Mental Stress and Coronary Artery Disease: A Multidisciplinary Guide

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Research suggests that acute and chronic stress are risk factors for the development and progression of coronary artery disease. Much of this work is multidisciplinary, using unfamiliar concepts deriving from disciplines other than cardiology and medicine. This article addresses and clarifies, for the cardiologist, some of the key concepts and issues in this area and provides an overview of evidence linking acute and chronic stress to cardiac pathology. Areas addressed include definitions and measurement of mental stress, methodological issues in stress research, and distinctions between stress and variables such as personality, emotion, and depression. Mental stress is a multifactorial process involving the environment, individual experiences and coping, and a set of neuroendocrine, autonomic, cardiovascular, and other systemic physiologic responses. There are difficulties identifying a single consensus physiologic stress measure because of individual differences in perceptions and physiologic response patterns. Nonetheless, important associations exist between mental stress and clinically relevant cardiovascular end points. As multidisciplinary research in this area continues, one major goal is the better integration of psychosocial knowledge and measures with cardiology research and practice.

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Among the lay public, it is widely believed that acute and chronic stress are important risk factors for the development and progression of coronary artery disease (CAD).1,2 In support of this view, epidemiologic studies, case reports, and human and animal research demonstrate effects of environmental, social, and psychological factors on cardiac pathology and pathophysiology.3-8 Despite this evidence, many in the medical community remain unsure of the meaning of this research.9-11 Some of this confusion is caused by the fact that much of this research is multidisciplinary, using unfamiliar behavioral science terminology and concepts that derive from disciplines other than cardiology and medicine. In other cases, research is difficult to evaluate because of imprecise definition and measurement of psychosocial factors, confounding by unmeasured variables that may be present in epidemiologic studies, and the multifactorial nature of CAD risk factors.

Several psychosocial variables have been identified as putative risk factors, including stress, emotional disorders, personality traits, depression, and poor social support.4,6,8,12-14 The present review will focus on the concept of psychosocial stress and will address and clarify, for the cardiologist, some of the key concepts and issues in this area of research.

Stress: Environment, Person, or Physiologic Response?

Stress has been an important focus of research on environmental and psychosocial factors and health. With respect to cardiovascular disease, animal and human research has documented associations between measures of stress and risk factors,15-17 intermediate pathophysiologic
markers in the CAD process (eg, inflammatory response, endothelial dysfunction, platelet aggregation, etc), and clinical CAD. Measures of stress and distress have been associated with the development of coronary artery atherosclerosis, increased left ventricular (LV) mass, and coronary artery calcification. In patients with CAD, stress has also been implicated as an acute trigger of myocardial ischemia and infarction, malignant arrhythmia, and sudden cardiac death. Despite these findings, issues in the definition and measurement of stress and inconsistencies in findings contribute to uncertainties regarding this research.

Definitions and Assumptions in Stress Research

There are differences in the way the term stress is defined, measured, and used in research. Despite these differences, most contemporary definitions of stress accept the following assumptions: (1) stress is a process that occurs when environmental demands exceed the adaptive capacity of the organism; (2) this process results in psychological and/or biologic changes that may have consequences for health; and (3) individual interpretations or “appraisals” are important in determining responses to stress.

In part, inconsistencies and controversies evident in the scientific literature on the effects of stress in the pathophysiology of disease are due to the fact that some stress research emphasizes elements of the environment, other studies focus on personal perceptions or emotions, and still others emphasize physiologic responses to threatening or challenging circumstances. Reflecting these differences are several approaches to measuring and studying stress. One perspective focuses on assessment of observable environmental events or circumstances (called stressors) that may place substantial demands on the individual. A second approach focuses on individuals’ subjective perceptions or evaluations (also called “appraisals”) of stressors and of their ability to cope with threats and demands created by stressors. A third approach focuses on cardiovascular, neural, endocrine, and other systemic responses produced as a result of exposure to threatening or demanding environmental events or situations. A fourth, more integrated conceptualization of stress incorporates environmental events or triggering stimuli; perceptions or appraisals of these events; and resulting physiologic responses (Fig 1). Each of these 3 parts represents a component or stage of a process of interaction between person and environment in which demands challenge or exceed the perceived ability to cope.

