Cleveland Clinic Journal of Medicine

Proceedings of the 2010 Heart-Brain Summit

Presented by the Earl and Doris Bakken Heart-Brain Institute at Cleveland Clinic
and the Society for Heart-Brain Medicine

September 23–24, 2010

Supplement Editor:

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Supplement to *Cleveland Clinic Journal of Medicine*
Supplement 1, Volume 78
August 2011

Acknowledgment of Grantors

The 2010 Heart-Brain Summit, on which this supplement is based, was supported in part by educational grants from BioControl Medical, Medtronic CRM, St. Jude Medical, and UCB Medical Education

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Supplement 1 to Volume 78, July 2011 • www.ccjm.org/content/78/Suppl_1

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The *Cleveland Clinic Journal of Medicine* [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published 12 times yearly by the Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal $115; institutional $143; single copy/back issue $20. Foreign: $160; single copy/back issue $20. Institutional (multiple-reader) rate applies to libraries, schools, hospitals, and federal, commercial, and private organizations. Individual subscriptions must be in the names of and paid by individuals.

Postmaster address changes: *Cleveland Clinic Journal of Medicine*, 1950 Richmond Road, TR4-04, Lyndhurst, OH 44124. Subscription orders, editorial, reprint, and production offices (same address): 216-444-2661 (phone); 216-444-9385 (fax); ccjm@ccf.org (e-mail); www.ccjm.org (Web).

Printed in USA.

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The *Bypassing the Blues* trial: Collaborative care for post-CABG depression and implications for future research

ABSTRACT

Depressive symptoms are reported by up to one-half of patients following coronary artery bypass graft (CABG) surgery, and are associated with numerous adverse outcomes, including poorer health-related quality of life, worse functional status, and delayed recovery. Strategies to detect and then manage depression in CABG patients and in cardiac populations are of great interest given the potential for depression treatment to reduce cardiovascular morbidity. Yet, many tested interventions have had little or no effect on mood symptoms in cardiac patients. "Collaborative care" is a safe and proven-effective strategy for treating depression in concert with patients' primary care physicians; however, it had not been tested previously in patients with cardiac disease. This article presents the design and main outcome findings from the National Institutes of Health–funded *Bypassing the Blues* study, the first trial to examine the impact of a collaborative care strategy for treating depression among patients with cardiac disease, and our efforts to improve upon and expand the model for testing in other cardiac conditions.

Coronary artery bypass graft (CABG) surgery is one of the most common and costly medical procedures performed in the United States.[1] However, up to one-half of post-CABG patients report significant increases in mood symptoms following surgery,[2] and these individuals are more likely to report poorer health-related quality of life (HRQoL) and worse functional status,[3] and to experience higher risk of rehospitalizations[4] and death[5] despite a satisfactory surgical result.

Strategies to detect and then manage depression in CABG patients and in cardiac populations are of great interest given the potential for depression treatment to reduce cardiovascular morbidity.

In recognition of the prevalence and excess burdens associated with this condition, a recent American Heart Association (AHA) Science Advisory has advocated regular screening and treatment of cardiac patients for depression.[6] Yet, the Advisory has been controversial,[7,8] as most depression treatment trials conducted in patients with cardiac disease have had less-than- anticipated impact on mood symptoms,[7,9–14] cardiovascular morbidity,[7,9,10,14] or mortality.[7,9–11,13–15] Possible explanations include: (1) dependence solely on single antidepressant agents[9,14] that, in general, are often ineffective,[16] untolerated, or otherwise discontinued by patients[17]; (2) reliance on psychologic counseling in elderly, medically ill populations who may be either unwilling or unable to adhere to successive face-to-face encounters with a therapist[10,13]; (3) inadequate consideration of patients' preferences for type and location of treatment[18,19]; (4) insufficient treatment adherence[20,21]; (5) perceived stigma of depression[22]; (6) brief duration of treatment and followup[9,13,14]; and (7) higher-than-expected spontaneous remission rates for depression.[10,14]

In an effort to overcome the limitations of earlier interventions, interest has turned toward "collaborative care" strategies for treating depression.[7,23–25] Based on Wagner's Chronic Care Model **(Figure 1)**,[26] collaborative care involves active followup by a nonphysician "care manager" who adheres to an evidence-based treatment protocol. The care manager contacts patients with the frequency necessary to educate them about their illness and proactively monitors their responses to treatment, all in collaboration with patients' primary care physicians (PCPs) and with specialty backup care when indicated.

Over the past 15 years, numerous trials have supported use of the flexible real-world collaborative care approach to improve outcomes for depression[27,28]

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

This work was supported by NIH grant R01 HL70007 (Rollman).

doi:10.3949/ccjm.78.s1.01

as well as a variety of other chronic medical conditions[29–32] and at a lower total cost of care.[33,34] This strategy is supported even outside the framework of a trial.[35,36] Moreover, collaborative care was the clinical framework[37] for a Robert Wood Johnson Foundation program to realign clinical and financial incentives for providing sustainable high-quality depression treatment in primary care.[38–41] It is also embraced by depression improvement initiatives supported by the MacArthur (http://www.depression-primarycare.org/)[42] and Hartford (http://impact-uw.org/)[43] Foundations. In recognition, a National Heart Lung and Blood Institute–sponsored working group on the assessment and treatment of depression in patients with cardiovascular disease endorsed testing of collaborative care strategies for treating depression in combination with "usual cardiologic care" as a method to improve clinical outcomes.[23] Collaborative care has also emerged as an integral part of the "patient-centered medical home" model presently advocated by leading professional organizations to organize and reimburse PCPs for providing high-quality chronic illness care.[44]

Despite this interest in collaborative care, to date, only the "Bypassing the Blues" (BtB) trial has reported the impact of this depression treatment strategy on the clinical outcomes of a population with cardiac disease.[45] In an effort to help disseminate collaborative care more broadly into routine practice as envisioned by the AHA Science Advisory, we present the key design elements and main outcome findings from BtB, along with our efforts to improve upon and expand the model for testing in other cardiac conditions.

STUDY OVERVIEW

BtB was designed to examine the impact of a telephone-delivered collaborative care strategy for treating depression after CABG surgery on HRQoL, physical functioning, health services utilization, and health care costs, as well as on mood symptoms and other measures that could influence uptake of this treatment strategy. The trial was powered to test the primary hypothesis: whether an 8-month course of collaborative care provided by a nurse care manager via telephone could produce a clinically meaningful improvement in HRQoL at 8 months post-CABG, as measured by the SF-36 Mental Component Summary Scale (MCS), versus physicians' "usual care" for depression. The 8-month period for testing our primary hypothesis allowed: (1) a therapeutic alliance to develop between patients, their PCPs, and our care managers; (2) patients initially unwilling or uninterested in trying any treatment modality time to change their minds, especially if their mood symptoms failed to remit; and (3) sufficient time for several therapeutic trials, if necessary, of antidepressant pharmacotherapy and counseling to take effect. Finally, BtB randomly sampled nondepressed post-CABG patients to better understand the impact of post-CABG depression and the benefits derived from its treatment **(Figure 2)**.[46]

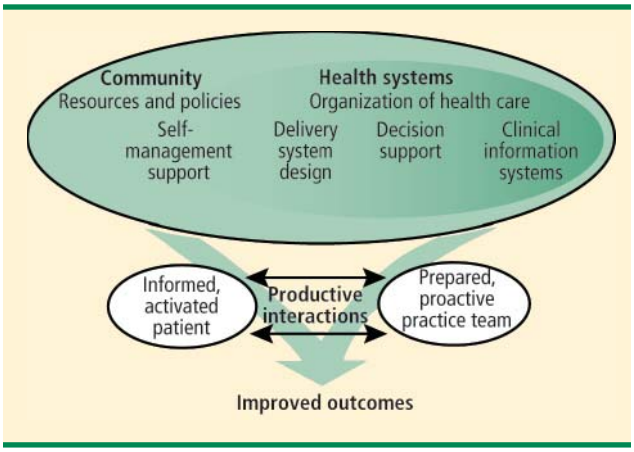

FIGURE 1. Overview of Wagner's Chronic Care Model.

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IDENTIFICATION OF DEPRESSION

Applying the two-step Patient Health Questionnaire (PHQ) depression screening strategy recently endorsed by the AHA Science Advisory,[6] BtB recruited medically stable post-CABG patients prior to hospital discharge from seven Pittsburgh-area hospitals between 2004 and 2007. To support our recruitment efforts, we developed press releases, wall posters, newsletter articles, and brochures to inform physicians, hospital staff, patients and their families about the impact of depression on cardiovascular disease and our study (available for download at: www.bypassingtheblues.pitt.edu).

Study nurse-recruiters obtained patients' signed informed consent to undergo screening with the two-item PHQ-2[22] ("Over the past 2 weeks have you had: little interest or pleasure in doing things or "felt down, depressed, or hopeless?").[47] We defined a positive PHQ-2 depression screen as patient endorsement of one or both of its items (90% sensitive and 69% specific for major depression among patients with cardiac disease when measured against the "gold-standard" Diagnostic Interview Schedule[48]).

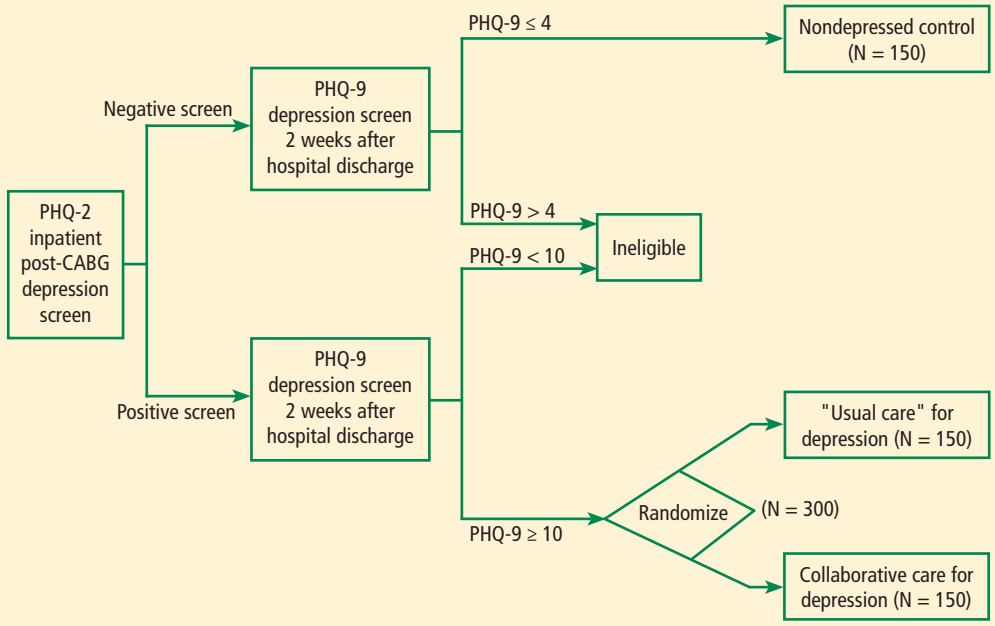

FIGURE 2. *Bypassing the Blues* study design. CABG = coronary artery bypass graft; PHQ = Patient Health Questionnaire

The psychologic and physical symptoms of depression often overlap with the post-CABG state (eg, fatigue, sleeplessness) and these elevations in depressive symptoms frequently remit spontaneously. Therefore, we administered the nine-item PHQ-9[49] over the telephone 2 weeks following hospital discharge to confirm the PHQ-2 screen. We required that patients score at least 10 to remain protocol-eligible, a threshold that signified at least a moderate level of depressive symptoms[49] and has been described as "virtually diagnostic" for depression among patients with cardiac disease (90% specific).[48]

ASSESSMENT AND OUTCOME MEASURES

Upon confirmation of all protocol-eligibility criteria prior to randomization, we conducted a detailed baseline telephone assessment that included the SF-36[50] to determine mental (MCS) and physical (PCS) HRQoL, the 12-item Duke Activity Status Index (DASI)[26] to determine disease-specific physical functioning, and the 17-item Hamilton Rating Scale for Depression (HRS-D)[27] to track mood symptoms. Telephone assessors blinded as to randomization status readministered these measures at 2, 4, and 8 months' followup and routinely inquired about any hospitalizations and mental health visits patients may have experienced since their last telephone assessment. Whenever they detected a potential "key event," we requested a copy of relevant medical records from the hospital where the event occurred. These were then forwarded to a physician adjudication committee that was blinded as to the patient's depression and intervention status to classify the nature of the event (cardiovascular, psychiatric, or "other").

COLLABORATIVE CARE INTERVENTION

Following randomization, a nurse care manager telephoned each intervention patient to: (1) review his or her psychiatric history, including use of any prescription medications, herbal supplements, or alcohol to self-medicate depressive symptoms; and (2) provide education about depression, its impact on cardiac disease, and basic advice for managing the condition (eg, exercise, sleep, social contact, alcohol avoidance); and (3) assess the patient's treatment preferences for depression.

Using a shared decision-making approach, patients then selected one or more of the following treatment options: (1) a workbook designed to impart self-management skills for managing depression[51]; (2) antidepressant pharmacotherapy, primarily a selective serotonin-reuptake inhibitor (SSRI) chosen according to patient preference, prior usage, and insurance coverage, but prescribed by the patient's PCP[46]; (3) referral to a local mental health specialist in keeping with the patient's insurance coverage; and (4) "watchful waiting" if the patient's mood symptoms were only mildly elevated and he or she had no prior history of depression.

Afterward, the nurse care manager telephoned the

FIGURE 3. Sample registry screenshot portraying an intervention patient's progress with our collaborative care program. Serial Patient Health Questionnaire (PHQ)-9 scores, pharmacotherapy usage, workbook lesson plans, and specialty referral (MHS) are all documented on this overview.

patient approximately every other week during the acute phase of treatment to practice skills imparted through workbook assignments, monitor pharmacotherapy, promote adherence with recommended care, and suggest adjustments in treatment as applicable. Depending upon the patient's motivation to complete workbook assignments and whether he or she accepted antidepressant pharmacotherapy, these followup contacts typically lasted 15 to 45 minutes and continued for 2 to 6 months. The patient subsequently transitioned to the "continuation phase" of treatment, during which the care manager contacted him or her less frequently until the end of our 8-month intervention.

WEEKLY CASE REVIEW

Our nurse care managers presented all new intervention patients and followup on ongoing cases to the study psychiatrist, internist, and project coordinator ("clinical team") at weekly case review sessions. To efficiently focus these sessions, we programmed our electronic registry to display each care manager's patient load on a conference room wall via an LCD projector so the information was current and visible to all **(Figure 3)**. Among the projected screens were: (1) the registry list of each nurse's intervention patients so as to focus group discussion on newly randomized patients and those with the highest levels of depressive symptoms; (2) an overview of a particular patient's progress, including serial PHQ-9 scores, pharmacotherapy usage, workbook lesson plans, and mental health specialty referral status; (3) additional clinical details to inform decision-making (eg, prior antidepressant experience); and (4) scores of individual PHQ-9 items to identify the precise domains where the patient was having difficulty (eg, sleep).

Following discussion, the clinical team typically

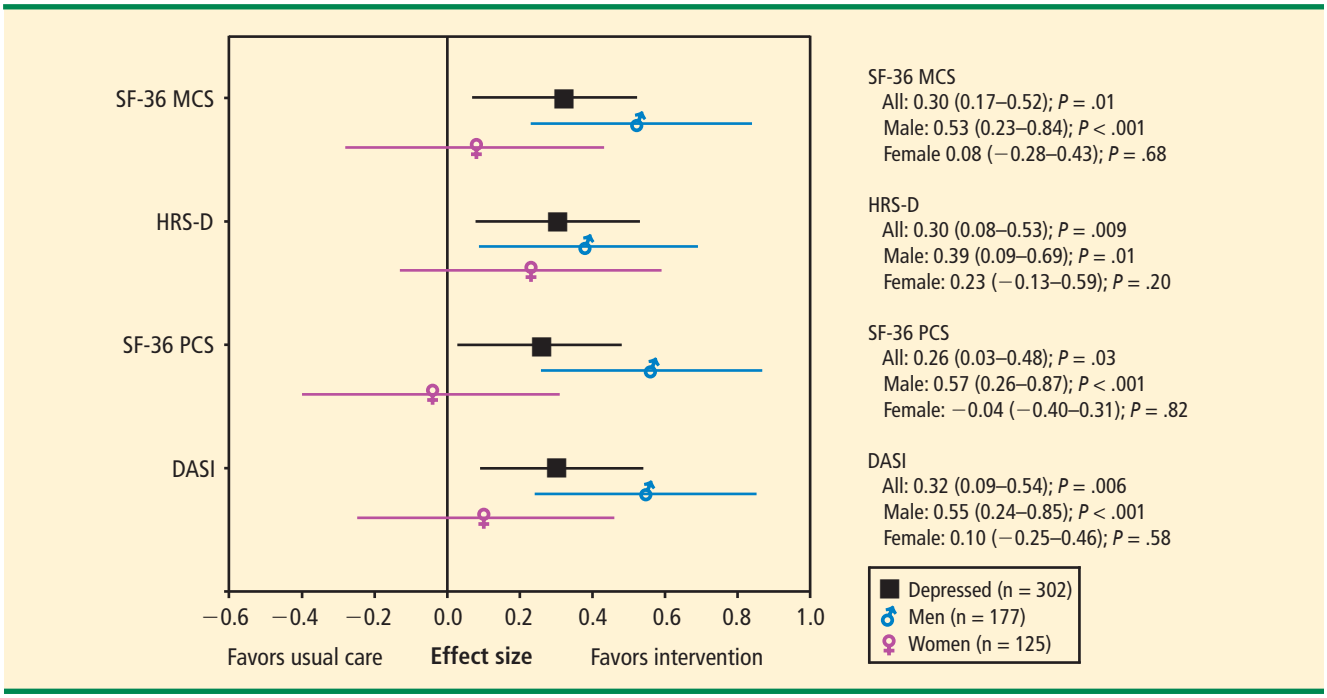

FIGURE 4. Main study outcomes.[45] DASI = Duke Activity Status Index; HRS-D: Hamilton Rating Scale for Depression (17-item); SF-36 MCS: Medical Outcomes Study 36-item Short Form Mental Component Summary; SF-36 PCS: Medical Outcomes Study 36-item Short Form Physical Component Summary

formulated one to three treatment recommendations that the nurse conveyed to the patient via telephone. As PCPs were responsible for prescribing all medications and dosage adjustments, we conveyed pharmacologic recommendations to them via telephone or fax. PCPs could accept or reject these recommendations at their discretion. If the patient demonstrated little response, had complex psychosocial issues (eg, impending divorce), or had an uncertain diagnosis (eg, bipolar disorder), we typically recommended referral to a mental health specialist. At quarterly intervals and at the end of the 8-month intervention, we mailed the PCP a summary of the patient's progress that included antidepressant dosages, PHQ-9 scores, and other pertinent information.[46]

PROMOTING MEDICATION ADHERENCE

To promote adherence with our treatment recommendations, our nurse care managers offered to call in antidepressant prescriptions to patients' pharmacies under their PCP's verbal orders, and then forwarded an order sheet for the PCP to sign and return to document it.

Some patients agreed to a trial of antidepressant pharmacotherapy but then declined or quickly discontinued it because of cost, side effects, or concerns about dependence, safety, or stigma. In these instances, particularly if the patient remained symptomatic, care managers attempted to overcome the patient's reluctance using various motivational interviewing approaches. Care managers also provided educational materials, including the workbook,[51] to mitigate any concerns, and emphasized they would monitor the patient's clinical status closely and report back to the clinical team and the patient's PCP for ongoing guidance. The care manager also informed the PCP of the patient's reason(s) for nonadherence, raising the possibility that the clinician could help overcome the patient's resistance.

OUTCOMES

Self-reported measures

BtB enrolled 453 post-CABG patients (101% target goal) who lived across western Pennsylvania, eastern Ohio, and West Virginia and met all protocol eligibility criteria. At the 8-month followup, depressed intervention patients reported significant improvements in mental and physical HRQoL, functional status, and mood symptoms versus those randomized to usual care **(Figure 4)**. Furthermore, intervention patients were more likely to achieve a 50% or greater decline from their baseline level of mood symptoms, as measured by the HRS-D, than patients randomized

to usual care (50% vs 30%), or an effect size (ES) improvement of 0.42 ($P < .001$)[45]; and they reported lower levels of pain.[52] As observed in other trials of depression treatment among patients with cardiac disease,[53–55] the intervention tended to be more effective in men than in women **(Figure 4)**.

PROCESSES OF CARE

Of the 150 patients randomized to our collaborative care intervention, 146 (97%) had one or more telephone care manager contacts and 83% had three or more contacts by the 4-month followup. At the 8-month conclusion of our intervention, the median number of care manager contacts per patient was 10 (range: 1–28). The proportion of intervention patients using antidepressants also increased from 15% at baseline to 44% by 8 months, and 4% reported a visit to a mental health specialist. In comparison, 31% ($P = .05$) and 6% (NS) of usual-care patients, respectively, were using an antidepressant or saw a mental health specialist during this period.[45]

HEALTH SERVICES UTILIZATION

Depressed patients reported a similar 8-month incidence of all-cause (33% intervention vs 32% usual care) and cardiovascular-cause (15% vs 18%) rehospitalizations by randomization status. However, male intervention subjects tended to have a lower incidence of cardiovascular-cause rehospitalizations than men randomized to usual care (13% vs 23%; $P = .07$) and one that was similar to that of nondepressed BtB male post-CABG patients (13%). Notably, we did not observe a similar pattern among female patients enrolled in BtB. To better examine the "business case" for treating post-CABG depression, we are presently analyzing claims data from Medicare and from two large western Pennsylvania insurance providers and hope to report these analyses shortly.

DISCUSSION

BtB was the first trial to examine the impact of a real-world collaborative care strategy for treating depression in post-CABG patients or in any other cardiac population. The generalizability of our treatment strategy is enhanced by multiple design features including: (1) use of a brief, validated, two-stage PHQ depression screening procedure that was endorsed by the AHA and can be routinely implemented by nonresearch clinical personnel; (2) a centralized telephone-delivered intervention; (3) reliance on a variety of safe, effective, simple-to-dose and increasingly generic pharmacotherapy options, a commercially available workbook, and community mental health specialists to deliver step-up care; (4) consideration of patients' prior treatment experiences, current care preferences, and insurance coverage when recommending care; (5) use of trained nurses as care coordinators across treatment delivery settings and providers across state lines; and (6) an informatics infrastructure designed to document and promote delivery of evidence-based depression treatment, care coordination, and efficient internal operations.

The ES improvement in HRS-D we observed in the BtB trial was at the upper end of a meta-analysis of 37 collaborative care trials for depression involving 12,355 primary care patients (ES: 0.25; 0.18–0.32).[27] It compared favorably with the improvements reported by the ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) randomized trial (ES: 0.22; 0.11–0.33),[10] the SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) (ES: 0.14; −0.06–0.35),[9] and the citalopram arm of the CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy) trial (ES: 0.29; 0.05–0.52).[13] However, our ES improvement was smaller than those generated by the more labor-intensive and face-to-face interventions provided by Freedland et al's trial of cognitive behavioral therapy (CBT) for post-CABG depression (ES: 0.73; 0.29–1.20; N = 123),[15] the COPES (Coronary Psychosocial Evaluation Studies) trial of problem-solving therapy (ES: 0.59; 0.18–1.00) that was the first to report a significant reduction in major adverse cardiac events from treating depression,[15,56] or a recent meta-analysis of psychologic treatments in patients with medical disorders (ES: 1.00; 0.57–1.44).[57]

Although the BtB intervention focused on depressed post-CABG patients, it is also generalizable to patients with other cardiovascular conditions. Moreover, the model can be readily adapted into practices at a variety of integrated health care delivery systems.[58] Therefore, we believe collaborative care interventions such as ours will become more widespread as elements of the 2010 Affordable Care Act are phased in.

FUTURE DIRECTIONS

Despite positive outcomes on HRQoL and mood symptoms generated by BtB and other recent trials,[15,56] it remains unclear whether effective depression treatment can reduce cardiovascular morbidity and mortality. Given the trend toward a reduced incidence of rehospitalization for cardiovascular causes among depressed male patients in BtB and findings

from COPES[56] and other trials,[7] we believe a comparative effectiveness trial of reasonable size (N < 2,000 study subjects) and cost will require an intervention capable of producing an ES reduction in mood symptoms of at least 0.50. Furthermore, because of declines in morbidity and mortality over the past decade following CABG surgery and myocardial infarction,[1] we also believe heart failure remains the only prevalent cardiovascular disorder for which to conduct this future comparative effectiveness trial.

Because an improvement of at least 0.50 ES in mood symptoms is higher than the ES improvements presently generated by collaborative care treatment approaches, it is critical to develop new interventions that blend the scalability and patient acceptability of telephone-delivered collaborative care with the greater efficacy of more intensive face-to-face counseling strategies. To address this need, we are investigating how best to incorporate Internet-delivered computerized cognitive behavioral therapy (CCBT) and other online strategies for treating depression into the BtB model. CCBT is a new and evolving technology that can improve patients' access to personalized, convenient, and effective treatment for depression.[59] Used primarily in the United Kingdom, Australia, and the Netherlands, CCBT has attracted growing interest by US investigators.[60] Importantly, some CCBT programs are able to produce the ES improvements in mood symptoms needed to potentially demonstrate a reduction of cardiovascular morbidity[61] and do so reliably, at scale, and at low cost compared with more labor-intensive methods of care.[62–64] Still, pilot testing of this innovative treatment approach is necessary to evaluate: (1) whether CCBT will be as effective among depressed patients with cardiovascular disease as among those recruited from primary care settings; (2) how best to integrate CCBT within a collaborative care program linked to cardiovascular patients' usual sources of cardiac and primary care; and (3) whether incorporating Internet-delivered CCBT into a "traditional" collaborative care program that provides active follow-up, pharmacotherapy monitoring, and mental health specialty referral as options provides either no additional benefit (ES ~0.30), benefit approaching that of CCBT alone (ES: ~0.60),[61] or an additive or synergistic benefit approaching face-to-face CBT (ES: ≥ 0.80).[15,65] Findings from these studies could also have profound implications for changing the way both cardiovascular and mental health conditions are treated[66] and direct further attention to the emerging field of e-mental health by other US investigators.[60]

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Type D personality and vulnerability to adverse outcomes in heart disease

ABSTRACT

General distress, shared across depression, anxiety and anger, partly accounts for the link between mind and heart. The type D (distressed) personality profile identifies individuals who are particularly vulnerable to the adverse effect of general distress. Type D individuals frequently experience negative emotions and are socially inhibited. This profile is more stable than that associated with episodes of clinical depression and describes the chronic nature of distress in some patients. Type D may also partly account for the effect of emotional distress on cardiac prognosis. Type D is associated with a threefold increased risk of adverse cardiovascular outcomes, even after adjustment for depression. This relationship is less obvious in patients with heart failure. Plausible pathways linking type D to cardiovascular complications include hypothalamic-pituitary-adrenal–axis hyperreactivity, autonomic and inflammatory dysregulation, and increased oxidative stress. Research needs to further clarify these pathways and investigate whether type D patients may benefit from closer monitoring of risk factors and a personalized approach to behavioral intervention. The DS14 is a brief, well-validated measure of type D that could be incorporated into clinical research and practice to identify high-risk patients.

Depression has been studied extensively in relation to cardiovascular disease.[1–3] In addition to depression, anger[4] and anxiety[5] also may promote coronary artery disease (CAD), suggesting that emotional distress in general may be related to increased cardiovascular risk. Evidence indicates that the general distress shared across depression, anger, and anxiety predicts CAD, even after controlling for each of these specific negative emotions.[6]

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

This work was supported by the Netherlands Organization for Scientific Research (The Hague, The Netherlands) with a VICI grant (453-04-004) to Dr. Johan Denollet.

doi:10.3949/ccjm.78.s1.02

THE CONCEPT OF TYPE D PERSONALITY

Lately, there is a renewed interest in broad individual differences in general distress and heart disease.[7] Since psychologic factors often cluster together in individual patients, biobehavioral research may benefit from the identification of discrete personality subtypes.[8] This focus on the identification of psychologically vulnerable patients who are at increased risk for adverse outcomes has led to the introduction of the *distressed*[9] or *type D*[10] personality profile in cardiovascular research. This personality construct is defined as follows:

"*The type D (distressed) personality profile refers to a general propensity to psychological distress that is characterized by the combination of negative affectivity and social inhibition.*"[10]

Negative affectivity, or the tendency to experience negative emotions across time and situations, is a major determinant of emotional distress in cardiac patients.[9,10] Patients who score high on this trait frequently report feelings of dysphoria, worry, and tension. Social inhibition, or the tendency to inhibit the expression of emotions or behavior, is a major determinant of social distress.[9,10] Patients who score high on this trait tend to avoid negative reactions from others.

Both traits define psychologically vulnerable patients and can be assessed with the type D scale (DS14).[10] This brief measure consists of a seven-item negative affectivity subscale (eg, *I often feel unhappy*) and a seven-item inhibition subscale (eg, *I am inhibited in social interactions*), and has a clear two-factor structure and good reliability (Cronbach's α = .88 and .86). Patients are classified as type D if they score 10 or higher on both DS14 subscales.[10] The prevalence of type D personality ranges between 20% and 40% across different types of cardiovascular conditions.

The type D construct was designed for the early identification of chronically distressed patients. This article reviews (1) the risk of adverse events associated with type D, (2) the extent to which type D is

TABLE 1

Type D and risk of clinical events in cardiovascular disease patients

Cardiovascular disease (n)	Clinical event (follow-up)	OR/HR (95% CI)	Meta-analytic review[23]
CAD			
CAD (303)[11]	Total mortality (6–10 y)	OR = 4.1 (1.9–8.8)*	Included in meta-analysis
CAD (319)[12]	Cardiac death, MI (5 y)	OR = 8.9 (3.2–24.7)†	Included in meta-analysis
CAD (337)[13]	Total mortality, MI (5 y)	OR = 4.8 (1.4–16.5)*	Included in meta-analysis
CAD (875)[14]	Total mortality, MI (9 mo)	OR = 5.3 (2.0–13.6)†	Included in meta-analysis
CAD (358)[15]	Total mortality, MI (2 y)	HR = 2.6 (1.1–6.0)‡	Included in meta-analysis
CAD (473)[16]	Cardiac death, MI (1.8 y)	HR = 2.2 (1.1–4.3)‡	Not included in meta-analysis
Other			
PAD (184)[17]	Total mortality (4 y)	HR = 3.5 (1.1–11.1)‡	Included in meta-analysis
CHF (87)[18]	Cardiac death, MI (6–10 y)	OR = 4.7 (1.9–11.8)*	Included in meta-analysis
CHF/HT (51)[19]	Mortality, rejection (5.4 y)	OR = 6.8 (1.4–30.9)‡	Included in meta-analysis
CHF (641)[20]	Cardiac death (3.1 y)	HR = 1.2 (0.6–2.1)	Not included in meta-analysis
ICD (391)[21]	Ventricular arrhythmia (1 y)	HR = 1.9 (1.1–3.1)‡	Not included in meta-analysis
ICD (371)[22]	Total mortality (1.7 y)	HR = 2.8 (1.2–6.2)*	Not included in meta-analysis

* $P < .01$; † $P < .0001$; ‡ $P < .05$

CAD = coronary artery disease; CHF = chronic heart failure; HR = hazard ratio; HT= heart transplantation; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; OR = odds ratio; PAD = peripheral arterial disease

distinct from depression, (3) the biologic pathways of type D, and (4) the implications of the type D personality profile.

RISK ASSOCIATED WITH TYPE D

Several prospective studies from our group have examined the notion that type D patients are particularly vulnerable to adverse events **(Table 1)**. In patients with CAD, evidence indicates that type D personality is an independent predictor of adverse events, including (cardiac) death, myocardial infarction, and need for revascularization procedures.[11–16] In these studies, type D also emerged as an independent predictor of adverse events after adjustment for anxiety,[11] stress,[13] depression,[16] disease severity,[11–16] and type of invasive treatment.[14] This increased risk associated with the type D profile was observed in the broader group of patients with CAD,[11–15] as well as in patients who survived an initial myocardial infarction.[16]

The relationship between type D personality and adverse events has also been investigated in other cardiovascular conditions. Type D has been associated with poor prognosis in patients with peripheral arterial disease,[17] but evidence for the prognostic role of type D in patients with chronic heart failure is mixed. In a study of patients with heart failure following myocardial infarction, type D predicted cardiac death independent of disease severity[18]; in a study of heart failure patients who underwent cardiac transplantation, type D was associated with early allograft rejection and increased mortality.[19] However, type D was not associated with cardiac death in a recent, larger heart failure study.[20] The link between psychologic factors and heart failure is complex[3] and may be less obvious than the type D-CAD link.[20] Type D has also been associated with the occurrence of life-threatening arrhythmias following implantable cardioverter defibrillator (ICD) treatment,[21] and it has been shown to predict an increased risk for mortality in ICD patients, independent from shocks and disease severity.[22]

The wide range in odds ratios and confidence intervals indicates disparity in data across these type D studies **(Table 1)**. We recently performed a meta-analysis of prospective studies between 1996 and 2009 to provide a more reliable estimate of the risk associated with type D. In this analysis, type D was associated with a threefold increased risk of adverse events[23]; the confidence interval of this pooled odds ratio ranged

from 2.7 to 5.1. In addition, type D personality was associated with a threefold increased risk (range, 2.6 to 4.3) of emotional distress over time.[23] From the recent studies that were not included in this meta-analysis, one reported negative findings[20] and three others positive findings[16,21,22] on the risk associated with type D.

COMPARING DEPRESSION AND TYPE D

Many studies report on depression and cardiac disease,[1–3] but both conceptual differences and clinical evidence indicate that type D and depression are distinct forms of distress **(Table 2)**. Conceptually, type D focuses not only on depressive affect but also on the general distress shared across negative emotions,[10] and it is based on the notion that social inhibition modulates the effect of negative emotions on cardiac prognosis.[24] While depression refers to an episodic distress factor (patients may go in and out of depressive episodes), the type D construct focuses on an underlying factor that predisposes patients to more chronic forms of distress.[8]

Clinical evidence shows that, after adjustment for depression, type D remained a predictor of adverse cardiac events in CAD.[16,24,25] Following ICD implantation, anxious type D patients were at risk of ventricular arrhythmias, whereas depression did not predict arrhythmias.[21] Type D also exerts an adverse effect on patients' health status following coronary bypass surgery,[26] heart failure,[27] or myocardial infarction,[28] adjusting for depressive symptoms. Type D is related to biomarkers of increased stress levels independent of depression[29–31] and, unlike depression, type D is not confounded by the severity of cardiac disorder.[32]

Following myocardial infarction, only one of four distressed patients met criteria for both type D and depression; most had one form of distress but not the other.[32] Research in healthy[33] and in cardiac[34] populations confirmed that items from depression and type D scales reflect different distress factors. After adjustment for depression at baseline, type D also predicted the incidence,[35] persistence,[36] and severity[37,38] of depression and anxiety. However, these findings do not imply that depression and type D are antonymous perspectives or that one perspective is better than the other in predicting outcomes; rather, we would like to argue that both constructs represent complementary perspectives that have added value.[23]

TABLE 2
Type D and depression are different forms of distress in cardiovascular disease patients

	Conceptual differences
Emotional	Type D focuses on general distress shared across negative emotions (anxiety, irritability, and others[10]) in addition to depressive affect
Social	Social inhibition is a factor in type D that may moderate the expression of emotions and behaviors in social interaction[24]
Duration	Emotional and social distress is a chronic factor (≥ 2 years) in type D, whereas it is an episodic factor (< 2 years) in depression [8–10]
	Cardiovascular outcomes
Clinical events	Type D personality predicts mortality and other clinical events in cardiac patients, even after adjustment for severity[16] and symptoms[24,25] of depression
Health status	Type D personality independently predicts poor health status over time in cardiac patients, above and beyond symptoms of depression[26–28]
Pathways of disease	Type D personality predicts increased oxidative stress and cortisol levels in cardiac patients after adjustment for depressive symptoms[29–31]
	Psychologic outcomes
Distinct diagnosis	There is only limited overlap between type D and depression classification[25,32]; items in type D and depression scales reflect different distress factors
Depressive symptoms	Type D personality predicts the onset and persistence of depressive symptoms in cardiac patients, controlling for depression at baseline[35,36]
Anxiety symptoms	Type D personality predicts the occurrence and severity of anxiety in cardiac patients, above and beyond symptoms of depression[37,38]

BIOLOGIC PATHWAYS OF TYPE D

A number of biologic pathways have been suggested to explain the effect of type D **(Table 3)**. Some have suggested dysregulation of the hypothalamic-pituitary-adrenal axis in patients with type D personality.[39] In fact, type D has been associated with greater cortisol reactivity to stress in healthy individuals[40] and with higher awakening[30] and daytime[31] cortisol levels in CAD patients. Autonomic dysregulation can also be inferred in type D individuals on the basis of a higher resting heart rate[41] and cardiovascular hyperreactivity[40,42] and decreased heart rate variability[43] in response to stress. In addition, type D has been related to reduced heart rate recovery after

TABLE 3
Potential biologic mechanisms underlying type D

	Healthy individuals	Cardiovascular patients
HPA-axis dysregulation	Increased cortisol reactivity to stress[40]	Higher CAR[30]; higher daytime cortisol[31]
Autonomic dysregulation	Higher HR[41]; increased CV stress reactivity[40,42]; decreased HRV[43]	Reduced HR recovery after exercise[44]
Inflammatory dysregulation	Higher concentration of CRP[41]	Increased plasma levels of TNF-α, TNFR1, TNFR2[46,47]
Reduced number of stem cells	Decreased EPC counts associated with NA[48]	Decreased EPC counts associated with type D[49]
Increased oxidative stress		Lower levels of Hsp70 and higher levels of XO[29]

CAR = cortisol awakening response; CRP = C-reactive protein; CV = cardiovascular; EPC = bone marrow-derived endothelial progenitor cells; HPA = hypothalamic-pituitary-adrenal; HR = heart rate; HRV = heart rate variability; Hsp70 = heat shock protein 70; NA = negative affectivity; TNF-α = tumor necrosis factor-α; TNFR1 = soluble TNF-α receptor 1; TNFR2 = soluble TNF-α receptor 2; XO = xanthine oxidase

exercise in patients with heart failure.[44] These indices of excessive sympathetic or inadequate parasympathetic modulation of heart rate predict poor cardiac prognoses.[45]

Other studies found that type D was associated with inflammatory dysregulation. In healthy adults, type D has been related to higher concentrations of C-reactive protein.[41] In heart failure patients, type D is associated with increased plasma levels of the proinflammatory cytokine tumor necrosis factor (TNF)-α and its soluble receptors 1 and 2.[46,47] Increased TNF-α levels may cause suppression of bone-marrow–derived endothelial progenitor cells (EPCs) that play an important role in maintaining vascular integrity. The negative affectivity component of type D has been shown to predict decreased circulating EPC counts in healthy individuals[48]; another study found that these EPC numbers were reduced by more than 50% in heart failure patients with a type D personality.[49] Type D personality is also associated with an increased oxidative stress burden in patients with chronic heart failure.[29] Studies on genetic linkage[50] and heritability[51] further support biologic underpinnings of the type D construct.

Regarding pathways that may explain the effect of type D, some issues are of special interest. First, genetic factors contribute to stability in type D personality, but environmental factors may induce changes in type D characteristics over time.[51] Hence, given this role of environmental influences over time, behavioral intervention would be feasible and useful in type D patients. Second, type D can promote heart disease indirectly through behavioral pathways. Type D has been associated with a sedentary lifestyle,[41,52] an unhealthy diet,[53] and a passive coping style.[54,55] Poor adherence to medical treatment[56,57] and reluctance to consult clinical staff[58] may jeopardize the working relationship with type D patients in clinical care. Intervention may focus on the management of these behavioral risk factors in type D patients. Third, many of these biologic[40–43,48,50,51] and behavioral[41,52–54] pathways have also been documented in healthy type D individuals, which suggests that these associations cannot be explained away by the confounding effect of underlying cardiovascular disease.

CLINICAL IMPLICATIONS OF TYPE D

The findings from type D research have a number of clinical implications. Type D is associated with an increased risk of adverse events,[23] chronic distress,[35–38] and suicidal ideation.[59] Type D may also have an adverse effect on the outcome of invasive treatment.[14,19,21,22,24,26,60]

Type D was associated with mortality and morbidity at 9 months[14] and 2 years[24] following coronary artery stenting, and with impaired health status 1 year following bypass surgery.[26] Type D also predicted mortality and allograft rejection following heart transplantation,[19] and an increased risk of ventricular arrhythmia[21] and mortality[22] in ICD patients. Researchers from the Cleveland Clinic have shown that type D is a risk factor for anxiety in ICD patients.[60]

Regarding the DSM-IV classification by the American Psychiatric Association,[61] type D qualifies for the diagnosis "psychological factors affecting medical condition" (Section 316). In keeping with this classification, the diagnostic category type D affects (1) the *course* of cardiovascular conditions,[23] (2) the *treatment* of these conditions,[56,57] and (3) the *working relationship* with medical staff.[58] At present, no clinical trial has examined whether intervention for distress among type D patients alters their risk for adverse events. Nevertheless, some have argued that it is plausible for type D patients to learn new strategies to reduce their level of general distress.[62] Previous research with patients experiencing symptoms like those of type D patients suggests that psychotherapy,

social skills training, stress management, and relaxation training may reduce stress in these patients and improve their ability to express their emotions to others.[62] Others have suggested that stress management training, including communication skills and problem-solving, may further improve the risk profile and health in cardiac patients.[63]

It is possible that type D patients may benefit from close monitoring of their clinical condition and from aggressive management of their risk factor profile to prevent adverse clinical events. Cardiac rehabilitation is an effective approach to treating risk factors and enhancing well-being in CAD.[63,64] A few studies have examined the effect of cardiac rehabilitation in type D patients. One study found a significant decrease in the social inhibition component of type D following cardiac rehabilitation, but there was no change in the prevalence of type D at 1-year follow-up.[65] Although the type D profile tends to remain stable during rehabilitation,[65,66] evidence shows that type D patients who participate in cardiac rehabilitation improve in physical and mental health status.[66] Cardiac rehabilitation may also ward off further deterioration in negative affect,[67] which, in turn, has been associated with better survival in patients who participated in rehabilitation.[68] Future studies need to examine the effect of cardiac rehabilitation and other personalized approaches to treatment in type D patients.

CONCLUSIONS

General distress shared across negative emotions[6,23] may partly account for the role of depression, anxiety, and anger in cardiovascular disorders.[1–5] Some cardiac patients are more likely to experience distress than others. Type D may identify these psychologically vulnerable patients who tend to experience general distress.[23] This propensity to general distress differs from depression, predicts adverse outcomes, is linked to plausible biologic pathways, and highlights the chronic nature of psychologic distress in some cardiac patients.

