

## Evaluating the Impact of Stress on Systemic Disease: The MOST Protocol in Primary Care

Jeffrey L. Boone, MD, MS  
Jeffrey P. Anthony, DO

**Mental stress has an enormous impact on physical health. This impact commonly manifests as headache, muscle tension, acne, peptic ulcer disease, or a compromised immune system. Stress is also associated with more serious adverse effects, such as cardiovascular disease and exacerbations of rheumatoid arthritis and systemic lupus erythematosus.**

As these effects are far-reaching, it is important for primary care physicians to identify and manage the symptoms of mental stress in their patients. This is increasingly possible with office-based mental stress testing, which uses cardiovascular markers to identify patients who are overresponders to mental stress, and, thus, at risk for stress-induced disorders. Mental stress in this population can be managed with nonpharmacologic and pharmacologic interventions to improve patients' responses to stress and decrease morbidity and mortality associated with this condition.

A broad definition of stress is that of an experience in which the demands of a situation exceed one's perceived ability to cope; an appraisal concludes with the belief that one is threatened, thereby initiating a stress response, including physiologic changes (eg, increases in blood pressure, heart rate, respiratory rate, output of stress hormones, changes in blood platelet activity). The stress response varies among individuals and is impacted by factors that include personality traits, psychosocial support, and affect (eg, depression, anxiety, anger).

Historically, discussion of the stress response and resultant physiologic alterations centered on acute physical threats. Today, however, a definition of mental stress and the impact it may have on systemic disease must incorporate the subtle, chronic stressors in a patient's life, such as stress that arises

from work activities and interactions, interpersonal relationships, and socioeconomic factors.

Mental stress as an underlying cause of systemic disease is of particular interest to primary care physicians because of the subtlety with which stress operates and the range of disorders it can affect. Its impact is devastating to systemic functions and dangerous in that oftentimes its immediate effects are not apparent. The philosopher Arthur Schopenhauer once quipped that a person is not conscious of his or her little toe until the shoe pinches. Likewise, one typically is not conscious of the intensity of his or her life until there are undesirable physical manifestations (headache, insomnia, fatigue, diarrhea, rash, increased blood pressure). Osteopathic physicians may be more likely than most primary care practitioners to understand this mind-body interaction.

Studies have found that between 75% and 90% of visits to primary care physicians can be attributed to the effects of stress,<sup>1</sup> yet physicians often fail to recognize mental stress as a causative factor behind many psychophysiologic symptoms, resulting in misdiagnosis and mistreatment. This article focuses on the impact of mental stress in patients as well as its diagnosis and treatment in the primary care setting.

### Stressing the System

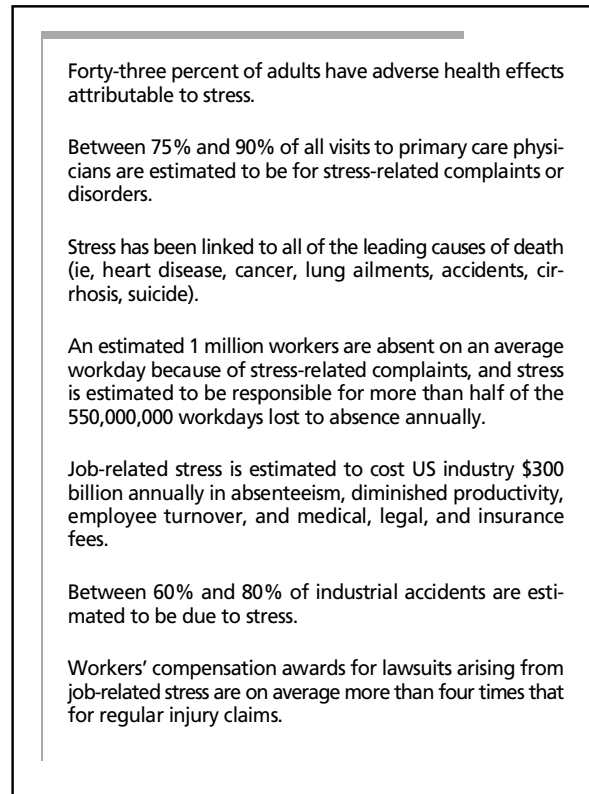
The American Institute of Stress<sup>1</sup> has compiled statistics on the prevalence and impact of mental stress in the United States (Figure 1). These data show that mental stress seriously affects many aspects of daily life and should be treated as an important health care concern. None of the body's organ systems is exempt from the pervasive effects of mental stress. Headache is the most common neurologic expression of stress seen in the clinical setting, along with dizziness, vertigo, and other balance disorders. Effects of stress on the gastrointestinal system contribute to numerous disorders (eg, peptic ulcer disease, esophagitis, irritable bowel syndrome). The musculoskeletal system manifests the effects of stress as muscular tension, cramping, and other enigmatic syndromes (eg, chronic fatigue syndrome, fibromyalgia). This interrelationship between the musculoskeletal system and all other systems of the body is emphasized in osteopathic medicine.