Acute Versus Chronic Stress

A temporal distinction between chronic and acute risk stress is useful in understanding the possible role of mental stress in CAD. Chronic stress is long standing and presumably exerts its influence over a period of time. Chronic stressors include persistent conditions associated with one’s occupation (eg, job demands), social relationships (eg, marital or family conflict), and the environment (eg, living in a low-income, high-crime neighborhood). Acute stress involves transient changes resulting from exposure to aversive environmental events of brief duration, often of abrupt onset, and both unpredictable and uncontrollable (eg, acute trauma, natural or man made disasters). Research on acute stress has contributed to the understanding of the timing of clinical coronary events by identifying the
importance of environmental triggers of those events in individuals with elevated chronic or episodic risk factors and/or known coronary disease (see Muller et al\textsuperscript{46}).  

**Environmental Stressors and CAD**

Some research on environmental stress is based on the notion that cumulative exposure to stressful life events is a predisposing factor for disease.\textsuperscript{42,47-50} In this regard, both human and animal research has linked chronic environmental and social stressors to the development and clinical course of CAD.

**Chronic Stress**

Controlled animal experiments demonstrate important effects of social stress and social status on the development of atherosclerosis. For example, primate models of social disruption support a relationship between exposure to chronic stressors and the development of coronary artery, aortic atherosclerosis, and endothelial dysfunction.\textsuperscript{34,51-55} In animal models of genetic cardiomyopathy, chronic stress has been shown to worsen the effects of heart failure and cardiac death.\textsuperscript{56,57} In the human literature, chronic job strain and occupational stress\textsuperscript{58,62} and marital strain\textsuperscript{63} have been linked to end points such as incident and recurrent myocardial infarction (MI). There is evidence that the chronic stress associated with poverty, crime, and economic hardship may contribute to increased cardiovascular risk associated with low socioeconomic status.\textsuperscript{59} In addition, post-MI patients with life stress and lack of supportive social relationships show an increased risk of recurrent MI and cardiac death.\textsuperscript{65,66} Supportive social networks, in turn, have been found to be protective against the potentially harmful effects of stress.\textsuperscript{67,68}

**Acute Stress**

Animal models have shown that acute, socially induced conflict producing an anger-like state can elicit coronary constriction\textsuperscript{69} and lower the threshold for ventricular fibrillation in dogs with experimentally induced coronary artery blockage.\textsuperscript{70} Induced anger also increases risk markers for malignant arrhythmias such as T-wave alternans.\textsuperscript{71}

Epidemiologic studies support the notion that in vulnerable individuals and patients with CAD, acute stressful or traumatic events can act as triggers for MI, malignant arrhythmias, and sudden cardiac death.\textsuperscript{26,39,40} Research has documented an increase in cardiovascular deaths and augmented rates of MI after several general disasters and personal traumas. During the 1994 Northridge earthquake, critical care unit admissions for acute MI were more than doubled (odds ratio, 2.4) in the week after the earthquake, as compared with the week before the disaster, particularly for hospitals within 15 miles of the earthquake epicenter.\textsuperscript{30,31} During the initial days of the 1991 Gulf War, incidence of fatal and nonfatal cardiac events was increased among the population living close to Tel Aviv.\textsuperscript{72} Cases of acute MI treated in the intensive care unit of a Tel Aviv medical center were elevated during the week after the missile attacks (January 17-25, 1991) compared with the week before the attacks and with an index period consisting of the same week a year earlier (Fig 2).

An increased incidence of ventricular arrhythmias was observed in patients in New York City following the 9/11 World Trade Center attacks.\textsuperscript{73} In 200 consecutive patients with implantable
cardioverter defibrillators scheduled for routine follow-up, incidence of tachyarrhythmias demonstrated a 2- to 3-fold increase, compared with the 30 days before 9/11 (Fig 3). These results were attributed to the stress associated with the terrorist attack. Interestingly, unlike other disasters, the increase in discharges did not occur until 3 days after the event. The increase in tachyarrhythmias after 9/11 was also demonstrated in patients living geographically distant from New York.74 However, other studies in the literature did not replicate these findings.26