After adjustment for depression, type D remains significantly associated with an increased risk of adverse events in patients with CAD.[16,24,25] However, this association is less obvious in patients with heart failure, and type D did not predict survival in one heart failure study.[20] Although initial findings suggest a number of plausible biologic and behavioral pathways, more research is needed to explain the adverse effect of type D on cardiovascular outcomes. Future research also needs to investigate whether type D patients may benefit from close monitoring of their risk factors and a more personalized approach to behavioral and cardiac treatment.

Overall, the current understanding of type D indicates that general distress should not be ignored in the link between mind and heart, and that cardiovascular patients who have a type D personality profile are particularly vulnerable to the adverse clinical effects of general distress. The DS14[10] is a brief, well-validated measure of type D that could be incorporated into clinical research and practice to identify patients who are at risk of chronic distress and poor prognosis.

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Biofeedback in the treatment of heart disease

ABSTRACT

Biofeedback is a method of training subjects to regulate their own physiology using feedback from physiologic sensors connected to an output display. Biofeedback-assisted stress management (BFSM) incorporates the physiologic signals with instructions on stress management. The goal of BFSM training is to give subjects the tools to control their own mental and physiologic reactions, leading to improved health and wellness. In cardiovascular disease, overactivation of the sympathetic component of the autonomic nervous system and psychologic stress together negatively affect quality of life and clinical status. BFSM targets both areas. We hypothesize that this intervention can be used in cardiovascular disease to improve clinical status and quality of life, as well as interfere with disease progression. We are conducting trials of BFSM in heart failure and stable coronary artery disease. Preliminary data suggest that use of BFSM by heart failure patients may actually cause cellular and molecular remodeling of the failing heart in the direction of normal. We are comparing the effects of BFSM with usual care in patients with stable coronary artery disease, testing the hypothesis that the intervention will decrease both sympathetic hyperarousal and activation of the inflammatory cascade. Since heart rate variability is abnormal in both cardiovascular disease and depression, and since BFSM has been successfully used to change heart rate variability, we also expect this intervention to have a positive impact on the depression that often accompanies cardiovascular disease.

BIOFEEDBACK: WHAT IS IT?

The term "biofeedback" refers to the instrumentation or training process that allows biologic information to be recorded, displayed, and communicated back to an individual, allowing the individual to make adjustments in physiologic processes that may enhance health or performance. The biofeedback display is analogous to a mirror, in which physiologic processes can be observed and adjusted much as one might adjust a hairstyle or a tie.

In our work with cardiovascular disease patients, biofeedback is a training process that involves a subject or patient, a biofeedback coach or therapist, and state-of-the-art biofeedback equipment. For biofeedback training to be effective, the subject who is trying to learn the skill must be engaged and willing to practice, the coach must be trained in psychophysiology, and the equipment must display accurate readings in real time, allowing the subject to monitor and change physiologic reactions appropriately. The coach teaches the subject about the physiologic parameters, establishes target ranges, and helps the subject learn how to move the physiologic parameters in the right direction.[1,2]

Training often begins with a session in which a brief mental stress test is followed by a period of relaxation while physiologic parameters are recorded and displayed. This process helps the subject to understand the link between mental processes and physiologic arousal.

Biofeedback training can involve a number of physiologic modalities, including those that reflect autonomic nervous system arousal, such as skin conductance and heart rate variability, and those that are not strictly correlated with autonomic activity, such as surface muscle tension. Each physiologic parameter is recorded by a specific sensor, and all sensors are noninvasive. Sensors feed signals into a computer, where they are processed and amplified, and subjects are able to view the output on a computer screen.

Typically, in our work, there is one screen for the subject, on which a single parameter can be displayed, observed and discussed, and another screen for the coach, on which all parameters are displayed simultaneously. During a single session of biofeedback training, the coach may choose to work on a single parameter or switch between parameters, depending on how much progress is being made with each. In our work with patients, we generally train to simple parameters first, such as respiratory rate, finger temperature, and skin conductance, moving on to surface muscle tension, heart rate, and eventually heart rate

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

doi:10.3949/ccjm.78.s1.03

variability, which is a more complex concept and more easily understood later in the training process.

It is important that the subject receive positive reinforcement for changing the physiologic parameters, and if the subject struggles too long with one parameter, it is generally useful to go back to a different parameter, where success may be more easily experienced. Ideally, by the end of six to eight training sessions, the subject will be able to make progress on all physiologic parameters, which will track together over time.

BIOFEEDBACK-ASSISTED STRESS MANAGEMENT

Pure biofeedback training consists of operant conditioning. That is, the subject learns to regulate his or her physiology in the right direction because of the feedback, which can be as simple as a pleasant image appearing on a computer screen or as complicated as a car moving faster around a racetrack; pure biofeedback involves changing physiology in response to positive reinforcement of some sort.

In practice, we generally employ biofeedback-assisted stress management (BFSM) rather than pure biofeedback. With BFSM, the subject learns to change physiology in the direction of health and wellness by learning techniques of stress management. The coach teaches the subject various relaxation techniques, such as slow and rhythmic breathing, guided imagery, progressive muscle relaxation, mindfulness, assertiveness, and how to change negative thought patterns. With regular practice, the subject learns to change the physiologic parameters by relaxing the body. For example, instead of instructing the subject to "increase your finger temperature" and assume that the subject will achieve this because doing so will make the light bulb on the screen glow more intensely, the BFSM coach may instead talk with the subject about eliminating stressful thoughts, learning to relax, and the fingers warming in response to the body relaxing.

We distinguish between techniques of stress management, some of which are mentioned above, and psychotherapy, which can certainly be effectively combined with biofeedback, but which we do not provide in our research studies. Coupling stress management techniques with biofeedback helps the subject change physiologic parameters in the direction of wellness and acquire tools that can be used in everyday life when stressful events arise. The objective of BFSM training is not just to change physiology, but also to change the way subjects respond to stressful events in daily life; ie, react to fewer events, react less intensely when they do react, and recover more quickly.

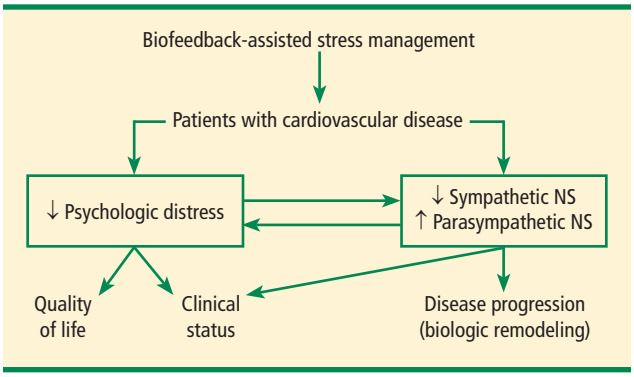

FIGURE. Proposed model by which biofeedback-mediated stress management interferes with symptoms and progression of cardiovascular disease. NS = nervous system

BIOFEEDBACK-ASSISTED STRESS MANAGEMENT IN CARDIOVASCULAR DISEASE

We are currently studying the effects of BFSM in patients with cardiovascular disease, including both heart failure and stable coronary artery disease. Patients with cardiovascular disease often are functionally limited, and they also experience psychologic distress related to physical limitations and other life stressors. Both the physical limitations and the psychologic distress impact quality of life. We hypothesize that BFSM will teach our patients techniques of stress management, both mental and physiologic, that will help relieve their psychologic distress and improve their quality of life. BFSM will also potentially decrease the overactivation of the sympathetic branch of the autonomic nervous system, which is common in cardiovascular disease, and correspondingly upregulate the contribution of the parasympathetic branch of the autonomic nervous system, which should be beneficial.[3]

We postulate that the decreased psychologic distress and improved balance of autonomic nervous system input to the heart will result in improved clinical status and biologic remodeling of the heart and blood vessels away from disease progression and toward health and wellness **(Figure)**.

A PROMISING TECHNIQUE IN HEART FAILURE

We are currently studying the effects of BFSM in patients with end-stage heart failure who are awaiting heart transplant at Cleveland Clinic.[4] As noted in a recent review, biofeedback is a promising technique in heart failure that patients may be able to use to consciously regulate their autonomic nervous systems.[5] We hypothesize that BFSM training will

interfere with the overactivation of the sympathetic nervous system that is characteristic of heart failure, and that this will reverse the cellular and molecular remodeling that occurs in the failing human heart.

To date, we have enrolled 25 patients; 10 are being studied in our National Institutes of Health–funded Clinic Research Unit and 15 are inpatients. All 25 patients are listed as heart transplant candidates and have given consent for us to study their hearts when they are explanted.

Each patient receives eight sessions with a certified biofeedback therapist. The first and last sessions include mental stress tests, while the remaining six are BFSM training sessions. Patients are assessed at the beginning and end of the study using the 6-minute walk test, the Kansas City Cardiomyopathy Questionnaire, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and measurement of plasma catecholamines.

The primary end point of the study is the measurement of cellular and molecular markers that have been shown to be altered in the failing human heart, testing the hypothesis that these markers will be reversed in the direction of normal in the BFSM therapy group. These markers are measured in the explanted failing heart when the patient receives a heart transplant.

It is too early to report the results of this study, since only seven patients have undergone transplantation to date. We are encouraged by several early findings, however, and hope these will be validated when the entire group is analyzed.

In early analysis, scores on the Kansas City Cardiomyopathy Questionnaire are improved in the last session compared with the first; patients have shown the ability to learn a slower breathing rate; and they are able to regulate their heart rate variability, as measured by the standard deviation of the N-to-N interval, or SDNN. Most important, measurements in the first seven hearts indicate that there is a degree of biologic remodeling of the failing heart after BFSM that is similar to what we have observed with left ventricular assist devices—hemodynamic pumps that take on the workload of the heart, permitting the heart to rest and recover while the patient is waiting for a transplant.[6,7] If BFSM could produce changes in the cellular and molecular properties of the heart that are equal in magnitude to those produced by a mechanical pump, this would be a revolutionary finding in the field of heart-brain medicine.

It should be noted that we are not the first group to study BFSM in patients with heart failure. Moser and colleagues first observed that a single session of skin temperature biofeedback could have significant functional effects in patients with heart failure.[8] Bernardi and coworkers showed that merely teaching patients to breathe six times per minute (a large component of BFSM training) improved oxygen saturation and exercise tolerance.[9] Swanson and colleagues in 2009 demonstrated that patients with heart failure were able to regulate their heart rate variability, although they observed this only in patients with a left ventricular ejection fraction greater than 30%.[10] Our preliminary data demonstrate regulation of heart rate variability in patients with lower ejection fractions, which is promising, but we have also added the biologic component of studying the explanted heart, allowing us to test the hypothesis that BFSM could potentially impact the remodeling process and thus have important therapeutic implications.

TRIAL UNDER WAY IN CORONARY ARTERY DISEASE

In addition to our studies of BFSM in heart failure, we have begun a randomized clinical trial of patients with stable coronary artery disease, type 2 diabetes, or multiple sclerosis. These three patient populations were chosen because evidence from numerous studies suggests that they all involve autonomic nervous system dysregulation as well as an inflammatory process.

It has already been mentioned that BFSM can interfere with overactivation of the sympathetic nervous system and potentially upregulate the contribution of the parasympathetic nervous system, which usually exists in juxtaposition to the sympathetic nervous system. Based on the work of Tracey,[11,12] upregulating the parasympathetic nervous system should be antiinflammatory. Thus, we hypothesize that by decreasing both sympathetic nervous system activation and inflammation, BFSM should have an impact on patients with one of these disease states, resulting in improved quality of life and clinical status, reduced anxiety and depression, and changed disease-specific indicators of severity.

We are currently enrolling patients who have coronary artery disease, type 2 diabetes, or multiple sclerosis and randomizing them to groups that will receive either BFSM or usual care. Outcome variables that will be assessed in all patients include heart rate variability; the response of temperature, skin conductance, respiratory rate, and heart rate variability to mental stress; plasma catecholamine levels; plasma C-reactive protein levels; and tumor necrosis factor alpha levels. At the first and last visits, all patients will complete the SF-36, the eight-item Patient

Health Questionnaire depression scale (PHQ-8), the Generalized Anxiety Disorder seven-item scale (GAD-7), and a visual analog pain scale. We will also assess disease-specific variables, including heart rate recovery after exercise, plasma lipids, and myeloperoxidase in patients with coronary artery disease; the Multiple Sclerosis Functional Composite (MSFC) test and the Modified Fatigue Impact Scale (MFIS) will be administered to patients with multiple sclerosis; and plasma glucose and hemoglobin A1C will be assessed in patients with type 2 diabetes.

Results of this study will provide data on the potential of BFSM to decrease common markers of autonomic nervous system activation and inflammatory cascades and the effect of those alterations on three specific disease states. To our knowledge, such a randomized study has not been conducted previously; our findings will add significantly to the literature on the mechanism of action of biofeedback-type interventions.

POTENTIAL IMPACT ON DEPRESSION IN CARDIOVASCULAR DISEASE

Depression is increasingly recognized as a component of many cardiovascular diseases; this raises the question of what effect BFSM therapy in cardiovascular disease patients will have on their depression. Of particular importance to this discussion, heart rate variability has been shown to be decreased both in cardiovascular disease and in depression, and BFSM is one treatment that can be used to regulate heart rate variability. Heart rate variability biofeedback has been shown to be useful in treating depression.

Work from Karavidas and colleagues showed that 10 weeks of heart rate variability biofeedback in patients with depression led to significantly improved scores on the Hamilton Depression Scale and the Beck Depression Inventory. Improvement was observed by the fourth week of training, with concurrent increases in the SDNN.[13] Siepmann and colleagues also used heart rate variability biofeedback in depressed subjects and demonstrated significant improvement in scores on the Beck Depression Inventory, as well as a concomitant decrease in anxiety.[14] In related work, Uhlmann and Fröscher used electroencephalographic biofeedback (also called neurofeedback) in epilepsy patients with depression and measured an increased sense of self control and a decrease in external locus of control; they postulated that biofeedback training provided an important opportunity for success, and thus increased internal control and decreased depression.[15]

Evidence suggests that BFSM should have an impact on depression in addition to impacting the cardiovascular disease itself, and both should work together to improve quality of life. For this reason we have added a depression inventory to our randomized trial of BFSM in patients who have coronary artery disease, diabetes, or multiple sclerosis.

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Electrical vagus nerve stimulation for the treatment of chronic heart failure

ABSTRACT

Autonomic dysregulation is a feature of chronic heart failure (HF) and is characterized by a sustained increase of sympathetic drive and by withdrawal of parasympathetic activity. Both sympathetic overdrive and increased heart rate are predictors of poor long-term outcome in patients with HF. Pharmacologic agents that partially inhibit sympathetic activity, such as beta-adrenergic receptor blockers, effectively reduce mortality and morbidity in patients with chronic HF. In contrast, modulation of parasympathetic activation as a potential therapy for HF has received only limited attention because of its inherent complex cardiovascular effects. This review examines results of experimental animal studies that provide support for the possible use of electrical vagus nerve stimulation (VNS) as a long-term therapy for the treatment of chronic HF. The review also addresses the effects of VNS on potential modifiers of the HF state, including proinflammatory cytokines, nitric oxide elaboration, and myocardial expression of gap junction proteins. Finally, the safety, feasibility, and efficacy trends of VNS in patients with advanced HF are reviewed.

Autonomic imbalance characterized by sustained sympathetic overdrive and by parasympathetic withdrawal is a key maladaptation of the heart failure (HF) state. This autonomic dysregulation has long been recognized as a mediator of increased mortality and morbidity in myocardial infarction and HF.[1,2] Sympathovagal imbalance in HF can lead to increased heart rate, excess release of proinflammatory cytokines, dysregulation of nitric oxide (NO) pathways, and arrythmogenesis. Diminished vagal activity reflected in increased heart rate is a predictor of high mortality in HF.[3,4] Sustained increase of sympathetic activity contributes to progressive left ventricular (LV) dysfunction in HF and promotes progressive LV remodeling.[5,6] Pharmacologic agents that reduce heart rate, such as beta-blockers and, more recently, specific and selective inhibitors of the cardiac pacemaker current *If*, have been shown to improve survival and prevent or attenuate progressive LV remodeling in animals with HF.[4,5,7,8]

During the past two to three decades, the emphasis on modulation of neurohumoral activition for treatment of chronic HF gave rise to angiotensin-converting enzyme inhibitors, beta-adrenergic receptor blockers, and aldosterone antagonists. In recent years, renewed interest has emerged in modulating parasympathetic or vagal activity as a therapeutic target for treating chronic HF. An alteration in cardiac vagal efferent activity through peripheral cardiac nerve stimulation can produce bradycardia and can modify atrial as well as ventricular contractile function.[9,10]

Electrical vagus nerve stimulation (VNS) was shown to prevent sudden cardiac death in dogs with myocardial infarction and to improve long-term survival in rats with chronic HF.[11,12] VNS has also been shown to suppress arrhythmias in conscious rats with chronic HF secondary to myocardial infarction.[13]

This article focuses primarily on the effects of chronic VNS on LV dysfunction and remodeling in dogs with HF produced by multiple sequential intracoronary microembolizations[14] or by high-rate ventricular pacing[15] and on the safety, feasibility, and efficacy trends of VNS in patients with advanced HF.[16]

VNS IN DOGS WITH MICROEMBOLIZATION-INDUCED HEART FAILURE

The CardioFit VNS system (BioControl Medical, Yehud, Israel), used in dogs with coronary microembolization-induced HF, delivered electrical stimulation to the right cervical vagus only when the heart rate increased beyond a preset level, thus operating on a negative-feedback loop **(Figure 1)**. The

Dr. Sabbah reported that he is a paid consultant for BioControl Medical, Ltd. and a member of the BioControl Medical, Ltd. Advisory Committee.

Supported, in part, by research grants from BioControl Medical, Ltd., and National Heart, Lung, and Blood Institute PO1 HL074237-06.

doi:10.3949/ccjm.78.s1.04

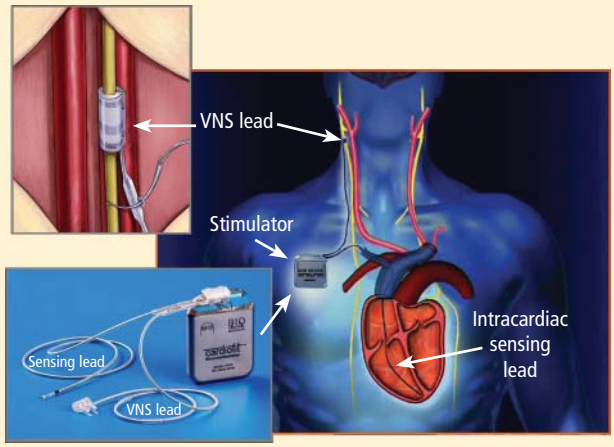

FIGURE 1. Right: Depiction of an implanted CardioFit vagus nerve stimulation (VNS) device showing the position of the VNS lead on the right vagus nerve, the intracardiac pacing lead in the right ventricular apex, and the implantable CardioFit neurostimulator in the right subclavicular region. Top left: Positioning of the CardioFit stimulation lead around the right vagus nerve. Bottom left: The CardioFit VNS implantable neurostimulator, sensing lead, and VNS lead.
Courtesy of BioControl Medical, Ltd., Yehud, Israel

stimulation lead was a modified bipolar cuff electrode designed to activate vagus cardioinhibitory B fibers while maintaining a large degree of unidirectionality with respect to low threshold fibers recruited in the 1- to 2-mA range. The lead is attached to a model 5000 electrostimulator fitted with a processing unit that adjusts the impulse rate and intensity to keep the heart rate within the desired range. Maximal stimulation current, pulse width, and operation algorithm are controlled by the physician programmer via wireless communication. A standard pacemaker bipolar ventricular electrode, also attached to the model 5000 electrostimulator, was used in all the animal studies for sensing the intracardiac electrocardiogram (ECG).

Monotherapy with VNS

Dogs with HF and LV ejection fraction of approximately 35% were randomized to 3 months of active VNS monotherapy (CardioFit on, n = 7) or to no therapy at all (sham-operated control, CardioFit off, n = 6). The feedback on-demand heart rate control was set to reduce basal heart rate by 10%.[17] Long-term (3 months) VNS monotherapy significantly improved LV ejection fraction and significantly decreased LV end-systolic and end-diastolic volumes compared with controls **(Table 1)**.[17] The reduction in LV size was in line with an observed decrease in plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP). In VNS-treated dogs, heart rate assessed using ambulatory ECG Holter monitoring showed a reduction of minimum, average, and maximum heart rate by 1, 10, and 28 beats per minute, respectively, compared with changes of heart rate in control dogs of 2, 1, and 0.5 beats per minute, respectively.

TABLE 1
Indices of LV systolic and diastolic function in control and VNS-treated dogs before (PRE) and 3 months after (POST) initiating therapy[17,33]

	Control (n = 6)		VNS (n = 7)	
	PRE	POST	PRE	POST
LV EF (%)	33 ± 1	29 ± 1*	34 ± 1	41 ± 1*
LV EDV (mL)	56 ± 2	60 ± 2*	58 ± 1	57 ± 3*
LV ESV (mL)	37 ± 1	42 ± 2*	38 ± 2	34 ± 3*
NT-proBNP (pg/mL)	487 ± 11	546 ± 126*	554 ± 84	260 ± 24*
LVEDP (mm Hg)	14 ± 1	15 ± 1	15 ± 1	11 ± 2*
PE/PA	2.0 ± 0.2	1.8 ± 0.2	2.0 ± 0.3	2.4 ± 0.4
DT (msec)	91 ± 1	85 ± 4	94 ± 5	111 ± 10*
EDWS (g/cm^2)	54 ± 3	57 ± 4	60 ± 5	46 ± 7*

DT = deceleration time of early rapid mitral inflow velocity; EDV = end-diastolic volume; EDWS = left ventricular end-diastolic circumferential wall stress; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE/PA = ratio of peak early rapid mitral inflow velocity (PE) to peak of mitral inflow velocity during left atrial contraction (PA); VNS = vagus nerve stimulation
* $P < .05$ vs PRE.

Long-term VNS therapy also elicited improvements in indices of LV diastolic function. VNS significantly decreased LV end-diastolic pressure **(Table 1)**, increased deceleration time of rapid mitral inflow velocity, tended to increase the ratio of peak mitral inflow velocity during early LV filling to peak mitral inflow velocity during left atrial contraction (PE/PA), and significantly reduced LV end-diastolic circumferential wall stress, a determinant of myocardial oxygen consumption **(Table 1)**. These measures suggest that VNS can reduce preload, improve LV relaxation and improve LV function without increasing myocardial oxygen consumption.

VNS in combination with beta-blockade

The effects of VNS in combination with beta-blockade were examined in dogs with HF. Dogs with LV ejection fraction of approximately 35% were randomized to 3 months of therapy with a beta-blocker alone (metoprolol succinate, 100 mg once daily, n = 6) or to

TABLE 2
Indices of LV systolic and diastolic function before (PRE) and 3 months after (POST) initiating therapy in heart failure dogs with beta-blocker alone or beta-blocker plus VNS[18,33]

	β-Blocker		β-Blocker + VNS	
	PRE	POST	PRE	POST
LV EF (%)	30.7 ± 0.9	36.2 ± 1.2*	33.3 ± 0.8	43.2 ± 0.7*
LV EDV (mL)	55.7 ± 3.7	56.3 ± 3.2	55.7 ± 1.6	56.3 ± 1.6
LV ESV (mL)	38.7 ± 2.7	35.8 ± 1.9*	37.2 ± 1.2	31.5 ± 1.0*
LV EDP (mm Hg)	13.3 ± 0.8	10.5 ± 0.6*	12.7 ± 0.8	8.5 ± 0.7*
PE/PA	1.7 ± 0.1	2.1 ± 0.2	1.5 ± 0.1	2.1 ± 0.1*
DT (msec)	80.2 ± 1.3	86.0 ± 1.3*	78.3 ± 1.3	91.3 ± 1.5*
EDWS (g/cm^2)	51.5 ± 3	40.0 ± 2.0	45.9 ± 4.0	29.6 ± 3.0*

Abbreviations as in **Table 1**.
* $P < .05$ vs PRE.

metoprolol (100 mg once daily) combined with active VNS with CardioFit (n = 6). As with the monotherapy study, the CardioFit VNS system was operated in the feedback on-demand heart rate responsive mode. Dogs were started on oral metoprolol therapy 2 weeks prior to randomization to VNS therapy. After randomization, all dogs continued to receive metoprolol succinate once daily for the duration of the study.[18]

In HF dogs receiving background therapy with metoprolol, the addition of VNS increased LV ejection fraction and decreased LV end-systolic volume compared with dogs treated with metoprolol alone **(Table 2)**.[18] These findings suggest that the addition of VNS improves LV systolic function beyond that seen with beta-blockade alone. Adding VNS therapy to metoprolol also elicited improvements in indices of LV diastolic function. Combination therapy resulted in greater lowering of LV end-diastolic pressure and LV end-diastolic wall stress and greater increase in deceleration time of rapid mitral inflow velocity compared with metoprolol alone.

The improvements in LV systolic and diastolic function with combination therapy were associated with important changes in heart rate. Twenty-four–hour ambulatory ECG Holter monitoring studies showed no differences in minimum and average heart rate between dogs treated with metoprolol and those treated with combination therapy with VNS. Maximum heart rate, however, was significantly lower in dogs treated with the combination therapy (114 ± 12 vs 149 ± 8 beats/min, $P < .05$). These observations suggest that preventing heart rate escape at the high end may further improve LV systolic function compared with beta-blockade alone. This added benefit of the combination of VNS and beta-blockade was likely the result of reducing the adverse impact of increased cardiac workload and increased myocardial oxygen consumption elicited by the heart rate increase.

VNS and left ventricular remodeling

In addition to improving LV systolic and diastolic function, long-term VNS in dogs with coronary microembolization-induced HF led to important changes in cellular and structural markers of LV remodeling.[19] Compared with untreated HF dogs, dogs treated with VNS as monotherapy showed a significant decrease in volume fraction of replacement and interstitial fibrosis; a decrease in oxygen diffusion distance, measured as half the distance between two adjoining capillaries; a decrease in myocyte cross-sectional area, a measure of cardiomyocyte hypertrophy; and an increase in capillary density **(Figure 2)**. These histomorphometric measures are often, if not always, adversely affected by the HF state. Their amelioration by VNS suggests that this form of therapy can help preserve myocardial structural integrity through direct or indirect action on the failing myocardium.

VNS and proinflammatory cytokines, nitric oxide, and gap junction proteins

Elevation of proinflammatory cytokines occurs in HF and is associated with increased morbidity and mortality. Electrical VNS has been shown to decrease the release of various cytokines, including tumor necrosis factor (TNF)-alpha and interleukin (IL)-6.[20] In dogs with microembolization-induced HF, LV tissue levels of TNF-alpha and IL-6 are elevated compared with LV tissue from normal dogs **(Table 3)**. Long-term monotherapy with VNS normalizes protein expression of both TNF-alpha and IL-6 in LV myocardium.[21]

Nitric oxide (NO) is formed by a family of NO synthases (NOS). The three isoforms of NOS identified to date are endothelin NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS). The three isoforms have differing characteristics and roles:

eNOS. NO produced by eNOS plays an important role in the regulation of cell growth and apoptosis[22] and can enhance myocardial relaxation and regulate contractility.[22,23]

iNOS. Overexpression of iNOS in cardiomyocytes in mice results in peroxynitrite generation associated with fibrosis, LV hypertrophy, chamber dilation,

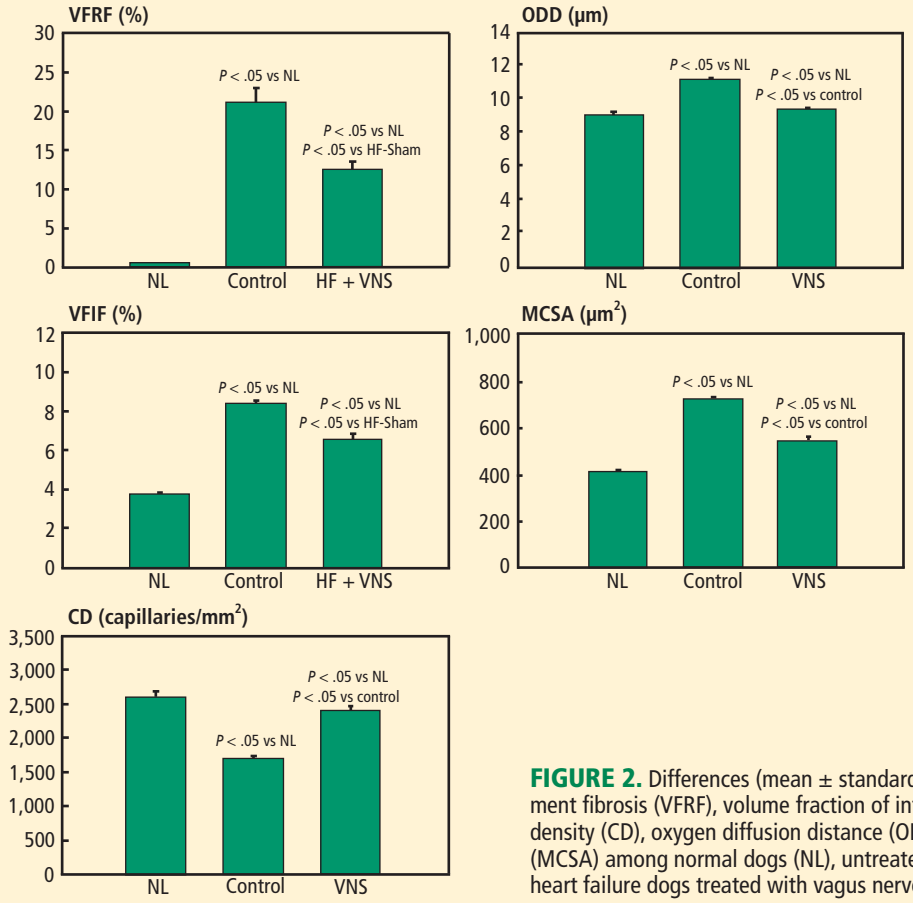

FIGURE 2. Differences (mean ± standard error) in volume fraction of replacement fibrosis (VFRF), volume fraction of interstitial fibrosis (VFIF), capillary density (CD), oxygen diffusion distance (ODD), and myocyte cross-sectional area (MCSA) among normal dogs (NL), untreated heart failure dogs (control), and heart failure dogs treated with vagus nerve stimulation (VNS).[33]

cardiomyopathic phenotype, heart block, and sudden cardiac death.[24]

nNOS. nNOS has been shown to be upregulated in the human failing heart and in rats following myocardial infarction.[25] In rats with HF, inhibition of nNOS leads to increased sensitivity of the myocardium to beta-adrenergic stimulation,[26] suggesting a role for nNOS in the autocrine regulation of myocardial contractility.[26]

In dogs with coronary microembolization-induced HF, mRNA and protein expression of eNOS in LV myocardium is significantly downregulated compared with normal dogs; therapy with VNS significantly improves the expression of eNOS **(Table 3)**.[27] Both iNOS and nNOS are significantly upregulated, and their expression tends to be normalized by long-term VNS therapy.[27]

Gap junction proteins or connexins are reduced or redistributed from intercalated disks to lateral cell borders in a variety of cardiac diseases, including HF.[28] This so-called "gap junction remodeling" is considered highly arrhythmogenic. In mammals, gap junctions exclusively contain connexin-43 (Cx43). Reduced expression of Cx43 occurs in the failing human heart and has been shown to result in slowed transmural conduction and dispersion of action potential duration with increased susceptibility to arrhythmia and sudden cardiac death.[29,30] In dogs with coronary microembolization-induced HF, mRNA and protein expression of Cx43 in LV myocardium was shown to be markedly downregulated compared with normal dogs, and long-term therapy with VNS was associated with a significant increase in the expression of Cx43 in LV myocardium **(Table 3)**.[31]

VNS IN DOGS WITH RAPID PACING–INDUCED HEART FAILURE

Electrical VNS as a potential therapy for HF was examined in dogs with HF secondary to high-rate ventricular pacing using the Cyberonics VNS system (Cyberonics Inc., Houston, TX), which does not operate on a negative feedback mechanism.[15] In this

TABLE 3
mRNA expression of proinflammatory cytokines, NOS, and connexin-43 in LV myocardium of normal (NL) dogs, untreated HF dogs (Control), and HF dogs treated with VNS[21,27,33]

	NL (n = 6)	Control (n = 6)	VNS (n = 7)
TNF-α (du)	173 ± 14	399 ± 12*	202 ± 21†
IL-6 (du)	75 ± 9	246 ± 23*	116 ± 19†
eNOS (du)	1.44 ± 0.15	0.51 ± 0.02*	0.90 ± 0.03†
iNOS (du)	1.68 ± 0.15	4.05 ± 0.14*	2.69 ± 0.28†
nNOS (du)	1.55 ± 0.11	4.41 ± 0.52*	1.98 ± 0.20†
Cx43 (du)	218 ± 16	11 ± 2*	106 ± 5†

Cx43 = connexin-43; du = densitometric units; eNOS = endothelial nitric oxide synthase; HF = heart failure; IL-6 = interleukin-6; iNOS = inducible nitric oxide synthase; LV = left ventricular; nNOS = neuronal nitric oxide synthase; TNF-α = tumor necrosis factor-alpha; VNS = vagus nerve stimulation.
* $P < .05$ vs NL; † $P < .05$ vs control.

study, VNS therapy was delivered continuously for the duration of the study with a duty cycle of 14 seconds on and 12 seconds off. VNS signals were delivered to the right cervical vagus nerve at a frequency of 20 Hz and a pulse width of 0.5 msec.[15] Dogs were randomized to control (n = 7) or to monotherapy with VNS (n = 8) and followed for 8 weeks. All measurements were made approximately 15 minutes after temporarily turning off the ventricular pacemaker and the vagus nerve stimulator.[15] VNS therapy resulted in a significant decrease in LV end-diastolic and end-systolic volumes and a significant increase in LV ejection fraction compared with controls.[15] This improvement was associated with significant reduction in plasma levels of norepinephrine, angiotensin II, and C-reactive protein. The study also demonstrated the effectiveness of VNS in restoring baroreflex sensitivity, thus improving cardiac autonomic control.[15] Because rapid pacing was maintained throughout the study except for short periods when measurements were made, one can argue that the benefits of VNS therapy in this model of HF are independent of heart rate.[15]

SAFETY AND TOLERABILITY OF VNS IN PATIENTS WITH ADVANCED HEART FAILURE

In patients with HF, reduced vagal activity is associated with increased mortality.[1] Vagal withdrawal has also been shown to precede episodes of acute decompensation.[32] In a recently published study, De Ferrari et al, on behalf of the CardioFit Multicenter Trial Investigators, examined the safety and tolerability of chronic VNS in 32 patients with symptomatic HF and severe LV dysfunction using the CardioFit system.[16] The CardioFit system used in this study differed from that used in dogs with microembolization-induced HF in that it did not operate on a negative feedback principle. A bradycardia limit causing interruption of VNS was set at 55 beats/min. A 3-week uptitration period was used to maximize current amplitude and duty cycle based on patient sensation. The intensity of the stimulation reached 4.1 ± 1.2 mA at the end of the titration period.[16]

This multicenter, open-label, phase 2 trial involved 3 to 6 months of followup with an optional 1 year followup. The results suggested that VNS may be safe and tolerable in HF patients with severe LV dysfunction. Trends for efficacy were also favorable, bearing in mind the nonrandomized and unblinded nature of the study design. The study showed significant improvements in New York Heart Association HF classification, 6-minute walk test, LV ejection fraction, and LV systolic volumes.[16]

CONCLUSIONS

A wealth of preclinical and clinical studies supports the concept that electrical VNS can favorably modify the underlying pathophysiology and course of evolving HF. In animals with HF, VNS improves LV function, attenuates LV remodeling and may prevent arrhythmias that provoke sudden cardiac death. VNS derives these potential clinical benefits from multiple mechanisms of action that include reduced heart rate and normalization of sympathetic overdrive. VNS also appears to have a favorable impact on other signaling pathways that are likely to elicit beneficial effects in patients with HF. These include restoration of baroreflex sensitivity, suppression of proinflammatory cytokines, normalization of NO signaling pathways, and suppression of gap junction remodeling. At present, there is no evidence to implicate a single mechanism of action for the benefits derived from VNS. Instead, it is likely that all of the mechanisms listed above act in concert to elicit the global benefit seen with VNS. In humans with HF, VNS may be safe, feasible, and apparently well tolerated. Full appreciation of its efficacy in treating chronic HF must await completion of pivotal randomized clinical trials.

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Treatment of chronic inflammatory diseases with implantable medical devices*

ABSTRACT

Implantable medical devices are finding increasing use in the treatment of diseases traditionally targeted with drugs. It is well established that the cholinergic anti-inflammatory pathway serves as a physiological regulator of inflammatory responses, but stimulation of this pathway therapeutically by electrical stimulation of the vagus nerve can also diminish excessive or dysregulated states of inflammation. Recent data from a wide variety of animal models, as well as evidence of reduced vagal tone in rheumatoid arthritis and other inflammatory diseases, support the rationale for, and feasibility of, developing implantable vagal nerve stimulation devices to treat chronic inflammation in humans.

Implantable devices are increasingly used in the treatment of diseases which have historically been targeted only with small molecule and biological therapeutic agents. In addition to well-established products such as subcutaneous insulin pumps and intra-arterial chemotherapy pumps, where the implantable device merely serves as a more efficient means of delivering the drug, there are a number of recently developed therapeutic approaches in which the implanted device itself functions to directly treat the underlying medical condition. One particularly successful example of this strategy is cardiac resynchronization using biventricular pacing devices for congestive heart failure (CHF). These devices were approved for marketing after having been proved to prolong survival in patients whose disease had progressed despite medical management.[1] Implantable device products are now approved or in late-stage development for many other traditional "medical" disorders such as hypertension, obesity, diabetes, Parkinson's disease, and glaucoma. Recent advances in understanding the interplay between the central nervous system and the immune system have made possible a feasible implantable device approach that may similarly find use in the management of rheumatoid arthritis (RA) and other chronic inflammatory diseases.[2]

NEUROSTIMULATION OF THE CHOLINERGIC ANTIINFLAMMATORY PATHWAY

The vagus nerve mediates an important neural reflex which senses inflammation both peripherally and in the central nervous system, and downregulates the inflammation via efferent neural outflow to the reticuloendothelial system. The efferent arm of this reflex has been termed the "cholinergic antiinflammatory pathway" (CAP). The CAP serves as a physiological regulator of inflammation by responding to environmental injury, pathogens, and other external threats with an appropriate degree of immune system activation.[3] An increasing body of evidence indicates that the CAP can also be harnessed to reduce pathological inflammation. Electrical neurostimulation of the vagus nerve (NCAP) in an appropriate manner with an implantable device is emerging as a novel and potentially feasible means of treating diseases characterized by excessive and dysregulated inflammation.

Our current understanding of the CAP began with the observations of Kevin Tracey and colleagues over a decade ago. They demonstrated that systemic, hepatic, and splenic tumor necrosis factor (TNF) production as well as the physiological manifestations of endotoxemic shock in rodents were worsened by vagotomy and ameliorated by electrical stimulation of the cervical vagus nerve (VNS). Further, based on in vitro experiments they postulated that this effect was mediated directly by acetylcholine acting through specific receptors on macrophages in the reticuloendothelial system.[4] It was later demonstrated that reducing the response to endotoxemia

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doi:10.3949/ccjm.78.s1.05

TABLE 1
CAP stimulation favourably affects many components of the immune system

Immune system component	Effect
Monocytes-macrophages	VNS or pharmacological manipulation of the CAP causes reduced production of: ▶ TNFα ▶ IL-1β ▶ IL-6 ▶ IFNγ ▶ HMGB1 ▶ CXCL-2 And no change or increased production of ▶ TGFβ ▶ IL-10
Neutrophils	VNS or pharmacological manipulation of the CAP causes reduced cellular trafficking to sites of inflammation, driven by reduction in cell surface CD11b expression
T cells	Vagotomy reduces T regulatory cells (CD4(+)FoxP3(+)), and long-term recovery from the immediate proinflammatory effects of vagotomy is associated with return of T regulatory cells Proinflammatory effect of vagotomy can be adoptively transferred Vagotomy increases and pharmacological CAP agonists decrease CD4(+)CD25(–) proliferation and production of Il-6, IFNγ and TNF
HPA axis	VNS increases systemic corticosteroid production via vagal afferent pathways

CAP = cholinergic anti-inflammatory pathway; HMGB = high-mobility group box 1; IFN = interferon; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor; VNS = vagus nerve stimulation

using NCAP required an intact spleen, and selective anatomical lesion experiments showed that an intact neural pathway to the spleen from the cervical vagus through the celiac ganglion and the splenic nerve was also necessary for this effect.[5] Within the spleen itself, nerve fiber synaptic vesicles are found in close apposition to TNF-secreting macrophages.[6] The α-7 nicotinic acetylcholine receptor, expressed on the surface of macrophages, is essential for the NCAP effect as demonstrated by antisense oligonucleotide and targeted disruption experiments.[7] In the macrophage, the α-7 nicotinic acetylcholine receptor does not appear to transduce signals through ion channels, as is the case in neuronal tissue. Rather, the NCAP effect is mediated at the subcellular level by alterations in the NF-κB and JAK/STAT/SOCS pathways.[8,9]

In addition to effects on macrophages, CAP stimulation has more recently been shown to alter the function of other components of the cellular immune system. The trafficking of neutrophils to sites of inflammation is reduced by VNS, accompanied by reductions in CD11b expression.[9,10] In rodent colitis models, disease severity is worsened by vagotomy, which simultaneously reduces the number of circulating Foxp3+ T regulatory cells. The proinflammatory effect of vagotomy can be adoptively transferred with a CD4+CD25− T-cell subpopulation.[11] Over time the proinflammatory effect of vagotomy wanes, accompanied by recovery of T regulatory cell numbers.[12,13] Finally, vagotomy and pharmacological manipulation of the CAP alter in vitro T-cell proliferation and production of the Th1 cytokines interferon γ, TNF, and interleukin 6 **(Table 1)**.[14]

When taken together, these studies show that NCAP has a dual set of immunological effects: it reduces production of systemically active cytokines by resident spleen cells and also causes circulating cells which traverse the spleen to develop an altered phenotype with reduced expression of inflammatory mediators and adhesion molecules upon trafficking to inflamed tissue.

An important characteristic of NCAP delivered by VNS is that very brief episodes of stimulation result in a remarkably prolonged biological effect. Huston et al delivered a single 30-second electrical VNS or sham treatment in rats, and then induced endotoxemia with intraperitoneal lipopolysaccharide (LPS) at varying times after VNS. Interestingly, this brief VNS stimulation reduced production of serum TNF in response to systemic LPS exposure for up to 48 hours. Similarly, after only 60 minutes of exposure to acetylcholine, cul-

TABLE 2
Efficacy of neurostimulation of the cholinergic anti-inflammatory pathway in animal models

Acute models
Endotoxemia and sepsis
Cecal puncture/acute peritonitis
Ischemia-reperfusion
Acute pancreatitis
Myocardial infarction
Subacute and chronic models
Inflammatory postoperative ileus
Congestive heart failure
Collagen-induced arthritis

tured human macrophages are changed in phenotype such that they become refractory to in vitro LPS stimulation for up to 48 hours thereafter.[15] The consistency of this phenomenon across species is corroborated by preliminary data in a canine model where 60-second VNS treatment results in reduced LPS-inducible TNF production in a whole-blood in vitro release assay for several days after the VNS (M Faltys, personal communication). A duration of biological effect lasting hours to days after periods of stimulation lasting for only seconds to minutes implies that an implantable device will probably only need to operate with very short daily duty cycles to effectively elicit an NCAP response. This will in turn greatly reduce the necessary size and complexity of the device itself, and increase its functional lifespan, with resultant reductions in overall cost of the treatment.

