Review

Autonomic Tone as a Cardiovascular Risk Factor: The Dangers of Chronic Fight or Flight

BRIAN M. CURTIS, MD, AND JAMES H. O'KEEFE, JR, MD

Chronic imbalance of the autonomic nervous system is a prevalent and potent risk factor for adverse cardiovascular events, including mortality. Although not widely recognized by clinicians, this risk factor is easily assessed by measures such as resting and peak exercise heart rate, heart rate recovery after exercise, and heart rate variability. Any factor that leads to inappropriate activation of the sympathetic nervous system can be expected to have an adverse effect on these measures and thus on patient outcomes, while any factor that augments vagal tone tends to improve outcomes. Insulin resistance, sympathomimetic medications, and negative psychosocial factors all have the potential to affect autonomic function adversely and thus cardiovascular prognosis. Congestive heart failure and hypertension also provide important lessons about the adverse effects of sympathetic predominance, as well as illustrate the benefits of β-blockers and angiotensin-converting enzyme inhibitors, 2 classes of drugs that reduce adrenergic tone. Other interventions, such as exercise, improve cardiovascular outcomes partially by increasing vagal activity and attenuating sympathetic hyperactivity.

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ACE = angiotensin-converting enzyme; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; LV = left ventricular; MI = myocardial infarction; PPA = phenylpropanolamine

Evolutionary pressures over millions of years have adapted the sympathetic nervous system as a major mediator of the fight or flight response. Adrenergic neurohumoral activation increases heart rate, blood pressure, and cardiac output and dilates large muscular arteries and the bronchioles. These changes are meant to prepare humans for physical confrontation or to respond to acute hemodynamic collapse or respiratory compromise. When the sympathetic nervous system is used in these settings, it improves a person's chance of survival and increases the likelihood that his or her genes will be passed on to the next generation.

Appropriate and intermittent stimulation of the sympathetic nervous system produces immediate improvement in various symptoms, from the mundane (fatigue, weakness, nasal congestion, etc) to the more serious (bronchial constriction, hypotension, and shock). Additionally, some of the exhilaration of life is mediated by adrenergic stimulation, commonly referred to as an *adrenaline rush*. Conversely, a reduction in sympathetic neurotransmitters such as dopamine and norepinephrine in the brain can produce dysphoria and lethargy. These factors have encouraged the liberal use of sympathomimetics for long-term therapy, ranging from prescription and over-the-counter drugs to "natural" supplements to illicit or illegal drugs. Although these agents produce short-term beneficial effects in many acute situations, long-term use not only results in tachyphylaxis but also exacts a toll on the integrity of the cardiovascular system.

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The status of the autonomic nervous system, although often ignored by clinicians, is a major determinant of cardiovascular health and prognosis. Any therapy that chronically activates the sympathetic nervous system and/or diminishes parasympathetic (vagal) tone will increase the risk of cardiovascular events. In contrast, therapies that tip the autonomic balance toward parasympathetic dominance and decrease sympathetic tone will improve prognosis. This simple axiom explains many observations and should be used as a guide in clinical decision making in the diagnosis and treatment of cardiovascular disease. In this article, we review the relationship between autonomic tone and cardiovascular risk and suggest strategies for recognizing and treating this risk factor.

AUTONOMIC DYSFUNCTION AS A RISK FACTOR

Many studies have established an elevated resting heart rate as a risk factor for cardiovascular disease and mortality.[1,2] Astute clinicians have long recognized the paradoxically worrisome nature of a "normal" sinus rhythm of 90 beats/min compared with a reassuringly "abnormal" sinus bradycardia of 50 beats/min. For example, the best prognostic marker on the admitting resting electrocardiogram

From the Mid-America Heart Institute of Saint Luke's Hospital and the University of Missouri, Kansas City.

Individual reprints of this article are not available. Address correspondence to James H. O'Keefe, Jr, MD, Cardiovascular Consultants, PC, 4330 Wornall Rd, Suite 2000, Kansas City, MO 64111 (e-mail: jhokeefe@cc-pc.com).

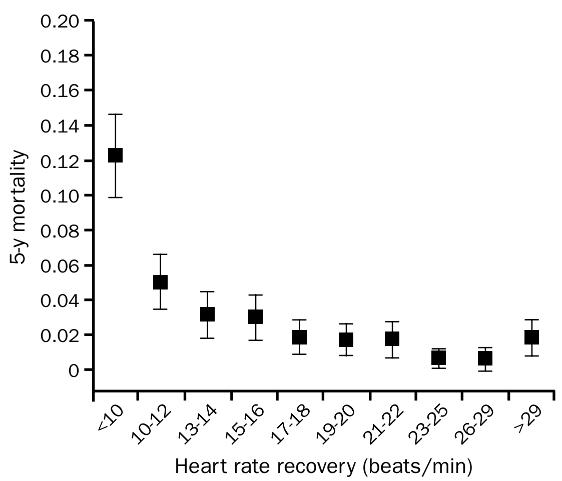

Figure 1. The 5-year Kaplan-Meier survival estimates in 9454 patients according to deciles of heart rate recovery 1 minute after exercise. Mortality was predicted by abnormal heart rate recovery, hazard ratio of 4.16 (95% confidence interval, 3.33-5.19; *P*<.001). Reprinted with permission from Nishime et al.[6]

of a patient suffering an acute myocardial infarction (MI) is the resting heart rate, not the extensiveness of Q waves or ST-segment deviation.[3]

Other indicators of the health of the autonomic system can be detected on a routine exercise tolerance test. An impaired chronotropic response to exercise is defined as a failure to achieve 85% of the age-predicted maximal heart rate. This abnormality is present in 11% to 26% of healthy middle-aged adults and increases mortality independent of findings on stress nuclear myocardial perfusion images and coronary angiography.[4,5]

Heart rate recovery after exercise, which is mediated primarily by vagal tone, has also been shown to be a significant prognostic factor. In a study of 9500 people, Nishime et al[6] showed that failure to decrease heart rate by more than 12 beats/min during the first minute after exercise (noted in 20% of apparently healthy middle-aged adults) increased mortality 4-fold over the ensuing 5 years (Figure 1). Another large study reported a relative risk of mortality of 2.58 in one third of 5200 healthy adults who had an abnormal heart rate recovery on a screening treadmill test.[7]