Dermatologic manifestations (eg, atopic dermatitis, inflammatory dermatoses, acne) may be precipitated by mental stress, and its effects may undermine the immune system,

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Dr Boone is assistant clinical professor of medicine and nursing in the Health Sciences Center at the University of Colorado, Denver. Dr Anthony is a clinical instructor in the Family Practice and Sports Medicine Department at the University of California, San Diego; assistant clinical professor in the Sports Medicine and Family Practice Department at Western University of Health Sciences, Pomona, Calif; and adjunct professor and team physician at San Diego State University, Calif.

Address correspondence to Jeffrey L. Boone, MS, MD, Preventive Cardiology, Stress Medicine, and Hypertension, Colorado Heart Imaging, 2490 W 26th Ave, Ste 260-A, Denver, CO 80211-5601.



**Figure 1.** The prevalence and impact of mental stress in the United States. (From *The American Institute of Stress*. Available at <http://www.stress.org/problem.htm>. Accessed October 1, 1999.)

rendering one more susceptible to the common cold and other viral and bacterial infections. Stress has also been linked to exacerbations of rheumatoid arthritis<sup>2,3</sup> and lupus erythematosus.<sup>4</sup> Selected effects of stress on the cardiovascular system are listed in *Figure 2*.<sup>5</sup>

**Stress and Cardiovascular Disease**

The role of traditional risk factors for cardiovascular disease (CVD) (eg, smoking, obesity, hypercholesterolemia, sedentary lifestyle) is well documented. However, not all sudden cardiac deaths and myocardial infarctions (MI) can be explained by the presence or severity of traditional cardiovascular risk factors.<sup>6</sup> Although mental stress as a factor in CVD has been assumed, recent findings validate that mental stress is an important nontraditional risk factor.

Gullette et al<sup>7</sup> determined the relative risk of myocardial ischemia triggered by negative emotions. In this trial, the occurrence of negative feelings during nonischemic (control) hours was compared to the frequency of negative feelings that occurred during ischemic (case) hours, using self-reported measures of activities and emotions.

Of 132 patients with coronary artery disease (CAD), 58 patients had ambulatory ischemia—defined as horizontal or downsloping ST-segment depression of  $\geq 1$  mm for at least 1 minute, compared with baseline—while undergoing 48 hours of ambulatory electrocardiographic (ECG) monitoring. In the hour after negative emotions, the relative risk of myocardial ischemia—adjusted for time of day and activity level—was 2.2 (95% CI, 1.1 to 4.5;  $P < .05$ ) for tension, 2.2 (95% CI, 0.7 to 6.4;  $P < .16$ ) for sadness, and 2.2 (95% CI, 1.1 to 4.3;  $P < .05$ ) for frustration.

The Determinants of Myocardial Infarction Onset Study<sup>8</sup> evaluated the role of anger in precipitating nonfatal MI in 1623 patients. This trial demonstrated a twofold increase in the baseline risk of MI during the 2 hours after episodes of self-reported anger (relative risk, 2.3; 95% CI, 1.7 to 3.2). Regular users of aspirin had a significantly lower risk of MI (relative risk, 1.4; 95% CI, 0.8 to 2.6). Similarly, the Veterans Administration Normative Aging Study,<sup>9</sup> which lasted more than 7 years, found that the relative risk of total coronary heart disease and of combined incident coronary events was increased threefold among men who reported high levels of anger.