NEUROSTIMULATION OF THE CAP IN ANIMAL MODELS OF DISEASE

CAP stimulation, delivered either by electrical VNS or by pharmacological agonists has proved quite effective in a wide variety of acute disease models of inflammation, including pancreatitis, myocardial infarction, ischemia-reperfusion injury, acute peritonitis, and hemorrhagic shock **(Table 2)** (reviewed by Tracey[3]). Until recently, testing for effectiveness of NCAP in more subacute and chronic rodent models of inflammation was not possible as the ability to deliver VNS was limited to "single sitting" surgical sessions because no reliable chronic rodent VNS system was available. However, a chronically implantable externalized lead with an external pulse generator, suitable for use in rodents, has now been developed **(Figure)**. This system allows testing of NCAP in a variety of standard inflammation models. In preliminary data presented in abstract form, NCAP has been shown to be effective in reducing clinical signs and histological joint damage in a rat collagen-induced arthritis model, even though active VNS was only delivered for 60 seconds daily.[16] Owing to the prohibitively large size of the current prototype rodent vagus nerve lead, at present it can only be used in rats and similarly sized animals. Future iterations of this delivery system will be smaller, self-contained, and fully implantable, allowing use over several months in more chronic models, and implantation in mice, both of which will greatly expand its usefulness as a research tool.

In a canine model of CHF induced by rapid ventricular pacing, inflammation and ventricular remodeling with fibrosis are typically accompanied by marked increases in serum C-reactive protein (CRP) levels. In addition to improving the physiological manifestations of CHF, VNS resulted in 60% to 80% reductions in CRP for up to 8 weeks.[17] In another canine CHF model induced by repetitive microembolization, which is similarly associated with systemic and myocardial inflammation, VNS markedly reduced circulating levels of interleukin 6 and TNF for up to 12 weeks.[18] Importantly, both these studies show that rapid tachyphylaxis does not appear to occur with NCAP over periods of time that are relatively chronic by the typical standards of animal models.

VAGAL NERVE STIMULATION FOR EPILEPSY AND DEPRESSION: EXPERIENCE IN HUMANS

VNS delivered using a surgically implanted cuffed cervical vagus nerve lead and pacemaker-style pulse generator device has been approved for the treatment of refractory epilepsy in the United States since the mid-1990s and has more recently been approved for treatment of depression. Over 50,000 patients have been implanted with these devices world wide since that time. The safety profile of both surgical implantation and VNS delivery in this setting is well established.[19] The major tolerability problem is laryngeal and pharyngeal symptoms, such as hoarseness and dysphonia, which are present almost solely during periods of active device stimulation. The frequency and severity of these treatments decreases after receiving treatment for an extended time.[20] With growing experience in VNS delivery over the first 5 years of use, it also became apparent that reducing the active

stimulation duty cycle from 40% to 10%, and keeping stimulation currents at ≤ 1.5 mA results in a marked reduction in these symptoms.[21] Of note, the stimulation currents necessary to evoke NCAP in animals are well below the 1.5 mA level, and as above, NCAP is effective even with very brief, once-daily periods of stimulation (ie, a duty cycle of 0.07% if given for 1 min each day). Thus it is likely that the laryngeal and pharyngeal adverse event profile of VNS will not be problematic in the setting of NCAP delivery for inflammation.

A POTENTIAL ROLE FOR THERAPEUTIC NCAP USING IMPLANTABLE DEVICES IN HUMAN INFLAMMATORY DISEASES

Autonomic nervous system activity can be measured indirectly by recording cardiac R-R interval variability and subjecting the data to power spectral analysis. Such heart rate variability (HRV) measurements are influenced by the levels of vagus nerve activity and by balance in cardiac sympathetic–parasympathetic tone. Reduced HRV is indicative of decreased vagal tone, and reductions in HRV have a strong inverse correlation with CRP levels, progression of atherosclerosis, and risk of sudden death.[22,23] HRV is also reduced relative to normal subjects in patients with RA, systemic lupus erythematosus, and Sjögren syndrome, and the extent of reduction in HRV within the patient groups correlates with disease severity.[24–26] Although these associations are only correlative and do not provide firm evidence of causality, they do provide additional epidemiological support for the hypothesis that driving increased vagal activity using implantable devices may have a favorable effect on inflammatory disease.

Implantable neurostimulation devices have not yet been tested in human patients with RA. However, preliminary evidence from a small study carried out in normal volunteers demonstrated that the CAP reflex can be elicited by brief mechanical stimulation of the afferent auricular branch of the vagus nerve, as shown by reduction of in vitro LPS-inducible cytokine production (T van der Poll, personal communication). Clinical testing of NCAP using implantable VNS devices will begin in the near future. The devices to be used for these initial studies will be very similar in design to those currently in use for epilepsy treatment. However, prototype versions of the device which will be used in follow-on studies are miniaturized to the point where they will be directly implantable on the vagus nerve, without the need for a pulse generator unit on the chest and will use a small self-contained battery system which can be recharged using transcutaneous radiofrequency induction. Given the long lifespan, relatively low cost, and potential for increased safety over currently available treatments, NCAP delivered using an implantable device holds great promise as a novel potential therapeutic approach for patients with RA and other inflammatory diseases.

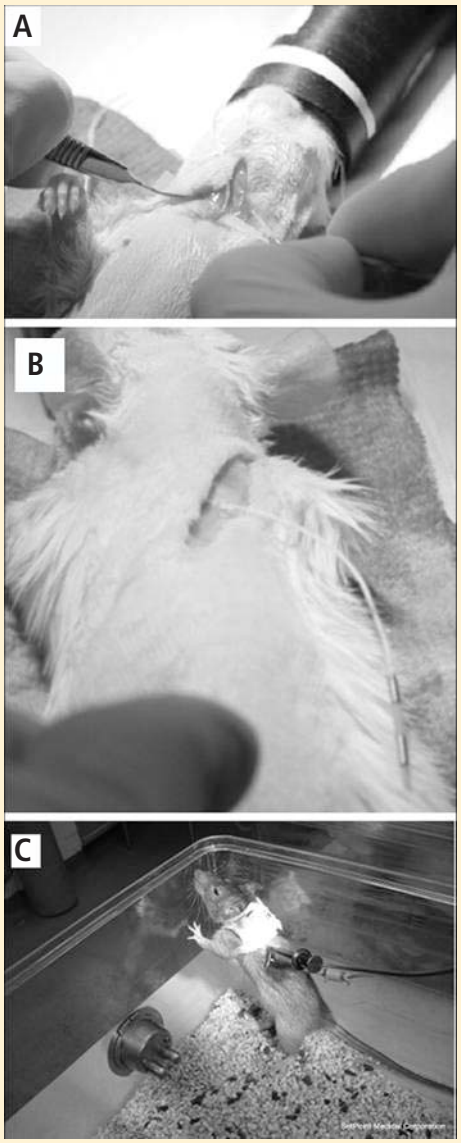

FIGURE. An implantable lead system for delivering neurostimulation of the cholinergic anti-inflammatory pathway (NCAP) in rodents. (A) Lead is wrapped circumferentially around left carotid sheath. (B) After anterior closure, lead is tunnelled subcutaneously and externalized posteriorly in the midline. (C) Animal is jacketed to prevent damage to externalized electrode. NCAP is delivered by temporarily connecting leads to an external electronic pulse generator.

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New frontiers in cardiovascular behavioral medicine: Comparative effectiveness of exercise and medication in treating depression

ABSTRACT

Exercise, considered a mainstay of cardiac rehabilitation, has been shown to reduce cardiac risk factors such as hyperlipidemia and hypertension. Growing evidence also suggests that exercise has beneficial effects on mental health, which is relevant for cardiac patients because of the prognostic significance of depression in patients with coronary heart disease (CHD). Depression has been associated with increased mortality and nonfatal cardiac events in patients with CHD; it is also associated with worse outcomes in patients who undergo coronary artery bypass graft surgery and those who have heart failure. The standard therapy for depression is pharmacologic treatment, often with second-generation antidepressants such as selective serotonin reuptake inhibitors. Despite their widespread use, antidepressants have only modest effects on depression for many patients compared with placebo controls. Exercise therapy, already an established component of cardiac rehabilitation, has potential efficacy as a treatment for depression in cardiac disease patients. Randomized controlled trials are needed to determine the clinical effects of exercise in this population and to compare the effects of exercise with those of antidepressants.

I am fortunate to be the recipient of the 2010 Bakken Institute Pioneer Award and feel especially honored to have my work recognized in this way. When informed that I was this year's recipient, it prompted me to reflect on the meaning of the term "pioneer," and how it related to me.

WHAT IS A PIONEER?

According to *Merriam-Webster's Collegiate Dictionary*, a pioneer is one who (a) ventures into unknown or unclaimed territory to settle; and (b) opens up new areas of thought, research, or development. One requirement for any pioneer is that there be a frontier to explore. Thirty years ago, my colleagues and I began our investigations into cardiac rehabilitation (CR), which at the time we considered to be a new frontier for behavioral medicine.[1]

EXERCISE-BASED CARDIAC REHABILITATION

Historically, patients who suffered an acute myocardial infarction (AMI) were often discouraged from engaging in physical activity; patients were initially prescribed prolonged bed rest and told to avoid strenuous exercise.[2] In the early 1950s, armchair therapy was proposed[3] as an initial attempt to mobilize patients after a coronary event. Over the years, the value of physical exercise has been increasingly recognized and exercise is now considered to be the cornerstone of CR.[4–7] Today, exercise-based CR, involving aerobic exercise supplemented by resistance training, is offered by virtually all CR programs in the United States.[8] Proper medical management is also emphasized, along with dietary modification and smoking cessation, but exercise is the centerpiece of treatment.

Exercise has been shown to reduce traditional risk factors such as hypertension and hyperlipidemia,[8] attenuate cardiovascular responses to mental stress,[9] and reduce myocardial ischemia.[10–12] Although no single study has demonstrated definitively that exercise reduces morbidity in patients with coronary heart disease (CHD), pooling data across clinical trials has shown that exercise may reduce risk of fatal CHD events by 25%.[13] A recent, comprehensive meta-analysis by Jolliffe et al[14] reported a 27% reduction in all-cause mortality and 31% reduction in cardiac mortality.

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

Supported by grants HL093374 and HL080664 from the National Heart, Lung, and Blood Institute. Based upon a presentation at the Cleveland Clinic Heart-Brain Summit, Las Vegas, NV, September 23, 2010.

doi:10.3949/ccjm.78.s1.06

Not only is exercise considered beneficial for medical outcomes, but is also recognized as an important factor in improved quality of life. Indeed, there has been increased interest in the value of exercise for improving not just physical health, but also mental health.[15–17] The mental health benefits of exercise are especially relevant for cardiac patients, as there is a growing literature documenting the importance of mental health, and, in particular the prognostic significance of depression, in patients with CHD.

PSYCHOSOCIAL RISK FACTORS: THE ROLE OF DEPRESSION IN CORONARY HEART DISEASE

There has long been an interest in psychosocial factors that contribute to the development and progression of CHD. More than three decades ago, researchers identified the type A behavior pattern as a risk factor for CHD.[18] When subsequent studies failed to confirm the association of type A with adverse health outcomes, researchers turned their attention to other possible psychosocial risk factors, including anger and hostility,[19] low social support,[20] and most recently, depression.[21] Indeed, the most consistent and compelling evidence is that clinical depression or elevated depressive symptoms in the presence of CHD increase the risk of fatal and nonfatal cardiac events and of all-cause mortality.[22]

Major depressive disorder (MDD) is a common and often chronic condition. Lifetime incidence estimates for MDD are approximately 12% in men and 20% in women.[23] In addition, MDD is marked by high rates of relapse, with 22% to 50% of patients suffering recurrent episodes within 6 months after recovery.[24] Furthermore, MDD is underrecognized and undertreated in older adults,[25] CHD patients, and, especially, minorities.[26–28]

Cross-sectional studies have documented a higher prevalence of depression in CHD patients than in the general population. Point estimates range from 14% to as high as 47%, with higher rates recorded most often in patients with unstable angina, heart failure (HF), and patients awaiting coronary artery bypass graft (CABG) surgery.[29–36]

Depression associated with poor outcomes

A number of prospective studies have found that depression is associated with increased risk for mortality or nonfatal cardiac events in a variety of CHD populations. The most compelling evidence for depression as a risk factor has come from studies in Montreal, Canada. Frasure-Smith and colleagues[31] assessed the impact of depression in 222 AMI patients, of whom 35 were diagnosed with MDD at the time of hospitalization. There were 12 deaths (six depressed and six nondepressed) over an initial 6-month follow-up period, representing more than a fivefold increased risk of death for depressed patients compared with nondepressed patients (hazard ratio, 5.7; 95% confidence interval [CI], 4.6 to 6.9). In a subsequent report,[36] in which 896 AMI patients were followed for 1 year, the presence of elevated depressive symptoms was associated with more than a threefold increased risk in cardiac mortality after controlling for other multivariate predictors of mortality (odds ratio, 3.29 for women; 3.05 for men).

Studies of patients with stable CHD also have reported significant associations between the presence of depression and worse clinical outcomes. For example, Barefoot et al[37] assessed 1,250 patients with documented CHD using the Zung self-report depression scale at the time of diagnostic coronary angiography and followed patients for up to 19.4 years. 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.

The presence of depression also has been associated with worse clinical outcomes in patients undergoing CABG surgery.[33,38–40] For example, Duke researchers[39] assessed the effect of depression on mortality after CABG surgery in 817 patients followed for up to 12 years (mean, 5.2 years). Patients with moderate to severe depression at the time of surgery were found to have a two- to threefold increased risk of death, even after statistically controlling for age, gender, number of grafts, diabetes, smoking, left ventricular ejection fraction, and history of AMI **(Figure 1)**.

Depression and heart failure outcomes

Patients with HF represent a particularly vulnerable group; a meta-analysis of depression in HF patients suggested that one in five patients are clinically depressed (range, 9% to 60%).[41] Not only is depression in HF patients associated with worse outcomes,[42–46] but recent evidence suggests that worsening of depressive symptoms, independent of clinical status, is related to worse outcomes. Sherwood et al[46] demonstrated that increased symptoms of depression, as indicated by higher scores on the Beck Depression Inventory (BDI) over a 1-year interval (BDI change [1-point] hazard ratio, 1.07; 95% CI, 1.02 to 1.12; $P = .007$), were associated with higher risk of death or cardiovascular hospitalization after controlling for baseline depression (baseline BDI hazard ratio, 1.1; 95% CI, 1.06 to 1.14, $P < .001$) and established risk factors, including HF

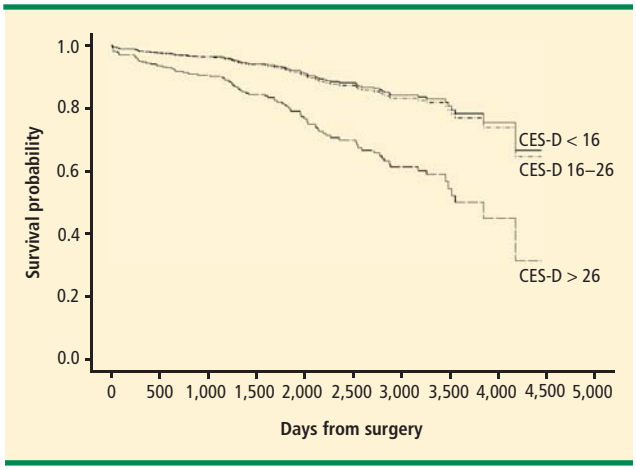

FIGURE 1. Patients with significant depressive symptoms assessed by the Center for Epidemiological Studies-Depression Scale (CES-D) were at increased risk of dying up to 12 years after they underwent coronary artery bypass graft surgery.[39]

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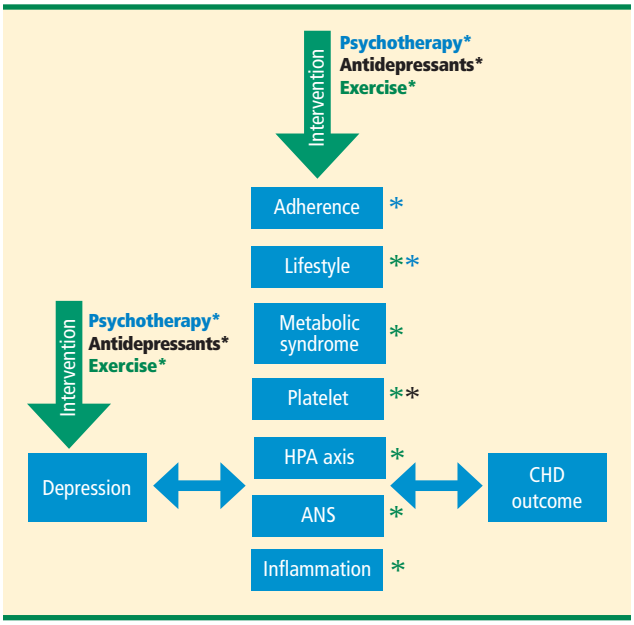

FIGURE 2. Proposed effects of different treatments for depression (psychotherapy, antidepressants, exercise) on hypothesized mechanisms by which depression is associated with adverse clinical events in coronary heart disease (CHD) patients. The potential mediators in the central column may increase risk for cardiac patients, and may be responsive to at least one intervention (identified by color-coded asterisks) that is used to treat depression. These interventions hold considerable promise for the management of cardiac disease. ANS = autonomic nervous system; HPA = hypothalamic-pituitary-adrenal

etiology, age, ejection fraction, N-terminal pro-B-type natriuretic peptides, and prior hospitalizations. Consequently, strategies to reduce depressive symptoms and prevent the worsening of depression may have important implications for improving cardiac health as well as for enhancing quality of life.

MECHANISMS LINKING DEPRESSION AND CHD

A number of biobehavioral mechanisms have been hypothesized to underlie the relationship between depression and CHD. There is evidence that depression is associated with traditional CHD risk factors such as hypertension, diabetes, and insulin resistance,[47,48] as well as changes in platelet reactivity,[49] dysregulation of the autonomic nervous system[50] and hypothalamic pituitary adrenal axis,[51] and alterations in immune response and inflammation.[52] Depression is also associated with behavioral factors that are, in turn, associated with CHD risk, such as treatment adherence,[53] smoking,[54] heavy alcohol use, and physical inactivity.[55] In considering strategies to maximize benefits in depressed cardiac patients, treatments that not only reduce depressive symptoms but also improve possible mediators responsible for the increased risk may hold particular promise **(Figure 2)**.

CONVENTIONAL APPROACHES TO TREATMENT OF DEPRESSION

Treatment of depression has focused on reduction of symptoms and restoration of function. Antidepressant medications are generally considered the treatment of choice.[56] In particular, second-generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are widely prescribed.[57] Current treatment guidelines suggest 6 to 12 weeks of acute treatment followed by a continuation phase of 3 to 9 months to maintain therapeutic benefit.[58] However, meta-analyses of antidepressant medications have reported only modest benefits over placebo treatments.[59,60] In particular, active drug–placebo differences in antidepressant efficacy are positively correlated with depression severity: antidepressants are often comparable with placebo in patients with low levels of depression but may be superior to placebo among patients with more severe depression. However, the explanation for this relationship may be that placebo is less effective for more depressed patients rather than antidepressants being more effective for more depressed patients.[59]

For acute treatment of MDD, approximately 60% of patients respond to second-generation antidepressants,[61] with a 40% relapse rate after 1 year.[62] A recent meta-analysis[60] of second-generation antidepressants summarized four comparative trials and 23 placebo-controlled trials and found that second-generation antidepressants were generally comparable with each

other. Interestingly, despite the modest benefit of antidepressants, the percentage of patients treated for depression in the United States increased from 0.73% in 1987 to 2.33% in 1997. The proportion of those treated who received antidepressants increased from 37.3% in 1987 to 74.5% in 1997.[63] The percentage of treated outpatients who used antidepressants has not increased significantly since 1997, but the use of psychotherapy as a sole treatment declined from 53.6% in 1998 to 43.1% in 2007.[64] Moreover, the national expenditure for the outpatient treatment of depression increased from $10.05 billion in 1998 to $12.45 billion in 2007, primarily driven by an increase in expenditures for antidepressant medications.

Uncertainty about value of antidepressant therapy

Despite compelling reasons for treating depression in cardiac patients, the clinical significance of treating depression remains uncertain. To date, only the Enhancing Recovery in CHD Patients (ENRICHD) trial has examined the impact of treating depression in post-MI patients on "hard" clinical end points.[65] Although more than 2,400 patients were enrolled in the trial, the results were disappointing. There were only modest differences (ie, two points on the Hamilton Depression Rating Scale [HAM-D]) in reductions of depressive symptoms in the group receiving cognitive behavior therapy (CBT) relative to usual-care controls and there were no treatment group differences in the primary outcome—all-cause mortality and nonfatal cardiac events. By the end of the follow-up period, 28.0% of patients in the CBT group and 20.6% of patients in usual care had received antidepressant medication. Although a subsequent reanalysis of the ENRICHD study revealed that antidepressant use was associated with improved clinical outcomes,[66] because patients were not randomized to pharmacologic treatment it could not be concluded that SSRI use was responsible for the improved outcomes.

In a randomized trial of patients with acute coronary syndrome (the Sertraline Antidepressant Heart Attack Randomized Trial, or SADHART),[67] almost 400 patients were treated with the SSRI sertraline or with placebo. Reductions in depressive symptoms were similar for patients receiving sertraline compared with placebo in the full sample, although a subgroup analysis revealed that patients with more severe depression (ie, those patients who reported two or more previous episodes) benefited more from sertraline compared with placebo. Interestingly, patients receiving sertraline tended to have more favorable cardiac outcomes, including a composite measure of both "hard" and "soft" clinical events, compared with placebo controls. These results suggested that antidepressant medication may improve underlying physiologic processes, such as platelet function, independent of changes in depression.[68] However, because SADHART was not powered to detect differences in clinical events, there remain unanswered questions about the clinical value of treating depression in cardiac patients with antidepressant medication.

In a second sertraline trial, SADHART-HF,[69] 469 men and women with MDD and chronic systolic HF were randomized to receive either sertraline or placebo for 12 weeks. Participants were followed for a minimum of 6 months. Results showed that while sertraline was safe, its use did not result in greater reductions in depressive symptoms compared with placebo (-7.1 ± 0.5 vs -6.8 ± 0.5) and there were no differences in clinical event rates between patients receiving sertraline compared with those receiving placebo.

In an observational study of patients with HF,[44] use of antidepressant medication was associated with *increased* risk of mortality or hospitalization. Although the potential harmful effects of antidepressant medication could not be ruled out, a more likely interpretation is that antidepressant medication use was a marker for individuals with more severe depression, and that the underlying depression may have contributed to their higher risk. Further, patients who are depressed, despite receiving treatment, may represent a subset of treatment-resistant patients who may be especially vulnerable to further cardiac events. Indeed, worsening depression is associated with worse outcomes in HF patients[46]; this is consistent with data from the ENRICHD trial, which showed that patients receiving CBT (and, in some cases, antidepressant medication) who failed to improve with treatment had higher mortality rates compared with patients who exhibited a positive response to treatment.[70]

A fourth randomized trial of CHD patients, the Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial,[71] used a modified "2 by 2" design; 284 CHD patients with MDD and HAM-D rating scores of 20 or greater were randomized to receive 12 weeks of (a) interpersonal therapy (IPT) plus clinical management (CM) or (b) CM only and citalopram or matching placebo. Because the same interventionists delivered the CM and IPT, patients assigned to IPT received IPT plus CM within the same (extended) session. Patients receiving citalopram had greater reductions in depressive symptoms compared with placebo, with a small to medium effect

size of 0.33, and better remission rates (35.9%) compared with placebo (22.5%). Unexpectedly, patients who received just CM tended to have greater improvements in depressive symptoms compared with patients who received IPT plus CM ($P < .07$); no clinical CHD end points were assessed, however.

Alternative approaches needed

Taken together, these data illustrate that antidepressant medications may reduce depressive symptoms for some patients; for other patients, however, medication fails to adequately relieve depressive symptoms and may perform no better than placebo. Adverse effects also may affect a subgroup of patients and may be relatively more common or more problematic in older persons with CHD.[72] Thus, a need remains to identify alternative approaches for treating depression in cardiac patients. We believe that aerobic exercise, the cornerstone of traditional CR, may be one such approach. Exercise is safe for most cardiac patients,[73,74] including patients with HF,[75] and, if proven effective as a treatment for depression, exercise would hold several potential advantages over traditional medical therapies: it is relatively inexpensive, improves cardiovascular functioning, and avoids the side effects sometimes associated with medication use.

EXERCISE THERAPY FOR DEPRESSION

Some studies of exercise treatment for CHD patients have tracked depressive symptoms and thus have provided information regarding the potential efficacy of exercise as a treatment for depression in this population.[76–81] Although most previous studies have reported significant improvements in depression after completion of an exercise program, many studies had important methodologic limitations, including the absence of a control group.

In one of the few controlled studies in this field, Stern et al[82] randomized 106 male patients who had a recent history of AMI along with elevated depression and anxiety or low fitness to 12 weeks of exercise training, group therapy, or a usual-care control group. At 1-year followup, both the exercise and counseling groups showed improvements in depression relative to controls.

Cross-sectional studies of non-CHD samples have reported that active individuals obtain significantly lower depression scores on self-report measures than sedentary persons.[83] Studies also have shown that aerobic exercise may reduce self-reported depressive symptoms in nonclinical populations and in patients diagnosed with MDD.[83] In 2001, a meta-analysis evaluating 11 randomized controlled trials of non-CHD patients with MDD[84] noted that studies were limited because of self-selection bias, absence of control groups or nonrandom controls, and inadequate assessment of exercise training effects; the authors concluded that "the effectiveness of exercise in reducing symptoms of depression cannot be determined because of a lack of good quality research on clinical populations with adequate followup."

Randomized controlled trials needed

A subsequent meta-analysis[85] included 25 studies; for 23 trials (907 participants) that compared exercise with no treatment or a control intervention, the pooled standardized mean difference (SMD) was −0.82 (95% CI, −1.12, −0.51), indicating a large effect size. However, when only the three trials (216 participants) with adequate allocation concealment, intention to treat analysis, and blinded outcome assessment were included, the pooled SMD was −0.43 (95% CI, −0.88, 0.03), with a point estimate that was half the size of that with all trials. As a result, the authors concluded that "exercise seems to improve depressive symptoms in people with a diagnosis of depression, but when only the methodologically robust trials are included, the effect size is only moderate."

To date, no randomized clinical trials (RCTs) have examined the effects of exercise on clinical outcomes in depressed cardiac patients. However, data from the ENRICHD trial suggest that exercise may reduce the rates of mortality and nonfatal reinfarction in patients with depression or in post-MI patients who are socially isolated.[86] Self-report data were used to categorize participants as exercising regularly or not exercising regularly. After controlling for medical and demographic variables, the magnitude of reduction in risk associated with regular exercise was nearly 40% for nonfatal reinfarction and 50% for mortality. The evidence that exercise mitigates depression, reduces CHD risk factors, and improves CHD outcomes suggests that exercise may be a particularly promising intervention for depressed CHD patients.

COMPARATIVE EFFECTIVENESS OF EXERCISE AND ANTIDEPRESSANT MEDICATION

In 2008, an Institute of Medicine (IOM) report called for a national initiative of research that would provide a basis for better decision-making about how to best treat various medical conditions, including depression. In 2009, the American Reinvestment Recovery Act provided a major boost in funding for comparative effectiveness research (CER). The act allotted

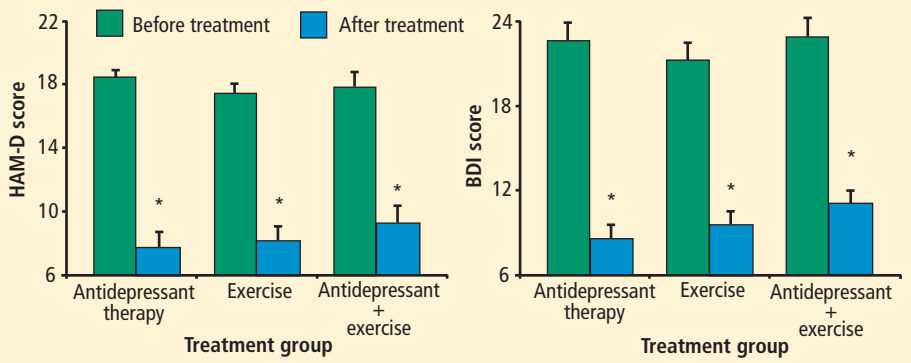

FIGURE 3. Changes in depressive symptoms measured by interview (Hamilton Depression Rating Scale [HAM-D]) and self-report (Beck Depression Inventory [BDI]) in patients who received antidepressant therapy, exercise, or a combination of antidepressant therapy and exercise.[90]
*Difference from baseline, $P < .001$.

$1.1 billion to support this form of research. CER refers to the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers in reaching informed decisions that will improve health care at both the individual and population levels.[87]

Two research categories inform decision-making

Two broad categories of research have been used to inform decision-making:

- Epidemiologic studies provide evidence linking various treatments with patient outcomes. These sources of data are limited because they seldom specify the basis for medical decisions and they fail to consider patient characteristics that affect both clinical decisions and clinical outcomes. Indeed, it has been suggested that "overcoming the limitations of observational research is the most important frontier of research on study methods."[88]
- RCTs address these limitations by randomly assigning patients to different treatment conditions. While this design may eliminate some of the uncertainty and potential confounders that characterize purely observational studies, most RCTs are efficacy studies; patients are carefully selected and a treatment is usually compared with a placebo or usual care.

The RCT design addresses the question of whether a given treatment is effective, but it does not necessarily address questions that many physicians want answers to: namely, is this treatment better than that treatment? Further, physicians want to know if one treatment is more effective than another for a given patient. For example, Hlatky et al[89] showed that mortality associated with percutaneous coronary interventions (PCIs) and CABG surgery was comparable; however, mortality with CABG surgery was significantly lower for patients older than 65 years while PCI was superior for patients younger than 55 years. Thus, examination of individual differences may also help to inform clinicians about the optimal therapy for their particular patients.

Treatment of depression not necessarily a research priority

The IOM committee sought advice from a broad range of stakeholders and prioritized areas for research. The top-ranked topic was comparison of treatment strategies for atrial fibrillation, including surgery, catheter ablation, and pharmacologic treatment. Coming in at #98 was comparison of the effectiveness of different treatment strategies (eg, psychotherapy, antidepressants, combination treatment with case management) for depression after MI and their impact on medication adherence, cardiovascular events, hospitalization, and death.

To date, only two RCTs have compared exercise training with antidepressant medication. In an initial study, Blumenthal et al[90] randomly assigned 156 middle-aged and older adults with DSM-IV MDD to one of three treatment groups: (1) aerobic exercise training, (2) standard pharmacotherapy (sertraline), and (3) a combination of exercise and pharmacotherapy. After 16 weeks of treatment, groups did not differ significantly on percentage remissions, self-reported depression severity (BDI), or clinician-rated depression severity (HAM-D). All treatment conditions demonstrated statistically and clinically significant reductions in depression **(Figure 3)**. At 6 months followup, participants who achieved remission with exercise alone exhibited significantly lower relapse rates compared with patients in the medication or combination groups who achieved remission.[91] Further, exercise during the followup period

(regardless of initial treatment group) was associated with reduced risk of depression diagnosis at 6 months posttreatment; ie, 50 minutes of exercise per week was associated with a 50% reduction in risk. While the study provided encouraging results, it was limited by the absence of a no-treatment control group and by the exercise being conducted in a group setting, so that social support may have confounded the effects of exercise.

In a second Duke study that compared exercise and antidepressant medication,[92] 202 adults (153 women; 49 men) diagnosed with MDD were randomly assigned to one of four groups: supervised exercise in a group setting, home-based exercise, antidepressant medication (sertraline, 50 to 200 mg daily), or placebo pill for 16 weeks. Once again, patients underwent the Structured Clinical Interview for Depression and completed the HAM-D. After 4 months of treatment, 41% of participants achieved remission, defined as no longer meeting criteria for MDD and a HAM-D score of less than 8 points. Patients receiving active treatments tended to have higher remission rates than placebo controls: supervised exercise, 45%; home-based exercise, 40%; medication, 47%; placebo, 31% (P = .057). All treatment groups had lower HAM-D scores after treatment; scores for the active treatment groups were not significantly different from the placebo group (P = .23). However, when immediate responders (ie, those patients who reported more than 50% reduction in depressive symptoms after only 1 week of treatment) were excluded from the analysis, patients receiving active treatments (ie, either sertraline or exercise) had greater reductions in depressive symptoms compared with placebo controls (P = .048). There was no difference between the exercise and antidepressant groups. We concluded that the efficacy of exercise appears generally comparable with antidepressant medication and both tend to be better than placebo in patients with MDD. Placebo response rates were high, suggesting that a considerable portion of the therapeutic response could be determined by patient expectations, ongoing symptom monitoring, attention, and other nonspecific factors. Similar to our previous trial, participants who continued to exercise following the completion of the program were less likely to be depressed.[93]

Another RCT[94] also demonstrated that exercise was associated with reduced depression, independent of group support. Participants exercised alone in a secluded setting, and the study included a no-treatment control group. Only 53 of 80 patients actually completed the 12-week trial, however, including only five of 13 no-treatment controls. Moreover, there was no active treatment comparison group, so that an estimate of comparative effectiveness could not be determined.

While these results are preliminary and should be interpreted with caution, it appears that exercise may be comparable with conventional antidepressant medication in reducing depressive symptoms, at least for patients who are willing to try it, and maintenance of exercise reduces the risk of relapse.

SUMMARY

Three decades ago, we recognized that CR was a new frontier for behavioral medicine. We now know that successful rehabilitation of patients with CHD involves modification of lifestyle behaviors, including smoking cessation, dietary modification, and exercise. Exercise is no longer considered unsafe for most cardiac patients, and exercise is currently the key component of CR services. Research also has provided strong evidence that depression is an important risk factor for CHD, although there is no consensus regarding the optimal way to treat depression in CHD patients.[95] Research on comparative effectiveness of established and alternative treatments for depressed cardiac patients is a new frontier for future pioneers in heart-brain medicine.

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Depression: A shared risk factor for cardiovascular and Alzheimer disease

ABSTRACT

Depression has been linked to cardiovascular disease and cognitive impairment, including Alzheimer disease, but the exact nature of the relationship is poorly understood. Although depression seems to progress little after the onset of Alzheimer disease, depression in earlier life increases the risk of dementia and cognitive impairment many years in the future. Depression is also associated with reduced vascular function and is a poorly recognized but significant risk factor for stroke.

The associations among depression, cardiovascular disease, and cognitive impairment are well known. Inflammation is increasingly recognized as playing an important role as well. However, the nature of their relationships and which may actually cause the other is not well understood. This article reviews studies over the past year that link depression with dementia and vascular disease. Desirable directions for future work are also explored.

DEPRESSION AND ALZHEIMER DISEASE

Several studies have shown significant correlations between depression and the risk of developing Alzheimer disease; the frequency of depressive episodes appears to be an important factor. Despite the risk relationship, however, depression and Alzheimer disease may not share a common pathology.

No shared pathology

Wilson and colleagues[1] analyzed data from the Chicago Health and Aging Project, a longitudinal cohort study of risk factors for Alzheimer disease that involved two groups of people aged 65 years and older; one group was composed of people who developed dementia during the study, while the other group had already developed dementia or had some degree of cognitive impairment. The investigators reasoned that if pathologic changes are common to depression and dementia, then there would be evidence of change in depressive symptoms along with the progression of dementia. They found only a barely perceptible increase in depressive symptoms among people who developed Alzheimer disease and concluded that there is no shared pathology between depression and Alzheimer disease.

Degree of depression signals risk

Depression has been associated with nearly double the risk of developing dementia and Alzheimer disease. Saczynski et al[2] evaluated 949 people in the Framingham study, mean age 79 years, using the 60-point Center for Epidemiologic Studies Depression Scale (depression defined as > 16 points). Individuals who had depression at baseline were 1.7 times more likely to develop dementia over the 17-year evaluation period. Results were similar when adjusted for major vascular risk factors (smoking, diabetes, hypertension, and cardiovascular disease). The correlation was slightly lower but still significant when subjects taking antidepressant medications were included in the depressed group.

The study also found a continuous relationship between the level of depression and the likelihood of developing dementia and Alzheimer disease: for every 10-point increase on the depression scale, the risk of developing dementia increased by nearly 50%. This study supports depression as a risk factor for dementia. One could also argue that depression as a simple prodrome to dementia seems unlikely because of the long followup between baseline assessment and the development of dementia.

Multiple episodes of depression increase risk

Dotson et al[3] analyzed data from 1,239 older adults from the Baltimore Longitudinal Study of Aging who

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

This article was developed from an audio transcript of Dr. Wint's lecture at the 2010 Heart-Brain Summit. The transcript was formatted and edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Wint.

doi:10.3949/ccjm.78.s1.07

did not have depression, dementia, or mild cognitive impairment at baseline. Every 1 to 2 years for about 25 years, cognitive status and mood of the subjects were evaluated. About 10% of the participants developed dementia during the course of the study. Of those who developed dementia, 35% had at least one episode of depression; among those who did not develop dementia, only 23% had a depressive episode. Findings were similar when investigators controlled for vascular risks and vascular dementia.

One episode of depression was associated with an 87% increase in risk of dementia; at least two episodes of depression more than doubled the risk (108%). Overall, each episode of depression conferred an additional 14% risk of developing dementia. Among subjects who had had two or more episodes of depression, the median age of developing dementia was 85 years versus 95 years for those without an episode of depression.

This study had the advantages of being prospective for both depression and dementia and of having a long followup period. A dose-effect relationship was observed, with the "dose" being the number of depressive episodes (rather than severity of depression). Because the definition of a depressive episode included subsyndromal depression (not likely to meet the criteria of clinical depression, but still clinically significant), the findings suggest that even minor depression increases the risk of dementia.

Baseline depression predicts cognitive impairment

Rosenberg et al[4] found depression to be associated with cognitive impairment in their evaluation of 436 women in their 70s; the women, who were participants in the Women's Health and Aging Study, were evaluated for up to 9 years. To be included in the evaluation, subjects needed a Mini-Mental State Examination score of at least 24 points (out of 30 possible) and could not be impaired in more than one basic functional capacity: mobility and exercise tolerance, upper extremity, higher functioning (eg, shopping), and basic self-care). Baseline depressive symptoms were measured using the Geriatric Depression Scale.

Cognitive testing included Hopkins Verbal Learning Tests (for immediate and delayed word recall) and Trail Making Tests (for psychomotor speed and executive functioning). Those who were not impaired (ie, having a cognitive test score below the 10th percentile for age-adjusted norms) were followed with up to six examinations over the next 9 years.

Baseline depression was found to be highly associated with incident impairment in all cognitive areas, especially in executive functioning. For every point increase in the depression scale, a 6% to 7% increase was found in the annual risk of impairment in each cognitive domain.

DEPRESSION AND VASCULAR DISEASE LINKED

It is somewhat easier to assess the relationship between depression and vascular disease than between depression and cognitive impairment because of the availability of objective measures of cardiovascular function.

The International Stroke Study (INTERSTROKE),[5] a case-control study in 22 countries with 3,000 cases of stroke and 3,000 age-, gender-, and ethnicity-matched controls, found nine risk factors that were correlated with 90% of ischemic stroke cases. Depression, with an odds ratio of 1.86, was found to be a more significant risk factor than physical activity, diet, or heavy drinking.

Paranthaman et al[6] evaluated a number of measures of arterial anatomy and function in 25 subjects with depressive disorder and in 21 nondepressed controls (mean age, 72 years). They found that depressed subjects had significantly higher mean carotid intima media thickness, reduced dilation in response to acetylcholine in preconstricted small arteries, and more dilated Virchow-Robin spaces in the basal ganglia observed on magnetic resonance imaging. This study provides evidence that arterial structure and function may mediate the relationship between depression and vascular disease.

FUTURE DIRECTIONS

Future studies into depression as a risk factor should use very well-characterized cohorts that are controlled for blood pressure and other vascular risk factors. Finding biomarkers for depression would be useful, permitting its detection earlier and with more certainty than is now possible. Prospective studies to evaluate the relationship of depression to cognitive impairment and dementia are needed that start earlier than in middle or old age. The key question that needs study is whether treatment of depression can actually change the onset of cognitive impairment, Alzheimer disease, and vascular disease.

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Inflammatory signaling in Alzheimer disease and depression

ABSTRACT

To help define the relationships among inflammation, Alzheimer disease, and depression, the Texas Alzheimer's Research Consortium analyzed an array of inflammatory biomarkers in a cohort of patients with Alzheimer disease and in controls. Inflammation severity was highly correlated with earlier age at onset of Alzheimer disease and was also associated with cognitive decline. The relationship between inflammation and depression was not as clear, and it varied with aspects of depression, gender, and the presence of Alzheimer disease.

The relationships among inflammation, Alzheimer disease, and depression have been the subject of recent research at several centers. Alzheimer disease and depression appear to be linked by several genetic and inflammatory processes, although the exact nature of the relationship is not clearly understood. The two disorders also share risk factors for vascular disease. This article reviews the current state of knowledge about inflammation and its implications for Alzheimer disease and depression, and it presents recent findings from the Texas Alzheimer's Research Consortium, which assessed an array of inflammatory markers in a cohort of patients with Alzheimer disease.

INFLAMMATION MAY MEDIATE DEPRESSION, COGNITIVE DECLINE, AND DEMENTIA

Alzheimer disease and depression share several vascular disease risk factors and appear to be linked through complex and integrated processes. The link may be mediated by long-term inflammatory processes. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction, chronic inflammation, and a deficit in neurotrophin signaling all may play roles in the pathogenesis of depression and Alzheimer disease.[1] Excessive release of glucocorticoids subsequent to HPA-axis dysfunction in chronic depression appears to damage the hippocampus: hippocampal atrophy is a feature in both depression and dementia, and recurrent depression is associated with greater atrophy. The direction of influence—whether depression leads to the factors that increase the risk of Alzheimer disease or the other way around—remains a controversial topic.

Symptoms of depression tend to appear early in Alzheimer disease and increase as dementia progresses to moderate severity. In advanced dementia, depression symptoms tend to decline, although this may reflect the difficulty in assessing depression at advanced stages of dementia.[2]

Numerous reports have linked inflammation to cognitive dysfunction or decline, as well as to the development of Alzheimer disease.[3–5] Evidence suggests that inflammation is a key mediator between cardiovascular risk factors and Alzheimer disease, although this is also still controversial.