Intact heart rate variability (beat-to-beat variability mediated by a dynamic autonomic nervous system, especially vagal tone) and baroreflex sensitivity (reflex-mediated changes in heart rate as a response to fluctuations in preload and venous return, such as those noted during postural changes) are characteristics of a healthy autonomic system and are potent independent predictors of cardiovascular prognosis. Low heart rate variability has been associated with increased risk of coronary heart disease (CHD) and mortality,[8,9] as well as with angiographic progression of coronary atherosclerosis[10] and sudden cardiac death[11] (Figure 2). Data from the Framingham Heart Study confirm that heart rate variability is related to the risk of all-cause mortality[12] and cardiac events.[13] The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study showed that both heart rate variability and baroreflex sensitivity were independent predictors of cardiovascular mortality.[14] Heart rate variability can be estimated at the bedside by observing the variation in heart rate for 1 minute during deep breathing[15] (Table 1).

HOW AUTONOMIC IMBALANCE INCREASES RISK

Simple markers like peak exercise heart rate and heart rate variability are powerful predictors of cardiovascular mortality because they are signs of an autonomic nervous system that has been disturbed by the strain of chronic, excessive sympathetic tone. A dramatic example of this phenomenon occurs under the extreme conditions of high-altitude mountain climbing. Elite alpinists are highly trained athletes who at sea level have a resting heart rate of less than 55 beats/min, a peak exercise heart rate of greater than 180 beats/min, and a brisk heart rate recovery within the first minute of resting. Within the days to weeks that climbers are acclimating to progressively higher altitudes, their resting heart rate gradually increases, peak exercise heart rate decreases, and heart rate recovery becomes delayed.[16,17] Altitudes greater than 26,000 feet are termed the *death zone*. As climbers ascend above this level, their resting heart rate typically increases to 120 to 140 beats/min, and their peak exercise heart rate decreases to this same level; thus, their heart rate recovery is nonexistent. Essentially, climbers are dying of hypoxia and exposure, and the sympathetic nervous system, while trying to compensate, is becoming less and less effective because of down-regulation of the adrenergic receptors in the face of continuous maximal sympathetic stimulation. These same adaptations, although less extreme, operate under normal ambient conditions.

Excessive sympathetic stimulation and diminished vagal tone not only are markers of an unhealthy cardiovascular system but also in part cause the adverse events. Chronic sympathetic hyperactivity increases the cardiovascular workload and hemodynamic stresses and predisposes to endothelial dysfunction, coronary spasm, left ventricular (LV) hypertrophy, and serious dysrhythmias.[18] Increased vagal activity exerts a protective effect against ischemia-related dysrhythmias and also reduces heart rate and blood pressure.[19] The risks of MI, sudden cardiac death, and stroke are highest during the first few hours after awakening in the morning, correlating with the circadian peak in sympathetic activity.[20] Mortality due to CHD is higher on Monday than on other days of the week but only in employed people.[21] β-Blockers normalize these increased risks related to circadian catecholamine peaks.[22]

In the setting of LV dysfunction, abnormal autonomic tone is the *most* sensitive predictor of cardiac and arrhythmic mortality, even more so than documented ventricular tachycardia.[23] Major noncardiac surgery is associated with activation of the sympathetic nervous system and increased CHD risk,[24] and β-blockers normalize this perioperative cardiovascular risk.[25,26]

The rates of sudden cardiac death and acute MI are increased in earthquake survivors during the days to weeks after the event. In a study of 12 patients who (by coincidence) were wearing a Holter monitor during a major earthquake in Taiwan, 9 showed enhanced sympathetic modulation and/or decreased vagal tone within 30 minutes.[27] Interestingly, the 3 people who did not show worsening autonomic tone were all taking a β-blocker at the time of the earthquake.

In animal models, β-blockers decrease both stress-induced and diet-induced atherosclerosis. Recently, in a 3-year randomized placebo-controlled trial involving 793 patients, low-dose metoprolol (25 mg/d) reduced progression of carotid atherosclerosis as effective as a statin.[28] Clearly, autonomic imbalance is much more than a surrogate marker of increased CHD risk.

INSULIN RESISTANCE AND AUTONOMIC DYSFUNCTION

The mechanisms whereby traditional risk factors (such as smoking, unhealthy diet, obesity, and sedentary lifestyle) predispose to adverse events are multifaceted, but activation of the sympathetic nervous system and diminished vagal tone appear to be important final common pathways through which a substantial portion of cardiovascular risk is conferred.[29] Some of the factors leading to chronic sympathetic activation are summarized in Table 2.

Diabetes and the metabolic syndrome (hypertension, insulin resistance, obesity, and atherogenic dyslipidemia) adversely affect cardiac autonomic function and are associated with increased risk of cardiovascular events.[30-32] Elevated fasting insulin has been shown to increase sympathetic activity and heart rate[33,34]; the insulin resistance syndrome also predisposes to cardiovascular hyperresponsiveness to sympathetic stimulation and has been shown to reduce heart rate variability.[35] A recent study showed that glucose intolerance was the strongest determinant of cardiovascular autonomic imbalance compared to the other standard risk factors.[36] Symptomatic autonomic neuropathy is common in patients with long-standing poorly controlled diabetes and is associated with increased 5-year mortality.[37] However, chronic hyperinsulinemia, even in the absence of type 2 diabetes mellitus, is associated with heightened sympathetic tone and decreased vagal tone.[38,39]

Data from the Framingham Heart Study recently confirmed that diabetes and impaired fasting glucose levels are associated with reduced heart rate variability.[40] Diabetic patients have a 3- to 5-fold increased risk of sudden death compared with nondiabetic patients.[41] Although β-blockers tend to worsen insulin sensitivity, they decrease mortality in diabetic patients partially by improving the autonomic imbalance and risk of sudden death.[42]