Numerous psychological and personality dimensions may factor into risk for coronary heart disease. The patient with mental stress due to certain personality traits or emotional lability must be distinguished from the patient with a mood disorder (eg, depression, anxiety). Nemeroff et al<sup>10</sup> published an excellent review of the relationship between depression and cardiac disease, noting that depression and other mood disorders are underdiagnosed and undertreated in patients with CVD.

Depression appears to be a biological risk factor for development of CAD and for death after MI. Musselman et al<sup>11</sup> identified enhanced susceptibility to platelet activation as the mechanism by which depression may contribute to an increased risk for CVD. In a study comparing in vivo platelet activation, secretion, and dose-response aggregation in patients with depression and a control group, patients with depression had increased susceptibility to platelet activation. In addition to modifications in platelet reactivity, depressed patients may be vulnerable to CVD due to alterations in heart-rate variability.<sup>10</sup>

**Correlation of Laboratory Mental Stress-induced Ischemia With Ambulatory Ischemia and Cardiovascular Events**

As mental stress in daily life leads to increased cardiovascular events, investigators have attempted to identify patients at risk for stress-induced CVD using laboratory mental stress testing. If a patient's response to office-based mental stress testing can predict risk for cardiovascular events, perhaps the causative mechanisms could be defined and effective treatment instituted.

The Psychophysiologic Investigations of Myocardial Ischemia (PIMI) Study<sup>12</sup> investigated three such issues: (1) the

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**Figure 2.** *The cardiovascular consequences of mental stress in the United States, compiled by the American Institute of Stress. (Reprinted with permission of The McGraw-Hill Companies. Boone JL, Christensen JF. Stress and disease. In: Feldman MD, Christensen JF, eds. Behavioral Medicine in Primary Care: A Practical Guide. Stanford, Conn: Appleton & Lange; 1997:265-276.)*

relationship between mental stress-induced ischemia and ischemia during daily life and physical exertion; (2) whether patients with daily life ischemia have augmented hemodynamic and catecholamine responses to mental or physical stress, compared with those without ambulatory ischemia; and (3) whether patients with daily life ischemia could be identified using mental or physical office-based stress testing. One hundred ninety-six patients with documented CAD and a positive exercise test underwent mental stress and bicycle exercise testing. The mental stress tests included a speech test in which patients were given 1 minute to compose and then deliver a 5-minute speech while being evaluated by laboratory staff, and a Stroop Color-Word Test in which subjects had to quickly interpret and match confusing information on a computer screen. Patients were monitored using radionuclide ventriculography and ECG during these mental and physical stress tests. Patients also underwent 48 hours of ambulatory ECG monitoring.

Results indicate that patients who had mental stress ischemia in the laboratory (58%) were more likely to have daily life ischemia than patients without mental stress ischemia despite similar exercise test results. During mental stress, patients with daily life ischemia had higher ejection fraction and cardiac output and a lower systemic vascular resistance, compared with patients without ambulatory ischemia; patients

with daily life ischemia also displayed a higher ejection fraction during rest and at peak exercise.

As patients with ambulatory ischemia had higher resting hemodynamics and exaggerated hemodynamic responses to mental stress, it is believed that these patients may chronically sustain a higher level of sympathetic arousal. More than 80% of patients with ST-segment depression during the speech test (mental stress) had daily life ischemia, while nearly 50% of patients with ST-segment depression during the bicycle test had daily life ischemia. A trial by Krittayaphong et al<sup>13</sup> showed similar results: Heart rate response during laboratory-induced mental stress correlates with the magnitude of ischemia on ambulatory ECG monitoring in patients with CAD.

A recent trial by Krantz et al<sup>14</sup> further demonstrates that laboratory mental stress testing is a useful means of assessing cardiovascular prognosis in patients with CAD. Using mental arithmetic and public speaking stress tests, this trial found that 44% of patients with mental stress ischemia had new cardiac events (eg, cardiac death, nonfatal myocardial infarction, revascularization procedures) more frequently than patients without mental stress ischemia (23%;  $P = .048$ ).