FINDINGS FROM THE TEXAS ALZHEIMER'S RESEARCH CONSORTIUM

The Texas Alzheimer's Research Consortium, composed of five medical centers, is pursuing a longitudinal, multi-institutional study of Alzheimer disease. The group recently published the results of a study assessing whether inflammatory markers were over- or underexpressed in patients with Alzheimer disease, and whether biomarkers could predict Alzheimer disease status and the age at onset of the disease.[4] The analysis included 197 patients with Alzheimer disease and 203 control subjects. The evaluation consisted of cognitive assessment, DNA analysis for human genome-wide association studies, and protein microarray analysis from blood. Cardiovascular risk factors were also measured, including serum lipids and blood factors for diabetes risk. The goal was to better under-

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

This article was developed from an audio transcript of Dr. Barber's lecture at the 2010 Heart-Brain Summit. The transcript was formatted and edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Barber.

doi:10.3949/ccjm.78.s1.08

TABLE
Inflammatory biomarkers panel

Alpha-1 antitrypsin	Intercellular adhesion molecule-1	Matrix metalloproteinase-3
Alpha-2 macroglobulin	Interferon gamma	RANTES
Beta-2 microglobulin	Interleukin (IL)-10	Stem cell factor
Brain-derived neurotrophic factor	IL-12p40	Tissue inhibitor of metalloproteinase-1
C-reactive protein	IL-15	Tumor necrosis factor (TNF) RII
Complement 3	IL-1ra	TNF-alpha
Eotaxin	IL-3	TNF-beta
Factor VII	IL-5	Vascular cell adhesion molecule-1
Ferritin	IL-7	Vitamin D binding protein
Fibrinogen	IL-8	Vascular endothelial growth factor
Granulocyte colony-stimulating factor	Monocyte chemotactic protein-1	von Willebrand factor
Haptoglobin		

RANTES = regulated upon activation, normal T-cell expressed and secreted

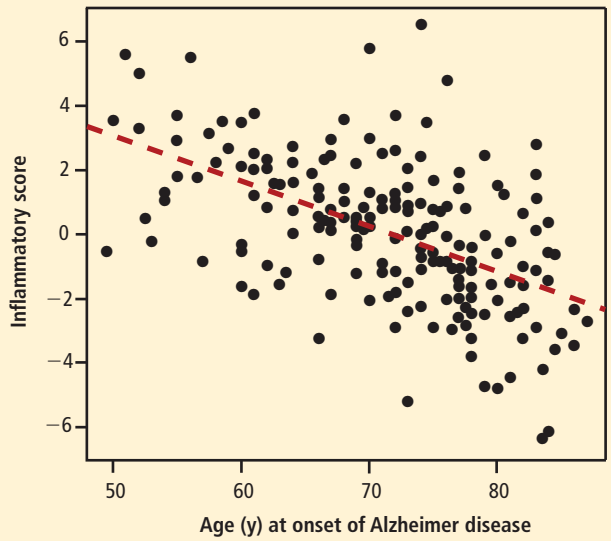

FIGURE. Principal component analysis showed that the degree of inflammation correlated with age at onset of Alzheimer disease. Greater degrees of inflammation were associated with early age at onset.[4]

stand the pathophysiology of cognitive decline and predict conversion of mild cognitive impairment to Alzheimer disease.

Researchers analyzed the levels of 34 inflammatory-related markers **(Table)** in the patient and control groups. Proteins were quantified by Rules-Based Medicine via Luminex, a multiplex fluorescent immunoassay using colored microspheres linked to protein-specific antibodies; this technology permits simultaneous measurement of several hundred proteins.

Significant differences were found in the study groups. For example, the median age in the Alzheimer group was significantly higher than in controls (79 vs 70 years, $P < .0001$), an issue that is being addressed as subjects are replaced due to attrition. The median educational level was higher in the control group (14 vs 16 years, $P < .0001$) than in the Alzheimer group. Subjects in the Alzheimer group were significantly more likely ($P < .001$) to carry at least one copy of the APOE ϵ4 allele.

Inflammation is associated with Alzheimer disease

The investigators applied principal component analysis to the data and found that inflammation correlated with onset of Alzheimer disease and with cognitive decline. Greater degrees of inflammation were associated with earlier age at onset of Alzheimer disease **(Figure)**.[4] The association was highly significant: risk of Alzheimer disease doubled with each increase in the score value of inflammation.

Degree of inflammation also correlated with Mini-Mental State Examination (MMSE) scores. Subjects with a high inflammatory score had a more accelerated decline in MMSE scores over a 3-year period than those with a low inflammatory score. The association was significant, although not as dramatic as the association between inflammation and age at onset of Alzheimer disease.

The investigators concluded that their findings, while considered preliminary, suggest the existence

of an inflammatory endophenotype associated with Alzheimer disease. The findings need to be validated in other populations, including ethnic groups other than Caucasian. The Consortium also will evaluate whether inflammatory biomarkers are associated with progression of mild cognitive impairment to Alzheimer disease.

Inflammation has a mixed association with depression

In a study whose results are not yet published, the Texas Consortium also examined the association between inflammatory markers and depression. Four subscales of depression were used, derived from the Geriatric Depression Scale (GDS) 30: dysphoria (consisting of 11 items), meaninglessness (seven items), apathy and withdrawal (six items), and cognitive impairment (six items).[5]

The GDS30 results as a whole suggested a trend toward an association between depression and inflammatory biomarkers, but the association was not significant. When the results were examined by subscale, however, striking differences were found between Alzheimer patients and the control group. For example, apathy was significantly associated with the C-reactive protein level, and the assocation was much stronger in patients with Alzheimer disease than in controls. Further, the association of apathy with C-reactive protein level was more significant in women than in men.

Other associations were found between several of the inflammatory and antiinflammatory cytokines and the various subscales; the relationship between inflammatory factors and depression appears to be complex and often gender-specific.

Inflammation-depression link is suggestive, not linear

Despite the relationships suggested by the data, no simple linear relationship was identified to indicate that more inflammation leads to more depression in Alzheimer disease. The relationship between inflammation and depression in Alzheimer disease appears to involve a complex interplay between many physiologic processes.

The effect of inflammation also varies with gender and with cognitive impairment. The mechanism that underlies these relationships remains to be determined and will be the focus of further studies with the Texas Alzheimer's Research Consortium.

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Vascular signaling abnormalities in Alzheimer disease

ABSTRACT

Our laboratory has documented that brain microvessels derived from patients with Alzheimer disease (AD) express or release a myriad of factors that have been implicated in vascular activation and angiogenesis. In addition, we have documented that signaling cascades associated with vascular activation and angiogenesis are upregulated in AD-derived brain microvessels. These results are consistent with emerging data suggesting that factors and processes characteristic of vascular activation and angiogenesis are found in the AD brain. Despite increases in proangiogenic factors and signals in the AD brain, however, evidence for increased vascularity in AD is lacking. Cerebral hypoperfusion/hypoxia, a potent stimulus for vascular activation and angiogenesis, triggers hypometabolic, cognitive, and degenerative changes in the brain. In our working model, hypoxia stimulates the angiogenic process; yet, there is no new vessel growth. Therefore, there are no feedback signals to shut off vascular activation, and endothelial cells become irreversibly activated. This activation results in release of a large number of proteases, inflammatory proteins, and other gene products with biologic activity that can injure or kill neurons. Pathologic activation of brain vasculature may contribute noxious mediators that lead to neuronal injury and disease processes in AD brains. This concept is supported by preliminary experiments in our laboratory, which show that pharmacologic blockade of vascular activation improves cognitive function in an animal model of AD. Thus, "vascular activation" could be a novel, unexplored therapeutic target in AD.

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

This work was supported in part by grants from the National Institutes of Health (AG15964, AG020569 and AG028367). Dr. Grammas is the recipient of the Shirley and Mildred Garrison Chair in Aging.

doi:10.3949/ccjm.78.s1.09

Alzheimer disease (AD) is a progressive, irreversible, neurodegenerative disease that affects more than 5.3 million people in the United States.[1] This number is significantly higher than the previous estimate of 4.5 million and is projected to increase sharply to nearly 8 million by 2030.[1] At present, the few agents that are approved by the US Food and Drug Administration for treatment of AD have demonstrated only modest effects in modifying clinical symptoms for relatively short periods; none has shown a clear effect on disease progression. New therapeutic approaches are desperately needed.

VASCULAR DISEASE AND ALZHEIMER DISEASE

Although AD is classified as a neurodegenerative dementia, there is epidemiologic and pathologic evidence of an association with vascular risk factors and vascular disease.[2–6] Vascular disease appears to lower the threshold for the clinical presentation of dementia at a given level of AD-related pathology.[7] The possible association of AD with vascular disease suggests that there are important pathogenic mechanisms common to both AD and vascular disease. For example, there is increasing evidence that perturbations in cerebral vascular structure and function occur in AD.[8]

It has been suggested that cerebral hypoperfusion/hypoxia triggers hypometabolic, cognitive, and degenerative changes in the brain and contributes to the pathologic processes of AD.[9] A study by Roher and colleagues reveals an association between severe circle of Willis atherosclerosis and sporadic AD.[10] These observations suggest that atherosclerosis-induced brain hypoperfusion contributes to the clinical and pathologic manifestations of AD.

Hypoxia is also known to stimulate angiogenesis, especially via upregulation of hypoxia-inducible genes such as vascular endothelial growth factor (VEGF).[11,12] VEGF, a critical mediator of angiogenesis, is present in the AD brain in the walls of intra-

parenchymal vessels, in diffuse perivascular deposits, and in clusters of reactive astrocytes.[13] In addition, intrathecal levels of VEGF in AD are related to clinical severity and intrathecal levels of amyloid-beta (Aβ).[14] Emerging data support the idea that factors and processes characteristic of angiogenesis are found in the AD brain.[15,16]

Our laboratory has documented that brain microvessels derived from AD patients express or release a myriad of factors that have been implicated in vascular activation and angiogenesis, including nitric oxide, thrombin, tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, transforming growth factor-β, macrophage inflammatory protein-1α, VEGF, monocyte chemotactic protein-1, matrix metalloproteinase-9, and integrins ($\alpha_V\beta_3$, $\alpha_V\beta_5$) **(Table 1)**.[17–22]

TABLE 1
Angiogenic mediators overexpressed by brain microvessels

NO	TGF-β
Thrombin	MIP-1α
TNF-α	VEGF
IL-1β	MCP-1
IL-6	MMP-9
IL-8	Integrin ($\alpha_V\beta_3$, $\alpha_V\beta_5$)

IL = interleukin-; MCP = monocyte chemotactic protein; MIP = macrophage inflammatory protein; MMP = matrix metalloproteinase; NO = nitric oxide; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

ENDOTHELIAL ACTIVATION AND ANGIOGENESIS

The angiogenic process is complex and involves several discrete steps, such as endothelial activation, extracellular matrix degradation, proliferation and migration of endothelial cells, and morphologic differentiation of endothelial cells to form tubes. Stimuli known to initiate angiogenesis, including hypoxia, inflammation, and mechanical factors such as shear stress and stretch,[23] either directly or indirectly activate endothelial cells. Activated endothelial cells elaborate adhesion molecules, cytokines and chemokines, growth factors, vasoactive molecules, major histocompatibility complex molecules, procoagulant and anticoagulant moieties, and a variety of other gene products with biologic activity.[24] The activated endothelium exerts direct local effects by producing at least 20 paracrine factors that act on adjacent cells.[25]

ANGIOGENIC SIGNALING MECHANISMS IN BRAIN MICROVESSELS

Signaling mechanisms that have been identified as important to endothelial cell viability and angiogenesis include PI3K/Akt, p38 kinase, ERK, and JNK. In this regard, intracellular Aβ accumulation is toxic to endothelial cells and decreases PI3K/Akt.[26] Extracellular Aβ peptides decrease phosphorylation and thus activation of ERK and p38 kinase.[26] VEGF promotes endothelial survival, proliferation, and migration through numerous pathways, including activation of ERK, p38 kinase, JNK, and Rho GTPase family members.[23]

The issue of proangiogenic and antiangiogenic signals in AD is complex. Wu and colleagues demonstrated that expression of the homeobox gene MEOX2 (also known as Gax), a regulator of vascular differentiation, is low in AD.[27] Furthermore, restoring expression stimulates angiogenesis. In mice, deletion of Gax results in reduced brain capillary density and loss of the angiogenic response to hypoxia in the brain.[27] On the other hand, other groups have shown that Gax is antiangiogenic and its expression inhibits endothelial cell proliferation and tube formation.[28,29] We have documented that signaling cascades associated with vascular activation and angiogenesis are generally upregulated in AD-derived brain microvessels **(Table 2)**.

VASCULAR ACTIVATION IN ALZHEIMER DISEASE

Despite increases in several proangiogenic factors in the AD brain, evidence for increased vascularity in AD is lacking. On the contrary, it has been suggested that the angiogenic process is delayed or impaired in aged tissues, with several studies showing decreased microvascular density in the AD brain.[30–33] Paris et al showed that wild-type Aβ peptides have antiangiogenic effects in vitro and in vivo.[34]

How can the data showing antiangiogenic effects of Aβ be reconciled with the presence or expression of a large number of proangiogenic proteins by brain microvessels in AD? These conflicting observations suggest an imbalance between proangiogenic and antiangiogeneic processes in the AD brain.

In our working model, we hypothesize that in response to a persistent stimulus such as cerebral hypoperfusion (a major clinical feature in AD), brain endothelial cells become activated and acquire an "activated-angiogenic phenotype." Despite the continued presence of the stimulus, an imbalance of proangiogenic and antiangiogenic factors or aborted angiogenic signaling prevents new vessel growth.

TABLE 2
Expression levels of some signaling kinases in human microvessels

Kinase	Mean expression ± SEM		Trend in AD	Significance
	Control	AD		
Phospho p38 MAPK	0.58 ± 0.01	0.97 ± 0.10	Increase	**
Phospho SAPK/JNK	0.44 ± 0.10	1.06 ± 0.18	Increase	**
Phospho ERK	0.22 ± 0.03	0.50 ± 0.11	Increase	*
Phospho Akt	0.19 ± 0.05	0.55 ± 0.09	Increase	**
Phospho c-Jun	0.73 ± 0.05	0.58 ± 0.07	No change	—

Protein levels of phosphorylated form of signaling kinases in human microvessels isolated from control (n = 6) and AD (n = 8) brains were determined by Western blot analysis.
$^{**}P < .01$; $^{*}P < .05$; AD = Alzheimer disease

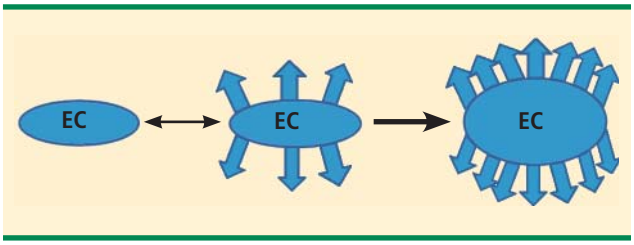

FIGURE. According to our hypothesis, in Alzheimer disease, endothelial cells (ECs) become irreversibly active and elaborate large numbers of proteases, inflammatory proteins, and other gene products (represented by the blue arrows) that can be toxic to neurons.

Therefore, in the absence of feedback signals to shut off vascular activation, endothelial cells become irreversibly activated and elaborate a large number of proteases, inflammatory proteins, and other gene products with biologic activity that can injure or kill neurons **(Figure)**.

Preliminary experiments in our laboratory show that pharmacologic blockade of vascular activation improves cognitive function in an animal model of AD. Thus, "vascular activation" could be a novel, unexplored therapeutic target in AD.

Acknowledgment

The authors gratefully acknowledge the secretarial assistance of Terri Stahl.

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Stress in medicine: Strategies for caregivers, patients, clinicians

The burdens of caregiver stress

By Michael G. McKee, PhD

The number of people in the United States who spend a significant part of each week working as unpaid caregivers is considerable, and the toll exacted for such work is high. Understanding the profile of the caregiver, the nature of the duties performed, the stress imposed by such duties, and the consequences of the stress can assist the clinician in recognizing the caregiver in need of intervention.

A PROFILE OF THE CAREGIVER

A recent survey estimated that more than 65 million Americans provide unpaid assistance annually to older adults with disabilities.1 The value of that labor has been estimated at $306 billion annually, or nearly double the combined cost of home health care and nursing home care.[2,3]

The typical caregiver is a woman, about 48 years old, with some college education, who spends 20 hours or more each week providing unpaid care to someone aged 50 years or older.[1] The recipients of care often have long-term physical disabilities; mental confusion or emotional problems frequently complicate care.

Caregivers help patients with instrumental activities of daily living (IADL), in addition to helping with tasks such as getting dressed and bathing. IADL might include assisting with transportation, housework, grocery shopping, preparing meals, managing finances, giving medications, and arranging for paid services such as nursing care **(Figure)**.[1]

PSYCHOLOGIC AND PHYSICAL COSTS

Caregiving may take a toll on the caregiver in a variety of ways: behavioral, in the form of alcohol or substance use[4]; psychologic, in the form of depression or other mental health problems[5]; and physical, in the form of chronic health conditions and impaired immune response.[6] About three-fifths of caregivers report fair or poor health, compared with one-third of noncaregivers, and caregivers have approximately twice as many chronic conditions, such as heart disease, cancer, arthritis, and diabetes, compared with noncaregivers.[2,7] Caregiving also exacts a financial toll, as employees who are caregivers cost their employers $13.4 billion more per year in health care expenditures.[8] In addition, absenteeism, workday interruptions, and shifts from full-time to part-time work by caregivers cost businesses between $17.1 and $33.6 billion per year.[9]

The cost of caregiving is higher for women, who exhibit higher levels of anxiety and depression and lower levels of subjective well-being, life satisfaction, and physical health.[10,11] The stress of caregiving has also been identified as a risk factor for morbidity among older (66 to 96 years old) caregivers, who have a 63% greater mortality than noncaregivers of the same age.[12]

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This article was developed from an audio transcript of the authors' presentations and panel discussion at the 2011 Heart-Brain Summit. The transcript was edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by each of the authors.

doi:10.3949/ccjm.78.s1.10

PSYCHOSOCIAL STRESS, UNHEALTHY BEHAVIORS, AND ILLNESS ARE LINKED

Psychosocial stress is a predictor of disease and can lead to unhealthy behaviors such as smoking, substance abuse, overeating, poor nutrition, and a sedentary lifestyle; these, in turn, can lead to physical and psychiatric illness. Behaviors adopted initially as coping skills may persist to become chronic, thereby promoting either continued wellness (in the case of healthy coping behaviors) or worsening levels of illness (in the case of unhealthy coping behaviors).

McEwen and Gianaros[13] have suggested that these stress mechanisms arise from patterns of communication between the brain and the autonomic, cardiovascular, and immune systems, which mutually influence one another. These so-called bidirectional stress processes affect cognition, experience, and behavior.

An integrated model of stress that maps the bidirectional causal pathways among psychosocial stressors, resulting unhealthy behaviors, and illness is needed. Although the steps from unhealthy behaviors to illness are fairly well understood, the links from psychosocial stress, such as those exhibited by caregivers, to unhealthy behaviors are not as clear. Several mediators are under study:

- Personality mediators can be either ameliorative (resilience, self-confidence, self-control, optimism, high self-esteem, a sense of mastery, and finding meaning in life) or exacerbating (neuroticism and inhibition, which together form the so-called type D personality).
- Environmental mediators include social support, financial support, a history of a significant life change, and trauma early in life, which may increase one's subsequent vulnerability to unhealthy behaviors.
- Biologic mediators may include prolonged sympathetic activation and enhanced platelet activation, caused by increased levels of depression and anxiety in chronically stressed caregivers.[14]

IMPLICATIONS FOR INTERVENTION

A significant percentage of caregivers do not need a clinician's intervention to help them cope with stress or unhealthy coping skills. Among caregivers aged 50 years or older, 47% indicated in a recent study that the burden of caregiving is low (ie, 1 or 2 on a 5-point scale).[1] Those who respond to stressors as challenges rather than threats tend to be resilient people who exert control over their lives, often through meditation or similar techniques, and have a strong social support network. Many report that caregiving provides them with an opportunity to act in accordance with their values and feel helpful rather than helpless.

FIGURE. Percentage of caregivers who assist with instrumental activities of daily living (IADL).[1]

Cognitive-behavioral interventions to alleviate stress-related symptoms appear to be more effective if offered as individual rather than group therapy. Teaching caregivers effective coping strategies, rather than merely providing social support, has been shown to improve caregiver psychologic health.[15] Chief among the goals of intervention should be to alter brain function and instill optimism, a sense of control and self-esteem.[13]

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Promoting better outcomes with stress and anxiety reduction

By A. Marc Gillinov, MD

The traditional paradigm for cardiac care has emphasized the use of technology to treat disease. Our focus on technologies such as echocardiography, advanced imaging instrumentation, and cardiac catheterization mirrors the preoccupation of society as a whole with technologic advances.

Attention has only recently been given to the patient's emotional experience and how this might relate to outcomes, recovery, and healing. An expanded paradigm of cardiac care incorporates pain relief, emotional support, spiritual healing, and a caring environment. These elements of patient-centered care aim to relieve stress and anxiety in order to achieve a better clinical outcome.

PATIENT-CENTERED CARE

The importance of patient-centered care is illustrated by the results of a 2007 survey in which 41% of patients cited elements of the patient experience as factors that most influenced their choice of hospital.[1] Accepted wisdom on patient choice has historically centered on medical factors such as clinical reputation, physician recommendations, and hospital location, each of which was cited by 18% to 21% of the patients surveyed. Elements of the patient experience cited in the study include stress-reducing factors such as the appearance of the room, ease of scheduling, an environment that supports family needs, convenience and comfort of common areas, on-time performance, and simple registration procedures.

Székely et al[2] found in a 4-year followup study that high levels of preoperative anxiety predicted greater mortality and cardiovascular morbidity following cardiac surgery. In a study by Tully et al,[3] preoperative anxiety was also predictive of hospital readmission following cardiac surgery. Preoperative stress and anxiety are reliable predictors of postoperative distress.[4]

The variety and relative efficacy of interventions to reduce stress and anxiety are not well studied. Voss et al[5] showed that cardiac surgery patients who were played soothing music experienced significantly reduced anxiety, pain, pain distress, and length of hospital stay. One Cleveland Clinic study of massage therapy, however, was unable to demonstrate a statistically significant therapeutic benefit, despite patient satisfaction with the therapy.[6]

THE ADVENT OF HEALING SERVICES

Identifying patients who exhibit significant preoperative stress and providing, as part of an expanded cardiac care paradigm, emotional care both pre- and postoperatively may ameliorate clinical outcomes. As such, the Heart and Vascular Institute at the Cleveland Clinic formed a healing services division, based on the concept that healing is more than simply physical recovery from a particular procedure. The division's mission statement is: "To enhance the patient experience by promoting healing through a comprehensive set of coordinated services addressing the holistic needs of the patient."

A healing services menu is offered to each patient **(Table)**. Referral for these services can come from the patient, family, physicians, or nurses. Of the first 898

patients admitted for heart surgery who were offered healing services on the third or fourth postoperative day, 582 chose one or more of the services (average, 2.7 interventions; total interventions, 1,514), most frequently spiritual or holistic nursing care. Ninety-three percent of these patients felt the services were helpful, and 90% said that they would recommend them to others. A personal connection between the patient and family and caregivers fosters feelings of a healing partnership that lessens stress and anxiety.

At the Cleveland Clinic, healing services are now integrated with standard services to enhance the cardiac care paradigm. Our standard medical services focus on areas of communication and pain control, both of which affect anxiety and stress. The need for enhanced communication is significant: 75% of patients admitted to a Chicago hospital were unable to name a single doctor assigned to their care, and of the remaining 25%, only 40% of responders were correct.[7]

It is worth noting that communicating more information to a patient is not necessarily better. Patients given detailed preoperative information about their disease and the potential complications of their cardiac surgery had levels of preoperative, perioperative, and postoperative stress, anxiety, and depression similar to those who received routine medical information.[8,9] On the other hand, patients desire information about their postoperative plan of care while they are experiencing it, and value communication with physicians, nurses, healing services personnel, and other caregivers when it is presented in a calm and forthright manner. Communications should emphasize that the entire clinical team is there to help the patient get better.

THE FIFTH VITAL SIGN

Pain control is an aspect of care that was long ignored. The goal of the pain control task force at the Cleveland Clinic is the development of effective, efficient, and compassionate pain management.

The fifth vital sign, one that escapes the electronic medical record, can be addressed by this question: "How are you feeling?" Treating pain will reduce stress and anxiety. Before surgery, pain management priorities are discussed with patients, and at each daily encounter the goal is to set, refine, and exceed expectations for pain control through discussion and frequent pain assessments.

Reducing anxiety and stress is the goal of both standard care services and healing services, resulting in more satisfied patients with better clinical outcomes.

TABLE
Healing services menu

Professional guidance and counseling	Spiritual, social, well-being, future visioning
Touch therapy teams	Reiki, healing touch, massage
Additional holistic interventions	Guided imagery, music, relaxation techniques

CASE: "YOU AND THE TEAM MADE ME GET OUT OF BED AND MOVE FORWARD"

Bobbi is a 78-year-old woman who was initially recovering well following cardiac surgery, including valve surgery, but had to return to the intensive care unit, which is difficult for patients. She was subsequently returned to the floor but was reluctant to walk and progressed slowly, despite normal electrocardiogram, radiographs, and blood panel results. We discovered that her husband was in hospice care in another state, causing Bobbi anxiety as she expressed concern over being her husband's caregiver while being weakened physically herself. She was fearful of moving forward and her recovery stalled.

The primary care nurse referred her to the healing services team. The healing services team provided support for her anxiety and stress, and reviewed options for managing her husband's care. She participated in Reiki, spiritual support, and social work services. During her admission her husband died, so the team provided appropriate support.

When asked about her experience upon leaving the hospital, Bobbi did not mention her surgeon or the success of her heart valve procedure, but commented instead on the healing services team that enabled her to get through the experience.

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Addressing the impact of clinician stress

M. Bridget Duffy, MD

The impact of clinician stress on the health care system is significant. It can adversely affect the patient experience, compromise patient safety, hinder the delivery of care in a manner that is inconsistent with producing quality outcomes, and increase the overall cost of care.

CLINICIAN STRESS IS PREVALENT

Models of health care that restore human interaction are desperately needed. Clinicians today are overwhelmed by performance assessments that are based on length of stay, use of evidence-based medication regimens, and morbidity and mortality outcomes. Yet clinicians have few opportunities to establish more than cursory relationships with their patients—relationships that would permit better understanding of patients' emotional well-being and that would optimize the overall healing experience.

Shanafelt et al[1] surveyed 7,905 surgeons and found that clinician stress is pervasive: 64% indicated that their work schedule left inadequate time for their personal or family life, 40% reported burnout, and 30% screened positive for symptoms of depression. Another survey of 763 practicing physicians in California found that 53% reported moderate to severe levels of stress.[2] Nonphysician clinicians have significant levels of stress as well, with one survey of nurses finding that, of those who quit the profession, 26% cited stress as the cause.[3]

THE EFFECT OF CLINICIAN STRESS ON QUALITY OF CARE

In the Shanafelt et al study, high levels of emotional exhaustion correlated positively with major medical errors over the previous 3 months.[1] Nearly 9% of the surgeons surveyed reported making a stress-related major medical mistake in the past 3 months; among those surgeons with high levels of emotional exhaustion, that figure was nearly 15%. This study also found that every 1-point increase in the emotional exhaustion scale (range, 0 to 54) was associated with a 5% increase in the likelihood of reporting a medical error.[1]

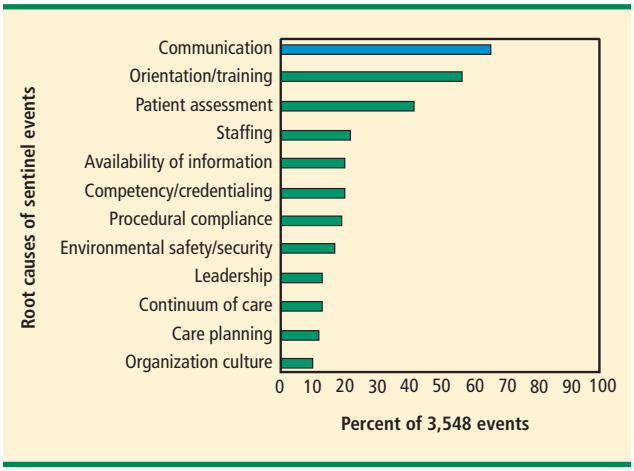

FIGURE. An analysis by the Agency for Healthcare Research and Quality concluded that communication was the most frequent contributor to 3,548 sentinel clinical events (eg, wrong-site surgery, medication errors) that occurred from 1995 through 2005.[6]

In a study of internal medicine residents, fatigue and distress were associated with medical errors, which were reported by 39% of respondents.[4]

STRESS AND COMMUNICATION

Stress can damage the physician-nurse relationship, with a significant impact not only on clinicians, but also on delivery of care. The associated breakdowns in communication can negatively affect several areas, including critical care transitions and timely delivery of care. Stress also affects morale, job satisfaction, and job retention.[5]

In an examination of sentinel events in US health care, the Agency for Healthcare Research and Quality determined that a communication breakdown was the most common root cause of sentinel events

in wrong-site surgery, delays in treatment, and medication errors, and the second most common cause (behind orientation/training) of adverse postoperative events.[6] When root causes of all clinical categories of sentinel events were tallied, communication was found to be the most frequent contributor (training, patient assessment, and staffing were next) **(Figure)**.[6] The quality of the communication among physicians and nurses is a major influence on overall patient satisfaction and a patient's willingness to recommend the hospital to others.

ADDRESSING THE IMPACT OF CLINICIAN STRESS

The traditional response to complaints registered by patients has been behavioral coaching, disruptive-behavior programs, and the punitive use of satisfaction metrics, which are incorporated into the physician's annual evaluation. These approaches do little to address the cause of the stress and can inculcate cynicism instead.

A more useful approach is to define and strive for an optimal working environment for clinicians, thereby promoting an enhanced patient experience. This approach attempts to restore balance to both the business and art of medicine and may incorporate biofeedback and other healing services to clinicians as tools to minimize and manage stress.

The business of medicine may be restored by enhancing the culture and climate of the hospital, improving communication and collaboration, reducing administrative tasks, restoring authority and autonomy, and eliminating punitive practices. The art of medicine may be restored by valuing the sacred relationship between clinician and patient, learning to listen more carefully to the patient, creating better healing environments, providing emotional support, and supporting caregivers.

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Biofeedback in the treatment of stress

By Richard N. Gevirtz, PhD

Traditionally, biofeedback was considered to be a stress management technique that targeted sympathetic nervous system (SNS) overdrive with an adrenal medullary system backup. Recent advances in autonomic physiology, however, have clarified that except in extreme situations, the SNS is not the key factor in day-to-day stress. Rather, the parasympathetic branch of the autonomic nervous system appears to be a more likely candidate for mediating routine stress because, unlike the SNS, which has slow-acting neurotransmitters (ie, catecholamines), the parasympathetic nervous system has the fast-acting transmitter acetylcholine.

VAGAL WITHDRAWAL: AN ALTERNATIVE TO SYMPATHETIC ACTIVATION

Porges[1] first proposed the concept of vagal withdrawal as an indicator of stress and stress vulnerability; this contrasts with the idea that the stress response is a consequence of sympathetic activation and the hypothalamic-pituitary-adrenal axis response. In the vagal withdrawal model, the response to stress is stabilization of the sympathetic system followed by termination of parasympathetic activity, manifested as cardiac acceleration.

Respiratory sinus arrhythmia (RSA), or the variability in heart rate as it synchronizes with breathing, is considered an index of parasympathetic tone. In the laboratory, slow atropine infusion produces a transient paradoxical vagomimetic effect characterized by an initial increase in RSA, followed by a flattening and then a rise in the heart rate.[2] This phenomenon has been measured in people during times of routine stress, such as when worrying about being late for an appointment. In such individuals, biofeedback training can result in recovery of normal RSA shortly after an episode of anxiety.

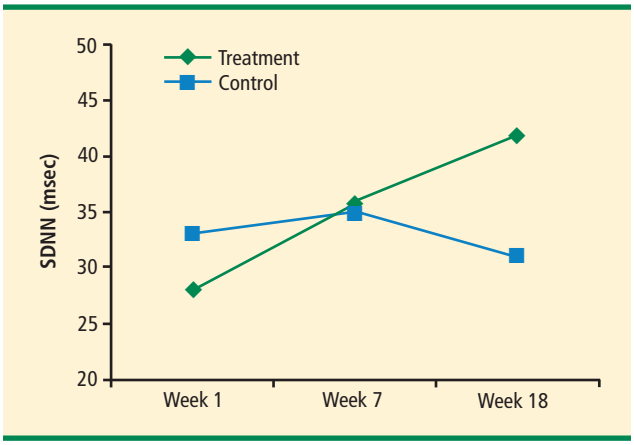

FIGURE. Patients who underwent heart-rate variability (HRV) biofeedback training achieved near-normal standard deviation of normal-to-normal QRS complexes (SDNN) after 18 weeks. The SDNN, which is the primary measure used to quantify a change in HRV, declined in patients in the control group.[3]

Historically, the focus of biofeedback was to cultivate low arousal, presumably reducing SNS activity, through the use of finger temperature, skin conductance training, and profound muscle relaxation. More sophisticated ways to look at both branches of the autonomic nervous system have since emerged that allow for sampling of the beat-by-beat changes in heart rate.

HEART RATE VARIABILITY BIOFEEDBACK

The concept of modifying the respiration rate (paced breathing) originated some 2,500 years ago as a component of meditation. It is being revisited today in the form of heart rate variability (HRV) biofeedback training, which is being used as a stress-management tool and a method to correct disorders in which autonomic regulation is thought to be important. HRV biofeedback involves training to increase the amplitude of HRV rhythms and thus improve autonomic homeostasis.

Normal HRV has a pattern of overlapping oscillatory frequency components, including:

- a high-frequency rhythm, 0.15 to 0.4 Hz, which is the RSA;
- a low-frequency rhythm, 0.05 to 0.15 Hz, associated with blood pressure oscillations; and
- a very-low-frequency rhythm, 0.005 to 0.05 Hz, which may regulate vascular tone and body temperature.

The goal of HRV biofeedback is to achieve respiratory rates at which resonance occurs between cardiac rhythms associated with respiration (RSA, or high-frequency oscillations) and those caused by baroreflex activity (low-frequency oscillations).

Spectral analysis has demonstrated that nearly all of the activity with HRV biofeedback occurs at a low-frequency band. The reason is that activity in the low-frequency band is related more to baroreflex activity than to HRV compared with other ranges of frequency. Breathing rates that correspond to baroreflex effects, called resonance frequency breathing, represent resonance in the cardiovascular system. Several devices are available whose mechanisms are based on the concept of achieving resonance frequency breathing. One such device is a slow-breathing monitor (Resp-e-rate) that has been approved by the US Food and Drug Administration for the adjunctive treatment of hypertension.

Biofeedback has demonstrated success in several clinical trials targeting populations with autonomically mediated disorders. Del Pozo et al[3] conducted a randomized study of HRV biofeedback in patients with coronary artery disease. Patients in the active intervention group underwent HRV biofeedback training that included breathing practice at home for 20 minutes per day. The standard deviation of normal-to-normal QRS complexes (SDNN), which is the primary measure used to quantify a change in HRV, improved from a mean of 28.0 msec to 42.0 msec after 18 weeks in the treatment group, and declined from a mean of 33.0 msec to 30.7 msec in the controls (**Figure**).

Improved HRV may suggest an improved risk status: Kleiger et al[4] found that the relative risk of mortality was 5.3 times greater for people with SDNN of less than 50 msec compared with those whose SDNN was greater than 100 msec. In Del Pozo's study, eight of 30 patients in the intervention group achieved an SDNN of greater than 50 msec (vs 0 at pretreatment) compared with three of 31 controls (vs two at pretreatment).[3] As an additional benefit of HRV biofeedback, patients in the intervention group who entered the study with hypertension all became normotensive.

In a meta-analysis, van Dixhoorn and White[5] found fewer cardiac events, fewer episodes of angina, and less occurrence of arrhythmia and exercise-induced ischemia from intensive supervised relaxation therapy in patients with ischemic heart disease. Improvements in scales of depression and anxiety were also observed with relaxation therapy.

Other studies have shown biofeedback to have beneficial effects based on the Posttraumatic Stress Disorder Checklist, the Hamilton Depression Rating Scale, and, in patients with mild to moderate heart failure, the 6-minute walk test.[6–8]

The proposed mechanism for the beneficial effects of biofeedback found in clinical trials is improvement in baroreflex function, producing greater reflex efficiency and improved modulation of autonomic activity.

CONCLUSION

A shift in emphasis to vagal withdrawal has led to new forms of biofeedback that probably potentiate many of the same mechanisms thought to be present in Eastern practices such as yoga and tai chi. Results from small-scale trials have been promising for HRV biofeedback as a means of modifying responses to stress and promoting homeostatic processes that reduce the intensity of symptoms and improve surrogate markers associated with a number of disorders.

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Biofeedback for extreme stress: Wounded warriors

By Carmen V. Russoniello, PhD

Posttraumatic stress disorder (PTSD) is a severe anxiety disorder whose symptoms emerge following exposure to extreme stress, such as those encountered in the battlefield or as a result of sexual abuse or natural disasters. The ability to employ coping mechanisms affects the disorder's presentation as well as the frequency, intensity, and duration of the symptoms. The "Wounded Warrior" program at East Carolina University (Greenville, NC) was developed to promote the functional independence of US Marines, including those with PTSD.

STRESS RESPONSE: INTERACTION OF THE BRAIN AND IMMUNE SYSTEM

Walter Cannon coined the "flight or fight" response to stress in the early 20th century, in which he emphasized the importance of the parasympathetic system.[1] In 1988, Folkow clarified the description as an immune response to stress.[2] The stress response is now understood to be a neuroendocrine function that includes a feedback loop between the hypothalamus and the pituitary and adrenal glands; stimulation of the hypothalamus promotes secretion of corticotropin-releasing hormone (CRH) into the hypophyseal portal system, which supplies the anterior pituitary with blood. CRH stimulates the secretion of adrenocorticotropic hormone into the bloodstream by the pituitary, prompting the adrenal glands to release the stress hormone cortisol.

Cortisol mobilizes the body's defenses to meet the challenge of an adverse situation. It modulates the stress response by inhibiting the further release of CRH by the hypothalamus. Cortisol thus protects healthy cells and tissues by inhibiting an overreaction from the immune system. Without this protective effect, the interaction between the brain and the immune system can become dysregulated, increasing the risk of immune disorders.

THE CENTRAL AUTONOMIC NETWORK

The central nervous system that regulates the overall balance of the autonomic nervous system (ANS) has been called the central autonomic network (CAN).[3] The CAN helps control executive, social, affective, attentional, and motivational functions. Therefore, the old paradigm of simply decreasing hyperarousal of the ANS to treat negative affective states and dispositions is inadequate. Instead, restoring the appropriate relationship between the ANS and the central nervous system is the aim behind interventions to treat PTSD.

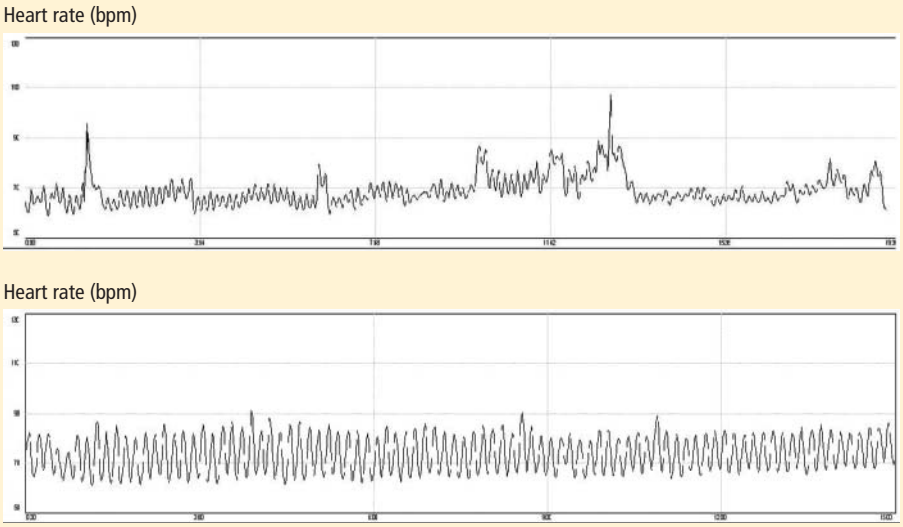

FIGURE. Before (top) and after (bottom) heart rate variability training training. The patient's heart rate after completing training has markedly less variation.

Autonomic, cognitive, and affective functions assist humans in maintaining balance when confronted with external challenges. The CAN controls inhibitory or negative processes that permit specific behavior and redeploy resources needed elsewhere. When negative circuits are compromised, positive circuits develop, resulting in hypervigilance, the symptoms of which can be devastating and, if not ameliorated, can develop into permanent conditions. In one study, Vietnam veterans with PTSD had an 8% reduction in the volume of their right hippocampus compared with veterans without PTSD. Another study calculated a 26% reduction in the left hippocampus and a 22% reduction in the right in veterans with the most severe PTSD compared with veterans who were in combat but had no PTSD symptoms.[4]

A common subcortical neural system regulates defensive behavior, including autonomic, emotional, and cognitive behavior. When the prefrontal cortex is taken "off line" for whatever reason, parasympathetic inhibitory action is withdrawn, and relative sympathetic dominance, associated with defense, occurs.

CONFRONTING HYPERAROUSAL

The question then arises of how to train the ANS to avoid hypervigilance. Growing evidence supports the use of heart rate variability as a predictor of hypervigilance and inefficient allocation of attentional and cognitive resources.

The overall objective of heart rate variability training is to decrease ANS hyperarousal and to improve its balance. "Wounded warriors" learn to control ANS responses to stress-producing stimuli (eg, thoughts, memories, and images associated with combat). The goal of training is to decrease arousal and maintain ANS balance for increasing lengths of time.

Once it was observed that alpha waves were dysfunctional in vulnerable populations, protocols were developed to train alpha and theta waves as a method of improving function. Peniston and colleagues[5–9] showed that increased alpha and theta brain wave production resulted in normalized personality measures and prolonged the period of time before relapse in alcoholics. This protocol has also shown efficacy as an intervention in depression and PTSD.

BIOFEEDBACK TRAINING PROGRAM

The US Department of Defense is studying a combination of central nervous system biofeedback with ANS biofeedback, with the goal of restoring and maintaining tone between the systems.

The training program used in the study lasts 1 month, and starts with a session for preassessment, 16 biofeedback sessions (four per week), a postprogram evaluation, and a 3-month followup. Each week, participants are exposed to stress-producing stimuli that increase in intensity:

- Week 1: Stroop Color Word Test, math stressor, talk stressor/everyday events
- Week 2: Talk stressor, combat experiences
- Week 3: Images and sounds of combat
- Week 4: Virtual Baghdad or Afghanistan (virtual reality exposure)

Each biofeedback session consists of 5 minutes of

baseline evaluation; 5 minutes in which the veteran is subjected to the weekly stressor; 20 minutes of heart rate variability and neurofeedback training; 5 more minutes of training with the weekly stressor; 20 more minutes of heart rate variability and neurofeedback training; and finally 5 minutes of recovery.