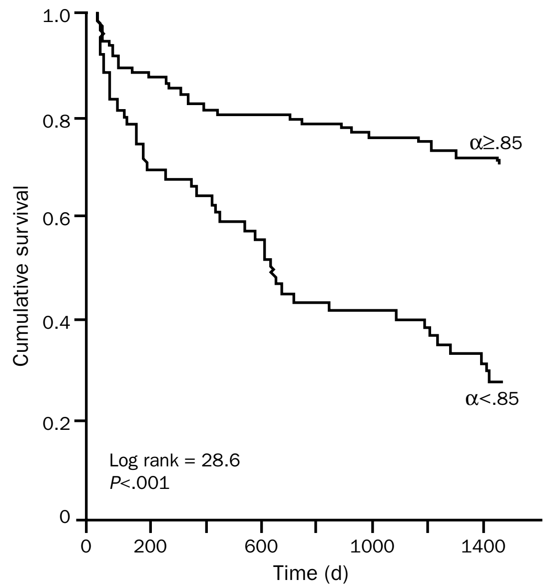

Figure 2. Fractal analysis with use of the α-variable documented heart rate variability as a powerful predictor of all-cause mortality in 159 patients with depressed left ventricular function after acute myocardial infarction. Impaired heart rate variability (α<.85) was associated with a relative risk of 3.17 (*P*<.001). Reprinted with permission from Mäkikallio et al.[9]

Table 1. **Practical Clinical Indicators of Abnormal Cardiac Autonomic Function**

Resting heart rate greater than 90 beats/min
Inability to achieve 85% of predicted maximal heart rate on treadmill testing
Abnormal heart rate recovery (failure to decrease heart rate >12 beats/min during the first minute after peak exercise)
Abnormal heart rate variability (failure to change heart rate, R-R interval, by ≥10 beats/min during 1 minute of slow deep breaths)

Table 2. **Factors Contributing to Chronic Sympathetic Activation**

Medical conditions
Obesity
Insulin resistance or diabetes
Hypertension
Depression, anxiety
Congestive heart failure
Sleep apnea
Psychosocial and behavioral conditions
Chronic stress
Social isolation
Hostility
Smoking
Sleep deprivation
Unhealthy diet
Sedentary lifestyle
Abuse of stimulants

RISKS OF SYMPATHOMIMETIC DRUGS

Illicit, powerful sympathomimetic drugs like cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine (also known as *ecstasy*) are popular because they produce a transient energized, euphoric state. Not surprisingly, these drugs markedly increase the risk of MI, stroke, cardiomyopathy, dysrhythmias, and other adverse cardiovascular effects (particularly with long-term use).[43-46] Legal sympathomimetic medications are widely used for various conditions, including weight loss, allergy or sinus problems, asthma, and chronic lung disease. Sympathomimetic agents are often found in over-the-counter products, including herbal preparations, and are frequently taken in combination with other stimulants and without supervision.

Two recently published studies (released early because of public health implications) renewed concerns about the safety of nonprescription sympathomimetic medications. In the first study, phenylpropanolamine (PPA), often used as a decongestant or appetite suppressant, was found to increase the risk of hemorrhagic stroke in women.[47] An accompanying editorial estimated that as many as 200 to 400 strokes related to the use of PPA may occur annually in the United States.[48] As a result, the Food and Drug Administration recommended that products containing PPA be removed voluntarily from the market. In a related study, ephedra alkaloids, found in herbal preparations like ma huang or Metabolife and used frequently for weight loss, were found to be associated with various adverse cardiovascular and central nervous system effects, including hypertension, stroke, and MI.[49]

The National Football League recently banned ephedra use because 4 players died in summer 2001 training camps; 3 had ephedra in their bloodstream, and 1 had an ephedra-containing drink in his locker.[50] Although a relationship between ephedra use and death was not proved in all cases, the National Football League policy was intended to protect the health of players until further study could be undertaken.

The Food and Drug Administration has been petitioned by the Public Citizen's Health Research Group to ban all over-the-counter products containing ephedra. Data from the American Association of Poison Control Centers show that, between January 1993 and February 2000, supplements containing ephedra accounted for 42% of all the reported adverse events related to nutritional supplements during that period.[51]

β-AGONIST BRONCHODILATORS

During the 1980s, asthma-related mortality increased in association with the liberal use of β-agonists.[52] Although this association remains controversial,[53] it has been established that even β_2-selective agents cause increased heart rate, decreased potassium levels, and increased QTc interval.[54] These agents have been associated with ventricular and atrial ectopy[55] as well as increased risk of acute cardiovascular mortality.[56] β-Agonists are used frequently in the setting of an acute upper respiratory tract infection, which has been independently associated with an increased risk of MI.[57] A recent case-control study showed that the use of inhaled β-agonists was associated with an increased risk of MI (adjusted odds ratio, 1.67; 95% confidence interval, 1.07-2.60) in patients with known cardiovascular disease.[58]

Patients with chronic lung disease often use a β-agonist (albuterol) and an anticholinergic medication (ipratropium) concurrently. Anticholinergic medications can increase heart rate and decrease heart variability.[59] A case-control study showed that, in patients with asthma, cardiovascular deaths were more common among those prescribed ipratropium at discharge (odds ratio, 3.55; 95% confidence interval, 1.05-11.94).[60] A wide variety of medications have anticholinergic effects, and caution is advised when sympathomimetic and anticholinergic medications are used together.

LESSONS LEARNED FROM CONGESTIVE HEART FAILURE

Nowhere in medicine is the importance of the autonomic nervous system more dramatic than in the patient with congestive heart failure (CHF). Under the old paradigm, the failing heart was "lazy" and needed sympathetic stimulation to improve systolic function and cardiac output. Indeed, the normal heart will respond to sympathetic stimulation by increasing cardiac output, but in the setting of an injured heart, adrenergic stimulation is analogous to "flogging a sick horse." A series of agents, from dopamine and dobutamine decades ago to more recent designer inotropes with associated vasodilatation like milrinone or vesnarinone, showed transient, inconsistent improvements in CHF symptoms that were offset by an exacerbation (often doubling) of mortality over a 6- to 12-month period (Figure 3).[61] Bouvy et al[62] recently reported that use of sympathomimetic drugs increased the risk of hospitalization for arrhythmias in patients with CHF.