Effects of Acute Stress on Myocardial Ischemia and Ventricular Arrhythmia

Laboratory and ambulatory clinical studies of patients with CAD provide additional evidence that mental stress acts as an acute trigger of myocardial ischemia and cardiac electrical instability. At least 3 studies found that risk of daily life myocardial ischemia was elevated during periods of daily life mental stress.75-77 Of interest, although stress-induced ischemia occurred relatively infrequently in patients with CAD, when it did occur, it was usually silent (asymptomatic) and accompanied by relatively low heart rate elevations. Moreover, stress was equal in potency to exercise as a trigger of ischemia.75,76

More than 20 laboratory studies using structured mental stress tests such as pressured mental arithmetic or simulated public speaking demonstrate that acute mental stress induces myocardial ischemia in 40% to 70% of patients with CAD.18,33,78-82 A variety of methods to assess ischemia have been used in this research, including radionuclide ventriculography, echocardiography, myocardial perfusion imaging, and positron emission tomography.40 As in the study of daily life mental stress, laboratory mental stress induces ischemia that is usually silent and occurs at lower heart elevations compared to exercise. In addition, mental stress–induced ischemia appears to occur more often in patients with reduced LV function.78

Factors involving both decreased myocardial supply and increased myocardial demand may be involved in mental stress ischemia. In patients with CAD, some,24,83 but not all studies have observed epicardial coronary constriction due to endothelial dysfunction during mental stress.84 Other studies 79,84,85 have reported impaired dilation in resistance vessels during mental stress. Blood pressure increases during mental stress are substantial, with systolic blood pressure increases comparable to exercise and diastolic responses greater than exercise.33,80 It has been observed that elevated total peripheral resistance is associated with the occurrence of mental stress–induced ischemia.80 Thus, factors relating to increased afterload and increased cardiac demand are also likely involved in this pathophysiologic process.

Stress-induced autonomic nervous system activation may predispose patients with CAD to lethal arrhythmias through alterations of cardiac neural transmission86 and through the combination of coronary occlusion and mental stress–induced ischemia.87 Acute mental stress in the laboratory can produce microvolt T-wave alternans, a marker of cardiac electrical instability, in patients vulnerable to ventricular arrhythmias.88,89 Lampert and colleagues29 found that mental stress alters ventricular tachycardia (VT) cycle length and termination without evidence of ischemia. Of 10 patients that underwent testing during mental stress (mental arithmetic and anger recall), induced VT was faster in 5 patients, VT became more difficult to terminate in 5 patients during mental stress, and 4 required implantable cardioverter-defibrillator therapy (Fig 4). These findings
suggest that the facilitation of lethal ventricular arrhythmias may be a mechanism through which mental stress leads to sudden death.

Self-Reported Distress, Perceived Stress, and CAD

The influential work of Lazarus emphasized the importance of individual perceptions as determinants of human responses to stress. This notion that individual perceptions can moderate stress responses has provided the basis for effective cognitive therapies to reduce the adverse effects of stress by modifying the individual’s interpretations of events and by enhancing coping abilities. Briefly, the notion here (see Fig 1) is that the individual makes an appraisal assessing whether the stimulus poses a danger or threat. Because of differences in prior experiences, personality, and other psychological factors, all individuals may not experience the same objective environmental event as equally stressful or aversive. Based on this initial evaluation or appraisal, coping behaviors are implemented that may or may not be effective in reducing or eliminating the threat or its emotional impact.

Individual differences in appraisal and coping effectiveness introduce changes in the magnitude of physiologic responses to stressors. The magnitude of physiologic responses to stressors may be influenced by other individual difference factors that may operate independently of appraisal and coping. Among these are temperament and other characteristics that reflect genetic factors, health habits such as regular exercise and environmental factors that influence autonomic, neuroendocrine, and cardiovascular systems. Nonetheless, the particular emphasis on appraisal and coping has come to dominate psychological perspectives on stress.