Preliminary clinical data indicate decreases in ANS hyperarousal and increases in parasympathetic activity (**Figure**). Reports on the Patient Health Questionnaire Short Form (PHQ SF-36) indicate positive changes in physical symptoms and decreases in symptoms of depression, panic, and anxiety.

Outcome measurements will include changes from heart rate variability training; the Posttraumatic Stress Checklist; PHQ SF-36; Profile of Mood States; salivary alpha-amylase changes; a behavioral questionnaire assessing nutrition habits and alcohol, drug, and nicotine use; and the Self-Satisfaction Inventory.

SUMMARY

Dysfunction in the balance of both the ANS and central nervous system is associated with symptoms of PTSD in combat veterans. Methods that are designed to restore balance in these systems are needed to ameliorate these symptoms. Biofeedback and neurofeedback are safe methods with which to achieve these goals.

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Panel discussion

Question from audience: Why does the Cleveland Clinic start its healing services program preoperatively rather than postoperatively?

Dr. Gillinov: We have a fairly well defined preoperative set of medical tests, and during this process nurses present patients with materials that explain the experience, and nurses and doctors make themselves available in special classes to answer patients' questions. In doing so, we have increasingly identified patients preoperatively who have stress or problems.

Last week I saw a woman who had a leaking mitral valve, but her symptoms were out of proportion to her disease. She had loss of energy and appetite, and she wasn't eating much. She was depressed and our team picked that up. She actually never had to undergo surgery. We referred her to a psychologist and, according to her son, she started to feel better. By starting preoperatively, we're sometimes able to pick out things that we should treat instead of heart disease.

We also provide guided imagery and massage preoperatively.

Dr. Duffy: Healing services is on standing preoperative orders at the hospital. The team goes in proactively and asks, "In addition to your open heart surgery on Wednesday, is there anything we can do to support your emotional and spiritual journey here today?"

Terminology also matters. The term "healing services" is a safe umbrella under which we include biofeedback as one of the services, but it encompasses pastoral care, hospice care, and palliative care. The way it's integrated into a care model is important. If it's reserved for end of life, it might be viewed as defective or as a death sentence, so we want the healing services team to be proactive.

Question from audience: How does the primary care physician fit into all of this? I believe that if the physicians in the hospital want to gain patient confidence, they'll show that they're communicating well with the primary care physician.

Dr. Gevirtz: The primary care physicians are incred-

ibly open to this idea. They have 12 minutes to deal with people with fibromyalgia, irritable bowel syndrome, chronic pain, noncardiac chest pain, etc. What are they going to do in 12 minutes? They're grateful if they have a handoff, especially if it's in the Clinic itself.

Question from audience: Are there any thoughts on making biofeedback part of general training rather than using it just for patients who've already experienced trauma?

Dr. Gevirtz: We did a study in which we showed that a biofeedback technician in the primary care setting saved the health maintenance system quite a lot of money, but the administration couldn't decide whose territory to take to give us an office, so it ended the program.

Dr. Russoniello: How we enable greater access to our intervention is an important question. I see people quit the program if they can't get access to biofeedback. In an effort to enhance compliance, we've incorporated biofeedback into video games, working with a couple of private companies to develop them. The idea is that persons playing the video game can accrue points to enhance their overall score if they perform paced breathing or some other form of biofeedback. Early indications from focus groups are that people will like this.

We have already shown in randomized controlled clinical studies of depression and anxiety that certain video games can improve mood and decrease stress. There is a big movement to get products in people's hands to help them manage their health.

Question from audience: How much overlap is there between biofeedback methodologies—enhancing heart rate variability, vagal withdrawal, neurofeedback, and electroencephalographic feedback—in the systems you're targeting and what are the unique contributions of each?

Dr. Gevirtz: We follow a stepped-care model. We start with the simplest and move on to the more complicated technologies. Two published studies with long-term followup showed the effectiveness of a learned breathing technique in alleviating noncardiac chest pain. Simple biofeedback wasn't even needed. Three years later, the patients were better than they were at the end of the actual training. If you can do it simply, then you do it, and if it doesn't work, then move on to more and more complicated techniques, with neurofeedback being the last resort.

Question from audience: Has anybody measured the physical impact of stimulating multiple systems on the study subject? In other words, can it be damaging to overstimulate these systems at the same time?

Dr. Gevirtz: We've been trying to do that. Recurrent abdominal pain or functional abdominal pain is the most common complaint to pediatric gastroenterologists. We have 1,800 patients a year who make it to the children's hospital level with this complaint. These are kids who are suffering with very great pain and we we're pretty sure it's an autonomically mediated kind of phenomenon. We're able to measure vagal activity in these kids in ambulatory settings at school and have found have very little vagal activity before treatment. After training, they were able to restore vagal activity, and it correlated at the level of 0.63 with a reduction of symptoms. I think it's important to try to tie the physiology to symptoms. It's not always easy to do but we're trying.

Question from audience: I'd like to pick up on two topics that Dr. Duffy raised: the business of medicine and the proposal for informed hope rather than an informed consent before surgery. Something that I see with patients and families at times is this magical expectation promoted by the business side that medicine can do these amazing and wonderful things and doesn't have any sort of weaknesses. I wonder what role unrealistic expectations promoted by the media, advertising, and others may play in the stress of patients, caregivers, and physicians who need to try to meet the expectations of infallible medicine?

Dr. Duffy: We've spun so far the other way with our advanced technology that we've lost the human side, especially the concept of a relationship and giving people hope even though they have a terminal condition. It's a balance between the art and the business of medicine. It's about setting realistic expectations and realistic hope.

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Key 2010 publications in behavioral medicine

ABSTRACT

Previous research has demonstrated an association between depression and incident coronary heart disease (CHD); in 2010, well-controlled studies and meta-analyses went beyond depression to include anxiety, anger expression, and negative affect as predictors of incident CHD. Emerging research suggests that positive emotions and resilience (including the ability to self-regulate) offer protection against CHD. New research is elucidating the pathophysiology to explain the effects of emotion and resilience on disease risk; for example, recent work has begun to consider how the relaxation response promotes resilience and found that it induces genomic changes that counter oxidative stress and associated cellular damage.

The effect of emotion on the heart is not confined to depression, but extends to a variety of mental states; as William Harvey described in 1628, "A mental disturbance provoking pain, excessive joy, hope or anxiety extends to the heart, where it affects its temper and rate, impairing general nutrition and vigor."

In going beyond the well-established role of depression as a risk factor for heart disease, 2010 delivered several important publications recognizing anxiety, anger, and other forms of distress as key factors in the etiology of coronary heart disease (CHD). Other papers of merit elucidated new and overlooked insights into the pathways linking psychosocial stress and cardiovascular risk, and also considered psychologic states that appear to promote healthy functioning.

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

This article was developed from an audio transcript of Dr. Kubzansky's lecture at the 2010 Heart-Brain Summit. The transcript was formatted and edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Kubzansky.

doi:10.3949/ccjm.78.s1.11

IMPACT OF NEGATIVE EMOTIONS ON RISK OF INCIDENT CORONARY HEART DISEASE

In a meta-analysis of 20 prospective studies that included 249,846 persons with a mean follow-up of 11.2 years, Roest et al[1] examined the impact of anxiety characterized by the presence of anxiety symptoms or a diagnosis of anxiety disorder on incident CHD. Most of the studies adjusted for a broad array of relevant potential confounders. Findings suggest the presence of anxiety increases the risk of incident CHD by 26% ($P < .0001$) and the risk of cardiac death by 48% ($P = .003$).

In a meta-analysis of 25 prospective studies of 7,160 persons with a mean follow-up exceeding 10 years, Chida and Steptoe[2] found that anger increased the risk of incident CHD by 19%, after adjustment for standard coronary risk factors. The effect was less stable than that associated with anxiety and depression, and when stratified by gender, the harmful effects of anger were more evident in men than in women. The effect of anger was attenuated when controlling for behavioral covariates. The association between anger and CHD did not hold for all ways of measuring anger, which suggests that the type of anger or the ability to regulate anger may be relevant to the relationship.

A study that did account for the type of anger expression on the risk of incident CHD was conducted by Davidson and Mostofsky.[3] The independent effect of three distinct types of anger expression (constructive anger, destructive anger justification, and destructive anger rumination) on 10-year incident CHD was examined, controlling for other psychosocial factors. In men, higher scores for constructive anger were associated with a lower rate of CHD; in both men and women, higher scores for destructive anger justification were associated with an increased risk of CHD.

Insights gained from these studies are as follows.

- The impact of anxiety appears to be comparable to depression, and the effects of anxiety and depression are largely independent.
- If anxiety and depression co-occur, the effect on CHD is synergistic.

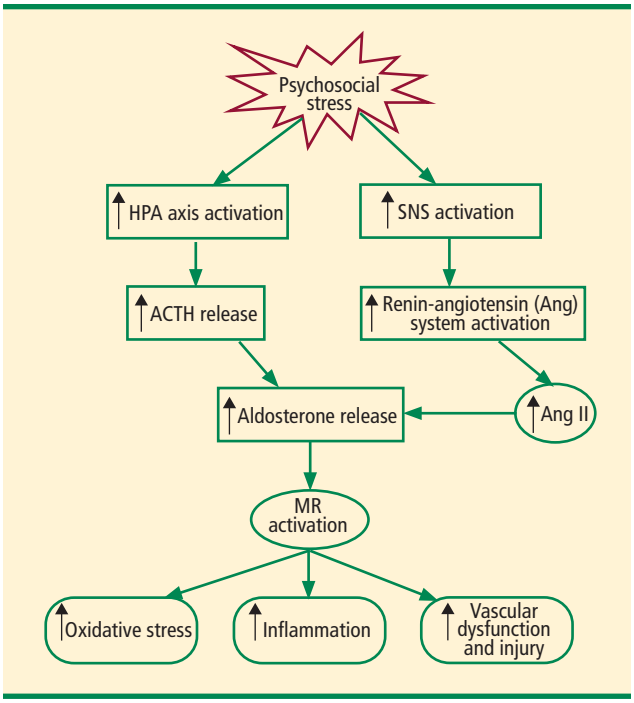

FIGURE 1. A model of aldosterone as a mediator of the relationship between distress and heart disease. ACTH = adrenocorticotropic hormone; HPA = hypothalamic-pituitary-adrenal; MR = mineralocorticoid receptor; SNS = sympathetic-adrenomedullary system

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- The effects of anger are less clear; its impact may be independent of or dependent on other forms of psychologic distress.
- Distress in general appears to serve as a signal that something is wrong and needs to be addressed. If ignored, it may become chronic and unremitting; because symptoms of distress may lead to systemic dysregulation and increased CHD risk, they may indicate the need for increased surveillance and intervention.

WHY FOCUS ON THE BIOLOGY OF EMOTIONS?

A clear biologic explanation for the influence of emotional factors on physical health would serve to assuage skeptics who doubt that such a link exists or who attribute a common underlying genetic trait to both negative affect and heart disease. Further, focusing on the biology may help answer key questions with respect to emotions and disease processes: What is the damage incurred by negative emotional states and is it reversible? Can compensatory pathways be activated to bypass the mechanisms causing damage or slow the progression of disease?

Cardiac response to worry and stress

In one study attempting to shed light on relevant emotion-related biologic process, the prolonged physiologic effects of worry were examined. Worry episodes and stressful events were recorded hourly along with ambulatory heart rate and heart rate variability in 73 teachers for 4 days.[4] Autonomic activity, as reflected by a concurrent elevation in heart rate and a decrease in heart rate variability, was increased up to 2 hours after a worry episode. The findings also suggested that the prolonged cardiac effects of separate worry episodes were independent.

Another study sought to determine whether heightened reactivity or delayed recovery to acute stress increases risk of cardiovascular disease.[5] This meta-analysis included 36 studies to assess whether acute cardiovascular response to various laboratory stressors (ie, cognitive tasks, stress interviews, public speaking). Findings indicated that heightened cardiovascular reactivity was associated with worse cardiovascular outcomes, such as incident hypertension, coronary calcification, carotid intima-media thickness, and cardiovascular events over time.

Role of aldosterone overlooked

Although identified by Selye as a stress-related hormone that may be relevant when considering health, few studies have considered aldosterone as a potential pathway linking emotional distress and heart disease. Aldosterone is an adrenocorticosteroid hormone that is released by activation of the hypothalamic-pituitary-adrenal (HPA) axis and the renin-angiotensin system in response to stress. Aldosterone, which activates the mineralocorticoid receptors, has widespread cardiovascular and metabolic effects beyond its effects on fluid and electrolyte balance. Clinical trials have shown that blocking activation of mineralocorticoid receptors in patients with heart failure reduces the incidence of cardiovascular mortality. Pharmacologic blockade of the renin-angiotensin system is also known to improve mood, leading to speculation that by activating the HPA axis and sympathetic nervous system, psychosocial distress may trigger the release of angiotensin II and aldosterone and activate mineralocorticoid receptors, thereby promoting pathophysiologic processes that can lead to heart disease **(Figure 1)**.

WHY CONSIDER RESILIENCE?

Because the absence of a deficit is not the same as the presence of an asset, greater insight into dysfunction may be gained by explicitly considering what promotes healthy functioning. Ameliorating distress has

proven difficult; so, in studying resilience (including the ability to regulate affect), new targets for prevention and intervention may be identified. Although no meta-analysis of resilience factors has been published to date owing to the paucity of data, the studies that have been performed are generally rigorous and have demonstrated consistent findings.

For example, one prospective, well-controlled study of 1,739 men and women demonstrated a protective effect of positive affect (as ascertained by structured interview) against 10-year incident CHD.[6] The risk of fatal or nonfatal ischemic heart disease events was reduced by 22% ($P = .02$) for each 1-point increase in positive affect, even after controlling for depression and negative emotions.

Recent work may suggest that considering the ability to regulate affect and behavior may provide further insight into why or how positive and negative affect levels per se influence CHD risk. For example, in one recent prospective study, a single measure of self-regulation in healthy men at baseline predicted the development of disease over 12.7 years, with higher levels of self-regulation associated with rates of disease-free survival (**Figure 2**).[7] This finding held after adjusting for standard coronary risk factors, as well as negative and positive affect. This study may suggest that effective self-regulation influences risk of CHD by maintaining emotional flexibility and preventing chronic negative states.

Biology of resilience: Counteracting cellular damage

Genomic changes can be induced by the relaxation response, as evidenced by the differential gene expression profiles of long-term daily practitioners of relaxation (ie, meditation, yoga), short-term (8-week) practitioners of relaxation, and healthy controls.[8] Alterations in cellular metabolism, oxidative phosphorylation, and generation of reactive oxygen species that counteract proinflammatory responses, indicative of an adaptive response, were observed in both groups that practiced relaxation.

FUTURE DIRECTIONS

Whether and how the sources and effects of psychosocial stress and response to treatment differ across men and women deserves closer examination. A review by Low et al[9] summarizes the current state of knowledge with respect to psychosocial factors and heart disease in women, noting that the sources of stress associated with increased CHD risk differ across men and women; psychosocial risk factors like depression and anxiety appear to increase risk for both men and women;

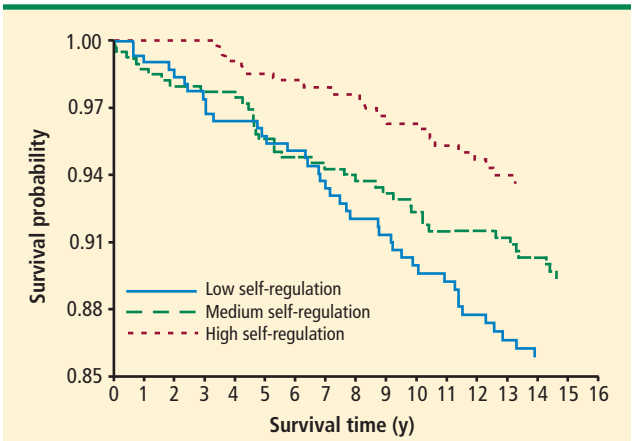

FIGURE 2. Kaplan-Meier survival curve for self-regulation and incident total coronary heart disease. The participant numbers in the self-regulation groups included 355 with low, 426 with medium, and 361 with high self-regulation.[7]

work-related stress has larger effects in men while stress related to relationships and family responsibilities appear to have larger effects in women.

Although responses to psychosocial stress are not clearly different between men and women, intervention targeted at reducing distress is much less effective in reducing the risk of adverse events in women versus men. The mechanism to explain this difference in effectiveness of intervention urgently requires further exploration.

In conducting this work, several factors are important. The best time to intervene in cases of psychosocial distress is unknown; a key consideration will be, what is the best etiologic window for intervention? Perhaps a life-course approach that targets individuals with chronically high levels of emotional distress who also have multiple coronary risk factors, and that enhances their capacity to regulate emotions would prove superior to waiting until late in the disease process.

Another area that may prove fruitful is to consider in more depth the biology of the placebo effect and whether and how it may inform our understanding of resilience.

More generally considering issues of why interventions seem to influence outcomes so differently across men and women, a life course approach to determine the best etiologic window for prevention and intervention strategies, and a more in-depth exploration of the biology of resilience may lead to improved capacity for population-based approaches to prevention and intervention of CHD.

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Imaging for autonomic dysfunction

ABSTRACT

Direct visualization of heart-brain interactions is the goal when assessing autonomic nervous system function. Cortical topology relevant to neuroimaging consists of the cingulate, insula, and amygdala, all of which share proximity to the basal ganglia. Significant cardiac effects stemming from brain injury are well known, including alteration of cardiac rhythms, cardiac variability, and blood pressure regulation; in some instances, these effects may correlate with neuroimaging, depending on the region of the brain involved. It is difficult to achieve visualization of areas within the brainstem that govern autonomic responses, although investigators have identified brain correlates of autonomic function with the use of functional magnetic resonance imaging and electrocardiographic data obtained simultaneously. The potential utility of brain imaging in sick patients may be limited because of challenges such as the magnetic resonance imaging environment and blunted autonomic responses, but continued investigation is warranted.

The autonomic nervous system (ANS), composed of the sympathetic and parasympathetic nervous systems, governs our adaptation to changing environments such as physical threats or changes in temperature. It has been difficult to elucidate this process in humans, however, because of limitations in neuroimaging caused by artifacts from cardiorespiratory sources. This article reviews structural and functional imaging that can provide insights into the ANS.

STRUCTURAL IMAGING

For purposes of imaging, it is helpful to visualize the neural anatomy at a primitive level. If we imagine the neural tube bisected and flayed open, and the folds smoothed out, we would see a simplified topology of the brain, revealing the forebrain (cerebral cortex, thalamus, and hypothalamus), midbrain, hindbrain (pons, medulla, cerebellum), and spinal cord. As the brain develops and appears more complicated, these simple underlying relationships are preserved. Of particular note are the relationships of the cingulate, insula, and amygdala, all of which share proximity to the basal ganglia and the gateways into and out of the brain. These regions control and influence the ANS, many of which are visible on a single coronal view, including the cingulate cortex, prefrontal cortex, insular cortex, amygdala, and hypothalamus **(Figure 1)**. However, the smaller individual hypothalamic and brainstem nuclei are typically not visible on conventional magnetic resonance imaging (MRI).

Similar to cortical and subcortical pathology (or stimulation) in areas of the brain that manifest as nonautonomic symptoms such as weakness, parasthesias, or seizures, pathology or stimulation in ANS areas of the brain manifest as autonomic symptoms. For example **(Table)**, electrical stimulation of the right insular cortex of animals and humans causes ANS manifestations in the form of changes in heart rate and blood pressure, whereas left-sided stimulation of the insular cortex causes a decrease in heart rate and depressor responses. Stimulation of the basolateral amygdalian nucleus increases blood pressure and decreases heart rate; stimulation of the rostral amygdalian nucleus results in depressor effects and variable changes in heart rate. Stimulation of the cingulated gyrus and some other regions within the prefrontal cortex causes decreases in heart rate and blood pressure.

The two main subcortical areas of interest for imaging are the lateral hypothalamic area and the paraventricular nucleus, but visualization is difficult. The hypothalamus occupies a volumetric area of the brain no larger than 20 voxels; individual substructures of the hypothalamus therefore cannot easily be viewed by conventional imaging. The larger voxel size of functional MRI (fMRI) mean that fMRI of the hypothalamus can display 1 voxel at most.

Most brainstem nuclei are motor nuclei that affect autonomic responses, either sympathetic or parasympathetic. These nuclei are difficult to visual-

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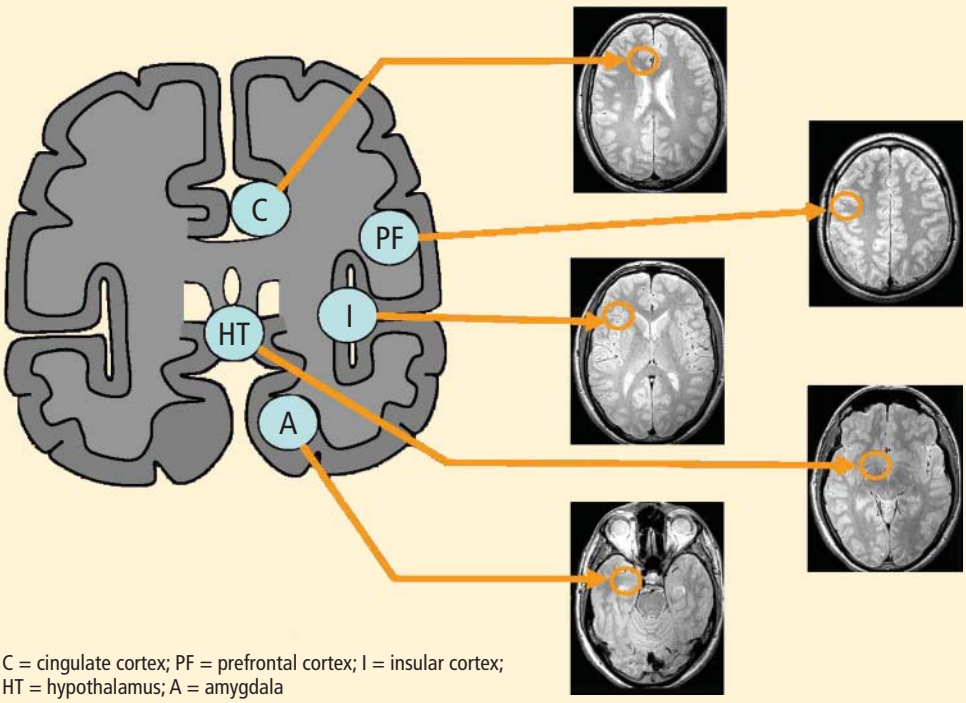
doi:10.3949/ccjm.78.s1.12



C = cingulate cortex; PF = prefrontal cortex; I = insular cortex; HT = hypothalamus; A = amygdala

FIGURE 1. With a coronal view, regions of cortical control of the autonomic nervous system are visible on magnetic resonance imaging.

ize on conventional MRI for two reasons: the nuclei are small, and may be the size of only 1 to 2 voxels. More important, MRI contrast between these nuclei and surrounding parenchyma is minimal because these structures "blend in" with the surrounding brain and are difficult to visualize singly. Examples of these major brainstem *sympathetic* nuclei are the periaqueductal gray substance, parabrachial nuclei, solitary nucleus, and the hypothalamospinal tract; examples of the major brainstem *parasympathetic* nuclei are the dorsal nucleus of the vagus nerve and the nucleus ambiguus.

The areas of the ANS under cortical control are more integrative, with influence from higher cognitive function—for example, the panic or fear associated with public speaking. Regions of subcortical control involve the basal ganglia and hypothalamus, which regulate primitive, subconscious activity, such as "fight or flight" response, pain reaction, and fear of snakes, all of which affect multiple motor nuclei. Several specific sympathetic and parasympathetic motor nuclei directly affect heart rate and blood pressure and act as relay stations for sensory impulses that reach the cerebral cortex.

NEUROLOGIC PROCESSES AND CARDIAC EFFECTS

Significant cardiac effects stemming from brain injury are well known, including alteration of cardiac rhythms, cardiac variability, and blood pressure regulation. Neurologic diseases such as parkinsonism, multiple sclerosis (MS), stroke, epilepsy, and tumors can have cardiac effects, although structural abnormalities on conventional MRI may be lacking. One notable exception is multiple systems atrophy, which can have strong autonomic symptoms and has a characteristic MRI finding called "hot cross buns" **(Figure 2)**. An example is a subtype formally known as Shy-Drager syndrome.

MS is classically a disease of white matter, although it can also affect gray matter. Autonomic dysfunction is common, affecting as many as 50% of MS patients with symptoms that include orthostatic dizziness, bladder disturbances, temperature instability, gastrointestinal disturbances, and sweating.[1–4] The effect of autonomic dysfunction on disease activity is unclear. Multiple brainstem lesions are evident on MRI, and may be linked to cardiac autonomic dysfunction. The variability of MS contributes to the difficulty of using imaging to identify culprit lesions.

Stroke causes autonomic dysfunction, with the specific manifestations dependent on the region of the brain involved. In cases of right middle cerebral artery infarct affecting the right insula, an increased incidence of cardiac arrhythmias, cardiac death, and catecholamine production ensues.[5–7] Medullary infarcts have been shown to produce significant auto-

nomic dysfunction.[8,9]

Ictal and interictal cardiac manifestations in epilepsy often precede seizure onset.[1] Common cardiac changes are ictal tachycardia or ictal bradycardia, or both, with no clear relationship to the location or type of seizure. Evidence suggests that heart rate variability changes in epilepsy result from interictal autonomic alterations, including sympathetic or parasympathetic dominance. Investigation of baroreflex responses with temporal lobe epilepsy has uncovered decreased baroreflex sensitivity. There is no reliable correlation between sympathetic or parasympathetic upregulation or downregulation and brain MRI findings, however.

Autonomic dysfunction in the form of orthostatic hypotension has been documented in patients with mass effect from tumors, for example posterior fossa epidermoid tumors, wherein tumor resection results in improved autonomic function.[10]

TABLE
Autonomic nervous system responses to cortical pathology[1]

Cortical region	Effect of electrical stimulation: Heart rate	Effect of electrical stimulation: Blood pressure
Cingulate	–	–
Prefrontal	–	–
Insula		
Right	+	+
Left	–	–
Amygdala	±	±
Hypothalamus		
Lateral	–	–
Ventromedial	+	+

– = decrease; + = increase

FUNCTIONAL BRAIN IMAGING IN GENERAL

Direct visualization of heart-brain interactions is the goal when assessing ANS function. Positron emission tomography (PET) produces quantitative images, but spatial and temporal resolutions are vastly superior with fMRI.[11] Further, radiation exposure is low with fMRI, allowing for safe repeat imaging.

Ogawa et al[12] first demonstrated that in vivo images of brain microvasculature are affected by blood oxygen level, and that blood oxygenation reduced vascular signal loss. Therefore, blood oxygenation level–dependent (BOLD) contrast added to MRI could complement PET-like measurements in the study of regional brain activity.

The relationship between neural activity and cerebral blood flow is indirect. Functional MRI has been used to locate the brain regions that are involved in simple tasks; for example, bilateral finger tapping results in increased cerebral blood flow that is detected by fMRI after a delay of several seconds. The increase in cerebral blood flow causes decreased intravascular deoxyhemoglobin which causes decreased extravascular susceptibility signal loss, which all together result in a net enhancement of the MRI signal. The signal-to-noise ratio is very low, with a signal change on the order of 1% to 3%.

Bilateral finger tapping with intermittent periods of rest is associated with a pattern of increasing and decreasing intensity of fMRI signals in involved brain regions that reflect the periods of activity and rest. This technique has been used to locate brain voxels with similar patterns of activity, enabling the creation of familiar color brain mapping. A challenge posed by autonomic fMRI in such brain mapping is that fMRI is susceptible to artifacts **(Figure 3)**. For example, a movement of the head as little as 1 mm inside the MRI scanner—a distance comparable to the size of autonomic structures—can produce a motion artifact (false activation of brain regions) that can affect statistical significance. In addition, many ANS regions of the brain are near osseous structures (for example the brainstem and skull base) that cause signal distortion and loss.

REQUIREMENTS FOR AUTONOMIC fMRI

The tasks chosen to visualize brain control of autonomic function must naturally elicit an autonomic response. The difficulty is that untrained persons have little or no volitional control over autonomic functions, so the task and its analysis must be designed carefully and be MRI-compatible. Any motion will degrade the image; further, the capacity for the MRI environment to corrupt the measurements can limit the potential tasks for measurement.

Possible stimuli for eliciting a sympathetic response include pain, fear, anticipation, anxiety, concentration or memory, cold pressor, Stroop test, breathing tests, and maximal hand grip. Examples of parasympathetic stimuli are the Valsalva maneuver and paced breathing. The responses to stimuli (ie, heart rate, heart rate variability, blood pressure, galvanic skin response, papillary response) must be monitored to compare the data obtained from fMRI. MRI-compatible equipment is now available for measuring many of these responses.

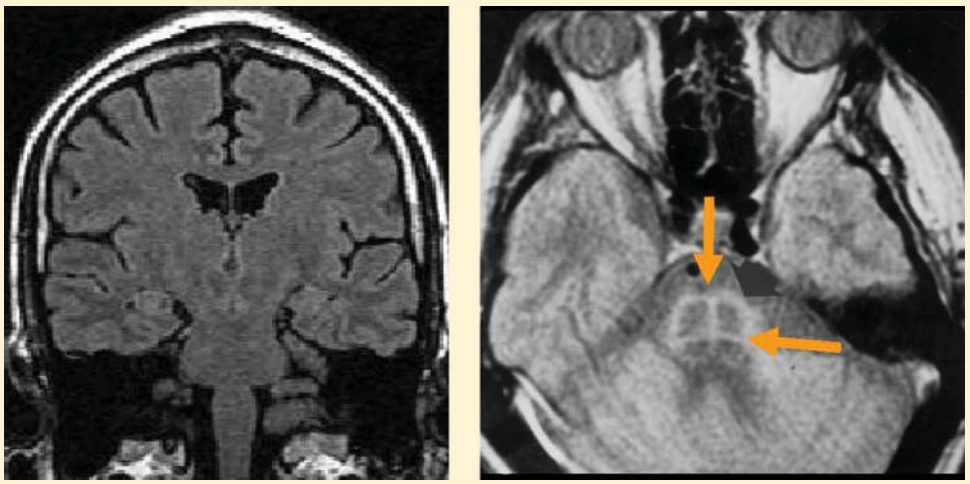


FIGURE 2. Magnetic resonance imaging in a patient with Shy-Drager (left) is normal; a "hot cross buns" sign may be evident in patients with multiple-system atrophy (right).

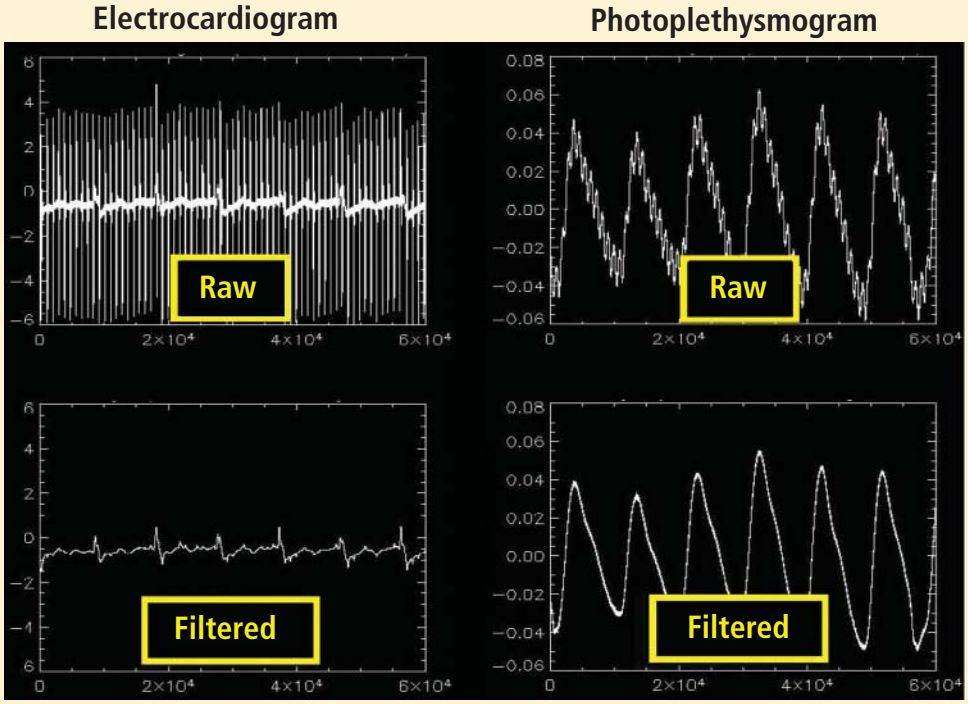


FIGURE 3. Examples of magnetic resonance imaging susceptibility to motion artifacts before and after filtering in an electrocardiogram and a photoplethysmogram.

Identifying areas activated during tasks

Functional neuroimaging with PET and fMRI has shown consistently that the anterior cingulate is activated during multiple tasks designed to elicit an autonomic response (gambling anticipation, emotional response to faces, Stroop test).[11]

In a study designed to test autonomic interoceptive awareness, subjects underwent fMRI while they were asked to judge the timing of their heartbeats to auditory tones that were either synchronized with their heartbeat or delayed by 500 msec.[13] Areas of enhanced activity during the task were the right insular cortex, anterior cingulate, parietal lobes, and operculum.

Characterizing brainstem sites

It is difficult to achieve visualization of areas within the brainstem that govern autonomic responses. These

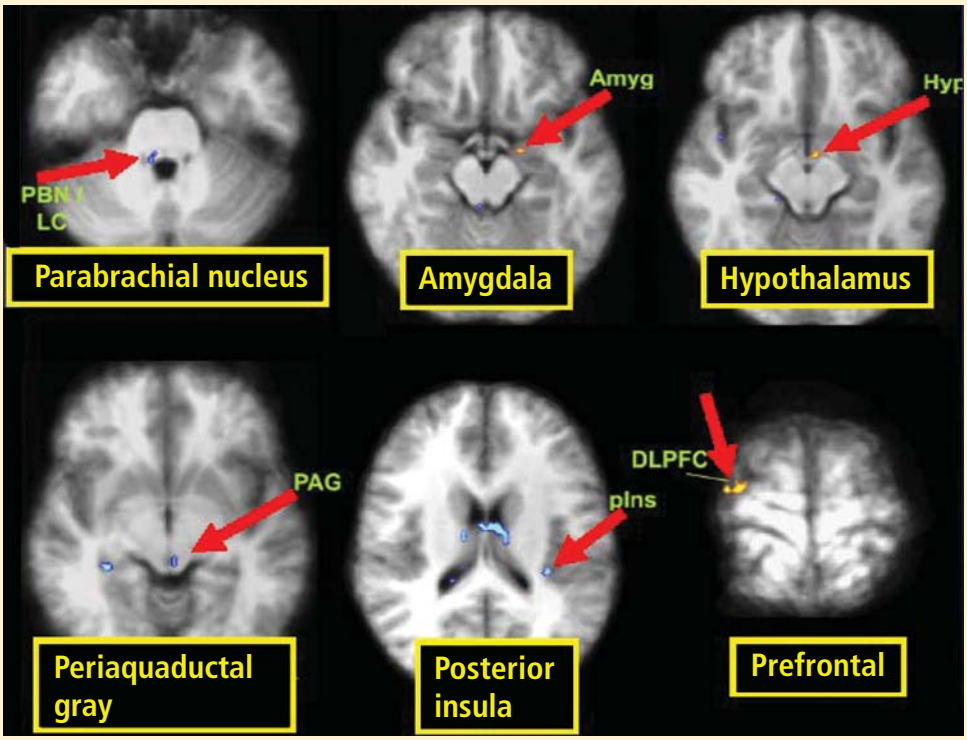


FIGURE 4. Despite the difficulty of visualizing brainstem areas that govern autonomic response, functional magnetic resonance imaging and electrocardiographic data demonstrated brainstem regions that correlated with autonomic involvement during a handgrip task.[16]

Reprinted from *NeuroImage* (Napadow V, et al. Brain correlates of autonomic modulation: combining heart rate variability with fMRI. NeuroImage 2008; 42:169–177), Copyright © 2008, with permission from Elsevier. http://www.sciencedirect.com/science/journal/10538119

regions are small and motion artifacts are common because of brainstem movement with the cardiac pulse. With fMRI, Topolovec et al[14] were able to characterize brainstem sites involved in autonomic control, demonstrating activation of the nucleus of the solitary tract and parabrachial nucleus.

Using fMRI and electrocardiographic data obtained simultaneously, Napadow et al[15] attempted to assess brain correlates of autonomic function in subjects performing an MRI-compatible handgrip task. Brainstem regions that co-localized with expected areas of autonomic involvement were the parabrachial nucleus, amygdala, hypothalamus, periaquaductal gray area, posterior insula, and prefrontal cortex **(Figure 4)**.

A review of four fMRI studies of stressor-evoked blood pressure reactivity demonstrated activation in corticolimbic areas, including the cingulate cortex, insula, amygdala, and cortical and subcortical areas that are involved in hemodynamic and metabolic support for stress-related behavioral responses.[16]

FUNCTIONAL BRAIN IMAGING IN DISEASE STATES

There are few studies of functional brain imaging in patients with disease because of the challenges involved. The studies are difficult to perform on sick patients because of the unfriendly MRI environment, with struct requirements for attention and participation. Furthermore, autonomic responses may be blunted, making physiologic comparisons difficult. In addition, there is evidence that BOLD may be intrinsically impaired in disease states. Unlike fMRI studies to locate brain regions involved in simple tasks such as finger tapping, which can be performed in a single subject, detecting changes in autonomic responses in disease states requires averaging over studies of multiple patients.

Woo et al[17] used fMRI to compare brain regions of activation in six patients with heart failure and 16 controls upon a forehead cold pressor challenge. Increases in heart rate were measured in the patients with heart failure with application of the cold stimulus. Larger neural fMRI signal responses in patients with heart failure were observed in 14 brain regions, whereas reduced fMRI activity was observed in 15 other brain regions in the heart failure patients. Based on the results, the investigators suggested that heart failure may be associated with altered sympathetic and parasympathetic activity, and that these dysfunctions might contribute to the progression of heart failure.

Gianaros et al[18] found fMRI evidence for a correla-

tion between carotid artery intima-media thickness, a surrogate measure for carotid artery or coronary artery disease, and altered ANS reaction to fear using a fearful faces paradigm.

CONCLUSION

Functional MRI of heart-brain interactions has strong potential for normal subjects, in whom the BOLD effect is small, within the limits of motion and susceptibility artifacts. Typically, such applications require averaging results over multiple subjects. Its potential utility in disease states is less significant because of the additional limitations of MRI with sick patients (the MRI environment, blunting of autonomic response in disease, possible impairment of BOLD), but continued investigation is warranted.

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Neurohormonal control of heart failure

ABSTRACT

For nearly three decades, starting in the early 1970s, the cardiology research laboratories at the University of Minnesota served as the focal point for the discovery and implementation of much of the information we now apply to the management of heart failure. Director Jay Cohn, building on his expertise in hypertension and hemodynamics, led many creative and committed investigators in the exploration of the mechanisms responsible for increased sensitivity to afterload in heart failure. The neurohormonal hypothesis of heart failure led to the development of several pharmacologic tools, such as angiotensin-converting enzyme inhibitors, β-adrenergic blockers, and, later, angiotensin-receptor blockers. By the late 1990s, it was understood that neurohormonal antagonists could prevent the progression of left ventricular remodeling and favorably influence the natural history of heart failure. Neurohormonal blockers are now considered standard therapy. Issues remain to be addressed, including early identification and treatment of patients at risk.

We have known for more than 100 years that heart failure is characterized by excessive sympathetic nervous system (SNS) activity. Thanks to refinement of this concept in the 1980s and 1990s, we now have a good understanding of SNS activity in both experimental and clinical heart failure. During those two decades, we also realized the pathophysiologic importance of the renin-angiotensin-aldosterone system (RAAS) in patients with heart failure.[1] By 2000, it was obvious that heart failure was inextricably intertwined with excessive neurohormonal activity.[2,3] This understanding of the pathophysiology of heart failure took on greater importance with the ability to pharmacologically block these neurohormonal systems, thereby demonstrating the detrimental role of neurohormones in the onset and progression of heart failure.

Dr. Francis reported that he has served on advisory boards for Sanofi-Aventis and on data safety monitoring boards for Novartis and Corthera.

doi:10.3949/ccjm.78.s1.13

This article is a brief historical and personal description of the study of neurohormonal control mechanisms as they relate to the clinical syndrome of heart failure. The article includes a personal account of how the story unfolded in the cardiology research laboratories at the University of Minnesota.

THE EARLY YEARS: NEUROHORMONAL HYPOTHESIS

A hypothesis emerged gradually in the 1980s suggesting that progression of heart failure was in part a product of excessive SNS and RAAS activity. Many believed that pharmacologic inhibition of these systems might mitigate against progressive cardiac remodeling and thereby reduce symptoms and extend life—the so called neurohormonal hypothesis.[4] SNS blockers and RAAS blockers are now widely used in tandem as first-line therapy to treat patients with heart failure,[5–11] but in 1980 we were just beginning to consider their therapeutic effects.

This major shift in thinking about neurohormonal systems and heart failure did not come about quickly. Early success was driven by the ability to quickly and precisely measure neurohormones in the laboratory coupled with the availability of drugs specifically designed to block the SNS and RAAS. It was also critically important to embrace the power of randomized controlled trials to test new therapies. Investigators, research nurses, and patients from many medical centers and laboratories should be credited with this astonishing success. I am proud to have been a part of this activity at the University of Minnesota.

THE COHN LABORATORY

Early work done in the 1960s by numerous investigators noted that the failing left ventricle (LV) was exquisitely sensitive to afterload conditions.[12–15] John Ross and Eugene Braunwald explored this observation in patients in 1964.[15] Jay Cohn, with his unique background in hypertension and hemodynamics, brought the concept back into the laboratory in the early 1970s, where he explored the mechanisms responsible for increased sensitivity to afterload in

patients with heart failure.[16]

I had the good fortune to join Cohn's laboratory in 1979, when this avenue of heart failure research was in full bloom. A team of investigators was gradually assembled that included Maria Teresa Olivari, who relocated from the Cardiovascular Research Institute in Milan, Italy, directed by Maurizio D. Guazzi. Also joining the group were T. Barry Levine from the University of Michigan, Ann Arbor; Steven Goldsmith from Ohio State University, Columbus; Susan Ziesche from the Minneapolis Veterans Affairs (VA) Medical Center; Thomas Rector, an expert statistician and pharmacologist at the University of Minnesota; and many research fellows, visitors, students, biochemists, statisticians, and research nurses. Joseph Franciosa joined the University of Minnesota group in 1974 and, after completing several important trials, left in 1979 to lead the cardiology group at the Philadelphia VA Medical Center.