In contrast, the use of β-blockers has revolutionized the prognosis of cardiomyopathy and CHF. After an initial or ongoing insult to the myocardium, such as MI, uncontrolled hypertension, excessive alcohol use, or viral myocarditis, the downward spiral of CHF is mediated by excessive sympathetic tone and activation of the renin-angiotensin system. This causes vasoconstriction, dysrhythmias, apoptosis, and progressive LV dysfunction.[18] Multiple studies have unequivocally documented that β-blockers are effective for improving outcomes in patients with CHF and LV dysfunction. These benefits have been found with carvedilol,[63,64] bisoprolol,[65] and metoprolol.[66] β-Blocker therapy not only reduces risk of sudden death but also consistently increases systolic function better than any other therapy[67] (Figure 4).

Because of the counterintuitive nature of the use of a β-blocker for the failing heart and the transient worsening of symptoms after initiation of therapy, many practicing physicians have been slow to embrace this life-saving therapy. Although β-blockers are the most important therapy for normalizing the prognosis of CHF, they are currently used in fewer than 1 in 5 eligible patients nationwide.

CHOICE OF AGENTS FOR HYPERTENSION

Sympathetic activity has been shown to be a factor in the development of hypertension.[68] When choosing an antihypertensive agent, it is important to consider the autonomic ramifications of the therapy. Direct vasodilators including short-acting calcium channel blockers (CCBs), particularly dihydropyridines such as nifedipine, cause a rapid decrease in blood pressure and a reflex increase in sympathetic activation, which may be associated with adverse cardiovascular outcomes.[69,70] Some studies have indicated that patients treated with a short-acting CCB are at increased risk for MI and have a higher mortality rate than patients treated with other types of medications.[71,72] This increased risk appears to be limited to short-acting CCB agents.[73]

Peripheral α-blockers (doxazosin, terazosin) lower blood pressure via peripheral vasodilation but activate the central sympathetic nervous system. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), doxazosin was found to increase the risk of CHF and stroke compared to a diuretic.[74] Drugs that normalize sympathetic hyperactivity, like β-blockers and angiotensin-converting enzyme (ACE) inhibitors,

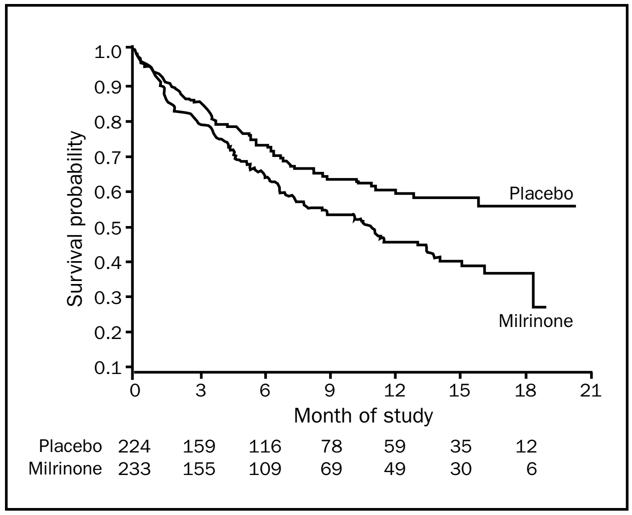

Figure 3. The Prospective Randomized Milrinone Survival Evaluation (PROMISE) randomized 1088 patients with congestive heart failure (CHF) (class III or IV) to oral milrinone or placebo. All-cause mortality was 28% higher in the patients taking milrinone and 53% higher among those with class IV CHF (95% confidence interval, 13%-107%; *P*=.006). Reprinted with permission from Packer et al.[61]

not only lower blood pressure but also reduce the risk of adverse cardiovascular events beyond what would be predicted based on the improvement in hypertension alone.[75,76]

ACE inhibitors block activation of the renin-angiotensin system and indirectly decrease sympathetic tone.[77,78] In the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril decreased death, MI, and stroke, as well as the occurrence of new-onset diabetes.[75] Other studies have shown that ACE inhibitors decrease sympathetic activation in patients with chronic renal failure[79] and CHF,[80] as measured by muscle sympathetic nerve activity, and improve heart rate variability in diabetic patients.[81]

β-Blockers lower heart rate and restore normal β-receptor responsiveness, improving peak exercise heart rate, heart rate recovery, and beat-to-beat variability. β-Blockers have also been shown to reduce the risk of sudden cardiac death by 30% to 50%[82] and decrease all-cause mortality,[83] especially in persons with an elevated resting heart rate (indicating an activated sympathetic nervous system at baseline).[84]

PSYCHOSOCIAL FACTORS

Psychosocial factors (like depression, anxiety, hostility, and social isolation) increase CHD risk both by their association with high-risk behaviors, such as smoking, and by direct pathophysiologic mechanisms, including activation of the sympathetic nervous system.[85] Depression has been

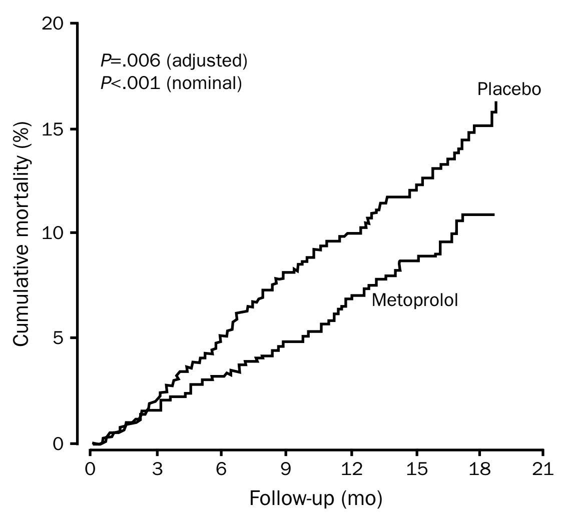

Figure 4. The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) (3991 patients with class II-IV congestive heart failure; ejection fraction ≤40%) showed a reduction in all-cause mortality with controlled release/extended release metoprolol, relative risk (RR), 0.66 (95% confidence interval [CI], 0.53-0.81; $P<.001$). Sudden death was also decreased, RR, 0.59 (95% CI, 0.45-0.78; $P=.002$). Reprinted with permission from MERIT-HF Study Group.[66]