Individual perceptions of stress and reported distress appear to be associated with several different forms of cardiovascular dysfunction. Studies have demonstrated an association between perceived work stress or strength of exposure to job strain and CAD incidence or prevalence. Recently published findings
from the INTERHEART study compared 11119 CAD and 13648 matched control subjects from 52 countries. Self-reported psychosocial factors (perceived stress at work or home, financial stress, stressful life events, depression, and perceived disempowerment) were associated with risk of the first acute MI (odds ratios ranging between 1.33 to 2.17, depending on the measure). These effects were comparable with those of standard CAD risk factors, were independent of socioeconomic status and smoking, and were generally consistent across geographic region, sex, age, and ethnic group. Potential shortcomings of this study include the use of psychological measures of unknown reliability and validity, and the case-control design of the study. Another follow-up study of over 7000 women found that those who had moderate to

Fig 5. Case study illustrating effects of internally generated emotional distress in provoking myocardial ischemia. Two-dimensional diastolic and systolic echocardiographic still frame images of Korean war veteran with CAD who was asked to visualize war experiences he would not verbalize. Echocardiography performed during mental imagery and subsequently during upright bicycle exercise. During rest, note normal systolic excursion of apical, anterior, and anterolateral walls. With mental imagery and during exercise, there is a similar pattern of inferoapical wall motion. These findings are consistent with myocardial ischemia induced by mental imagery and by exercise stress in a left anterior descending branch culprit distribution, confirmed subsequently at cardiac catheterization.
severe perceived stress were more likely to have a new diagnosis of coronary heart disease at follow-up, as compared to those with no perceived stress. This result was obtained after controlling for traditional nonpsychosocial risk factors, and perceived stress was the only psychosocial variable found to be an independent risk factor for new diagnosis. Perceived stress was also associated with cardiovascular mortality in a large sample of Japanese men and women.

A powerful effect of individual psychological processes in the provocation of myocardial ischemia is illustrated in a case study (Krantz and Gottdiener, unpublished data) of a war veteran with known CAD who was asked to imagine a previously experienced traumatic situation. Echocardiographic imaging of ventricular function was conducted during imagery and subsequently during bicycle exercise (Fig 5). The patient demonstrated normal LV function at rest and ischemic wall motion abnormalities during exercise and while imagining the traumatic situation. This case study illustrates that internally generated emotion and distress may elicit clinically important pathophysiologic processes such as myocardial ischemia.

Biologic Perspectives in Stress Research

A foundation for the extensive body of research on pathophysiologic effects of stress was provided by the physiologist Walter Cannon, who observed in an animal model that environmental threats provoked a general discharge of the sympathetic nervous system (SNS), marked by increases in circulating catecholamines, preparing the animal for fighting or fleeing. This response was viewed as part of a homeostatic process that was important for survival. Later, Selye described a generalized physiologic stress response to a variety of noxious stimuli, marked by activation of the pituitary adrenal cortical axis and corticosteroid responses and their physiologic effects. Measures of corticosteroid responses (eg, cortisol and corticosterone) are frequently used as stress indicators in contemporary human and animal research. Mason, among others, presented evidence for the specificity of responses to stress—namely, that distinctive cardiovascular and endocrine response patterns are specific to particular types of stressors. The notion that the nature and direction of cardiovascular and neuroendocrine responses depend on the type of environmental stressor challenges the idea that a single unitary measure of physiologic response to stress can be identified that is adequate for all stressful situations.

Physiologic responses to stress involve the coordinated responses of multiple systems, including central, autonomic, endocrine, cardiovascular, musculoskeletal, gastrointestinal, and immune/inflammatory systems. Assessment of these parameters, in particular, cardiovascular and neuroendocrine responses, is used to measure the presence of stress and its effects or outcomes. Current research on the effects of mental and physical stress on cardiac pathophysiology emphasizes effects of stress-induced central and autonomic nervous system activation in the development and progression of CAD. This activation might predispose to MI and to sudden cardiac death by promoting coronary endothelial dysfunction, immune/inflammatory responses, and atherosclerosis; influencing pathophysiologic processes that occur in the presence of atherosclerosis and increase vulnerability to clinical events; and/or by directly triggering lethal arrhythmias through alterations of neural transmission to the heart.