The Cohn group developed a working hypothesis that activation of the SNS and RAAS in heart failure was most likely an adaptive mechanism intended for short-term circulatory support, such as in the setting of blood loss, dehydration, shock, volume depletion, or flight response. In patients with heart failure, according to the hypothesis, the SNS and RAAS activity persisted beyond that needed for adaptation, with chronic release of norepinephrine (NE), renin, angiotensin II, aldosterone, and other neurohormones. The neurohormones ultimately became "maladaptive." Thanks to the assaying skills of Ada Simon, we had the early advantage of precise and rapid radioenzyme measurement of plasma norepinephrine and renin activity in the blood of patients and animals.

We believed that neurohormonal activation contributed in part to the excessive afterload conditions observed in heart failure. We also thought that excessive neurohormonal activation directly impaired cardiac systolic function. The obvious next step was to explore whether neurohormonal antagonists would improve myocardial performance.

Under the leadership of Steven Goldsmith, many studies were performed to investigate reflex control mechanisms and their pathogenic role in patients with heart failure. The accumulating data suggested that persistent, excessive neurohormonal activity was characteristic of heart failure and that it was associated with a poor prognosis.[17] The precise mechanism that drives activation of the SNS remained elusive, however, and is poorly defined even today. In that era, when β-adrenergic blockers were believed to be contraindicated, we inhibited the central SNS with bromocriptine, clonidine, and guanfacine with modestly favorable responses. We inhibited circulating arginine vasopressin antibody (thanks to Prof. Alan Cowley for noting an acute favorable response).

THE PHARMACOLOGIC ERA

The 1980s and 1990s saw the availability of several pharmacologic tools for assessing the roles of the SNS and RAAS in heart failure. The hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors and, later, angiotensin-receptor blockers (ARBs) were sources of concern, since many patients with advanced heart failure had low- to normal-range blood pressures before they received RAAS blockers. However, our group as well as others observed that abrupt blood pressure reduction occurred primarily in patients with very hyperreninemic responses to intravenous diuretics (ie, volume-depleted patients). Eventually, we learned that low baseline blood pressure did not adversely affect outcomes when vasodilators were used in patients with heart failure,[18,19] leading us to titrate these drugs upward over days to weeks.

Several different combinations of vasodilators were used successfully to treat heart failure, including hydralazine, isosorbide dinitrate,[20] ACE inhibitors,[21,22] and ARBs.[8,23–28] Direct-acting calcium channel blocking vasodilators, such as amlodipine, did not improve survival in patients with systolic heart failure, although they appeared to be safe in this setting.[29] The aldosterone receptor blockers spironolactone[30] and eplerenone[31] were later demonstrated to improve survival of patients with advanced systolic heart failure when added to vasodilator therapy.

By the end of the 1990s, it was evident that drugs that blocked the SNS and RAAS were not just vasodilators or "afterload reducers," similar to α-blockers, hydralazine, nitrates, and amlodipine. Neurohormonal blockers were doing something profoundly beneficial not observed with more direct-acting vasodilators.[32–37] Simple afterload reduction was not enough in patients with systolic heart failure.

Neurohormonal antagonists were acting more directly on the myocardium. They were preventing the progression of LV remodeling and, in some cases, promoting reverse remodeling, thus improving myocardial function and favorably influencing the natural history of heart failure.[31–39] We were astonished to discover that the failing, dilated heart could revert to normal size in response to neurohormone blockade with ACE inhibitors and β-adrenergic blockers; these findings were soon reported by other laboratories as well.

Contrary to our concept of heart failure in the 1970s, we now understood that the heart has inherent plasticity. It can dilate in response to abnormal loading conditions or myocardial injury, and it can restore itself to normal size when neurohormones are blocked and perverse loading conditions are improved. This reversal can occur spontaneously if an offending agent such as chronic alcohol use or inflammation is removed, but it is likely facilitated by SNS and RAAS blockers.

THE REMODELING ERA

Ken McDonald joined the University of Minnesota lab in 1989 as a research fellow. His skill in conducting both animal and clinical mechanistic studies was pivotal to our achieving our research goals. The inspired animal work by Boston-based Marc and Janice Pfeffer revealed the significance of the LV remodeling concept in the development of heart failure[36]: ventricular remodeling was a hallmark of systolic heart failure, and pharmacologic inhibition of LV remodeling by blocking neurohormones had profound clinical implications.

Under the direction of Wenda Carlyle, a molecular biology laboratory was established at the University of Minnesota whose work was dedicated solely to exploration of remodeling at a very basic level. Alan Hirsch was recruited from Victor Dzau's laboratory at Brigham and Women's Hospital in Boston to extend our efforts to understand the molecular basis of cardiac remodeling. Ken McDonald guided the use of magnetic resonance imaging to study remodeling in dogs.

The late 1970s saw the initiation and eventual execution of several important clinical trials, including the Vasodilator Heart Failure Trials (V-HeFT I and V-HeFT II)[40,41] under our leadership, and Studies of Left Ventricular Dysfunction (SOLVD)[5,6] under the leadership of Salim Yusuf and others at the National Heart Lung and Blood Institute (NHLBI). Many neurohormonal and remodeling substudies sprang from these large clinical trials. Spencer Kubo joined our group from the Medical College of Cornell University in the mid-1980s, and he immediately demonstrated his prowess in clinical research. He also recruited Alan Bank to study the endothelium in both experimental and human heart failure.

Integrating the molecular, animal, and clinical laboratories allowed us to pursue many mechanistic studies. Laboratory meetings, often held on Saturday mornings, generated ideas for program projects that were subsequently funded by NHLBI. Birthday parties and other social events with laboratory staff and their families were part of our fabric. Late-night trips to the Post Office to send off abstracts for national meetings before the midnight deadline were a regular feature.

Our coordination of and participation in the large clinical trials allowed us to meet frequently in Bethesda with colleagues from other major centers, fostering many collaborations and friendships that continue to thrive. Susan Ziesche deserves much of the credit for coordinating many groups that were part of these large, complex trials. Cheryl Yano, our administrator, also played a key role. All National Institutes of Health (NIH) grants passed through Cheryl, and she worked tirelessly to ensure that the proposals were in the best possible shape before we submitted them. Inder Anand joined our group in the early 1990s and became a major analytical force. Jay Cohn was the intellectual leader of the group, as well as our soul and inspiration. People worked hard for him, and he taught us much in a setting that valued creativity and new ideas above all.

THE LATER YEARS

By 1997, the face of heart failure had changed. New treatments were effective, but there were new challenges to face. I moved that year to the Cleveland Clinic, where I spent 11 enjoyable and productive years. I returned to Minnesota in 2008 to help build a new cardiovascular division.

It is gratifying to look back and see what has become of the "neurohormonal hypothesis." Today, nearly all major medical centers have heart failure programs, and certification in advanced heart failure/heart transplantation is a reality. Training programs in advanced heart failure and heart transplant are common. The Heart Failure Society of America sprang up in the early 1990s, dedicated to patients with heart failure. Jay Cohn founded the *Journal of Cardiac Failure*, which flourished under his leadership. Neurohormonal blockers are now considered standard, conventional therapy and are widely used throughout the world.

CONCLUSIONS

Still, there is much work to do. An increasing number of devices are being developed, largely for patients with more advanced heart failure, but attention is also being directed to prevention of heart failure. Identification and possible treatment of patients at risk for the development of heart failure, and identification of those who already have some early structural and functional perturbation without advanced symptoms,

are critically important. Since event rates are so low in these patients, we need to create new strategies for studying interventions. In the long term, the best treatment for nearly any condition is early diagnosis and perhaps early treatment with a goal of prevention.

One consequence of our progress over the years may be that heart failure now primarily affects a more elderly group—patients who often have many associated comorbidities. The consequences include more frequent readmissions, large numbers of patients with intractable signs and symptoms, and the emergence of difficult end-of-life decisions. If we could truly prevent heart failure rather than forestall its emergence to a later point in life, perhaps we could do more good.

For me, the study of neurohormonal mechanisms in the setting of heart failure was the centerpiece of my early career. Jay Cohn had asked several of us early in our laboratory experience to choose a neurohormonal system and learn about it in great depth and detail. My assignment was the SNS. Since then, I have never tired of learning about its control mechanisms, how it achieves circulatory homeostasis, how its excess quantities can be directly toxic to the heart, and the variety of pharmacologic ways that we can control it. I am indeed fortunate to have been part of this amazing study group.

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Poster Abstracts

BHBI-Funded Research*

1 Biofeedback in Coronary Artery Disease, Type 2 Diabetes, and Multiple Sclerosis

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Biofeedback-mediated stress management can be used to train patients to regulate their autonomic nervous system. Particularly in diseases where sympathetic activation has been shown to be excessive and parasympathetic activation insufficient, biofeedback may be a useful method for balancing autonomic nervous system input. Coronary artery disease, type 2 diabetes and multiple sclerosis are all diseases of increasing prevalence in the US population, and all are diseases where heart rate variability (HRV) has been shown to be decreased, suggesting an inappropriate balance of sympathetic/parasympathetic nervous system activation. We hypothesize that biofeedback-assisted stress management can be used to restore a healthy balance of autonomic activation in patients with these three diseases, and that less sympathetic and more parasympathetic input will result in altered symptoms of each disease, as well as enhanced quality of life. In this ongoing study, we are enrolling 180 patients, with 60 in each of the three disease groups, and randomizing them to receive eight sessions of biofeedback-mediated stress management or usual medical care. All participants, regardless of treatment group, receive an initial and final assessment of physiologic reactivity to three mental stressors and complete the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), the Patient Health Questionnaire (PHQ-9), and the Generalized Anxiety Disorder 7-Item Scale (GAD-7). In addition to disease-specific markers, we are also measuring HRV, plasma norepinephrine (NE), plasma C-reactive protein (CRP), and plasma tumor necrosis factor alpha (TNF) in all patients before and after the biofeedback training period. Across all three groups of patients, we will test the hypothesis that biofeedback-mediated stress management will result in decreased sympathetic nervous system activity (as evidenced by changes in HRV and plasma NE) and increased parasympathetic nervous system activity (as evidenced by changes in HRV and the inflammatory markers CRP and TNF). The overall goal of the study is to demonstrate that, regardless of disease etiology, biofeedback training can effectively restore a healthy balance of autonomic nervous system input, retard disease progression, and significantly improve clinical status and quality of life.

BHBI-Funded Research

2 Biofeedback in Heart Failure Patients Awaiting Transplantation

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Biofeedback training can be used to alter the balance of autonomic input to the cardiovascular system. Studies from our own group and others have shown that heart failure is accompanied by overactivation of the sympathetic nervous system, and that decreasing this activation (for example, with a beta-blocker or left ventricular assist device) not only has a positive impact on clinical status, but also reverses cellular and molecular alterations associated with the failing myocardium. In this study, we hypothesized that biofeedback-mediated stress management could also be used to remodel the failing myocardium in the direction of normal cardiac muscle function. A total of 20 patients with end-stage heart failure were studied, including four stable outpatients awaiting transplantation at home, who were studied in the Clinical Research Unit, and 16 inpatients awaiting transplantation in the hospital, who were studied in their rooms. All patients were subjected to the same protocol, which included an initial assessment of physiologic reactivity to mental stress, six sessions of training with a certified biofeedback therapist, and a final assessment of physiologic reactivity to mental stress. Patients also completed the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and Kansas City Cardiomyopathy questionnaires before and after the biofeedback protocol. A measurement of plasma norepinephrine and 6-minute walk distance were also collected at these times in outpatients only. At the time of heart transplantation, which occurred after the biofeedback training protocol, each explanted heart was obtained and transported to the laboratory. Trabecular muscles were dissected from the endocardial surface of the heart and hung in an oxygenated bath to study the inotropic response to sympathetic stimulation. Changes in developed tension were measured after exposing the muscles to isoproterenol, a synthetic norepinephrine analogue. Beta- adrenergic receptors on the myocardial cell membranes were also assessed by radioligand binding and Scatchard analysis. Data from this study demonstrate that biofeedback-mediated stress management training can decrease sympathetic nervous system activity and produce positive remodeling of the myocardium in patients with end-stage heart failure, similar to what has been previously observed for other more invasive therapeutic options.

* BHBI = Bakken Heart-Brain Institute

BHBI-Funded Research

3 Prevalence of Anxiety and Type D Personality in an Outpatient ICD Clinic

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Background: Implantable cardioverter defibrillator (ICD) patients can exhibit significant psychosocial stress including anxiety. Type D personality, characterized by negative emotions and social inhibition, has been shown to negatively impact perceived quality of life and have an adverse effect in cardiovascular illnesses. We sought to measure the incidence of type D personality and the prevalence of overall anxiety in an ambulatory ICD population.

Methods: To date, 244 patients have been enrolled in a prospective study of anxiety in ICD patients, with recruiting in the ICD device clinic at the Cleveland Clinic. Patients are enrolled at least 4 weeks after implantation of an ICD, seen in routine followup, and administered the Type D Scale-14 (DS-14) questionnaire, from which the individual constructs of negative affectivity (NA) and social inhibition (SI) are also scored. The Beck Anxiety Inventory (BAI) was also administered, with total scores of 0 to 9 correlating with no or low anxiety; 10 to 18, mild to moderate anxiety; 19 to 29, moderate to severe anxiety; and 30 to 63, severe anxiety. SAS statistical software was used to analyze the data.

Results: This outpatient population consisted of 74% males with a prevalence of 18% type D that was equally distributed among gender. The median BAI score was 4.0, with 73% scoring no or low anxiety. Female patients had higher median BAI anxiety scores compared with males (8.5 vs 4.0, $P < .001$). Patients with type D personality had higher median BAI anxiety scores (12.0 vs 4.0, $P < .001$) and NA correlated with elevation of anxiety more so than SI (Pearson coefficient 0.59 vs 0.33).

Conclusions: In our ambulatory ICD population, overall anxiety rates were surprisingly low. The presence of type D personality is a risk factor for increased anxiety. Screening for type D personality may assist detecting at-risk psychosocial ICD patients. Outcome studies of this patient population, including time from implantation and incidence of firings, warrant further study for quantification of overall ICD quality of life.

BHBI-Funded Research

4 Sudden Unexpected Death in Epilepsy: Finding the Missing Cardiac Links

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Introduction and Objectives: Sudden unexpected death in epilepsy (SUDEP) is a significant cause of mortality in patients with refractory epilepsy, accounting for up to 17% of all deaths in epilepsy, and exceeding the expected rate of sudden death in the general population by nearly 24 times.

Most of the identified SUDEP risk factors are unavoidable, and patients with refractory epilepsy currently face a lifelong SUDEP risk as high as 1% per year. Elucidating the mechanisms of this devastating condition might offer an opportunity for preventive measures, and therefore could have significant implications in reducing mortality in this patient population.

One commonly postulated mechanism is cardiac arrhythmia precipitated by seizure discharges acting via the autonomic nervous system.

Project Goals: Our long-range goal is to allow early identification of patients at risk for SUDEP so that appropriate preventive and protective interventions can be instituted.

The specific aims of this pilot study are the following:

(1) To evaluate the interictal (between seizures) and ictal (during seizures) cardiac rhythm characteristics of patients with SUDEP compared with the general population and other patients with epilepsy.

(2) To study the cardiac and neurologic clinical characteristics of patients with SUDEP compared with the general population and other patients with epilepsy

(3) To evaluate the interictal and ictal electroencephalographic characteristics of patients with SUDEP in relation to any identified interictal and ictal cardiac rate/rhythm changes.

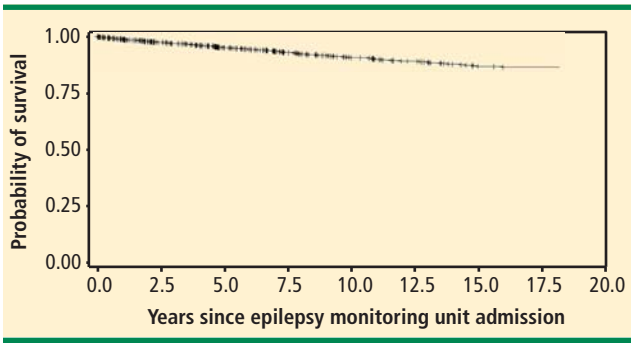

FIGURE. Survival curve.

Results: We identified 3,852 patients who were evaluated in the epilepsy monitoring unit between 1995 and 2005.

Among those, we identified 301 deaths based on the Social Security Death Index database. The overall survival curve is shown in the **Figure**. Of those who died, 237 (77%) had epilepsy, 41 (13%) had nonepileptic seizures, and 29 (9%) had both recorded. Mean age at death was 49.9 years (18.6–99.6 years; SD, = 17.9). The cause of death was identified in 211. The death certificates need to be obtained for the remainder.

SUDEP accounted for 21% of the deaths in our cohort with epilepsy.

Identified Characteristics of SUDEP Cases: Significant differences were observed in the mean epilepsy duration and mean monthly seizure frequency between SUDEP and controls: 22.9 ± 2.3 years epilepsy duration in SUDEP versus 13.7 ± 1.5 years in controls; $P = .005$; and 31.3 ± 16.9 seizures per month in SUDEP versus 1.4 ± 0.7 in controls; $P = .005$. Patients with SUDEP were more likely to have been discharged from the epilepsy monitor-

ing unit on valproic acid. Valproic acid was only used in controls on admission. In SUDEP cases, it was used 50% of the time on admission only, 33% on admission and discharge, and 17% on discharge only [P = .01]). The risk for SUDEP was independent of epilepsy type or localization.

Our current data collection efforts are now focused on obtaining the cardiac data elements and obtaining the remaining death certificates to identify the remaining SUDEP cases.

Young Investigator Research Award Winner

5 Low Levels of Depressive Symptoms Predict the Combined Outcome of Good Health-Related Quality of Life and No Cardiac Events in Patients with Heart Failure

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Background: Depressive symptoms predict health-related quality of life (HRQOL) and cardiac event-free survival (free from hospitalization or emergency department visits due to cardiac reasons) in patients with heart failure (HF). However, researchers have examined these two outcomes separately. It is unknown whether depressive symptoms are associated with a combined end point of good HRQOL and without cardiac events.

Purpose: To determine whether depressive symptoms independently predicted a combined end point of good HRQOL and no cardiac events among patients with HF who were alive at a 1-year follow up.

Methods: A total of 209 community-dwelling patients with HF (aged 62 years, 32% female, 29% minority, 46% New York Heart Association (NYHA) class III/IV) were followed for 1 year to determine cardiac events. Depressive symptoms were measured at baseline with the Beck Depression Inventory-II (BDI-II). HRQOL was defined as the scores of the Minnesota Living with HF Questionnaire (LHFQ) at 1 year and categorized into good or poor HRQOL based on the median split of LHFQ scores (cutoff point, 37). Patients who survived at 1 year were placed in one of two groups based on 1-year LHFQ scores and cardiac events: (1) good HRQOL without cardiac events and (2) all other outcomes. Logistic regression was used to test whether depressive symptoms were an independent predictor of good HRQOL without cardiac events after controlling for age, gender, ethnicity, body mass index, total comorbidity scores (Charlson Comorbidity Index), HF etiology, NYHA class, and perceived social support (Perceived Social Support Scale).

Results: Of the 209 patients, 90 (43%) had good HRQOL without cardiac events. In the regression, only depressive symptoms at baseline predicted the combined outcome. For each point increase in the BDI-II score, patients were 14% less likely to have good HRQOL without cardiac events (odds ratio 0.86, 95% confidence interval 0.80–0.91).

Conclusion: This was the first study to show that low levels of depressive symptoms independently predicted the combined outcome of good HRQOL and no cardiac events. The result suggests that the management of depressive symptoms may be essential to achieving the ideal outcome of good HRQOL without cardiac events.

Young Investigator Research Award Nominee

6 Spectral HRV and C-Reactive Protein in a Community-Based Sample of African Americans

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Introduction: Heart rate variability (HRV) and C-reactive protein (CRP) have been reported as independent predictors of heart disease and cardiovascular mortality. CRP levels are associated with various negative conditions, such as depression, diabetes, and the metabolic syndrome. HRV has also been linked to these conditions, providing evidence of a possible overlap between the two biomarkers. However, very few studies have focused on HRV and CRP concurrently while considering various demographic factors. The purpose of this study was to explore the association between HRV and CRP in a community-based sample of African Americans.

Method: Seventy-six (female = 29; male = 47) African Americans from the Washington, DC, metropolitan area were recruited to participate in the study. Upon entry, participants had blood drawn and completed demographic questionnaires that included medical histories. CRP was obtained via venipuncture by a nurse in the General Clinical Research Center at Howard University Hospital. Five minutes of beat-to-beat intervals were used to derive the baseline measurements of the frequency domain metrics of HRV.

Results: Preliminary findings showed significant correlations between CRP and body mass index (BMI [r = .530; P = .000]), hypertension (r = .228; P = .024), and low frequency (LF) HRV (r = −.242; P = .018). Hierarchical multivariate regression analysis revealed that BMI (β = .500, P = .000) and LF (β = −.210, P = .043) accurately predicted CRP levels while adjusting for demographic factors.

Conclusion: The association of LF and CRP while adjusting for various factors suggests a link between the autonomic nervous system and inflammation. Sympathetic activation is initiated throughout both the acute and chronic phases of the immune response, and the findings in the current study suggest HRV may have a direct impact on CRP levels.

*The **Young Investigator Research Award** is a competition open to graduate students, postdoctoral fellows, residents, fellows, and junior faculty (within 2 years of their first appointment). It is made possible by the continued support of **Thomas F. Peterson, Jr.**, who also supports the Thomas F. Peterson, Jr. Center for Heart-Brain Research within the Earl and Doris Bakken Heart-Brain Institute at Cleveland Clinic. The 2010 recipient is **Kyoung Suk Lee, PhD**.*

Young Investigator Research Award Nominee

7 Symptoms of Depression and Anxiety Determine Fatigue but Not Physical Fitness in Patients With CAD

Adomas Bunevicius,[1,2] Albinas Stankus,[1] Julija Brozaitiene,[1] and Robertas Bunevicius[1]

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Introduction: Fatigue is the most frequently reported symptom in patients with coronary artery disease (CAD) and is associated with increased morbidity and mortality as well as with decreased quality of life. Similarly, depression is also prevalent in CAD patients and has a significant negative effect on morbidity and morality of CAD patients. However, no studies have evaluated the relationship between symptoms of fatigue and symptoms of depression and anxiety in CAD patients.

Methods: A total of 1,536 (63% male; mean age 57 ± 11 years) consecutive CAD patients admitted for rehabilitation to the Institute of Psychophysiology and Rehabilitation of the Kaunas University of Medicine, Palanga, Lithuania, agreed to participate in the study. Within 3 days of admission all patients were evaluated by cardiologists for demographic characteristics, CAD risk factors, and severity of heart failure according to New York Heart Association (NYHA) classes. All patients were also evaluated for symptoms of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) and for fatigue using the Multidimensional Fatigue Inventory (MFI-20). All patients underwent physical fitness evaluation using standard exercise stress-testing procedures.

Results: Multivariate stepwise regression analyses revealed that when age, gender, education, hypertension, heart failure, NYHA class, and severity of angina were included in the model, the determination coefficients for scores on the MFI-20 subscales were low, covering less than 7% of variance. Gender was the strongest predictor of the MFI-20 scores on subscales of general fatigue (β = .211, *P* = .000), physical fatigue (β = .125, *P* = .000), mental fatigue (β = .208, *P* = .000) and decreased motivation (β = .138, *P* = .000). Education was the strongest predictor of the score on MFI-20 decreased activation subscale (β = .132, *P* = .000). On the other hand, NYHA class was a moderate predictor for physical fitness (β = .393, *P* = .000) and together with age, gender, education, hypertension, and heart failure covered 34% of variance.

When HADS scores for depression and anxiety were added, models for MFI-20 subscales strengthened significantly. HADS depression and anxiety scores were the strongest predictors of scores on the MFI-20 subscales of general fatigue (β = .298, *P* = .000 and β = .259, *P* = .000, respectively), physical fatigue (β = .243, *P* = .000 and β = .139, *P* = .000, respectively), mental fatigue (β = .298, *P* = .000 and β = .267, *P* = .000, respectively) and decreased motivation (β = .328, *P* = .000 and β = .113, *P* = .000, respectively), and together with other significant variables covered from 16% to 30% of variance. The HADS depression score was the strongest predictor for the MFI-20 subscale of decreased activation (β = .336, *P* = .000) and together with other significant predictors covered 19% of variance. The HADS score did not predict physical fitness and NYHA class remained the strongest predictor (β = .393, *P* = .000).

Conclusion: Fatigue in CAD patients has a stronger relationship with symptoms of depression and anxiety than with symptoms of CAD. On the other hand, physical fitness is mostly related to symptoms of CAD, but not to symptoms of anxiety and depression.

Young Investigator Research Award Nominee

8 Depression, Cardiovascular Symptom Reporting, and Functional Status in Heart Failure Patients

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Background: Depression is common among heart failure (HF) patients and can influence reporting of cardiovascular symptoms; depression may precipitate psychosomatic symptom reporting and worsen functional health status. This study examines the relationship between depression and cardiovascular symptoms through self-reports and objective measures.

Methods: Eighty-one patients (64 males; mean = 55.8 ± 11.2 years at baseline) with HF (ejection fraction ≤ 40) were examined at intake and again 3 months later. The Beck Depression Inventory (BDI) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) as subjective measures along with the Six-Minute Walk Test (6MWT) as a measure of objective functional status were administered at both time points.

Results: Baseline BDI scores correlated negatively with nine of the 10 subscales of the KCCQ (physical limitation: r = −0.44; symptom frequency: r = −.52; symptom burden: r = −0.50; total symptoms: r = −0.53; self-efficacy: r = −0.27, *P* = .019; quality of life: r = −0.72; social limitation: r = −0.56; clinical summary: r = −0.55; overall summary: r = −0.67; all *P* < .001 unless noted) but was not related to symptom stability. Mean BDI scores significantly decreased from baseline (13.6 ± 10.5) to 3 months (9.2 ± 7.7) indicating less depressive symptoms over 3 months (*P* > .001). In addition, changes in BDI scores and the KCCQ from baseline to 3 months were also negatively related to all KCCQ subscales (r range: −0.52 to −0.32, *P* < .05) except for symptom stability. Increasing BDI scores were related to decreased 6MWT performance (r = −.33, *P* = .024); after controlling for age, gender, body mass index, current smoking status, diabetic status, and serum creatinine, only worsening BDI scores significantly predicted a decrease in distance walked on the 6MWT (β = −.38, *P* = .017; overall model R^2 = 0.18, *P* = .039) between baseline and 3-month follow-up.

Conclusions: In HF patients studied prospectively, depressive symptoms were related to poorer self-reported HF symptoms at baseline; over time, increases in depression were related to increased subjective symptom reporting and worsening functional status. These findings suggest that depression can negatively impact both subjective and objective health outcomes in HF patients; mechanisms of this association require further investigation.

9 Cardiotopic Organization of the Functionally Associated Axons Within the Cervical Vagus Nerves That Project to the Ventricles of the Cat Heart

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Introduction: Data obtained in the cat model indicate that there is a regional organization of functionally associated vagal preganglionic cardioinhibitory neurons in the CNS, and vagal postganglionic cardioinhibitory neurons within the heart. These data have been confirmed, in part, in other models, including the rat, dog, pig, primates, and humans. Succinctly stated, these data indicate that anatomically separated and functionally selective cardioinhibitory neurons are found in both the CNS and the intrinsic cardiac nervous system. These neurons are interconnected via the vagus nerves. In the heart parasympathetic postganglionic cardioinhibitory neurons are found within fat pads on the epicardial surface as well as within the myocardium. A total of three separate intracardiac ganglia innervate the left ventricle; however, the interventriculoseptal (IVS) ganglion provides the major source of innervation to the anterior surfaces of both the left and right ventricles. Although considerable evidence has been accumulated that describes the origin, distribution, and functions of cardioinhibitory neurons within the brain and within the heart, much less morphologic information is available on the main neural circuit that interconnects these two sites; ie, the vagus nerves. Electrical stimulation of the vagi has important effects upon cardiac function. The vagus nerves contain substantial populations of both myelinated and unmyelinated axons. By varying the parameters and methods of vagal stimulation, it is possible to *selectively* activate *either* myelinated or unmyelinated axons. Stimulation of either myelinated or unmyelinated vagal axons caused negative chronotropic, dromotropic, or inotropic cardiac effects; however, there are both *qualitative* and *quantitative* differences in the evoked cardiac effects depending upon which type of fiber was activated. If vagal axons projecting to different intracardiac targets are differentially *spatially organized* within the vagi, and/or differ in the *numbers* of myelinated or unmyelinated axons that participate in eliciting desired physiologic effects, then it should be possible to induce extraordinarily selective effects upon cardiac performance by selecting the appropriate stimulation parameters and/or geometry. The present experiments were designed to test the hypotheses that: (1) vagal axons projecting to the IVS ganglion are differentially *spatially organized* within the vagi; and/or (2) different *numbers* of myelinated or unmyelinated vagal axons project to the IVS ganglion, where they may participate in eliciting selective physiologic effects on the ventricles.

Methods: Cholera toxin beta subunit conjugated to horseradish peroxidase (CTB-HRP) was microinjected into the IVS or pericardial space of eight cats to retrogradely label axons in the cervical vagus nerves. Animals were anesthetized and perfused intravascularly with fixatives after a 4-day survival. Retrogradely labeled axons in the vagi were identified by a histochemical method. Tissues were subsequently processed for electron microscopic visualization of both right and left vagus nerves at 2,500× magnification. Overlapping digitized photomontages of approximately 2,500 images each were assembled for each nerve. Custom software was developed to localize and count retrogradely labeled myelinated or unmyelinated axons in each of four quadrants superimposed sequentially at 90-degree intervals. Raw data were normalized by conversion to percent of total labeling. Subsequent data were analyzed using ANOVA with significance at $P < .05$. If the F test was significant, least significant difference post hoc tests were performed.

Results: The cervical vagus nerves in the cat contain one large fascicle (A), one moderate-size fascicle (B) below fascicle A, and 0 to 4 significantly smaller fascicles, irregularly distributed. Quantitative data were restricted to fascicles A and B in order to have a large enough sample size to achieve statistical significance. The regional distribution of myelinated labeled axons within the four quadrants of fascicle A ($P < .004$), or unmyelinated labeled axons within fascicle B ($P < .05$), of the *left* vagus nerve was not random. In contrast, the regional distribution of either myelinated or unmyelinated labeled axons in fascicles A or B of the *right* vagus nerve is random ($P > .05$). There were no statistically significant differences between the number of myelinated versus unmyelinated labeled axons in either bundle A or B of both vagus nerves.

Conclusions: These data are consistent with the hypothesis that vagal axons projecting to some intracardiac targets are cardiotopically organized within the vagus nerve. Although the total numbers of labeled myelinated and unmyelinated axons observed in the vagi were not statistically significantly different, this remains a potential mechanism for vagal projections to other intracardiac targets. Therefore, precise electrical stimulation of selected quadrants of the vagi may potentially elicit potent effects on the ventricles without directly influencing cardiac rate or atrioventricular conduction.

Supported in part by grants 2 G12 RR003048 from the RCMI Program, Division of Research Infrastructure, NCRR, NIH; 1KL2 RR031974-01, NCRR, NIH; and by Boston Scientific, Inc.

10 Significance of Carotid Intimal Thickening in Hypertensive Patients

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Background: Detection of early atherosclerosis is of utmost clinical importance. Although abnormal intima-media thickness (IMT) measurements correlate well with atherosclerosis and increased cardiovascular events, little attention has been placed on intimal thickening (IT). IT may result from damage caused by retained lipoproteins before they migrate to the media. IT may thus be an early indicator of endothelial dysfunction. IT may precede reduced vessel elasticity, abnormal IMT, stenotic carotid lesions or symptomatic carotid artery disease. Its Doppler presence may therefore be an earlier warning sign of future cerebrovascular events.

Aim of Study: This study was done to evaluate the presence and significance of intimal thickening in the carotid arteries of hypertensive patients.

Methods: Carotid duplex scans of 119 consecutive hypertensive patients were retrospectively reviewed. Bilateral common carotids, carotid bulbs, internal carotids, and external carotids were studied using a linear array 7- to 10-MHz transducer. Intima was considered thickened if it was visualized as an echodense area, similar to the media-adventia interface in the far wall of the

artery. Plaque was present if there was a protrusion into the lumen wall. Patients with IMT were excluded from the study.

Results: Of the total, 71 (59.7%) were male and 48 (40.3%) were female. Their ages ranged from 46 to 88 years. Eighty-three (52 [62.7%] males; 31 [37.3%] females) (69.7%) of the 119 patients showed areas of thickened intima in the carotid arteries. Twenty-one (12 [57.1%] males; 9 [42.9%] females) (17.6%) of the 119 patients had plaque detected. Of these 21 with abnormal plaque, all (100%) showed IT while 62 (40 [64.5%] males; 22 [35.5%] females) (63.3%) of the 98 with no plaque showed IT. Twenty-one (12 [57.1%] males; 9 [42.9%] females) (25.3%) of the 83 with IT revealed an abnormal plaque while none of the 36 (19 [52.8%] males; 17 [47.2%] females) with no IT revealed an abnormal plaque.

Conclusions: We found a high incidence of intimal thickening in the carotid arteries of hypertensive patients. There appeared to be a correlation with atherosclerotic plaque. Since intimal damage precedes media thickening, ultrasound evidence of an abnormal intima may be the first indication of carotid atherosclerosis and prognosticate future progression to IMT and plaque. Further studies are needed to correlate isolated intimal thickening with morbidity and mortality in cardiovascular disease.

11 Lacunar Infarcts in a Hypertensive Population and Their Correlation With Systemic Vascular Resistance

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Introduction: Lacunar infarcts (LI) result from disease of the small cerebral arteries. An LI is a subcortical ischemic lesion at the level of a single perforating artery, with a diameter ranging from 100 to 400 µm and generally originating at right angles directly from the main arteries. Single lesions may result in no significant loss of function. We studied 67 consecutive hypertensive patients who underwent brain MRI for suspected central nervous system (CNS) pathology and compared their systemic vascular resistance (SVR) data with 133 hypertensive patients without suspected CNS pathology. All hypertensive patients were on antihypertensive medications. Since elevated SVR in treated hypertensives may represent small artery constriction, we postulated that patients with documented LIs may have higher SVR compared with those without suspected LIs.

Methods: Hypertensive patients with suspicion of CVS pathology underwent magnetic resonance imaging (MRI) of the brain. Neuroradiologists read the MRI scans in a standard fashion and diagnosed LI as subcortical infarcts measuring 3 to 20 mm. Cerebral infarcts (CI) and white matter disease (WMD) were also noted. SVR was measured using BioZ ICG Monitor (CardioDynamics, San Diego, California) and was considered elevated if it was more than 1,378 dynes × s/cm^5.

Results: We studied 200 patients with ages ranging from 37 to 94 years. Of these 200 patients (114 [57.0%] males and 86 [43.0%] females), 67 (41 [61.2%] males and 26 [38.8%] females) had undergone a brain MRI. Of the latter group, 49 (73.1%) were abnormal. Of these 49, 29 (43.3%) had LI, 8 (11.9%) had CI, and 15 (22.4%) had WMD. Of the 49 with pathology, 36 (73%) had elevated SVR. Of those with LI, 19 (65.5%) had elevated SVR. Of those with CI, 5 (62.5%) had elevated SVR. Of those with WMD, 12 (80.0%) had elevated SVR. Of the 18 (26.9%) normals, 12 (66.7%) had elevated SVR. In the group of 133 patients (73 [54.9%] males and 60 [45.1%] females) without brain MRI, 60.8% of patients had high SVR.

Conclusions: The majority of hypertensive patients undergoing brain MRIs for evaluation of clinical symptoms or signs of CNS disorder show abnormalities. The most common finding is LI. Most hypertensive patients on treatment maintain a high SVR. Patients with CNS disease appear to have a tendency toward higher SVR compared with hypertensive patients without suspected CNS pathology. We found no relationship between elevated SVR and LI in this hypertensive population.

12 Age-Matched Attenuation of Both Autonomic Branches in Chronic Disease: I. Hypertension

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Background: Autonomic dysfunction, as evidenced by reduced low frequency (LF) and high frequency (HF) power of baseline heart rate variability (HRV), has been implicated in chronic hypertension. However, thus far there is very little consensus on the validity of the correlation between LF power and hypertension. Moreover, LF power from traditional HRV analysis has been shown to be an inaccurate indicator of sympathetic activity. Parasympathetic and sympathetic (P&S) nervous system profiling using HRV and respiratory activity (RA) simultaneously, known as P&S monitoring, yields accurate measures of sympathetic activity (LF area or LFa), parasympathetic activity (respiratory frequency area or RFa), and sympathovagal balance (SB = LFa/RFa ratio).

Methods: Serial P&S monitoring (ANX-3.0 Autonomic Monitor, ANSAR, Medical Technologies, Inc., Philadelphia, Pennsylvania) was performed on 74 hypertensive patients (females = 21; age = 66.6 ± 12.2 years) with and without comor-

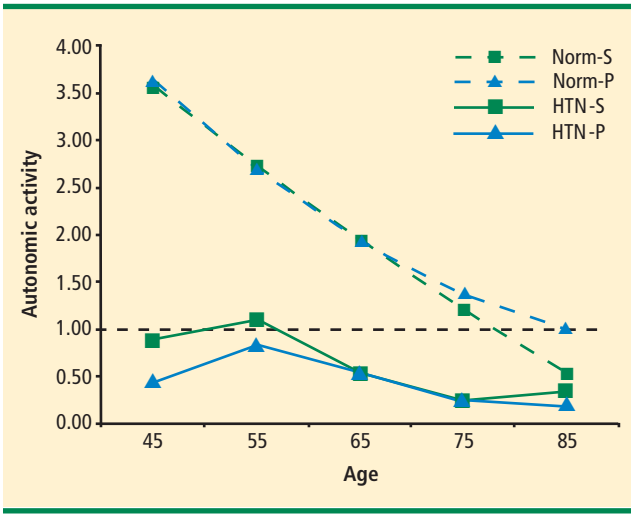

FIGURE. Serial parasympathetic (P) and sympathetic (S) monitoring in hypertension (HTN) patients compared with normal (NORM) controls.

bidities (diabetes = 43; coronary artery disease = 43). The data are compared with preexisting data for normal controls (ages 40–90 years) with no history of diabetes or cardiovascular or autonomic disorders. The broken horizontal line indicates the threshold for cardiovascular autonomic neuropathy **(Figure)**.

Results: Baseline P&S levels were found to be significantly reduced in chronic hypertensive patients compared with normal controls. An age-distributed investigation reveals that the P&S activity decreases with age, a trend similar to that of normal controls. However, the differences between normal controls and hypertensives are much more marked, especially in the younger population. The differences gradually decrease with age. These trends were observed regardless of comorbidities or medications. The P&S values for 45-year-old hypertensive patients are similar (or lower) in magnitude than those of 85-year-old normal controls.

Conclusion: Both parasympathetic and sympathetic activity appears to be significantly decreased in chronic hypertensive patients compared with age-matched normal controls. Whether these observations suggest P&S decline is an effect of hypertension, or contributes to the cause of hypertension, remains to be established.

13 Age-Matched Attenuation of Both Autonomic Branches in Chronic Disease: II. Diabetes Mellitus

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Background: Autonomic assessment using parasympathetic and sympathetic (P&S) monitoring (see Background in: I. Hypertension) yields accurate measures of sympathetic activity (low-frequency area, or LFa), parasympathetic activity (respiratory frequency area, or RFa), and sympathovagal balance (SB = LFa/RFa ratio).

Methods: Serial P&S monitoring (ANX-3.0 Autonomic Monitor, ANSAR, Medical Technologies, Inc., Philadelphia, Pennsylvania) was performed on 511 patients diagnosed with type 2 diabetes (females = 248; age = 63.4 ± 13.1, range 25 to 96 years) with and without comorbidities (hypertension, 56.1%; coronary artery disease, 25.2%). The data are compared with preexisting data for normal controls (ages 25–90 years) with no history of diabetes or cardiovascular or autonomic disorders. The broken horizontal line indicates the threshold for cardiovascular autonomic neuropathy (CAN). Diabetic autonomic neuropathy (DAN) is also indicated **(Figure)**.

Results: Baseline P&S levels were found to be significantly reduced in patients with diabetes compared with normal controls. An age-distributed investigation reveals that P&S activity decreases with age, a trend similar to that of normal controls. However, the differences between normal controls and diabetics are much more marked in the younger population. These differences gradually decrease with age. These trends were observed regardless of comorbidities or medications. P&S values for 35-year-old patients are similar (or lower) in magnitude than those of 70-year-old normal controls.

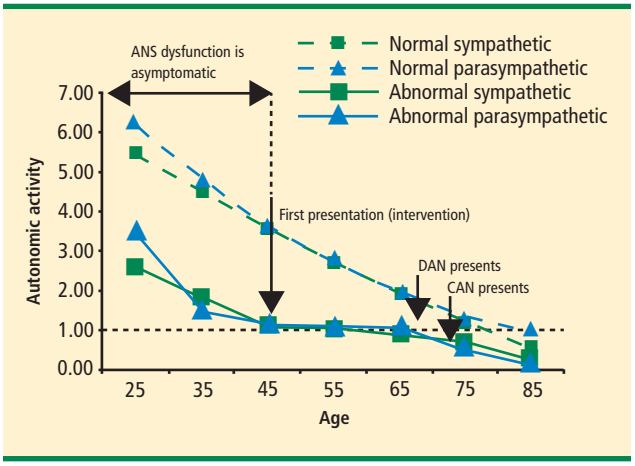

FIGURE. Autonomic nervous system (ANS) changes with age. CAN = cardiovascular autonomic neuropathy; DAN = diabetic autonomic neuropathy

Conclusion: Both parasympathetic and sympathetic activity appears to be significantly decreased in diabetics compared with age-matched normal controls. Whether these observations suggest autonomic decline is an effect of diabetes, or contributes to the cause of diabetes, remains to be established.

14 Age-Matched Attenuation of Both Autonomic Branches in Chronic Disease: III. Coronary Artery Disease

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Background: Chronic coronary artery disease (CAD) may lead to a reduction in parasympathetic and sympathetic (P&S) activity as measured by P&S monitoring (see Background in: I. Hypertension). P&S monitoring yields accurate measures of sympathetic activity (low-frequency area, or LFa), parasympathetic activity (respiratory frequency area, or RFa), and sympathovagal balance (SB = LFa/RFa ratio).

Methods: Serial P&S monitoring (ANX-3.0 Autonomic Monitor, ANSAR Medical Technologies, Inc., Philadelphia, Pennsylvania) was performed on 52 CAD patients (females = 1; age = 65.5 ± 13.3) with and without comorbidities (hypertension = 42; diabetes = 25). The data are compared with preexisting data for normal controls (age range, 40–90 years) with no history of diabetes or cardiovascular or autonomic disorders. The broken horizontal line indicates the threshold for cardiovascular autonomic neuropathy **(Figure)**.