associated with elevated resting heart rate,[86] decreased heart rate variability,[87] impaired vagal control,[88] and elevated levels of plasma norepinephrine,[89] suggesting chronic inappropriate activation of the sympathetic nervous system. All 11 prospective studies evaluating a possible link between major depression and CHD showed positive results.[90] A history of major depression is a potent independent predictor for the future risk of CHD events, with an odds ratio of approximately 6.0, placing it among the strongest of cardiovascular risk factors.[91,92]

Chronic anxiety has been shown to decrease heart rate variability,[93] impair vagal control,[94] and increase the risk of sudden cardiac death.[95] Multiple studies support the relationship between hostility[96,97] or anger[98] and CHD. Additionally, lack of social support disturbs normal autonomic tone and is associated with increased risk of cardiovascular events, in both healthy populations and those with known CHD.[99-101] An exaggerated heart rate and blood pressure response to stressful situations, labeled the *hot responder trait*, has been linked to an increased risk of cardiac events.[102,103]

In contrast, some lifestyle factors appear to be cardioprotective. The support provided by marriage,[104] religiosity or faith,[105] and other forms of social connection, such as dog ownership, have been associated with activation of the parasympathetic nervous system and decreased risk of future cardiovascular events. Interventions that have used psychosocial support programs for patients with CHD have shown mixed results, but some studies have shown benefit.[106,107]

Table 3. **Interventions to Improve Autonomic Function**

Lifestyle modifications
Exercise
Social support
Religiosity or faith
Meditation
Restoration of normal sleep
Weight loss
Smoking cessation
Stress reduction
Medications
β-Blockers
Angiotensin-converting enzyme inhibitors
Omega-3 fatty acids

EXERCISE

Interventions for improving autonomic function are listed in Table 3. In today's world, sympathetic activation usually occurs in response to emotional stress, but our body prepares as if it were responding to a physical threat. Increased sympathetic tone that occurs with exercise is physiologic and facilitates increased capacity for physical work. After exertion, sympathetic tone is decreased from baseline, and vagal tone is augmented.[108] This "relaxation response" does not occur after anxiety or extrinsic sympathomimetic stimulation.[94]

Although nonphysiologic stresses increase the risk of adverse cardiovascular events, normal physiologic sympathetic activation (eg, during exercise or sexual activity) improves physical conditioning, mood, and cardiovascular prognosis. Exercise transiently stimulates the sympathetic nervous system, but because it strongly augments background vagal activity, it is an effective and practical means to restore a healthy balance of autonomic tone.[109]

The sympathetic activation that occurs during exercise can trigger sudden death or acute MI, predominantly in sedentary persons and especially during extreme exertion.[110] Thus, exercise has been referred to as a *two-edged sword*, increasing risk in the short term in susceptible persons, while reducing chronic risk in regular exercisers.[111]

Epidemiological studies have shown that physical activity is important for reducing the risk of cardiovascular disease.[112] Regular exercise is associated with lower resting heart rate and improved heart rate recovery.[113,114] Regular physical activity also improves other indicators of autonomic function, including heart rate variability and baroreflex sensitivity,[19] and has been associated with decreased risk of sudden cardiac death[115] and slower progression of carotid atherosclerosis.[116] In a recent study, regular walking was shown to decrease blood pressure and sympathetic nerve activity in men with mild hypertension.[108] Frequent physical activity reduces sympathetic activity through many indirect mechanisms, including weight loss, reduced anxiety and depression, improved insulin sensitivity, and as an aid in smoking cessation efforts.

OMEGA-3 FATTY ACIDS

The cardiovascular benefits of omega-3 fatty acids, principally docosahexaenoic acid and eicosapentaenoic acid, appear to be mediated by a reduction in the risk of sudden cardiac death.[117] Several clinical trials have shown improved outcomes in patients with higher intakes of omega-3 (from dietary intake and supplements).[118,119] The Mediterranean diet appears to protect against cardiovascular disease. In prospective studies, the benefits of this diet are specifically correlated with high omega-3 content, and cardiovascular outcomes are improved predominantly by preventing sudden cardiac death.[120,121]

Several studies suggest that omega-3 fatty acids (especially docosahexaenoic acid) may improve parameters of autonomic function, including baroreflex sensitivity and heart rate variability.[122-126] Intake of omega-3 may help to prevent serious ventricular ectopy, particularly in the setting of acute myocardial ischemia.[127-130] However, routine use of omega-3 fatty acids for this indication should be deferred until further prospective randomized trials are completed.

CONCLUSION

Autonomic dysfunction, as measured by resting and peak exercise heart rate, heart rate recovery after exercise, and heart rate variability, is a prevalent and potent CHD risk factor. Therefore, we urge clinicians to develop an increased awareness of the effects of various therapies on autonomic function; consider carefully the risks involved before prescribing medications with sympathomimetic effects, especially in patients with cardiovascular disease; and place greater emphasis on interventions (like regular, moderate-intensity exercise, β-blockers, and ACE inhibitors) that have been shown to improve autonomic function and outcomes in patients with CHD.