In a trial of patients with implantable cardioverter-defibrillators, Lampert et al<sup>15</sup> demonstrated that ventricular arrhythmias have a faster onset and are more difficult to terminate

## Checklist

- Interventions related to mental stress perception and coping
  - Improve time management.
  - Improve sense of humor.
  - Pursue personal and vocational activities consistent with life values.
  - Explore the meaning and purpose of life.
  - Cultivate spiritual and transcendent activities:
    - Prayer
    - Communal religious observances
    - Spiritual retreat
    - Seasonal ritual celebrations
    - Increase emotional self-disclosure.
    - Pursue short-term psychotherapy.
    - Clarify values.
    - Cultivate social support network.
    - Increase assertiveness.
    - Reduce exposure to unnecessary stressors.
    - Practice meditation or biofeedback techniques.
    - Monitor sensory input.
    - Consider osteopathic manipulative treatment.
    - Help others.
- Interventions for treatment of stress-induced high blood pressure
  - Pursue daily aerobic exercise.
  - Improve physical fitness and stamina.
  - Reduce excess body weight and fat.
  - Reduce alcohol intake to >1 ounce per day.
  - Reduce dietary sodium.
  - Increase dietary potassium, calcium, and omega-3-rich fish.

**Figure 3.** *Nonpharmacologic measures to improve patients' perception of stress. (Adapted with permission of The McGraw-Hill Companies. Boone JL, Christensen JF. Stress and disease. In: Feldman MD, Christensen JF, eds. Behavioral Medicine in Primary Care: A Practical Guide. Stanford, Conn: Appleton & Lange; 1997:265-276.)*

during mental stress testing (mental arithmetic and anger recall). This trial linked sympathetic arousal to the increased incidence of arrhythmic events in patients undergoing mental stress testing, as norepinephrine levels increased significantly during psychologic stress.

### Neurohormonal Responses to Mental Stress: Defense and Defeat Reactions

It is the neurohormonal responses elicited by mental stress that lead to increased cardiovascular risk. These neurohormonal responses are known as the defense and defeat reactions.

The defense reaction is a natural and necessary instinct in life that enables one to respond to stressful situations. It is known that this response (also known as the "fight-or-flight" response) is induced in life-threatening situations. This response can also be mildly activated in response to smaller stresses

found in the mentally engaging activities of ordinary life. The defense reaction causes sympathetic activation with resulting increases in blood pressure, heart rate, cardiac output, and skeletal muscle blood flow, concurrent with vasoconstriction in the kidneys, splanchnic, and skin vasculature.

Despite the benefits of the defense reaction in appropriate situations, excessive and intense repetition of this response accelerates psychophysiologic reactions in the organ systems, which may precipitate adverse cardiovascular events, such as heart disease and stroke. Excessive neurohormonal responses to stress are believed to involve coronary flow, lipid metabolism, blood coagulation, and thrombocyte and endothelial cell function.<sup>16</sup>

The defeat reaction, mediated by cortisol, is induced by periods of prolonged mental stress that tend to overwhelm coping mechanisms and eventually result in feelings of hope-

lessness and despair. It is characterized by increased levels of circulating corticosteroids, catecholamines, and opioids as well as decreases in growth hormone and prolactin.<sup>5</sup>

Although a direct connection is not proven, similar endocrine abnormalities are associated with increased visceral fat accumulation and insulin resistance, which are important cardiovascular risk factors.<sup>17</sup> In addition to serious adverse effects on the gastrointestinal tract (ie, increased pepsin, gastric ulcers) and immune system suppression, hemodynamic changes that contribute to cardiovascular disease occur with the defeat reaction. These include vasoconstriction, which causes a rise in blood pressure levels, and a slowed heart rate. Thus, the defeat reaction can be equally—and sometimes more—devastating to health and survival as the defense reaction.

Early clinical recognition and treatment of both the defense and defeat responses to stress may prevent a variety of illnesses and protect against the possibility of premature death. Office-based tests used to determine the response to mental stress may be as important as traditional evaluations of cholesterol, blood pressure, and blood glucose levels as well as body weight.