Results: Resting P&S levels were found to be significantly reduced in chronic CAD patients compared with normal controls. An age-distributed investigation reveals that P&S activity decreases with age, a trend similar to that of normal controls. However, the differences between normal controls and CAD patients are much more marked in the younger population. The differences gradually decrease with age. These trends are observed regardless of any comorbidities or medications. P&S values for 45-year-old CAD patients were similar (or lower) in magnitude than those of 85-year-old normal controls.

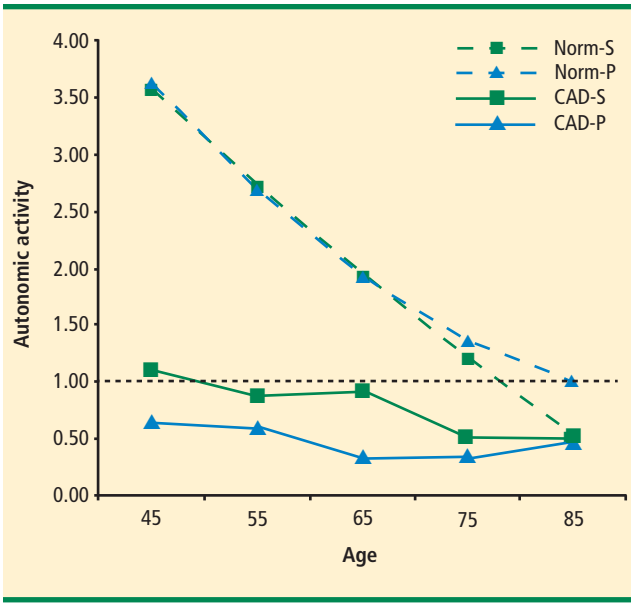

FIGURE. Serial parasympathetic (P) and sympathetic (S) monitoring in coronary artery disease (CAD) patients compared with normal (NORM) controls.

Conclusion: Overall autonomic activity appears to be significantly decreased in CAD patients compared with age-matched normal controls, suggesting that CAD may affect an acceleration in the physiologic aging process of patients compared with age-matched controls. Whether decreases in P&S activity in CAD patients is a cause or an effect needs to be established.

15 Age-Matched Attenuation of Both Autonomic Branches in Chronic Disease: IV: HIV/AIDS

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Background: Chronic disease is known to lead to early cardiovascular autonomic neuropathy (CAN). CAN indicates increased risk of morbidity and mortality. Autonomic dysfunction (AD), defined as abnormal autonomic, or sympathovagal, balance (SB, normal = 0.4 < SB < 3.0) prior to CAN is asymptomatic. Early intervention provides physicians with more therapy options. Treating AD by establishing and maintaining normal SB reduces morbidity and mortality risk. Low-normal SB minimizes morbidity and mortality risk in patients with CAN. High SB indicates sympathetic excess. CAN with high SB indicates high risk of mortality. Early intervention in response to early testing is justified based on the diagnosis of chronic diseases. Our hypothesis is that the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) lead to early AD.

Methods: Serial parasympathetic and sympathetic (P&S) monitoring (ANX-3.0 Autonomic Monitor, ANSAR, Medical Technologies, Inc., Philadelphia, Pennsylvania; see Background in: I. Hypertension) was performed on 232 consecutive patients (47 female) at an ambulatory clinic in Missouri. HR variability and respiratory activity data were collected concurrently and analyzed independently and simultaneously to compute parasympathetic and sympathetic (P&S) activity. The results were analyzed and are presented here against 234 aged-matched normals from our nationwide database. The level that defines the threshold for

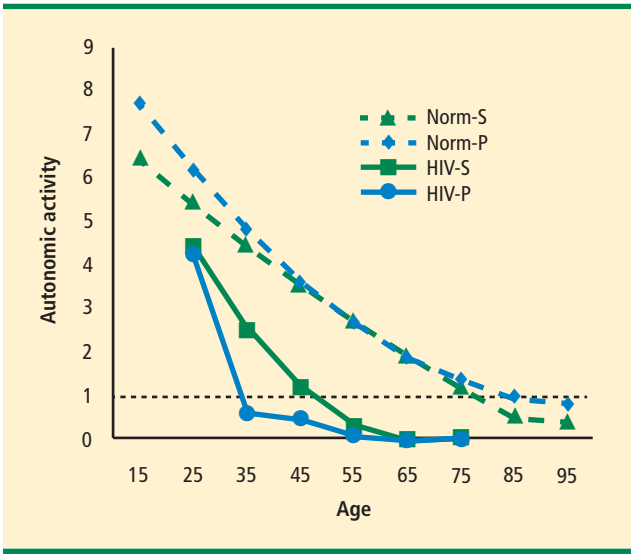

FIGURE. Age-matched human immunodeficiency virus (HIV). Serial parasympathetic (P) and sympathetic (S) monitoring in HIV patients compared with normal (NORM) controls.

CAN (P activity = 0.1 bpm^2) is shown on the **Figure**.

Results: Upon first diagnosis (approximately age 25 on average), patients' P&S levels are near normal with SB (1.77). Within one decade patients are near CAN, presenting with advanced AD and high SB (5.30). At age 55, patients demonstrate CAN with continued high SB (3.60). Normal subjects present with CAN around age 75, yet with normal SB (1.66), which mitigates the risk.

Conclusions: Patients present with AD and CAN earlier than normal subjects do. Patients also demonstrate high SB, indicating sympathetic excess compared with normal subjects. This suggests that patients have a higher mortality and morbidity risk, which leads to greater health care costs because of increased medications and hospitalizations.

16 The Existential Dilemma of Coronary Artery Disease: Nurse as Agent of Change in the Emerging Field of Behavioral Cardiology

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To Be or Not To Be

Shakespeare wrote those words for Hamlet no doubt with lengthy consideration for content and delivery. If all the world is a stage, then there is an act being played out every day in every hospital when health care professionals deliver the concept of "aggressive risk factor management" to persons with coronary artery disease (CAD). In essence the abridged version may be interpreted as, "Do you want to be or not be? And the corollary, "You must make these changes in your life or you *won't* be."

In a perfect world, and in a more therapeutic fashion this scene should be a dialogue. But health care professionals often lack the time, inclination, and empathic compassionate connection to the person, so this vital teaching becomes a monologue—a lecture, if you will. A case of classic Shakespearean "mistaken identity" occurs when the wholly integrated person who entered the hospital and who had a sense of who he is in the world, now becomes an accidental passive audience—that is, a patient.

The Evidence for the Existential Phenomenon as Experienced by Persons with CAD

1. "But my wife smokes. I would almost have to move out of the house to have even a chance to stop." (Person with CAD after stent placement, circa 2010.)

2. "Stress! Are you kidding? His job is killing him! But we have three daughters in college!" (Wife of person with CAD, circa 2009.)

3. "I have been praying for a miracle to undo all my bad habits; guess it's too late." (Overheard from person with CAD on her way into the catheterization lab minutes before receiving a stent, circa 2010.)

4. "The first time I got chest pain I renewed my health club membership." (Person with CAD after myocardial infarction, circa 2009.)

5. "I know my slothlike ways may be taking me straight to the big final void." (Person with CAD on the evening of receiving his fourth stent, circa 2010.)

The Nurse and the New Discipline of Behavioral Cardiology

So, is anyone listening to the person with CAD? Yes. The Nurse. And the emerging field of behavioral cardiology. They are ready to explore methods of delivering this age-old script of "risk factor modification." The nurse and behavioral cardiology are prepared to diagnose the internal struggle people face when they discover the way they live their lives may be in direct conflict with their cardiovascular health. Aye, there's the rub, and the beginning of what may be quite an existential crisis questioning the very meaning and purpose of life. And the alternative.

17 Phantom Shocks as Markers of Underlying PTSD and Depression

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Implantable cardioverter defibrillator recipients sometimes report *phantom shocks*, defined as a patient's report of having experienced a shock without objective evidence of having received one. This mixed-methods study aimed to gain an understanding of the phenomenologic experience of phantom shocks. It was also hypothesized that phantom shocks are related to an increased level of posttraumatic stress disorder (PTSD) symptoms.

Methods: Nine phantom shock participants were recruited and matched on sex and age with participants who had received objective shocks only (n = 8, 100% male). Participants were interviewed and completed measures of PTSD (PTSD Checklist—Civilian Version [PCL-C]), depression and anxiety (Hospital Anxiety and Depression Scale [HADS]), disease-specific distress (Cardiac Anxiety Questionnaire, Florida Patient Acceptance Survey), psychologic vulnerability to trauma (Pain Anxiety Symptoms Scale [PASS-20]), pain quality ratings (short-form McGill Pain Questionnaire), and social desirability (Socially Desirable Response Set).

Results: Three themes emerged from the qualitative analysis: (1) phantom shocks—a somatic experience, (2) the emotional impact of phantom shocks, (3) searching for meaning. Quantitative analysis showed that both groups exhibited elevated trauma and anxiety levels. Medium-effect size differences, where the phantom shock group showed elevated levels compared with the objective shock group, were found on HADS depression (M = 8.02, SD = 3.87 vs M = 5.50, SD = 3.38, respectively, eta^2 = .12), PCL-C avoidance (M = 4.00, SD = 2.00 vs M = 3.13, SD = 1.89, eta^2 = .06) and numbing (M = 11.31, SD = 5.01 vs M = 9.00, SD = 3.89, eta^2 = .07), and PASS-20 (M = 41.57, SD = 33.11 vs M = 28.28, SD = 23.16, eta^2 = .06). A small effect was seen on the PCL-C re-experiencing subscale (phantom shock group: M = 10.38, SD = 4.63 vs objective shock group: M = 9.63, SD = 4.10, eta^2 = .01).

Conclusion: Phantom shocks are often indistinguishable from objective shock therapy, evoking alarm, frustration, and confusion for the individual. Taken together, the data suggest that for some participants, symptoms of PTSD and depression contribute to the experience of phantom shocks.

18 Psychologic Markers of Stress, Anxiety, and Depression Are Associated With Indices of Vascular Impairment in Women With High Stress Levels and Advanced Coronary Artery Disease

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[1]University of Minnesota, School of Nursing, and Department of Kinesiology, Minneapolis, MN; [2]The Women's Heart Health Program of the Minneapolis Heart Institute® at Abbott Northwestern Hospital, and Minneapolis Heart Institute Foundation, Minneapolis, MN; and [3]Kyungpook National University School of Nursing, South Korea

Background: Psychologic stress, anxiety, and depression have been linked in several epidemiologic studies to the development and progression of coronary artery disease (CAD). However, the mechanism of the negative impact of these psychologic factors on CAD progression remains to be fully elucidated. Recent studies have suggested that depression and negative mood may adversely impact the vascular endothelium, which may represent one link between these psychologic factors and CAD.

Purpose: The purpose of this study was therefore to investigate the association between psychologic markers of perceived stress, anxiety, depression, and indices of vascular health and function in women with high stress levels and advanced CAD. We hypothesized that there would be significant associations between psychologic markers of mood and impaired vascular health and function.

Methods: Twenty-two non-Hispanic white female patients (mean age = 64.8 years), who were stressed per Holmes and Rahe Life Change, or Perceived Stress Scales, with advanced CAD (> 50% stenosis) underwent assessment of vascular endothelial function via brachial artery reactive hyperemia following 5 minutes of forearm occlusion using Doppler ultrasound (FMD) and concurrent assessment of peripheral arterial tone (RHI-PAT) in the second digit. Other indices of vascular health included carotid intima media thickness, carotid compliance (internal elastic modulus), high sensitivity C-reactive protein (CRP), and pro-brain natriuretic peptide hormone. Psychologic makers included depression (Center for Epidemiological Studies Depression Scale), perceived stress (Perceived Stress Scale [PSS-14]), 12-Item Short-Form Health Survey Mental Component, social support (Enhancing Recovery in Coronary Heart Disease [ENRICHD]) intervention, control, and anxiety. Spearman's rho was used to assess associations between variables.

Results: Statistically significant moderate associations were found between indices of vascular health and psychologic measures of anxiety, perceived stress, and depression **(Table)**. RHI-PAT was associated with social support (ENRICHD, rs = .51, *P* = .02), but it was not associated with other markers or indices although a trend for an inverse association was observed with perceived stress (rs = −.40, *P* = .076). CRP was associated with the SF-12 Mental Component (rs = −.48, *P* = .04).

Conclusions: Results suggest that depression is a major factor associated with impaired vascular endothelial function and arterial health in women with high levels of stress and advanced CAD. This study supports the need to consider depression in CAD risk factor profiling, and underscores the need to investigate interventions that target depression to attenuate its putative adverse effects on vascular health and function. Moreover, the presence of increased stress and anxiety may pose an additional CAD risk burden that should be investigated further.

TABLE
ASSOCIATION BETWEEN SELECTED INDICES OF VASCULAR HEALTH AND PSYCHOLOGICAL MARKERS

Variables (n = 22)	Peak % FMD	TP FMD	FMD-AUC	Pro-BNP	CRP	CIMT	CIEM
Mean (SD)	4.3 (2.7)%	84 (59)	421 (340)	248 (244)	1.9 (1.5)	0.68 (0.16)	.092 (.039)
Depression 8.8 (6.9)	rs = −.61 *P* = < .01	rs = .61 *P* = < .01	rs = −.51 *P* = .03	rs = .59 *P* = < .01	rs = .57 *P* = .01	rs = .07 *P* = .71	rs = −.44 *P* = .06
Perceived stress 23.2 (6.1)	rs = −.03 *P* = .88	rs = .08 *P* = .72	rs = −.01 *P* = .98	rs = .43 *P* = .05	rs = .41 *P* = .06	rs = −.51 *P* = .02	rs = .01 *P* = .95
Anxiety 0.61 (0.48)	rs = −.18 *P* = .44	rs = .47 *P* = .04	rs = −.12 *P* = .60	rs = −.10 *P* = .69	r s= −.64 *P* = < .01	rs = −.22 *P* = .35	rs = .27 *P* = .25

CIEM = carotid internal elastic modulus; CIMT = carotid intima media thickness (mm); CRP = C-reactive protein (mg/dL); FMD = flow mediated vasodilation (percent); FMD-AUC = flow mediated vasodilation area under the curve (percent × seconds); pro-BNP = pro-brain natriuretic peptide hormone (pg/mL); TP FMD = time to peak flow mediated vasodilation (seconds)

19 Personality Dimensions and Health-Related Quality of Life in Patients with Coronary Artery Disease

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Objective: Health-related quality of life (HRQoL) is an important outcome parameter in patients with coronary artery disease (CAD). The aim of the study was to examine the effects of personality dimensions on HRQoL in patients with CAD.

Methods: Five hundred fourteen consecutive patients attending a CAD rehabilitation program were invited to participated in the study. Patients completed the Ten-Item Personality Inventory (TIPI), and the 36-item Short Form Medical Outcome Questionnaire (SF-36). A stepwise linear regression analysis was used to examine whether personality dimensions determine HRQoL.

Results: Multivariate stepwise regression analyses revealed that when age, gender, and five TIPI personality dimensions were included in the model, TIPI personality dimension of emotional stability had an impact on seven of eight SF-36 subscales of qual-

ity of life in patients with CAD and strongly determined the scores on subscales for mental health (β = .451, *P* = .000), role limitations due to emotional problems (β = .193, *P* = .000), social functioning (β = .118, *P* = .007), energy/vitality (β = .284, *P* = .000), pain (β = .123, *P* = .005), and general health perception (β = .276, *P* = .000). Personality dimension of conscientiousness had an impact on the physical function subscale (β = .093, *P* = .025), the role limitations due to physical problems subscale (β = .112, *P* = .010), the social functioning subscale (β = .157, *P* = .000), and the energy/vitality subscale (β = .092, *P* = .026). Personality dimension of the extraversion had an impact only on the mental health subscale (β = .097, *P* = .012) and reverse impact on the general health perception subscale (β = −.129, *P* = .002). Another significant determinant was gender, which had an impact on the SF-36 subscales of physical function (β = −.377, *P* = .000), role limitations due to physical problems (β = −.151, *P* = .001), social functioning (β = −.195, *P* = .000), mental health (β = −.107, *P* = .006), energy/vitality (β = −.247, *P* = .000), pain (β = −.116, *P* = .010), and general health perception subscale (β = −.118, *P* = .005). Age was a significant determinant only in role limitations due to physical and emotional problems and pain. While significance was found in most of the regressions, the determination coefficients were rather low. Only on the subscale for mental health, it covered 25% of the variance; on other subscales it varied from 17% to 5%.

Conclusion: In patients with CAD , the personality trait of emotional stability has a significant effect on the HRQoL, especially on the mental aspects of the HRQoL. Psychologic interventions in CAD should be extended to the management of personality traits.

20 Behavioral Stress Results in Reversible Myocardial Dysfunction in a Rodent Model

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Clinical reports suggest that emotional stress alone is sufficient to cause reversible myocardial dysfunction in patients. We report that a combination of prenatal stress followed by restraint stress (PS + R) results in echocardiographic evidence of myocardial dysfunction compared with control rats subjected to the same restraint stress (control + R) (45.8 ± 3.9 vs 61.9 ± 2.4%; *P* < .01). Catheter-based hemodynamic studies in freely ambulatory awake rats revealed both systolic (+dp/dt; 10,438 ± 741 vs 12,111 ± 652) and diastolic (−dp/dt; −8,287 ± 444 vs 10,440 ± 364) dysfunction in PS + R vs control + R (*P* < .05, for both). PS + R also demonstrated a significantly attenuated (*P* < .05) hemodynamic response to increasing doses of the beta-adrenergic agonist, isoproterenol. Pretreatment with the p38 MAP kinase inhibitor, SB203580, prevented the baseline reduction in +dp/dt and −dp/dt as well as the blunted isoproterenol response in vivo. Cardiac myocytes from PS + R also revealed diminished fractional shortening (6.7 ± 0.8 vs 12.7 ± 1.1%, *P* < .01) and blunted inotropic responses to isoproterenol (*P* < .01). In vitro treatment with SB-203580 blocked p38 MAP kinase phosphorylation, reversed the depression in fractional shortening, and partially ameliorated the blunted adrenergic signaling seen in adult rat ventricular myocytes from PS + R. We conclude that p38 MAP kinase activation in cardiac myocytes by behavioral stress may lead to reversible myocardial dysfunction in this animal model of human disease.

21 Perceived Stress, Psychosocial Stressors, and Behavioral Factors: Association With Inflammatory, Immune, and Neuroendocrine Biomarkers in a Cohort of Healthy Very Elderly Men and Women

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Introduction: By 2030, it is estimated that 20% of the US population will be over 65 years of age, and that 75% of adults will have one or more severe disabilities by age 80. Determining preventive models for age-related diseases, frailty, and functional decline is critical. Dysregulation of inflammatory pathways and desynchronization of hormonal axes have been identified in age-related diseases including cardiovascular disease, dementia, and mood disorders.

Methodology: In this 12-month prospective study, 28 healthy elderly and very elderly (> 85 years of age) subjects who met strict inclusion/exclusion criteria were enrolled. Twenty-one psychosocial, cognitive-behavioral, and nutritional factors that were associated with eight immunologic and neuroendocrine/endocrine biomarkers at different times of the day and at different levels of physiologic stress were measured at baseline and at 6, 9, and 12 months. Mean age of participants was 85 years with 79% female and 21% male.

Results: Perceived stress as determined by Holmes-Rahe revealed a mean of 304.46 ± 156.33, with 26% of subjects reporting high financial stress. In addition, 29.62% of subjects had experienced childhood health issues and 18.51% experienced a traumatic home environment. Assessment of quality of life with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) revealed mean values of 46.43 for the mental component (MC), and 36.15 for the physical component (PC) at baseline, and 37.12 for MC 41.65 for PC at follow-up. Social interactions averaged 24.47 activities per month and 85% of subjects reported active spiritual beliefs. Completed educational level completion was high school or higher. Nutritional assessments showed that 89% consumed prudent diet selections with no significant change over time, mean body mass index (BMI) was 25.98 (SD, 4.30), and 89% took dietary supplements. Behavioral findings revealed that 3.5% used tobacco; 28.5% drank alcohol at least once weekly, 28.57% exercised daily, and 71.43% exercised at least twice weekly with no significant change over 12 months. Neuroendocrine measures revealed mean Folstein Mini-Mental Status Exam score, 28; mean insulin-like growth factor-1, 36.98 ng/mL; mean cortisol/dehydroepiandrosterone sulfate ratio 3.2; mean tumor necrosis factor-alpha, 1.73 pg/ml; mean interleukin-6, 0.34 pg/mL; mean C-reactive protein (CRP), 3.25 mg/L; mean fibrinogen, 9.66 mg/dL; mean dehydroepiandrosterone sulfate, 3.06 ng/mL; mean testosterone, 22.69 pg/mL in women, 81.93

pg/mL in men; mean estrogen 1.94 pg/mL in women. Recursive partitioning (RP) was used to "grow trees" for each biologic marker at both the morning and evening as well as the high and low cortisol-collecting intervals. Each tree identified multiple combinations of the 21 factors/stressors (predictor variables) that led to each of the biologic markers (target variables), referred to as pathways. Two at-risk target variables were identified: CRP from the immune system and testosterone from the endocrine system at both time intervals and at the low- and high-risk cortisol levels. Predictor variables that showed the greatest frequency of both target variables were BMI, education level, socialization/activities, nutrition, marital status, and whether or not they lived alone.

Conclusion: It is plausible that proadaptive psychosocial and lifestyle choices, despite high perceived stress, may influence neuroendocrine and immune regulatory processes, and thus, may protect against age-related changes in proinflammatory pathways. Preventive counseling models in younger adults may be expanded to assess nontraditional clinical markers of neuroendocrine/immune function that are associated with psychosocial/behavioral/nutritional factors in efforts to prevent later age-related diseases, frailty, and functional decline.

22 Prognostic Significance of PD2i in Heart Failure Patients

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Background: Heart rate variability and heart rate dynamics are useful in identifying heart failure patients at increased risk of mortality. A new nonlinear deterministic model, the automated point correlation dimension (PD2i), was evaluated regarding its prognostic significance for predicting cardiac events in chronic heart failure patients.

Methods: The study population consisted of chronic heart failure patients who were observed for 44 months on average with total mortality as the primary end point and cardiac mortality, sudden cardiac death, and heart failure death as secondary end points. The PD2i was computed based on 20-minute supine high-resolution Holter recording and was categorized as positive (PD2i ≤ 1.4) or negative (PD2i > 1.4) based on prespecified criteria.

Results: Among 651 chronic heart failure patients, 537 had successful PD2i analyses resulting in 144 (27%) patients showing positive results and 393 (73%) negative results **(Figure)**. After adjustment for clinical covariates, PD2i was found predictive for total mortality (heart rate [HR] = 1.55; *P* = .026). Predictive value of PD2i was observed in heart failure patients with left ventricular ejection fraction of 35% or less (HR = 1.95; *P* = .004), but not in patients with ejection fraction greater than 35% (HR = 0.87; *P* = .716); *P* for interaction 0.072. Further analyses revealed that among patients with ejection fraction ≤ 35%, PD2i was also predictive for cardiac death and for heart failure death.

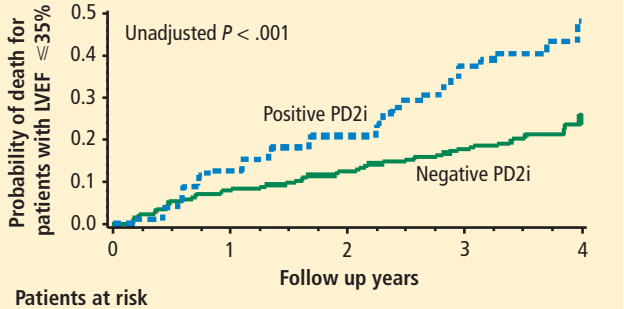

FIGURE. Predictive value of point correlation dimension (PD2i) in heart failure patients with left ventricular ejection fraction (LVEF) of 35% or less.

Conclusions: The PD2i, a novel nonlinear heart rate dynamics parameter, is predictive for total mortality, cardiac death, and heart failure death in heart failure patients with left ventricular ejection fraction of 35% or less There was no predictive value of PD2i in heart failure patients with ejection fraction greater than 35%.

23 Sympathovagal Imbalance Assessed by Heart Rate Variability Correlates With Percent Body Fat and Skeletal Muscle, Independent of Body Mass Index

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Introduction: Heart rate variability (HRV) has been used to assess sympathovagal balance and it has been described as correlating with obesity. Body mass index (BMI) is one of the most accurate ways to determine when overweight translates into health risks. We propose that bioelectric impedance may be used as an alternative measure to correlate with sympathovagal balance using body fat percentage (%BF), skeletal muscle percentage (%SM), and %BF/%SM ratio.

Methods: Two hundred twenty-eight healthy volunteers, 110 males (20.7 ± 2.0 years) and 118 females (20.2 ± 1.6 years), participated in the study. Five-minute recordings of HRV time-and frequency-domain indices were analyzed and correlated with bioelectric impedance variables **(Table)**: The root mean of the squared successive interbeat intervals differences (RMSSD) was taken as the time domain measure of HRV. High-frequency (HF: 0.15–0.4 Hz), low-frequency (LF: 0.04–0.15 Hz), very-low-frequency (VLF: < 0.04 Hz) band power, and HF power or LF/HF ratio were calculated on the electrocardiogram (ECG) recordings obtained. All time- and frequency-domain indices were automatically calculated by the commercially available Norav ECG Management System (Wiesbaden, Germany). Standard measures for BMI and bioelectric impedance for %BF, %SM, and %BF/%SM ratio were measured with the commercially available Omron BF500 Body Composition Monitor (Kyoto, Japan).

Results: Bioimpedance variables: For all volunteers mean BMI was 23.9 ± 4.2, %BF 29.6 ± 9.4, %SM 31.6 ± 7.0, and

TABLE
HEART RATE VARIABILITY AND BIOIMPEDANCE VARIABLES

		Heart rate variability (frequency-domain)			
		HF	LF	VLF	LF/HF
Bioimpedance	BMI	.034 (P = ns)	−.097 (P = ns)	−.029 (P = ns)	−.032 (P = ns)
	%Fat	.336 (P < .001)	−.222 (P = .001)	−.224 (P = .001)	−.217 (P = .001)
	%Skeletal muscle	−.396 (P < .001)	.221 (P = .001)	.254 (P < .001)	.252 (P < .001)
	%Fat/%SM	.359 (P < .001)	−.228 (P = .001)	−.240 (P < .001)	−.228 (P = .001)

HF = high frequency; LF = low frequency; VLF = very low frequency

%BF/%SM 1.0 ± 0.5.

HRV variables: For all volunteers mean average RR 883.9 ± 144.7, RMSSD 57.5 ± 30.7, LF 157.0 ± 79.3, HF 240.3 ± 96.7, LF/HF 0.88 ± 0.79.

No correlation was observed between BMI and any of the HRV analyzed.

BMI had a direct correlation with %BF/%SM ratio (.464, P < .001). %BF had an inverse correlation with LF (−.222, P = .001), a positive correlation with HF (.336, P < .01), and an inverse correlation with VLF (−.224, P = .001). %SM had a direct correlation with LF (.221, P = .001), an inverse correlation with HF (−.396, P < .01), and a direct correlation with VLF (.254, P = .001). %BF/%SM ratio had an inverse correlation with LF (−.228, P = .001), a positive correlation with HF (.359, P < .001), and an inverse correlation with VLF (−.240, P = .001) and with LF/HF ratio (−.228, P = .001).

Conclusion: Sympathovagal balance is affected by weight gain and its measurement correlates with %BF, %SM, and %BF/%SM ratio, and not BMI. Sympathetic tone (LF) and VLF (related to thermogenesis) have a direct correlation with greater %SM and less %BF. Vagal tone (HF) has a direct correlation with greater %BF and less %SM. Studies to measure sympathovagal balance assessed by HRV may help to distinguish bioelectric impedance measurements as additional cardiovascular risk factors independent of BMI, and may help address focused training and followup programs in overweight patients.

24 Trajectory of Depressive Symptoms in Patients With Heart Failure: Influence on Cardiac Event-Free Survival

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Background: Patients with heart failure (HF) experience depressive symptoms that adversely affect mortality and morbidity. Little is known about whether a change in depressive symptoms over time influences cardiac events.

Purpose: To determine whether a change in depressive symptom status is associated with cardiac event-free survival in patients with HF.

Methods: We used a prospective, longitudinal design with repeated measures. The sample consisted of 250 patients with HF (35% female, 61 ± 12 years, 57% New York Heart Association class III/IV, 32% inpatient) enrolled in a multicenter quality of life registry. Depressive symptoms were measured with the Patient Health Questionnaire-9 at baseline, 3, or 6 months; scores 10 or higher indicate depressive symptoms. Patients were categorized into four groups based on change in depressive symptoms from baseline to 3 to 6 months: symptom free, symptoms improved, developed symptoms, and persistent symptoms. Patients were followed for a median of 12 months to determine cardiac event-free survival. Survival curves were computed using the Kaplan-Meier method; groups were compared using log rank test.

Results: Patients who remained symptom free (n = 173) had the best cardiac event-free survival (**Figure**, P = .02), followed by patients whose symptoms improved (n = 29), patients with persistent symptoms (n = 34), and patients who developed symptoms (n = 14).

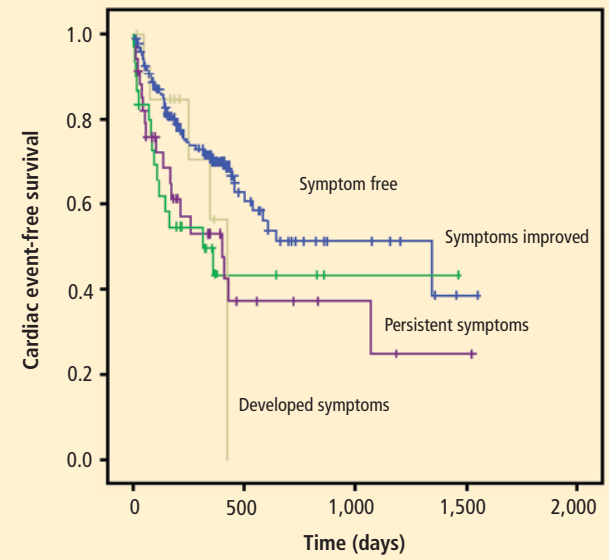

FIGURE. Relationship between depressive symptoms and event-free survival.

Conclusion: Patients with HF and persistent or developing depressive symptoms had shorter cardiac event-free survival. Research is needed to test whether interventions that prevent new onset of or reduce depressive symptoms also improve event-free survival.

25 Autonomic Modulation of Ankle Brachial Index Assessed by Heart Rate Variability in Healthy Young Male and Female Volunteers

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Introduction: Autonomic regulation analysis is useful as risk stratification in a wide variety of cardiac, neurologic, and metabolic diseases. Sympathovagal balance assessed by heart rate variability (HRV), both in time and frequency domains, correlates with peripheral arterial disease determined by ankle-brachial index (ABI) in patients with known cardiovascular disease. The aim of this study is to assess the association of HRV and ABI in healthy young volunteers.

Methods: Two hundred twenty-eight healthy volunteers, 110 males (20.7 ± 2.0 years) and 118 females (20.2 ± 1.6 years) participated in the study. Five-minute recordings of HRV time- and frequency-domain indices were analyzed and correlated with ABI. The root mean of the squared successive interbeat intervals differences (RMSSD) was taken as the time domain measure of HRV. High-frequency (HF: 0.15–0.4 Hz), low-frequency (LF: 0.04–0.15 Hz), very-low-frequency (VLF: < 0.04 Hz) band power, and HF power or LF/HF ratio were calculated on the electrocardiogram recordings obtained. All time- and frequency-domain indices were automatically calculated by the commercially available Norav ECG Management System (Wiesbaden, Germany). ABI was measured by noninvasive methods.

Results: For all volunteers: mean RMSSD, 57.5 ± 30.7; LF, 157.0 ± 79.3; HF, 240.3 ± 96.7; VLF, 144.8 ± 82.2; LF/HF, 0.88 ± 0.79; and ABI, 1.05 ± 0.09. RMSSD had a direct correlation with ABI (.191, P = .005). No correlation was observed between ABI and any of the other HRV data.

Independent analysis of male and female groups was as follows:

Male: Mean ABI (1.05 ± .08) and RMSSD (53.3 ± 30.9) had a positive correlation (.229, P = 0.19). No other correlation was observed.

Female: Mean ABI (1.04 ± .09) and RMSSD (61.3 ± 30.2), had no correlation with each other or with other HRV variables.

T-test for equality of means: RMSSD, male (53.3 ± 30.9) and female (61.3 ± 30.2), (P = .05); LF, male (174.0 ± 84.0) and female (141.3 ± 71.6), (P = .02); HF, male (201.4 ± 81.7) and female (276.1 ± 96.0), (P < .001); and LF/HF, male (1.09 ± 0.86) and female (0.69 ± 0.67), (P < .001).

Conclusion: Differences in sympathovagal balance in time and frequency domain analysis between male and female healthy volunteers was observed. RMSSD only correlates with ABI in healthy young male volunteers, and may be related to an augmented sympathetic tone (LF).

Even though no difference in ABI between sexes is found at this age, autonomic balance control related to time-domain analysis may explain its correlation with a higher sympathetic tone in healthy young men compared with healthy young women.

26 Toward Uncovering Key Factors in Adherence in a Post–Heart Transplant Population: A Project in the Making

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Background: Adherence to immunosuppressant medications is variable among heart transplant recipients with potentially life- threatening outcomes. It is understood that patients with psychosocial barriers are at increased risk of poor outcomes due to a variety of factors, such as stress related to the procedure, medication nonadherence, recidivism of substance abuse, and mental status changes with steroid exposure.

Hypothesis: Specific issues related to depression, anxiety, cognitive dysfunction, and external locus of control have been documented in the literature as likely reasons for nonadherence to prescribed medication regimens in a number of patient populations. Data are lacking for heart transplant recipients, however. Our aim is to understand the impact of these psychologic factors in post–heart transplant recipients' nonadherence to immunosuppressant medication regimens. In particular, we seek to understand the post–heart transplant recipients' locus of control.

Locus of control is a concept from Rotter's social learning theory. Internal locus of control refers to the perception of positive or negative events as being a consequence of one's own actions and thereby under one's own personal control. External locus of control refers to the perception of positive or negative events as being unrelated to one's own behavior and therefore beyond personal control. The literature suggests that patients with an internal locus of control have a sense of responsibility for their health and therefore do better in terms of adherence. Thus, knowledge of the locus of control of heart transplant recipients would be key to predicting adherence with immunosuppressant medication and follow up care.

Method: In an effort to understand the profile of adherence we began collecting data on post-transplant recipients. Recruitment was conducted by contacting all the post-transplant patients followed by the Kaiser Permanente Northern California transplant service and asking for voluntary participation. Data collection consisted of self-report questionnaires and one cognitive screening test conducted by the transplant psychologist. To date, we have collected data on 24 participants; it is hoped that data will be available for 46 participants. This number will adequately power the study and allow meaningful statistical interpretation of data.

Data Summary: Averages for 24 patients:

Demographic: male, 79%; female, 21%; age, 61.12 years; years post-heart transplant, 4.35.

Psychologic: coping (self-report 0–10), 7.73; adherence to immunosuppressant medication (0–12),11.16 (high); depression (Beck Depression Inventory-II: 0–13 minimal), 6.47 (low); state anxiety at appointment (cardiac: 25.81–48.71 = normal), 28.66 (average); trait anxiety in general (cardiac: 25.64–43.50 = normal), 28.87 (average); cognitive assessment (Montreal Cognitive Assessment): normal = 26–30), 26.54 (low normal).

Locus of control: internal (6–36), 23.21 (above average); chance (6–36), 15.37; doctor (3–18), 16.3 (high); other people (3–18), 10.3.

Limitations: The study is limited in terms of accuracy by patient self-reporting.

Results: Preliminary data on 24 patients included self-reported high adherence. This suggests a profile of patients who cope relatively well, have minimal depression and average state and trait anxiety, and whose cognitive function is in the normal range. The locus of control data suggests that both internal and external (doctor-specific) orientations are meaningful to our understanding of adherence.

Discussion: Additional data and recruitment of more patients will validate the findings of this preliminary analysis. It is hoped that locus of control may yield a better predictive profile of adher-

ence compared with traditional identification with mood disorders. Our clinical experience suggests that patients will be more truthful with the questionnaire about locus of control because this concept is less loaded for them. The concepts of depression and anxiety are negatively perceived by patients, which may cause them to be more guarded in the ways they answer those questions. Therefore this subset of data might yield more meaningful results. In addition to collecting the data summarized above, we will check each patient's chart to verify episodes of rejection and potential nonadherence.

Future Directions: Objective data on patient adherence will be collected and potential nonadherence will be correlated with future rejections. This data collection phase is under way.

27 Sympathovagal Tone Assessed by Heart Rate Variability Is Directly Related to Body Mass Index, Percent Body Fat, and Skeletal Muscle in Healthy Male and Female Young Volunteers

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Introduction: Sympathovagal balance has been described as related to obesity and metabolic syndrome, assessed by heart rate variability (HRV) and body mass index (BMI). Bioelectric impedance (BI) is used, among other variables, to measure body fat percentage (%BF), skeletal muscle percentage (%SM), and %BF/%SM ratio. BMI takes into account only body weight and height. In order to determine whether HRV relates to body composition in healthy young males compared with females, we analyzed HRV and BI variables.

Methods: Two hundred twenty-eight healthy volunteers, 110 males (20.7 ± 2.0 years) and 118 females (20.2 ± 1.6 years) participated in the study. Five-minute recordings of HRV time-and frequency-domain indices were analyzed and correlated with BI variables: The root mean of the squared successive interbeat intervals differences (RMSSD) was taken as the time domain measure of HRV. High-frequency (HF: 0.15–0.4 Hz), low-frequency (LF: 0.04–0.15 Hz), very-low-frequency (VLF: < 0.04 Hz) band power, and HF power or LF/HF ratio were calculated on the electrocardiogram recordings obtained. All time- and frequency-domain indices were automatically calculated by the commercially available Norav ECG Management System (Wiesbaden, Germany). Standard measures for BMI and BI for %BF, %SM and %BF/%SM ratio were measured with commercially available Omron BF500 Body Composition Monitor (Kyoto, Japan).

Results: T-test for equality of means between male and female volunteers is shown in the **Table**.

Conclusion: Differences in sympathovagal balance between male and female healthy volunteers were observed. We found an augmented sympathetic tone (LF) and VLF (related to thermogenesis) in healthy male volunteers related to a higher %SM, and an augmented vagal (HF) and parasympathetic tone (LF/HF) in healthy female volunteers, related to an increase in %BF. Bioelectric impedance parameters should also be used to estimate cardiovascular risk factors related to sympathovagal equilibrium.

TABLE
T-TEST FOR EQUALITY OF MEANS BETWEEN MALE AND FEMALE VOLUNTEERS

	Mean	SD	*P*
Bioimpedance			
Weight (kg)			
Male	75.2	14.5	.000
Female	60.2	11.1	
BMI			
Male	24.7	4.4	.007
Female	23.2	3.8	
%Fat			
Male	23.7	7.9	.000
Female	35.2	7.0	
%Skeletal muscle			
Male	37.8	4.4	.000
Female	25.8	2.6	
%Fat/%SM			
Male	.66	.30	.000
Female	1.3	.37	
HRV			
RMSSD			
Male	53.3	30.9	.05
Female	61.3	30.2	
VLF			
Male	166.4	91.1	.000
Female	124.9	67.7	
LF			
Male	174.0	84.0	.000
Female	141.3	71.6	
HF			
Male	201.4	81.7	.000
Female	276.1	96.0	
LF/HF			
Male	1.09	0.86	.000
Female	0.69	0.67	

BMI = body mass index; HF = high frequency; HRV = heart rate variability; LF = low frequency; RMSSD = root mean of the squared successive interbeat intervals differences; VLF = very low frequency

28 Biofeedback Training to Promote ANS Resilience in Army ROTC Cadets

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Introduction: Stressors experienced by military personnel encompass both operational and environmental challenges. These challenges are both chronic (requiring sustained vigilance) and acute (requiring immediate action). Exposure to these stressors can eventually lead to fatigue and physical and emotional exhaustion. Preliminary data suggest that prewar physiologic stress reactivity and recovery may be important determinants of immediate postdeployment physical health in soldiers returning home from Iraq or Afghanistan. Therefore, the investigation of methods to modulate stress reactivity and promote autonomic nervous system resilience in military personnel is warranted. This study investigated the impact of biofeedback training, with an empha-

sis on heart rate variability (HRV) training, on the physiologic and stress reactivity patterns of Army ROTC cadets.

Methods: Forty-two cadets were recruited from the Army ROTC. Participants were randomly assigned to either the wait-list control group or the treatment group. The treatment group received an 8-week course of 45-minute multimodality biofeedback sessions with a primary emphasis on HRV training utilizing the resonant frequency protocol described by Lehrer, Vaschillo, and Vaschillo. Both groups underwent a psychophysiologic stress profile (PSP) in weeks 1, 8, and 16 of participating in the study. The PSP data were utilized to determine the impact of biofeedback training on autonomic nervous system (ANS) indices. Program Post-Training Self-Report Measurement (PTSRM) forms were administered at week 16 to assess changes in energy level, ability to focus, emotional regulation, quality of sleep, and recovery skills.

Results: There were no significant differences in retrospective self-reports of preintervention average daily energy level ratings for the treatment-versus-control groups. Postintervention daily energy ratings for the treatment group revealed perceived improvement; however, there was no significant difference between the postintervention treatment and control group scores. This is as we might expect, given that both groups have now completed the intervention. The results of the impact of the training on ANS indices are pending physiologic data analysis.

Discussion: The study intervention was designed to increase autonomic flexibility in the service of helping individuals utilize their full autonomic capacity in case of strong metabolic need (ie, military service). The data to address the overall hypothesis are not yet available. Retrospectively, those in both the treatment and wait-list control groups perceived better energy and improved emotional regulation, quality of sleep, recovery skills, and ability to focus after the intervention than before. In addition, the lack of difference in posttraining energy ratings for the treatment and control groups suggests that the gains the control group perceived immediately posttraining were still maintained by the treatment group another 8 weeks after the intervention. In future studies it would be optimal to take self-report measurements both pre- and postintervention rather than retrospectively. Modulation of stress reactivity and faster recovery could prove beneficial for soldiers in combat and may ultimately result in improved postdeployment physical health and emotional well-being.

29 Trait Hostility Is Associated With Endothelial Cell Apoptosis in Healthy Adults

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Background: Trait hostility is associated with increased risk of incident cardiovascular disease (CVD) events. The underlying biologic mechanisms remain poorly characterized. Endothelial cell-derived microparticles (EMPs) are phospholipid-rich, submicron particles shed from the membranes of activated or apoptotic endothelial cells (ECs). EMPs play an important role in the pathobiology of atherosclerosis formation and thus CVD development by inhibiting nitric oxide bioavailability, promoting inflammation via leukocyte activation and transendothelial migration, and activating the coagulation cascade. The relation between trait hostility and EMPs in healthy adults without CVD is unknown.