REFERENCES

1. Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. *Am Heart J.* 1993;125:1148-1154.
2. Hjalmarson A. Significance of reduction in heart rate in cardiovascular disease. *Clin Cardiol.* 1998;21(12, suppl 2):II3-II7.
3. Hathaway WR, Peterson ED, Wagner GS, et al, GUSTO-I Investigators. Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. *JAMA.* 1998;279:387-391.
4. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *JAMA.* 1999;281:524-529.
5. Dresing TJ, Blackstone EH, Pashkow FJ, Snader CE, Marwick TH, Lauer MS. Usefulness of impaired chronotropic response to exercise as a predictor of mortality, independent of the severity of coronary artery disease. *Am J Cardiol.* 2000;86:602-609.
6. Nishime EO, Cole CR, Blackstone EH, Pashkow FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA.* 2000;284:1392-1398.
7. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med.* 2000;132:552-555.
8. Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. *Circulation.* 2000;102:1239-1244.
9. Mäkikallio TH, Høiber S, Køber L, et al, TRACE Investigators. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. *Am J Cardiol.* 1999;83:836-839.
10. Huikuri HV, Jokinen V, Syvanne M, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol.* 1999;19:1979-1985.
11. Fauchier L, Babuty D, Cosnay P, Fauchier JP. Prognostic value of heart rate variability for sudden death and major arrhythmic events in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol.* 1999;33:1203-1207.
12. Tsuji H, Venditti FJ Jr, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort: the Framingham Heart Study. *Circulation.* 1994;90:878-883.
13. Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. *Circulation.* 1996;94:2850-2855.
14. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ, ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet.* 1998;351:478-484.
15. Katz A, Liberty IF, Porath A, Ovsyshcher I, Prystowsky EN. A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction. *Am Heart J.* 1999;138(1, pt 1):32-38.
16. Ponchia A, Noventa D, Bertaglia M, et al. Cardiovascular neural regulation during and after prolonged high altitude exposure. *Eur Heart J.* 1994;15:1463-1469.
17. Farinelli CC, Kayser B, Binzoni T, Cerretelli P, Girardier L. Autonomic nervous control of heart rate at altitude (5050 m). *Eur J Appl Physiol Occup Physiol.* 1994;69:502-507.
18. Metra M, Nodari S, D'Aloia A, Bontempi L, Boldi E, Cas LD. A rationale for the use of β-blockers as standard treatment for heart failure. *Am Heart J.* 2000;139:511-521.
19. Iellamo F, Legramante JM, Massaro M, Raimondi G, Galante A. Effects of a residential exercise training on baroreflex sensitivity and heart rate variability in patients with coronary artery disease: a randomized, controlled study. *Circulation.* 2000;102:2588-2592.
20. Muller JE. Circadian variation and triggering of acute coronary events. *Am Heart J.* 1999;137(4, pt 2):S1-S8.
21. Willich SN, Lowel H, Lewis M, Hormann A, Arntz HR, Keil U. Weekly variation of acute myocardial infarction: increased Monday risk in the working population. *Circulation.* 1994;90:87-93.

22. Peters RW. Propranolol and the morning increase in sudden cardiac death: the beta-Blocker Heart Attack Trial experience. *Am J Cardiol*. 1990;66:57G-59G.
23. La Rovere MT, Pinna GD, Hohnloser SH, et al, Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) Investigators. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. *Circulation.* 2001;103:2072-2077.
24. Mangano DT, Hollenberg M, Fegert G, et al, Study of Perioperative Ischemia (SPI) Research Group. Perioperative myocardial ischemia in patients undergoing noncardiac surgery, I: incidence and severity during the 4 day perioperative period. *J Am Coll Cardiol*. 1991;17:843-850.
25. Mangano DT, Layug EL, Wallace A, Tateo I, Multicenter Study of Perioperative Ischemia Research Group. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med*. 1996;335:1713-1720.
26. Poldermans D, Boersma E, Bax JJ, et al, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med.* 1999;341:1789-1794.
27. Huang JL, Chiou CW, Ting CT, Chen YT, Chen SA. Sudden changes in heart rate variability during the 1999 Taiwan earthquake. *Am J Cardiol.* 2001;87:245-248.
28. Hedblad B, Wikstrand J, Janzon L, Wedel H, Berglund G. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation.* 2001;103:1721-1726.
29. Grassi G, Seravalle G, Calhoun DA, et al. Mechanisms responsible for sympathetic activation by cigarette smoking in humans. *Circulation.* 1994;90:248-253.
30. Laakso M. Insulin resistance and coronary heart disease. *Curr Opin Lipidol*. 1996;7:217-226.
31. O'Keefe JH Jr, Miles JM, Harris WH, Moe RM, McCallister BD. Improving the adverse cardiovascular prognosis of type 2 diabetes. *Mayo Clin Proc.* 1999;74:171-180.
32. Timar O, Sestier F, Levy E. Metabolic syndrome X: a review. *Can J Cardiol*. 2000;16:779-789.
33. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest.* 1991;87:2246-2252.
34. Festa A, D'Agostino R Jr, Hales CN, Mykkänen L, Haffner SM. Heart rate in relation to insulin sensitivity and insulin secretion in nondiabetic subjects. *Diabetes Care.* 2000;23:624-628.
35. Liao D, Sloan RP, Cascio WE, et al. Multiple metabolic syndrome is associated with lower heart rate variability: the Atherosclerosis Risk in Communities Study. *Diabetes Care.* 1998;21: 2116-2122.
36. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Glucose tolerance and other determinants of cardiovascular autonomic function: the Hoorn Study. *Diabetologia.* 2000;43:561-570.
37. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care.* 1985;8:491-498.
38. Laitinen T, Vauhkonen IK, Niskanen LK, et al. Power spectral analysis of heart rate variability during hyperinsulinemia in nondiabetic offspring of type 2 diabetic patients: evidence for possible early autonomic dysfunction in insulin-resistant subjects. *Diabetes.* 1999;48:1295-1299.
39. Emdin M, Gastaldelli A, Muscelli E, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. *Circulation.* 2001;103:513-519.
40. Singh JP, Larson MG, O'Donnell CJ, et al. Association of hyperglycemia with reduced heart rate variability (the Framingham Heart Study). *Am J Cardiol.* 2000;86:309-312.
41. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. *Circulation.* 1995;91:2591-2595.
42. Jonas M, Reicher-Reiss H, Boyko V, et al, Bezafibrate Infarction Prevention (BIP) Study Group. Usefulness of β-blocker therapy in patients with non-insulin-dependent diabetes mellitus and coronary artery disease. *Am J Cardiol.* 1996;77:1273-1277.
43. Mittleman MA, Mintzer D, Maclure M, Tofler GH, Sherwood JB, Muller JE. Triggering of myocardial infarction by cocaine. *Circulation.* 1999;99:2737-2741.
44. Petitti DB, Sidney S, Quesenberry C, Bernstein A. Stroke and cocaine or amphetamine use. *Epidemiology*. 1998;9:596-600.
45. Lester SJ, Baggott M, Welm S, et al. Cardiovascular effects of 3,4-methylenedioxymethamphetamine: a double-blind, placebo-controlled trial. *Ann Intern Med*. 2000;133:969-973.
46. Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. *Circulation.* 2001;103:502-506.
47. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med.* 2000;343: 1826-1832.
48. Fleming GA. The FDA, regulation, and the risk of stroke [editorial]. *N Engl J Med*. 2000;343:1886-1887.
49. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833-1838.
50. Mihoces G. Ephedrine: safe or lethal? debate intensifies as supplement becomes the energy booster of choice for athletes. *USA Today*. November 8, 2001:C1, C2.
51. Bergmann CF. FDA asked to ban ephedra products. *Cardiol Today*. November 2001;4:24.
52. Spitzer W, Suissa S, Ernst P, et al. The use of β-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992; 326:501-506.
53. Beasley R, Pearce N, Crane J, Burgess C. β-Agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? *J Allergy Clin Immunol*. 1999;104(2, pt 2):S18-S30.
54. Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet.* 1990; 336:1396-1399.
55. Newhouse MT, Chapman KR, McCallum AL, et al. Cardiovascular safety of high doses of inhaled fenoterol and albuterol in acute severe asthma. *Chest.* 1996;110:595-603.
56. Suissa S, Hemmelgarn B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med.* 1996;154(6, pt 1):1598-1602.
57. Meier CR, Jick SS, Derby LE, Vasilakis C, Jick H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet.* 1998;351:1467-1471.
58. Au DH, Lemaitre RN, Curtis JR, Smith NL, Psaty BM. The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. *Am J Respir Crit Care Med.* 2000;161(3, pt 1):827-830.
59. Yeragani VK, Pohl R, Balon R, et al. Effect of imipramine treatment on heart rate variability measures. *Neuropsychobiology.* 1992;26:27-32.
60. Guite HF, Dundas R, Burney PG. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax*. 1999; 54:301-307.