Evidence suggests several specific components of the physiologic responses to stress that may promote coronary vasoconstriction, platelet aggregation, or plaque rupture. Mental stress can produce arterial pressure surges, often comparable with those elicited by acute exercise. In patients with vulnerable plaque, a vascular pressure surge may cause a plaque to rupture and lead to occlusive or nonocclusive coronary thrombosis. In the presence of atherosclerosis, stress-induced elevations in blood pressure, heart rate, and catecholamines increase myocardial oxygen demand and result in acute myocardial ischemia. Furthermore, if mental stress has induced coronary vasoconstriction or a state of hypercoagulation, small thrombi may trigger a blood clotting cascade, resulting in acute coronary occlusion and subsequent MI, ischemia, or vulnerability to arrhythmias or sudden death. Evidence also suggests that mental stress can lead to arterial vasoconstriction in diseased coronary vessels with damaged coronary endothelium.
Physiologic Stress Responses as Predictors of CAD Prognosis and Outcomes

In human and animal research, there are well-established individual differences in cardiovascular and neuroendocrine response to stress. These physiologic responses to stress have been used as markers of stable individual differences that may be predictors of subsequent CAD outcomes.

“Stress reactivity” involves the assessment of physiologic changes in response to stressors, as opposed to the sole assessment of resting/baseline levels of physiologic variables. The notion that excessive reactivity to stress may itself be a risk factor for coronary disease has been examined in several studies. Exaggerated blood pressure responses during mental stress are predictive of enhanced carotid atherosclerosis in men. One study of men followed up for 23 years found that the magnitude of diastolic blood pressure reactions to a cold pressor test predicted later incident heart disease, although another study failed to replicate this finding. Programmatic studies of cynomolgus monkeys fed a cholesterol-rich diet showed that high heart rate reactors in response to a standard laboratory stress (threat of capture) had nearly twice the amount of coronary atherosclerosis than did low heart rate reactors. In cardiac patients, high blood pressure reactors to acute stress are more likely to evidence mental stress–induced ischemia and to show worsened clinical outcomes over time. At least 4 studies have demonstrated that patients with CAD with myocardial ischemia inducible by mental stress demonstrate increased risk of subsequent clinical events. For example, in patients with mental stress–induced LV wall motion abnormalities, 44% experienced new cardiac events, compared with 23% in those without mental stress ischemia. Another study prospectively followed up 126 patients with stable angina for an average of 3.2 years. A transient decrease in ejection fraction of greater than 5% during mental stress was associated with an increased risk of clinical events (odds ratio, 2.4). A study of total mortality reported that, in 196 patients with CAD followed up over 5 years, new or worsened wall motion abnormalities during the speech test were present in 40% of those who died, compared with 19% of survivors, and significantly predicted total mortality. Because most of the patients in all these studies had prior positive exercise stress tests, the predictive value of mental stress testing may only be applicable in this population.

Stress and Similar Psychosocial Variables: Personality, Emotion, and Depression

Variables that overlap with the concept of stress are also promising psychosocial risk factors for CAD, a fact that both enriches and complicates the picture. Personality attributes in general, and especially anger-related traits, have long been studied for their possible role in predisposing individuals to experience cardiovascular disease. More recently, psychiatric syndromes and conditions such as anxiety and, in particular, depression, have attracted enormous attention in this area. Personality and emotion share certain characteristics with stress, but these 3 concepts are best seen as referring to distinctive factors.

Personality Factors and CAD

Personality involves patterns of thought, feeling, and action that are stable both over time and across different situations. Interest in the role of personality in coronary disease spurred research on type A behavior, which consists of anger and hostility, competitive drive, and impatience. Early epidemiologic studies demonstrated that Type A behavior was associated with increased CAD incidence in men over an 8 1/2–year period. Subsequent evidence did not support the predictive utility of a broader type A behavior pattern and indicated that anger-related aspects of type A may account for its risk-enhancing effects. These observations led to a focus on trait hostility as a promising CAD risk factor. Hostility is defined as a personality attribute involving negative attitudes, easily aroused anger, and aggressive behavior. Methods for assessing hostility differ in their emphasis on each of these behavioral components. One frequently used method, the Cook and Medley hostility scale (Ho), reflects attitudes of cynicism and mistrust and anger experience. Evidence has provided support for an association
between hostility and incidence of CAD.\textsuperscript{115,120} Evidence that type A and hostility operate independently of traditional risk factors led to a focus on other mechanisms, including some that involve behavioral and physiologic responses to stress.\textsuperscript{121,122}