### The MOST Protocol

The response to mental stress testing in the office or laboratory can identify patients who are sympathetic overresponders and who are thus at risk for CVD.<sup>12-15</sup> Over the past decade, the Mental Office-based Stress Testing (MOST) protocol has been used to evaluate physiologic responses to mental stress. The MOST protocol includes simple, cost-effective tests that are done in the physician's office. By measuring alterations in blood pressure levels and heart rate—both clinically accessible psychophysiologic responses to mental stress—the MOST protocol is able to identify patients with sympathetic hyperreactivity.<sup>18</sup>

This protocol includes the following components: (1) baseline assessment in which blood pressure level and heart rate are measured at rest in the sitting position; (2) relaxation assessment (deep-breathing relaxation); and (3) stress assessment.

In the relaxation assessment, the patient is asked to breathe deeply and consistently for 5 breaths over 15 seconds; blood pressure level and heart rate are measured at the end of the final breath.

The stress assessment consists of three tests. The first is a mathematics challenge in which patients are asked to serially subtract 7 from 777 (eg, 777, 770, 763, 756) with blood pressure measurements taken after 1 and 3 minutes of subtraction. The second stress assessment is the cold pressor test, which involves inserting the patient's hand into ice water past the wrist while blood pressure level and heart rate are taken in the opposite arm within 60 seconds. The grip challenge is the last of the stress assessments. This isometric test requires patients to hold 30% of maximum handgrip while blood pressure level and heart rate are taken in the opposite arm within 60 seconds.

These mental and physical stress tests have been used in clinical trials to evaluate sympathetic reactivity as well as hemodynamic responses of antihypertensive classes and agents.<sup>14,15,19-22</sup> The stress response induced by these tests is mediated by increased sympathetic outflow, resulting in increased mean arterial pressure due to increased cardiac output, accelerated heart rate, and increased systolic and diastolic pressure.<sup>19,20,23</sup> Furthermore, patients with CVD have greater hemodynamic responses to such tests.<sup>24,25</sup> Studies have shown that office-based mental stress tests more closely approximate average ambulatory blood pressure than casual office-based blood pressure level measurements.<sup>23</sup>

Assessment of results from the MOST protocol includes an evaluation of baseline, peak, and change from baseline blood pressure levels and heart rate responses to stress. These measures are used to predict ambulatory blood pressure levels and heart rate oscillations during stressful times throughout the day.<sup>26</sup> The theory that underlies the MOST protocol is that the absolute values of blood pressure and heart rate at baseline and at peak levels during mentally stressful activity, as well as the change in these measures from rest to stress, may have clinical diagnostic and prognostic significance. For example, patients with a stress increase in blood pressure from 100/60 mm Hg to 140/90 mm Hg and a stress increase in heart rate from 60 beats/min to 90 beats/min may require attention despite apparently normal blood pressure levels and heart rate values. Patients with a resting blood pressure greater than 130/85 mm Hg and a resting heart rate of more than 80 beats/min should receive clinical intervention independent of increases in blood pressure and heart rate elicited by MOST protocol testing.

### Treatment Strategies

Once patients with sympathetic hyperreactivity are identified in clinical practice, nonpharmacologic and pharmacologic interventions can be instituted to reduce the risk of CVD. These interventions not only target reduction of blood pressure levels and heart rate directly, but also improve a patient's skills in coping with stress. After treatment is instituted, therapeutic effectiveness can be evaluated over time by repeat office-based stress testing. As a patient's stress response improves as the result of these interventions, MOST protocol hemodynamic measures also should fall. Furthermore, as stress-related increases in blood pressure level and heart rate fall, other physiologic signs of stress in the body (eg, headache, irritable bowel, anxiety, sleeplessness) should improve.