61. Packer M, Carver JR, Rodeheffer RJ, et al, PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med.* 1991;325:1468-1475.
62. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med.* 2000;160:2477-2480.
63. Packer M, Bristow MR, Cohn JN, et al, U. S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.
64. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet.* 2001;357:1385-1390.
65. Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet.* 1999;353:9-13.
66. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
67. O'Keefe JH Jr, Magalski A, Stevens TL, et al. Predictors of improvement in left ventricular ejection fraction with carvedilol for congestive heart failure. *J Nucl Cardiol.* 2000;7:3-7.
68. Julius S, Majahalme S. The changing face of sympathetic overactivity in hypertension. *Ann Med.* 2000;32:365-370.
69. Ruzicka M, Leenen FH. Relevance of 24 H blood pressure profile and sympathetic activity for outcome on short- versus long-acting 1,4-dihydropyridines. *Am J Hypertens.* 1996;9:86-94.
70. Singh BN. The relevance of sympathetic activity in the pharmacological treatment of chronic stable angina. *Can J Cardiol.* 1999;15(suppl A):15A-21A.
71. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA.* 1995;274:620-625.
72. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation.* 1995;92:1326-1331.
73. Alderman MH, Cohen H, Roque R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet.* 1997;349:594-598.
74. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2000;283:1967-1975.
75. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145-153.
76. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet.* 1999;353:611-616.
77. O'Keefe JH, Wetzel M, Moe RR, Bronsnahan K, Lavie CJ. Should an angiotensin-converting enzyme inhibitor be standard therapy for patients with atherosclerotic disease? *J Am Coll Cardiol.* 2001;37:1-8.
78. Domanski MJ, Exner DV, Borkowf CB, Geller NL, Rosenberg Y, Pfeffer MA. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol.* 1999;33:598-604.
79. Ligtenberg G, Blankestijn PJ, Oey PL, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. *N Engl J Med.* 1999;340:1321-1328.
80. Grassi G, Cattaneo BM, Seravalle G, et al. Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. *Circulation.* 1997;96:1173-1179.
81. Athyros VG, Didangelos TP, Karamitsos DT, Papageorgiou AA, Boudoulas H, Kontopoulos AG. Long-term effect of converting enzyme inhibition on circadian sympathetic and parasympathetic modulation in patients with diabetic autonomic neuropathy. *Acta Cardiol.* 1998;53:201-209.
82. Hjalmarson A. Prevention of sudden cardiac death with β-blockers. *Clin Cardiol.* 1999;22(suppl 5):V11-V15.
83. Heidenreich PA, Lee TT, Massie BM. Effect of β-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol.* 1997;30:27-34.
84. Kjekshus JK. Importance of heart rate in determining β-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol.* 1986;57:43F-49F.
85. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation.* 1999;99:2192-2217.
86. Carney RM, Freedland KE, Veith RC, et al. Major depression, heart rate, and plasma norepinephrine in patients with coronary heart disease. *Biol Psychiatry.* 1999;45:458-463.
87. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression with reduced heart rate variability in coronary artery disease. *Am J Cardiol.* 1995;76:562-564.
88. Watkins LL, Grossman P. Association of depressive symptoms with reduced baroreflex cardiac control in coronary artery disease. *Am Heart J.* 1999;137:453-457.
89. Lake CR, Pickar D, Ziegler MG, Lipper S, Slater S, Murphy DL. High plasma norepinephrine levels in patients with major affective disorder. *Am J Psychiatry.* 1982;139:1315-1318.
90. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. *BMJ*. 1999;318:1460-1467.
91. Lesperance F, Frasure-Smith N, Juneau M, Theroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med*. 2000;160:1354-1360.
92. Ziegelstein RC. Depression in patients recovering from a myocardial infarction. *JAMA*. 2001;286:1621-1627.
93. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). *Am J Cardiol.* 1995;75:882-885.
94. Watkins LL, Grossman P, Krishnan R, Sherwood A. Anxiety and vagal control of heart rate. *Psychosom Med.* 1998;60:498-502.
95. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Symptoms of anxiety and risk of coronary heart disease: the Normative Aging Study. *Circulation.* 1994;90:2225-2229.
96. Iribarren C, Sidney S, Bild DE, et al. Association of hostility with coronary artery calcification in young adults: the CARDIA study. *JAMA.* 2000;283:2546-2551.
97. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. A meta-analytic review of research on hostility and physical health. *Psychol Bull.* 1996;119:322-348.
98. Mittleman MA, Maclure M, Sherwood JB, et al, Determinants of Myocardial Infarction Onset Study Investigators. Triggering of acute myocardial infarction onset by episodes of anger. *Circulation.* 1995;92:1720-1725.
99. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. *N Engl J Med.* 1984;311:552-559.