Methods: Twenty-seven apparently healthy participants (age 37 ± 12 years, 63% female) without any clinical evidence of CVD, hypertension, diabetes, hypercholesterolemia, smoking, family history of premature CVD, rheumatologic disorders, active or recent infection, or any chronic medication use (including over-the-counter drugs or herbal medications) were recruited. Circulating EMPs in blood were assessed by flow cytometry. EMPs were defined as the number of particles with a diameter less than 1.5 μm that were negatively labeled by fluorescein isothiocyanate-conjugated monoclonal antibody to CD42b (specific to platelets) and positively labeled by phycoerythrin-conjugated monoclonal antibody to CD31 (EC apoptosis marker), CD51 (EC apoptosis and activation marker) or CD62E (EC activation marker). Hostility was assessed using the 50-item Cook-Medley Hostility scale, from which the Barefoot Hostility (Ho) 27-item score was calculated.

Results: There was a significant relationship between hostility and levels of EMPs expressing CD31 (beta = .409, P = .034) and CD51 (beta = .399, P = .039), but not CD62E (P = .170). The relationships were similar after adjusting for age, sex, and body mass index (for CD31, beta = .681, P = .007; for CD51, beta = .524, P = .036; for CD62E, P = .240).

Conclusion: These findings demonstrate that higher trait hostility scores are associated with greater circulating levels of EMPs, mostly phenotypic for EC apoptosis. Given the important role of EMPs in the pathobiology of atherosclerosis, these findings suggest that trait hostility may contribute to incident CVD events through EC injury and death.

30 Vascular Depression Impairs Health-Related Behavior

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This study investigated the relationship between subclinical depression and health behaviors in 100 African Americans (72% of whom were women) with a mean age of 72 years and education of 12 years. Depressive symptoms were significantly related to life stress, vascular burden, sleep quality, exercise, and dietary behavior patterns. Both life events and vascular burden predicted subclinical depression. Age and life events predicted exercise. Life events and education predicted diet. The effect of life events on diet, exercise, and sleep was partially mediated by depressive symptoms. The effect of vascular burden on diet, exercise, and sleep was partially mediated by depressive symptoms. Health promotion efforts may do well to incorporate stress management, depression assessment and intervention, and chronic disease management into their programs.

31 Detection of Acute Mild Hypovolemia by Nonlinear Heart Rate Variability

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The pattern of heart rate variability (HRV) has been shown to correlate well with measures of autonomic activity. In turn, changes in HRV pattern have been proposed as markers of altered physiologic states, including disease, and a variety of linear and nonlinear measures of HRV have been evaluated for this purpose. In both animals and humans, changes in minimum point correlation dimension (PD2i), a nonlinear measure of the degrees of freedom of the HRV, correlates well with the effects of severe blood loss during trauma. However, the response of PD2i to mild blood loss has not yet been evaluated. As in more severe blood loss, during even mild blood loss, such as occurs during blood donation, several neurohormonal mechanisms are called into play as the central nervous system attempts to compensate and restore homeostasis. This should acutely cause a noticeable change in PD2i, which is known to decrease in the face of sympathetic stimulation.

Subjects were volunteers who presented for a standard single unit whole blood donation. A 15-minute electrocardiogram recording was made predonation and the recording was then continued during the donation period and a rest afterwards.

Eighteen subjects (mean age, 48 ± 18 years) participated. Three were taking beta-blockers and two were taking antidepressants; one had diabetes. At baseline the minimum PD2i had a mean of 2.6 ± 0.8 dimensions, whereas after donation it fell to 1.8 ± 0.5 dimensions (P = .0011).

The minimum PD2i is a sensitive metric for the detection of mild blood loss, as seen in the controlled environment of donation of a whole unit of blood. Thus, PD2i may serve as a marker for mild hemorrhage in hospital (eg, surgery) and trauma environments. In addition, given PD2i's association with autonomic activity, these results suggest significant sympathetic activation with even standard blood donation, suggesting that PD2i can be used to track a patient's autonomic response to insult.

32 Metabolic Pathway Perturbation of Patients With Chronic Heart Failure and Comorbid Major Depressive Disorder

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Background: Metabolomics* is the systematic and theoretically comprehensive study of the small molecules that comprise a biological sample, eg, sera or plasma and enables detection and quantification of small molecules involved in metabolic and signaling pathways. Metabolic signatures for a disease may provide valuable biomarkers and insights about mechanisms of the disease and indication of future therapeutic search. Previous study using metabolomics indicated that depression and ischemic heart disease may be associated with alterations in the metabolism of lipids and neurotransmitters. In this study, we evaluate whether metabolomics differentiate depressed heart failure (HF) patients from their nondepressed counterparts.

Methods: We performed a metabolomic analysis of blood plasma from 80 patients who have chronic heart failure with a New York Heart Association class II or greater and left ventricular ejection fraction 45% or less. Of these, 40 had a diagnosis of major depressive disorder (MDD) and the other 40 had never experienced depression. Approximately 400 metabolites were analyzed, with comparisons made between the two groups. Two parameters were evaluated when considering statistical significance, namely the P value and the q-value.

Results: Several systems of metabolites were identified to be significantly altered in currently depressed HF patients compared with HF patients who had no depression, including elevation of several excitatory amino acids that are activators of glutamatergic receptors, reduction of 3-hydroxybutyrate level, increase in dicarboxylic acid (DCA) formation with fatty acids metabolism, reduction of inositol metabolism, elevation of phenylalanine, and elevation of muscle protein catabolism.

Conclusion: These observations suggest that among patients with significant HF, metabolomics is able to differentiate metabolic profiles for the depressed from the nondepressed, which may enhance understanding of underlying pathology of depressed population. Whether treatment of depression may modify those alterations needs to be examined.

* Metabolomics: A global biochemical approach to the study of neuropsychiatric diseases. Metabolomics, the omics science of biochemistry, is a global approach to understanding regulation of metabolic pathways and metabolic networks of a biological system. Metabolomics complements data derived from genomics, transcriptomics, and proteomics to assist in providing a systems approach to the study of human health and disease. The metabolome defines a metabolic state as regulated by a net of interactions between genes and environment and provides useful information to bridge the gap between genotype and phenotype. Metabolomics became part of the NIH Roadmap vision in 2003 and is a rapidly expanding field.

33 Headache: An Unusual Presenting Symptom of Guillain-Barré Syndrome

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Guillain-Barré syndrome (GBS) is a immune-mediated heterogeneous condition generally characterized by motor, sensory, and autonomic dysfunction. In its classic form, GBS is an acute inflammatory demyelinating polyneuropathy characterized by progressive symmetric ascending muscle weakness, paralysis, and hyporeflexia with or without sensory or autonomic symptoms; however, it has several variant forms that include pure cranial nerves involvement, pure motor involvement, or back pain as presenting symptoms. We present an unusual case of Guillain-Barré syndrome in which headache is a presenting symptom.

A 35-year-old Hispanic woman with past medical history of gestational diabetes presented with bilateral throbbing

tempero-occipital headache. She was alert and fully oriented. General examinable was unremarkable. Neurologic examination on presentation showed unilateral left-sided facial weakness and global depressed reflex with preserved motor strength. Her motor weakness gradually progressed to 3/5 and she had bilateral facial palsy by day 2. She denied any sensory abnormalities and difficulty breathing throughout her hospital stay. Laboratory findings were unremarkable and computed tomography and magnetic resonance imaging of the brain along with magnetic resonance venography were normal. Cerebrospinal fluid examination showed cytoalbumin dissociation. Electromyography and a nerve conduction study showed slowed conduction consistent with diagnosis of GBS. She was started on intravenous immunoglobulin and showed slight improvement after a 5-day course. She was discharged in stable condition. When she followed up after a month, her symptoms had improved, but she had residual facial palsy.

GBS is a group of autoimmune syndromes consisting of demyelinating and acute axonal degeneration forms of the disease. In some patients with GBS, low back and leg pain can dominate the presentation, suggesting nerve root irritation and paresthesia of the legs and feet. Headache as presenting symptom of GBS has never been reported in the English language literature. Irritated, inflamed, or damaged cranial nerves, spinal roots, or peripheral nerves can cause aching and throbbing pain. Our patient's only initial complaint was headache without any physical signs, and she thus was discharged on pain medication from other institutions. Unexplained headache with second presentation in less than a week in our emergency department led to a concern for subarachnoid hemorrhage and meningitis. A lumbar puncture revealed the unexpected finding of albuminocytologic dissociation, and further investigation led to a final diagnosis of GBS variant. In any patient with acute unexplained headache, the differential diagnosis needs to include GBS.

34 Effect of Stress Reduction Using the BREATHE Technique on Inflammatory Markers and Risk Factors for Atherosclerosis

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Purpose: We propose that patients with the metabolic syndrome will have lower serum C-reactive protein (CRP), blood glucose, and triglyceride levels following a 6-week course using a stress reduction exercise known as the B-R-E-A-T-H-E technique.

Background: Emotional stress and the metabolic syndrome are both associated with increased cardiovascular risk.[1,2] Data show that emotional stress leads to increased blood concentrations of adrenaline and cortisol that alter blood glucose and lipid metabolism. Additionally, stress leads to a proinflammatory state and increased levels of tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6. Inflammation is thought to be an integral part of atherosclerosis and has been associated with higher cardiovascular risk.[3]

Previous studies have shown that stress reduction lowers cardiovascular risk factors and cardiac events; however, the mechanisms for these findings have not been clearly defined. Possible explanations include behavioral changes such as better compliance with diet and exercise, or beneficial physiologic effects such as improved lipid and blood glucose metabolism, and antiinflammatory properties.

Stress activates the sympathoadrenal system and the hypothalamic-pituitary-adrenocortical (HPA) axis. Defense reactions involve catecholamine release, vagal withdrawal, cortisol secretion, and activation of the renin-angiotensin system. These mediators subserve functions that help the individual during short-term stress. When stress is frequent, adaptation (coping) is lacking, the ability to shut off the stress response is deficient, or the responses to stress are inadequate and compensatory mechanisms are activated, the allostatic load may become overwhelming and the adaptive processes become maladaptive. Stress is involved in the pathophysiology of cardiovascular disease, as nicely demonstrated in animal experiments, though human research in this area is complicated.

Stress is a nebulous concept that is subjective and difficult to measure. Thus, it is difficult to extrapolate from the laboratory environment to everyday life, to quantitate and categorize stress over time in the individual, and to pinpoint the role of stress in multifactorial cardiovascular diseases. However, epidemiologic studies have shown associations between psychosocial factors and cardiovascular disease.[4,5]

The "metabolic syndrome" (also referred to as "syndrome X" or the "insulin resistance syndrome") has emerged as an important cluster of risk factors for atherosclerotic disease, the exact definition of which is not fully agreed on.

Common features are central (abdominal) obesity, insulin resistance/hyperinsulinemia, hypertension, and dyslipidemia (high triglycerides, low high-density lipoprotein cholesterol, and small atherogenic low-density lipoprotein particles). There are indications that neurohormonal activity may be causally involved in all of these conditions. Finally, obesity, insulin resistance, and diabetes are associated with a proinflammatory state, which is associated with increased cardiovascular risk.[2,6]

Methods: Fifty patients with the metabolic syndrome, defined by the American Diabetes Association[2] criteria (fasting blood sugar > 100 mg/dL, serum triglycerides > 150 mg/dL, body mass index > 19, systolic blood pressure > 130 mm Hg, and diastolic blood pressure > 80 mm Hg) will be randomly assigned to test or control groups. The test group will include 25 patients trained to use the BREATHE technique by a physician and a registered nurse, both versed in behavioral cardiology; the control group will consist of 25 patients receiving standard medical care for the metabolic syndrome.

Instructional and therapeutic DVDs and audio CDs describing the BREATHE technique will be used twice weekly for 15 minutes per session over 6 weeks. The BREATHE technique is a novel relaxation exercise designed to elicit the relaxation response, the opposite of the stress response. BREATHE uses two proven forms of relaxation therapy, breath work and guided imagery and is an acronym where each letter represents a different step in the exercise: B-begin, R-relax, E-envision, A-apply, T-treat, H-heal, and E-end. http://www.johnmkennedymd.com/breathe-technique.htm

Anticipated Results: We expect those in the study group to have lower fasting serum triglycerides, blood sugar, and CRP levels compared with those in the control group.

We propose that the BREATHE technique will allow patients to elicit the *relaxation response*, which is the opposite of the stress response. By decreasing sympathetic tone and lowering cortisol and adrenaline/noradrenaline levels, the relaxation response will ultimately lower triglycerides, fasting blood sugar, and CRP.

BREATHE also has antianxiety effects that may help those in the study group exercise more frequently and improve compliance with diet and medications, further improving blood glucose, triglyceride, and CRP levels.

Conclusion: Previous studies suggest that stress reduction techniques decrease cardiovascular risk.[7–10] Yoga, tai chi, biofeedback, and transcendental meditation have all been shown to lower blood pressure and heart rate primarily by attenuating sympathetic tone. In addition, studies have shown that eliciting the relaxation response increases vagal tone which may have an anti-inflammatory effect yielding lower serum levels of CRP.[11]

BREATHE is a simple, easy-to-learn, self-directed relaxation tool that can be practiced anywhere and anytime, does not require a gym membership or yoga mat, and may be a helpful clinical tool for those at increased cardiovascular risk.

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35 The Lite HEARTEN Study: How Exercise and Relaxation Techniques Affect Subclinical Markers of Heart Disease in Women: Patterns of Change and Effect Sizes to Power Future Studies of Treatment Efficacy

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Background: Stress has been linked in epidemiologic studies to the development and progression of coronary artery disease (CAD). However the mechanism is elusive and methods to reduce the impact of stress on cardiovascular health are not well defined.

Purpose: This feasibility study was designed to assess the feasibility and potential efficacy of strategies to reduce the impact of life stress and improve cardiovascular health and function of women with heart disease.

Methods: An experimental three-group pretest/posttest randomized control group design was used to study the effects of aerobic walking exercise versus mindfulness-based stress reduction (MBSR) with support group versus control on measures of subclinical markers of heart disease. Female patients from one cardiovascular clinic, aged 18 years or older, who were stressed (per Holmes and Rahe Life Change, or Perceived Stress Scales [PSS]), with diagnosed CAD (history of stenosis ≥ 50% of one or more coronary arteries) were eligible to participate. Subjects (N = 25) were randomized to MBSR (n = 11), exercise (n = 9), or control (n = 5) groups for 12 weeks. An exercise stress test assessed exercise and aerobic capacity (peak MET). Measures at baseline and 12 weeks included vascular flow mediated dilation (FMD peak % dilation) as primary outcome; and reactive hyperemia peripheral arterial tone index (RHI) as a secondary outcome. Other secondary outcomes included blood biomarkers (pro-B-type natriuretic peptide, cortisol, and high-sensitivity C-reactive protein [hs-CRP]), psychosocial (depression [Center for Epidemiological Studies Depression Scale, or CES-D], perceived stress [PSS-14], mental function [12-Item Short-Form Health Survey Mental Component Score, or SF-12 MCS], life stress [Holmes and Rahe Life Change], control [Control Attitudes Scale-Revised, or CAS-R], anxiety [Brief Symptom Inventory, or BSI], social support [Enhancing Recovery in Coronary Heart Disease intervention, or ENRICHD]; health perceptions (SF-12), physical functioning (SF-12 Physical Component Scale, [PCS]), and 6-Minute Walk Test (6MWT). Patterns of change of variables within and between groups were examined and effect sizes generated to calculate sample size estimates for future investigations to determine treatment efficacy.

Results: Of 25 enrolled, 18 completed the study. Women completing were white, aged 36 to 81 years (mean, 64.8), all with some college education or degree. Eight were retired and 10 were employed full- or part-time; a majority were currently or previously married; a majority had family histories of CAD, and histories of hypercholesterolemia, hypertension, and previous myocardial infarction or stent; none were diabetic. The protocol was judged feasible, safe (no adverse events), and acceptable to participants despite variable adherence and some attrition. Analysis of patterns of change, from pre- to posttreatment for all variables for all subjects, then for selected variables by group, notably revealed trends for improvement in psychosocial variables (CES-D, PSS, CAS-R, BSI) in all groups. There were patterns for improvement in exercise capacity (peak metabolic equivalent [MET]), inflammation (hs-CRP), and social support (ENRICHD) in the MBSR group. There were trends for improvement in the FMD peak % dilation, Mental Component Score, and walking distance for women in the exercise group. The control also had patterns for improvement in several study variables. Effect sizes, calculated for selected variables to power future investigation for moderate effects of interventions (80% power to detect differences between groups), were examined for sample sizes (N = 20–90 women pre/post). Projecting these sample sizes, there would be sufficient power to detect improvements for MBSR in hs-CRP, peak MET, PSS, ENRICHD, and MCS for exercise; and, with n = 50 in each of the three groups, sufficient power to detect differences between groups for MCS,

peak MET and RHI. A sample size of N = 157 per group would be required to detect improvement in FMD peak % dilation.

Conclusions and Recommendations: The study protocol was feasible as designed and implemented, and patterns of improvement were observed in stress and psychosocial variables, and in cardiovascular health and function. Future study with a larger sample size will extend the period of intervention and focus on adherence enhancement to explore effects of exercise and MBSR on biobehavioral outcomes of women with heart disease.

This study was funded by the Women's Heart Health Program of the Minneapolis Heart Institute at Abbott Northwestern Hospital and the Minneapolis Heart Institute Foundation, Minneapolis, MN.

36 Cardiovascular Effects of Spinal Cord Stimulation in Hypertensive Patients

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Background: A number of animal studies have shown that thoracic spinal cord stimulation (SCS) may decrease mean arterial pressure (MAP). A recent study demonstrated a trend towards reduction in MAP at the T5-T6 spinal level in sedated normotensive subjects. Another study sponsored by Medtronic (Minneapolis, Minnesota) demonstrated that chronic SCS at subthreshold stimulation level (85% of the voltage that causes paresthesia) significantly improved angina attacks and 6-minute hall walk distance in drug-refractory angina patients. This study was an acute, single-center, randomized feasibility study and was designed to determine if SCS at two different stimulation strengths would decrease MAP and heart rate (HR) during baseline conditions and during activation of the sympathetic nervous system by the cold pressor test (CPT).

Methods: Six hypertensive patients and 11 normotensive patients were evaluated in this study. All subjects were clinically indicated for SCS therapy to manage their neuropathic pain. Arterial BP was continuously measured at the finger using beat-to-beat photoplethysmographic recordings (Finometer; Finapres Medical Systems, Amsterdam, The Netherlands) at rest and during CPT. SCS at threshold (100%: SCS-100) and subthreshold (80%: SCS-80) intensities were randomly performed in the T5-T6 region of the spinal cord during normal conditions as well as during CPT. Each subject underwent three CPTs with the placebo (control) CPT always performed first. The approximate recovery time between the serial CPTs was 10 to 12 minutes. CPT was performed by immersion of the right hand of each subject into slurry of ice water for 90 seconds. Thirty seconds of beat-to-beat data prior to starting each CPT (baseline) was analyzed. During the 90-second CPT, the median values of the last 30 seconds of data were used for analysis. Heart rate variability (HRV) during baseline and SCS (3–5 minutes of inter-beat-interval data derived by the Finometer) was computed using the Kubios HRV Analysis software (University of Kuopio, Finland). The HRV analysis included measurements in both the time and frequency domain. Repeated measures ANOVA and the Wilcoxon's signed rank test were used to compare groups.

Results: SCS did not significantly alter MAP or HR at baseline nor did it appear to blunt changes in MAP or HR in response to CPT. In the normotensive group, the MAP was significantly elevated by 19.3 mm Hg ($P < .001$) during the placebo phase, and by 16.1 and 15.3 mm Hg during the SCS-80 and SCS-100 phases ,respectively. However, in hypertensive subjects, an enhanced response to the CPT was observed. In the hypertensive group, the MAP was significantly elevated by 26.9 mm Hg ($P < .001$) during the placebo phase, and by 20.8 and 23.4 mm Hg during the SCS-80 and SCS-100 phases respectively. The HR in both the groups did not show any significant changes during the three CPTs. Compared with normotensive subjects, HRV tended to decrease in both the time and frequency domain in hypertensive subjects, although this decrease was not statistically significant.

Conclusion: Acute SCS at the T5-T6 region did not significantly alter MAP or HR compared with baseline (no SCS) in subjects without sedation, supporting our previous findings in sedated subjects. In contrast to acute SCS, chronic SCS may have a different effect on BP and HRV and should be explored in the future.

37 Screening for Depression and Anxiety in Patients Admitted for Coronary Artery Bypass Graft: Comparison of Nurses' Reports vs Hospital Anxiety and Depression Scale

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Aims: To evaluate the validity of nurses' reports as a screening tool for anxiety and depression in hospitalized patients admitted for coronary artery bypass graft.

Methods: This study was performed on a cohort admitted to cardiac surgery wards of Tehran Heart Center. Within 72 hours of admission, the patients were assessed using the Hospital Anxiety and Depression Scale (HADS). Simultaneously, the nurses who provided care for the patients were asked whether they believed the patients had significant levels of depression or anxiety. They were also asked to rate the degree of depression and anxiety of their patients in a 5-point Likert scale. Assessments were completed for 150 patients. The chi-square test, correlation coefficients, and ROC-curve were implemented for statistical analysis.

Results: According to HADS score, 67 (44.66%) patients had probable depressive disorders (HADS-D score > 7) and 57 (38%) had probable anxiety disorders (HADS-A score > 7). Nurses recognized 31 (20.66%) patients who had depressive disorders and 24 (16%) who had anxiety disorders. The correlation coefficient between nursing diagnosis and diagnosis according to HADS was small (phi = 0.24, $P < .01$). No significant correlation was observed between HADS scores and the nurses' assessment of severity of depression and anxiety. Comparing with HADS, the sensitivity, specificity, and positive predictive value for nursing reports was 0.25, 0.55, and 0.41 for depression and 0.66, 0.57, and 0.72 for anxiety respectively.

Conclusion: This study indicates nurses' reports may have not enough validity and sensitivity to be used as the only way to screen for anxiety and depression in patients admitted for cardiac surgery. A consultation-liaison psychiatry service that includes an active case-finding strategy using standard instruments and educational programs for nurses may be helpful.

38 Hormonal Heart-Mind Connections: Clinical and Research Implications

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Oxytocin (OX) is an 8-amino acid peptide that is secreted in greatest concentration from the pituitary. It is best known for its roles in parturition and milk letdown reflex in nursing mothers, but males have OX in as great quantities in the brain and pituitary as females and have equal receptors. Recent discoveries have established OX as an essential hormone to facilitate prosocial behaviors such as trust, empathy, compassion, and generosity. It was shown to be deficient in children who spent their early years in orphanages with little human contact and has been shown to promote social engagement in autistic children. It is released by nurturing behavior such as massage, singing, and dog-owner bonding as well as exercise, sex, and fatty and sweet foods. This study looks at the OX system and demonstrates CNS-cardiac connections and their implications.

There is an extensive OX receptor network in multiple organs in the body, including the brain, hypothalamus, pituitary, uterus, breast, and kidney, with the heart demonstrating a concentration of both receptors and an OX synthetic system second only in size to the hypothalamus. The role of OX in the heart has yet to be established. OX is secreted in a pulsatile manner and has a plasma $t_{1/2}$ of 10 to 15 minutes.

OX causes release of atrial natriuretic peptide (ANP), which has been shown to account for most cardiovascular effects of OX. ANP has been shown to suppress adrenocorticotropic hormone secretion and turn off the sympathetic stress response. Additionally, it has been shown to have significant antiinflammatory effects, promote myocardial revascularization and vascular endothelialization, lower heart rate, prevent endothelial disruption, antagonize the effects of aldosterone and renin on the myocardium and cardiac vasculature, decrease myocardial and endothelial fibrosis, limit cellular damage and post-myocardial infarction death, and decrease reperfusion injury.

The biobehavioral psychophysiologic implications of these connections for disease prevention, and postincident survival in patients who are post-MI, poststent and post-CABG are vast. Some questions: Does heart rate variability training increase OX and ANP? Does change in these hormones predict survival? Does caregiver compassionate behavior influence ANP and OX secretion and survival? What relationship do OX and ANP have with telomerase and telomere length, which are known stress markers and survival predictors? Can peptide analogues be used therapeutically? Can prosocial behavior training of patients and significant others change OX and ANP levels and influence survival? Are one-time measurements or salivary and urine measurements reliable for assessment?

39 Gender Differences in Longevity and Sympathovagal Balance

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Background: Female longevity is not yet understood. Aging is associated with progressive decline in autonomic (parasympathetic and sympathetic, or P&S) function. The decline in the absolute levels of P&S function seems similar for both female and males. Holter monitoring studies suggest that the relative levels of P&S activity differ between the genders. Geriatric females demonstrate more parasympathetic activity relative to sympathetic activity than do age-matched males. This study considers the sympathovagal balance (SB) for female and male by age group to further investigate the dichotomy found in the Holter data.

Methods: Autonomic assessment of more than 5,000 patients, age 65 years or older was performed (ANX 3.0, ANSAR Medical Technologies, Inc., Philadelphia, Pennsylvania). P&S monitoring analyzes the two independent, simultaneous respiratory and

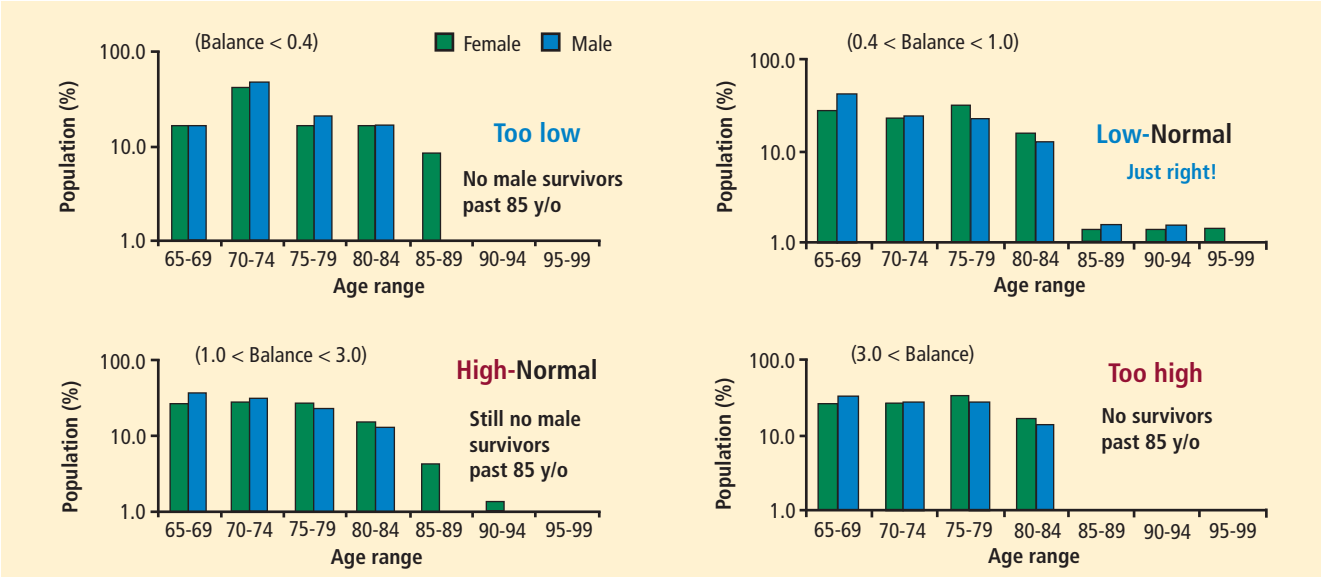

FIGURE. Gender differences.

HR variability activity signals to measure P&S activity. After omitting patient records with high-quality arrhythmia, 4,911 patients remained (3,007 females, average age = 73.6 ± 5.9 years). These patients were not screened for comorbidities or numbers of comorbidities. SB is defined as resting sympathetic activity over resting parasympathetic activity (S/P). "Perfect" SB is 1.0. The normal range of SB is 0.4 < SB < 3.0. Therefore, there are at least four logical ranges for SB: (1) *high*, SB > 3.0, indicating sympathetic excess (SE); (2) *low*, SB < 0.4, indicating parasympathetic excess (PE); (3) *high-normal*, 1.0 < SB < 3.0, indicating more sympathetic activity, and (4) *low-normal*, 0.4 < SB < 1.0, indicating more parasympathetic activity.

Results: No one survived beyond 85 years of age with *high* SB (> 3.0). No males survived beyond 85 years with *high-normal* SB (> 1.0) or *low* SB (< 0.4). Only males with *low-normal* SB (0.4 < SB < 1.0) survived beyond 85 years, with some surviving into their mid-90s. Females with *low* SB survived longer than those with *high* SB, some living into their late 80s. Females with *high-normal* SB survived even longer, some living into their early 90s. Females (similar to males) with *low-normal* SB survived the longest, into their late 90s **(Figure)**.

Conclusion: Holter data indicate that geriatric females demonstrate more parasympathetic activity relative to sympathetic activity than do age-matched males. However, Holter data cannot differentiate normal levels of parasympathetic activity from PE. Low-normal SB appears to correlate ($P < .001$) with greater longevity, and as shown elsewhere, reduced morbidity and mortality leading to reduced medication load and hospitalization. Gender differences in longevity are associated with autonomic function.

40 Neuroendocrine, Inflammatory, and Immune Biomarkers Associated With Body Composition, Depression, and Cognitive Impairment in Elderly Men and Women

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Introduction: By 2030, it is estimated that 20% of the US population will be over 65 years of age and that 75% of adults will have one or more severe disabilities by age 80. Cardiovascular disease, depression, and dementia are significant concerns in our aging global population. Determining preventive models for age-related diseases, frailty, and functional decline is critical. Dysregulation of inflammatory pathways and steroid hormonal axes have been identified in age-related diseases including mood disorders, dementia, and cardiovascular disease.

Methodology: In this correlational study, 156 men and women 60 years of age and older who met strict inclusion/exclusion criteria underwent evaluation with the Patient Health Questionnaire (PHQ)-2, PHQ-9, Geriatric Depression Scale (GDS), Folstein Mini-Mental Status Exam (MMSE), and Clock Drawing Test (CDT). Subjects underwent waist circumference measurement, along with whole blood sampling for C-reactive protein (CRP), insulin-like growth factor (IGF)-1, progesterone, estradiol, and testosterone levels. Saliva samples were collected for analyses of cortisol circadian rhythm, estradiol, progesterone, testosterone, and dehydroepiandrosterone sulfate (DHEA-S). Mean age of participants was 73.99 (SD, 9.63) years with 62.9% female 37.1% male. Educational level completion was high school or higher, and ethnicity was 93.7% Caucasian.

Results: For elderly males the study found significant relationships between age and cognition as measured by the MMSE ($r = -.28$, $P < .05$) and CDT ($r = .27$, $P < .05$) and between increased nocturnal cortisol levels and impaired cognition as measured by the CDT. Male data revealed a significant relationship between low levels of DHEA-S and between higher estradiol levels correlated with depressive disorder ($r = .36$, $P < .05$) as measured by the GDS-30. No significant relationships were found between cognition (as measured by the MMSE and CDT) and depressive mood (as measured by the GDS-30) with C-reactive protein, insulin-like growth factor-1, testosterone, progesterone, and waist circumference in male subjects. In female subjects, age was significantly associated with depressed mood as measured by the GDS-30 ($r = .30$, $P < .01$). Cognition in females as measured by the CDT was significantly associated with increasing age ($r = .42$, $P < .01$), awakening cortisol ($r = .45$, $P < .05$), nocturnal cortisol, cortisol amplitude, DHEA-S, estradiol ($r = .35$, $P < .01$), and CRP levels. MMSE scores in females were significantly associated with increasing age ($r = -.50$, $P < .01$), awakening cortisol ($r = -.57$, $P < .05$), nocturnal cortisol ($r = -.63$, $P < .01$), and cortisol amplitude. Waist circumference, IGF-1, progesterone, and testosterone in female subjects did not significantly impact cognition or mood in female subjects. Demographic factors revealed significant associations of improved mood and cognition in married subjects, subjects residing in an independent living facility, and nutritional supplement use in female subjects.

Conclusion: These data suggest that preventive counseling models in younger adults may be expanded to assess nontraditional clinical markers of neuroendocrine and immune function that are associated with inflammatory pathways in efforts to prevent later age-related cardiovascular disease, depression, and cognitive decline.

41 Short-Term Heart Rate Complexity Determined by the PD2i Algorithm Is Reduced in Patients With Type 1 Diabetes Mellitus

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Background: Diabetic autonomic dysfunction is one of the least understood complications of diabetes mellitus (DM). Using the *P* value as a measure of discriminability between the means of DM patients and young age-matched controls, various traditional and complexity algorithmic assessments of heart rate variability (HRV) were considered, and it was found that multiscale entropy (MSE) at scale 3 had the smallest-order *P* value.[1] A new measure of HRV complexity, the point correlation dimension (PD2i), has similarly been found superior in comparison with various traditional and complexity algorithmic assessments of HRV.[2]

Objective: The objective is to test the ability of PD2i to discriminate between young DM patients without neuropathy and age- and gender-matched controls.

Methods: Seventeen DM patients with known autonomic dysfunction and 17 age- and gender-matched controls were studied. The

		Disease		
		Positive	Negative	
Test	Positive	True positive (TP) 16	False positive (FP) 5	TP + FP 21
	Negative	False negative (FN) 1	True negative (TN) 12	FN + TN 13
		TP + FN 17	FP + TN 17	

FIGURE. Sensitivity = TP/(TP + FN) = 94%, specificity = TN/(TN + FP) = 71%, negative predictive value = TN/(TN +FN) = 92%, positive predictive value = TP/(TP + FP) = 76%, relative risk = TP/FN × (TP + FN)/(TN + FP) = 16

same R-R interval data (3,200 heartbeats per subject) in the Javorka study[1] were analyzed (blinded) to determine the PD2i values.

Results: PD2i was able to detect autonomic nervous system (ANS) dysfunction **(Figure)** with P = .0006, similar to the best discriminating MSE scale, with P= .0002.

Conclusion: The performance of PD2i to discriminate asymptomatic DM patients and controls is similar to the best discriminative power of previously published complexity measures. PD2i is able to discriminate among asymptomatic DM patients and controls for the presence of ANS dysfunction and may prove to be useful clinical tool.

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42 Heart Rate Variability Biofeedback and Mindfulness: A Functional Neuroimaging Study

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Mindfulness has become an integral component in many treatments for a wide variety of psychologic and stress-related disorders. Unfortunately, most treatments involve multiple interventions and procedures ranging from individual therapy, group therapy, exercise, meditation, yoga, and health and wellness strategies. In an effort to isolate the components that increase levels of mindfulness in these treatments, we utilized heart rate variability (HRV) biofeedback training to increase an individual's awareness of heart rate and decreased respirations. HRV biofeedback isolates the slow breathing and relaxation components utilized in the aforementioned traditions and interventions. Altering the autonomic nervous system through slow respirations, we contend that HRV biofeedback could increase subjective levels of mindfulness and decrease physiologic stress after the presentation of stimulus from the International Affective Picture Set.

In addition to measuring HRV and subjective measures of mindfulness, we utilized functional magnetic resonance imaging (fMRI) to establish neural correlates of HRV training. Previous functional imaging research across disciplines typically indicates increased levels of activation in the anterior cingulate cortex (ACC) and decreased activation in the limbic system when in a mindful or relaxed state. In this pilot study, we utilized fMRI pre- and post-HRV biofeedback training to identify differential activations pre- and posttraining, inquiring whether these activations parallel previous meditation, mindfulness, and biofeedback imaging studies.

In our two subjects, we found increased activation in the amygdala and the anterior cingulate cortex following HRV biofeedback training. The participants increased levels of mindfulness following training, but these results were not statistically significant. The participants reported increased levels of emotional arousal in reaction to disturbing images following the training.

43 Heart, Brain, and the Octopus Connection

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Introduction: Intense vasospasm of the coronary arteries following a stressful event may cause myocardial stunning and lead to chest pain similar to that occurring after an acute coronary syndrome.

Case Report: Mr. F is a 62-year-old white man with past medical history of deep venous thrombosis and pulmonary embolism that occurred 7 years ago. He presented with a chief complaint of chest pain that started after he had an episode of dizziness while working outside cleaning a pool. The initial physical examination revealed nothing of significant note except a systolic murmur. The patient had no clinical signs of heart failure. Initial electrocardiogram showed ST-segment elevation in lateral leads with no reciprocal changes. Coronary angiography did not reveal any significant flow-limiting obstruction, but it showed a large area of lateral wall dyskinesis, significant left ventricular dysfunction with an ejection fraction of 30%, and significant mitral regurgitation. The first set of troponin, creatine phosphokinase, and creatine kinase MB fraction indices were elevated at 44.5, 932, and 47.3, respectively. The D-dimer was within normal limits. The patient was started on low-dose angiotensin converting enzyme inhibitor, beta-blocker, aspirin, and an HMG-CoA reductase inhibitor. He was symptom free on the second day of hospitalization and remained asymptomatic throughout his hospital stay. A repeat two-dimensional (2D) echocardiogram showed improvement of the patient's ejection fraction (45% to 50%) and resolution of his mitral regurgitation.

Conclusions: Takotsubo syndrome (also called broken-heart syndrome or stress cardiomyopathy) was first described in Japan. Classically, it is a transient cardiomyopathy that occurs after a stressful event, usually observed in women, and is described as apical ballooning of the heart with basal hyperkinesis. We report the first case of Takotsubo variant involving the lateral wall associated with electrocardiographic changes in a 62-year-old man. This transient cardiomyopathy usually improves with time. Our patient's cardiomyopathy improved, along with improvement of his mitral regurgitation as shown on 2D echocardiography. Mitral regurgitation in this case was likely due to dysfunction of papillary muscle associated with this condition.

Reason Case Chosen: Takotsubo syndrome is an important consideration in the presentation of acute coronary syndrome. It usually presents after an acute stressful event. However, in recent times, it has been described after even minor stresses such as steroid injection in asthma exacerbation, a court appearance, surprise parties, and, as in this patient, an episode of dizziness. It is important to recognize this syndrome, its presentation after even minor stressors, and its prognosis, which is usually very good.

44 Relationship Between Depressive Symptoms and Cardiovascular Risk Factors in Black Individuals

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Background: Cardiovascular disease (CVD) is the leading cause of mortality in the United States. Blacks have a disproportionate burden of death and disability from CVD. Studies have shown that socioeconomic status underlies a substantial portion, but not all, of the higher rate of CVD in blacks. Other factors may explain this disproportionate burden of CVD. Depression is a significant predictor of cardiovascular mortality and there is evidence that depression prevalence and severity may differ in blacks compared with other racial groups. The present investigation examined the prevalence of depression in a group of black individuals and the relationship between depression status and traditional CVD risk factors.

Methods: Participants were recruited by advertisements (N = 253; age 43.7 ± 11.6 years). All of the participants included are Black. The measure of depression used was the Center for Epidemiological Studies Depression Scale (CES-D).

Results: When the traditional CES-D cutoff of 16 or greater was used as an indicator of depression, 38% of the sample reached this level (see **Table** for sample characteristics; data in the table are unadjusted for potential confounding variables). Regression analyses were performed to assess the relationship of depression with traditional cardiovascular risk factors (body-mass index [BMI], waist-to-hip ratio, blood pressure, smoking, and cholesterol) while controlling for potential confounding variables (gender, age, sleep quality, perceived stress level, marital status, educational level, and income). This analysis demonstrated that those with higher levels of depressive symptoms had larger waist-to-hip ratios (r = 0.04) and higher systolic blood pressures (r = 0.05), and were more likely to be smokers (r = 0.06).

Discussion: It is well known that higher levels of depression are associated with higher CVD risk. However, this evidence is derived primarily from samples of predominantly white men and women. The present investigation demonstrates that not only is there a high prevalence of depression in a relatively healthy black population, but that depression status is related to traditional CVD risk factors in black individuals. As has been previously demonstrated in black samples, cholesterol measurements may not be a strong indicator of cardiovascular risk due to racial differences in lipoprotein lipase activity.

TABLE
SAMPLE CHARACTERISTICS

	Total	CES-D ⩾ 16	CES-D < 16	*P* value
N	253	96	157	
Male (%)	94 (37%)	32 (34%)	62 (39%)	> .20
Age (yr)	43.7 ± 11.6	44.9 ± 11.0	42.8 ± 11.8	> .20
BMI (kg/m^2)	30.3 ± 8.5	30.7 ± 8.3	30.1 ± 8.7	> .20
Waist-to-hip ratio	0.86 ± 0.09	0.87 ± 0.09	0.85 ± 0.08	> .10
Systolic blood pressure (mm Hg)	132 ± 17	132 ± 18	132 ± 16	> .20
Diastolic blood pressure (mm Hg)	82.4 ± 12.8	82.3 ± 12.4	82.4 ± 12.9	> .20
Smoking (%)	93 (36%)	46 (48%)	47 (30%)	< .01
Total cholesterol (mg/dL)	157 ± 37	161 ± 38	155 ± 37	> .20
LDL (mg/dL)	86 ± 31	85 ± 31	86 ± 31	> .10
HDL (mg/dL)	50 ± 15	52 ± 17	49 ± 14	> .10

BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; HDL = high-density lipoprotein; LDL = low-density lipoprotein

45 History of Depression Affects Patients' Depression Scores and Inflammatory Biomarkers in Women Hospitalized for Acute Coronary Syndromes

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A history of major depression is identified as a significant predictor of the development of acute coronary syndromes (ACS); the role of increased inflammatory proteins has been suggested as a possible mechanism to explain the link between depression and ACS. The purpose of this study was to compare, in women with and without reported history of depression, their depression scores and inflammatory biomarkers at three time points (when hospitalized for ACS and 3 and 6 months post-hospitalization). A secondary purpose was to examine whether age and body mass index (BMI) differed by group.

Methodology: Forty-three consecutive economically disadvantaged women with ACS were recruited and divided into two groups based on self-reported prior history of depression. Depression (measured by Beck Depression Inventory [BDI]-II), and inflammatory biomarkers including interleukin (IL)-6 and high-sensitivity C-reactive protein (hs-CRP) were collected during hospitalization (baseline) and at 3 and 6 months. A linear mixed model was used to compare group differences across time.

Results: When hospitalized for ACS, 44% (n = 19) reported a history of depression. These women were significantly ($P < .05$) younger (55 ± 7) and heavier (BMI = 37 ± 13) than those who did not report a history of depression (n = 24) (60 ± 6, BMI = 32 ± 8). No significant interaction was observed between depression group and time. However, for BDI-II scores, we found a significant group effect ($F_{1, 43.8} = 4.74$, $P = .03$), indicating that those who reported a history of depression were more depressed regardless of time; we also found a significant time effect ($F_{2, 77.2} = 3.74$, $P = .02$), indicating an increase in BDI-II scores from baseline to 3 months followed by a decrease to baseline level at 6 months regardless of prior depression history. For IL-6, there was no significant interaction or group effect. However, there was a significant time effect ($F_{2, 72} = 10.32$, $P < .01$).

Conclusions: This is the first study to compare the depression scores and inflammatory biomarkers over time between women with and without a prior history of depression. Further research is needed to determine how to identify a subgroup of depressed patients at particularly high risk for cardiac events among patients with a history of cardiovascular disease.