### Patient Communication, Nonpharmacologic and Pharmacologic Measures

#### Patient Communication

Effective communication with patients about the impact and management of stress is an important first step in treatment. As patients understand and accept their condition, the potential for treatment compliance is greatly enhanced; however,

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**Figure 4.** The pharmacologic treatment of blood pressure elevations related to stress: rank-order of medications for control of sympathetic hyperreactivity. (Reprinted with permission of The McGraw-Hill Companies. Boone JL, Christensen JF. *Stress and disease*. In: Feldman MD, Christensen JF, eds. *Behavioral Medicine in Primary Care: A Practical Guide*. Stanford, Conn: Appleton & Lange; 1997:265-276.)

describing the role of stress in illness to patients is difficult. It is a common misconception that if a symptom or disease is stress-related, it is all in the patient's head and not to be taken seriously. It is, therefore, crucial to avoid conveying this misconception to patients. Indeed, it is likely that between 75% and 90% of reported symptoms in clinical practice are stress-related,<sup>1</sup> thus supporting a real connection between stress and disease.

The current paradigm of stress analysis in clinical practice may benefit from new terminology in communicating with patients. Some suggest applying the term *intense* or *hot reactor* to the patient, rather than *stressed*, as the latter implies a fault in the patient. Patients may more readily accept a discussion of the intensity of their lives as it relates to stress and disease, rather than approaching stress and its negative connotations directly. The goal of this delicate communication process is to assist the patient in appreciating the mind-body connection. Further, using the MOST protocol to assess stress levels in clinical practice confines discussion of stress to objective clinical criteria. This approach may be less threatening to the patient than a discussion with more psychological or psychiatric overtones.

### **Nonpharmacologic Measures**

A review of the patient's coping skills is facilitated once the physiologic effects of stress are established. Education on nonpharmacologic interventions aimed at improving the patient's perception of stress and stress-coping mechanisms, as well as reducing blood pressure levels related to stress, can be initiated.

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**Figure 5.** Pharmacologic treatment guidelines and outcome goals. (Reprinted with permission of The McGraw-Hill Companies. Boone JL, Christensen JF. *Stress and disease*. In: Feldman MD, Christensen JF, eds. *Behavioral Medicine in Primary Care: A Practical Guide*. Stanford, Conn: Appleton & Lange; 1997:265-276.)

Psychotherapeutic interventions may include stress reduction techniques (eg, meditation, hypnosis), relaxation training, and biofeedback. In addition, clinical psychosocial management should include education regarding cardiac risk factors and identification of social and environmental stressors. *Figure 3* lists these and other nonpharmacologic measures.<sup>5</sup>

### Pharmacologic Measures

An important factor in choosing antihypertensive treatment for mental stress-induced hypertension is selecting an agent that will most effectively counteract the increased sympathetic tone while maintaining quality of life. Pharmacologic options for the treatment of stress-related blood pressure increases are ranked in *Figure 4*, and cardiovascular disease treatment guidelines and outcome goals are given in *Figure 5*. For the patient whose depression, anxiety disorder, or other mood disorder is diagnosed according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*,<sup>26</sup> pharmacologic intervention with psychotherapeutic agents may be a necessary component of therapy.

Nondihydropyridine calcium channel blocking drugs (eg, verapamil) appear to be the most effective agents for controlling sympathetic hyperactivity in response to stress, reducing heart rate and total peripheral resistance and decreasing norepinephrine levels.<sup>22,28-30</sup> Verapamil also blunts stress-induced hemodynamic and hemostatic changes, including increased platelet aggregability, in response to assumption of upright posture, mental challenge, and cold pressor testing.<sup>30</sup>

A second choice for control of mental stress-induced CVD are the angiotensin-converting enzyme inhibitors and angiotensin II receptor blocking agents. These agents inhibit the effects of angiotensin on the release of epinephrine and norepinephrine; thus, they can indirectly attenuate sympathetic reactivity.<sup>32</sup> Although  $\beta$ -adrenergic receptor blocking agents (beta-blockers) reduce heart rate during mental stress, these agents increase total peripheral resistance during isometric stress and mathematics challenges,<sup>19,24</sup> making these drugs less desirable than nondihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blocking agents. The  $\alpha_1$ -adrenergic receptor blocking agents (eg, doxazosin) and centrally acting  $\alpha$ -adrenergic receptor agonists (eg, clonidine) can inhibit sympathetic reactivity; however, these agents are further down in ranking for control of mental stress-induced hemodynamic changes based on their adverse effect profiles. Diuretics, while beneficial for hypertension, are not optimal for treatment of sympathetic arousal. These agents cause a baroreceptor-mediated increase in sympathetic activity that results in increased plasma norepinephrine concentrations. Sympathetic activity is an major determinant of blood pressure responsiveness and resistance to diuretic therapy.<sup>33</sup> Finally, dihydropyridine calcium channel blockers (eg, nifedipine, amlodipine) are generally a last choice for sympathetic inhibition because of their ability to increase heart rate and norepinephrine levels.<sup>29</sup>