100. Case RB, Moss AJ, Case N, McDermott M, Eberly S. Living alone after myocardial infarction: impact on prognosis. *JAMA.* 1992;267:515-519.
101. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction: a prospective, population-based study of the elderly. *Ann Intern Med.* 1992;117:1003-1009.
102. Kamarck TW, Everson SA, Kaplan GA, et al. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. *Circulation*. 1997;96:3842-3848.
103. Kral BG, Becker LC, Blumenthal RS, et al. Exaggerated reactivity to mental stress is associated with exercise-induced myocardial ischemia in an asymptomatic high-risk population. *Circulation*. 1997;96:4246-4253.
104. Chandra V, Szklo M, Goldberg R, Tonascia J. The impact of marital status on survival after an acute myocardial infarction: a population-based study. *Am J Epidemiol.* 1983;117:320-325.
105. Oxman TE, Freeman DH Jr, Manheimer ED. Lack of social participation or religious strength and comfort as risk factors for death after cardiac surgery in the elderly. *Psychosom Med.* 1995; 57:5-15.
106. Linden W, Stossel C, Maurice J. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. *Arch Intern Med.* 1996;156:745-752.
107. Blumenthal JA, Jiang W, Babyak MA, et al. Stress management and exercise training in cardiac patients with myocardial ischemia: effects on prognosis and evaluation of mechanisms. *Arch Intern Med.* 1997;157:2213-2223.
108. Iwane M, Arita M, Tomimoto S, et al. Walking 10,000 steps/day or more reduces blood pressure and sympathetic nerve activity in mild essential hypertension. *Hypertens Res.* 2000;23:573-580.
109. Pardo Y, Merz CN, Velasquez I, Paul-Labrador M, Agarwala A, Peter CT. Exercise conditioning and heart rate variability: evidence of a threshold effect. *Clin Cardiol.* 2000;23:615-620.
110. Albert CM, Mittleman MA, Chae CU, Lee I-M, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med*. 2000;343:1355-1361.
111. Maron BJ. The paradox of exercise [editorial]. *N Engl J Med.* 2000;343:1409-1411.
112. Kannel WB, Wilson P, Blair SN. Epidemiological assessment of the role of physical activity and fitness in development of cardiovascular disease. *Am Heart J.* 1985;109:876-885.
113. Mensink GB, Ziese T, Kok FJ. Benefits of leisure-time physical activity on the cardiovascular risk profile at older age. *Int J Epidemiol.* 1999;28:659-666.
114. Bijnen FC, Feskens EJ, Caspersen CJ, et al. Physical activity and cardiovascular risk factors among elderly men in Finland, Italy, and the Netherlands. *Am J Epidemiol.* 1996;143:553-561.
115. Lemaitre RN, Siscovick DS, Raghunathan TE, Weinmann S, Arbogast P, Lin DY. Leisure-time physical activity and the risk of primary cardiac arrest. *Arch Intern Med.* 1999;159:686-690.
116. Lakka TA, Laukkanen JA, Rauramaa R, et al. Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann Intern Med.* 2001;134:12-20.
117. O'Keefe JH Jr, Harris WS. From Inuit to implementation: omega-3 fatty acids come of age. *Mayo Clin Proc*. 2000;75:607-614.
118. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet.* 1999;354:447-455.
119. Rissanen T, Voutilainen S, Nyyssonen K, Lakka TA, Salonen JT. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Circulation*. 2000;102:2677-2679.
120. de Lorgeril M, Salen P. Diet as preventive medicine in cardiology. *Curr Opin Cardiol.* 2000;15:364-370.
121. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet.* 1989;2:757-761.
122. Weisser B, Struck A, Gobel BO, Vetter H, Dusing R. Fish oil and baroreceptor function in man. *Klin Wochenschr.* 1990;68(suppl 20):49-52.
123. Christensen JH, Gustenhoff P, Korup E, et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomised controlled trial. *BMJ.* 1996;312:677-678.
124. Christensen JH, Skou HA, Fog L, et al. Marine n-3 fatty acids, wine intake, and heart rate variability in patients referred for coronary angiography. *Circulation.* 2001;103:651-657.
125. Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension.* 1999;34: 253-260.
126. Christensen JH, Korup E, Aaroe J, et al. Fish consumption, n-3 fatty acids in cell membranes, and heart rate variability in survivors of myocardial infarction with left ventricular dysfunction. *Am J Cardiol.* 1997;79:1670-1673.
127. Sellmayer A, Witzgall H, Lorenz RL, Weber PC. Effects of dietary fish oil on ventricular premature complexes. *Am J Cardiol*. 1995;76:974-977.
128. Billman GE, Hallaq H, Leaf A. Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. *Proc Natl Acad Sci U S A*. 1994;91:4427-4430.
129. Leaf A, Kang JX. Prevention of cardiac sudden death by n-3 fatty acids: a review of the evidence. *J Intern Med.* 1996;240:5-12.
130. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA.* 1995;274: 1363-1367.