### Conclusion

The connection between stress and disease is well established. Mental stress can adversely affect almost all of the body's systems and is an important cause of morbidity and mortality. Primary care physicians must be able to recognize and appropriately manage patients with mental stress-induced disease

to improve treatment outcomes. The availability of inexpensive, time-efficient, office-based mental stress testing may allow physicians to better diagnose stress-induced disease. Once identified, patients with stress-induced disease can be appropriately managed, using both nonpharmacologic and pharmacologic means. Hopefully, enhanced efforts at identifying and controlling the effects of mental stress on disease will ultimately improve patient outcomes.

### References

1. American Institute of Stress. *America's #1 Health Problem*. Available at: <http://www.stress.org/problem.htm>. Accessed October 1, 1999.
2. Marcenaro M, Prete C, Badini A, Sulli A, Magi E, Cutolo M. Rheumatoid arthritis, personality, stress response style, and coping with illness. A preliminary survey. *Ann NY Acad Sci*. 1999;876:419-425.
3. Zautra AJ, Hoffman JM, Matt KS, Yocum D, Potter PT, Castro WL, et al. An examination of individual differences in the relationship between interpersonal stress and disease activity among women with rheumatoid arthritis. *Arthritis Care Res*. 1998;11:271-279.
4. Da Costa D, Dobkin PL, Pinard L, Fortin PR, Danoff DS, Esdaile JM, et al. The role of stress in functional disability among women with systemic lupus erythematosus: a prospective study. *Arthritis Care Res*. 1999;12:112-119.
5. Boone JL, Christensen JF. Stress & disease. In: Feldman MD, Christensen JF, eds. *Behavioral Medicine in Primary Care: A Practical Guide*. Stanford, Conn: Appleton & Lange; 1997:265-276.
6. Pasternak RC, Grundy SM, Levy D, Thompson PD. 27th Bethesda Conference: Matching the intensity of risk factor management with the hazard for coronary events. Task force 3. Spectrum of risk factors for coronary heart disease. *J Am Coll Cardiol*. 1996;27:978-990.
7. Gullette ECD, Blumenthal JA, Babyak M, Jiang W, Waugh RA, Frid DJ, et al. Effects of mental stress on myocardial ischemia during daily life. *JAMA*. 1997;277:1521-1526.
8. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. *Circulation*. 1995;92:1720-1725.
9. Kawachi I, Sparrow D, Spiro A III, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. *Circulation*. 1996;94:2090-2095.
10. Nemeroff CB, Musselman DL, Evans DL. Depression and cardiac disease [review]. *Depress Anxiety*. 1998;8(suppl 1):71-79.
11. Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, et al. Exaggerated platelet reactivity in major depression. *Am J Psych*. 1995;152:1313-1317.
12. Stone PH, Krantz DS, McMahon RP, Goldberg AD, Becker LC, Chaitman BR, et al. Relationship among mental stress-induced ischemia and ischemia during daily life and during exercise: The Psychophysiological Investigations of Myocardial Ischemia (PIMI) study. *Am Coll Cardiol*. 1999;33:1476-1484.
13. Krittayaphong R, Light KC, Biles PL, Ballenger MN, Sheps DS. Increased heart rate response to laboratory-induced mental stress predicts frequency and duration of daily life ambulatory myocardial ischemia in patients with coronary artery disease. *Am J Cardiol*. 1995;76:657-660.
14. Krantz DS, Santiago HT, Kop WJ, Bairey Merz CN, Rozanski A, Gottdiener JS. Prognostic value of mental stress testing in coronary artery disease. *Am J Cardiol*. 1999;84:1292-1297.

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## REVIEW ARTICLE

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15. Lampert R, Jain D, Burg MM, Batsford WP, McPherson CA. Destabilizing effects of mental stress on ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *Circulation*. 2000;101:158-164.
16. Verrier RL, Mittelman MA. Cardiovascular consequences of anger and other stress states. *Baillieres Clin Neurol*. 1997;6:245-259.
17. Bjorntorp P. Stress and cardiovascular disease. *Acta Physiol Scand Suppl*. 1997;640:144-148.
18. Boone JL. The cardiovascular consequences of mental intensity. *JAMA*. 1996;12(suppl—Southeast Asia edition):26-28.
19. Garavaglia GE, Messerli FH, Schmieder RE, Nunez BD. Antihypertensive therapy and cardiovascular reactivity during isometric stress. *J Hum Hypertens*. 1988;2:247-251.
20. Cardillo C, Musumeci V, Savi L, Guardigli R, Mores N, Folli G. Effect of sustained-release verapamil therapy on the blood pressure at rest and on the pressor response to isometric exertion in hypertensive patients. *Eur J Clin Pharmacol*. 1988;34:549-553.
21. Velasco M, Gomez J, Blanco M, Rodriguez I. The cold pressor test: Pharmacological and therapeutic aspects [review]. *Am J Ther*. 1997;4:34-38.
22. Dimitrow PP, Krzanowski M, Nizankowski R, Szczeklik A, Dubiel JS. Verapamil improves the response of coronary vasomotion to cold pressor test in asymptomatic and mildly symptomatic patients with hypertrophic cardiomyopathy. *Cardiovasc Drugs Ther*. 1999;13:259-264.
23. McKinney ME, Miner MH, Ruddle H, McIvain HE, Witte H, Buell JC, et al. The standardized mental stress test protocol: Test-retest reliability and comparison with ambulatory blood pressure monitoring. *Psychophysiology*. 1985;22:453-463.
24. Ruddle H, Langewitz W, Schachinger H, Schmieder R, Schulte W. Hemodynamic response patterns to mental stress: Diagnostic and therapeutic implications. *Am Heart J*. 1988;116:617-627.
25. Sevre K, Rostrup M. Blood pressure and heart rate responses to cold pressor test in patients admitted to hospital due to chest pain. *Blood Press*. 1999;8:110-113.
26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Arlington, Va: American Psychiatric Press; 1995.
27. Morales-Ballejo HM, Eliot RS, Boone JL, Hughes JS. Psychophysiological stress testing as a predictor of mean daily blood pressure. *Am Heart J*. 1988;116(pt 2):673-681.
28. Nazzaro P, Merlo M, Manzari M, Cicco G, Pirrelli A. Stress response and antihypertensive treatment. *Drugs*. 1993;46(suppl):133-140.
29. Kailasam MT, Parmer RJ, Cervenka JH, Wu RA, Ziegler MG, Kennedy BP, et al. Divergent effects of dihydropyridine and phenylalkylamine calcium channel antagonist classes on autonomic function in human hypertension. *Hypertension*. 1995;26:143-149.
30. Grossman E, Messerli FH. Effect of calcium antagonists on sympathetic activity [review]. *Eur Heart J*. 1998;19(suppl F):F27-F31.
31. Gebara OC, Jimenez AH, McKenna C, Mittleman MA, Xu P, Lipinska I, et al. Stress-induced hemodynamic and hemostatic changes in patients with systemic hypertension: effect of verapamil. *Clin Cardiol*. 1996;19:205-211.
32. de Champlain J, Karas M, Toal C, Nadeau R, Larochelle P. Effects of anti-hypertensive therapies on the sympathetic nervous system [review]. *Can J Cardiol*. 1999;15(suppl A):8A-14A.
33. Freis ED, Reda DJ, Materson BJ. Volume (weight) loss and blood pressure response following thiazide diuretics. *Hypertension*. 1988;12:244-250.