### Anger and Other Emotions

Thought to be one of several basic emotions, anger may be defined as an acute state, comprised of behavioral changes (eg, facial muscle movements), subjective feelings (eg, mild irritation, rage), and physiologic responses including increased sympathetic outflow and adrenergic stimulation of the heart and blood vessels.\textsuperscript{123} Emotions are most commonly assessed by self-reports of emotional experience. Measures of the experience and expression of anger, involving self-report rating scales, have been prospectively linked to cardiovascular morbidity and mortality.\textsuperscript{124} One study indicated that the experience of anger was associated with increased risk for an MI for up to 2 hours, with additional anger episodes within the 2-hour period further increasing risk of MI\textsuperscript{125} (Fig 6).

Moreover, both laboratory-induced\textsuperscript{126-128} and daily life experiences of anger\textsuperscript{75,76} have been linked to the development of myocardial ischemia during daily life. For example, one study demonstrated that recalling an anger-provoking experience produced a reduction in LV ejection fraction in coronary patients.\textsuperscript{127} Another study showed that anger experiences in the naturalistic setting induced ST-segment depression in coronary patients undergoing Holter monitoring,\textsuperscript{75} and still another study reported a similar association using a measure that reflected negative emotions including frustration.\textsuperscript{76}

Much of this work has been facilitated by the development of reliable methods for assessment of daily life experiences of stress, emotion, and activities.\textsuperscript{129,130} Short-term emotional states such as anxiety and hostility can also be measured by several reliable instruments.\textsuperscript{131-133}

### Clinical and Subclinical Psychiatric Syndromes

Anxiety and depression have been studied in relation to CAD, both as dimensions describing normal-range and subclinical individual differences and also as clinical diagnostic categories such as anxiety disorders and major depressive disorder. Although epidemiologic findings point to anxiety syndromes involving worry or panic disorder as possible CAD risk factors,\textsuperscript{120,7} the role of depression has received particular attention. Depressive symptoms include components of emotion or affect (eg, feeling sad or blue), cognition or thoughts (eg, negative views of self and the future), and somatic/vegetative states (eg, lack of energy, disturbances of sleep and appetite). These symptoms may be assessed using self-report questionnaires such as the Beck Depression Inventory\textsuperscript{134} and Center for Epidemiologic Studies Depression Scale.\textsuperscript{135} Major depression as a diagnostic category is usually assessed by a structured interview according to criteria specified in the \textit{Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition}.\textsuperscript{136} Both subclinical levels of depressive symptoms and major depressive disorder have been implicated in the development of CAD and sequelae.
including MI and cardiac mortality.\textsuperscript{7,13} Possible mechanisms for these effects include immune/inflammatory processes, hemodynamic changes, and other factors responsible for endothelial damage, effects on heart rhythm, and alterations in blood platelet coagulability.\textsuperscript{7,13}

**Stress, Personality, and Emotion: Similarities and Differences**

Within the epidemiologic literature linking anger/hostility, depression, and anxiety to CAD endpoints, studies typically focus on a single psychosocial variable, rather than taking a multivariate approach.\textsuperscript{7,120} It is therefore difficult to say conclusively whether these variables each have unique effects on CAD or whether their influence is overlapping and involves shared common pathways. It is well known that emotional states such as anxiety, anger, and sadness are moderately correlated with one another.\textsuperscript{137} Personality characteristics such as hostility also include elements of anger in their definition. On the other hand, these characteristics also exhibit some independence from one another.

Clinical syndromes such as major depression and anxiety disorders are rigorously defined and can be clearly distinguished from the normal range of emotions, such as anger or irritability, and also from the distress encountered during normal daily activities. Yet it is almost always possible to attribute the findings of one of these emotional factors either to the person (eg, personality hostility, anxiety, or depressive syndrome) or to an environmental stressor that may have produced or exacerbated the emotional condition. Unfortunately, sorting out the distinctions and interactions of stress, personality, and emotion as they are relevant to CAD is at an early stage and must await future research for a resolution.

**Stress: One Response or Many?**

As noted previously, because the stress process involves objective environmental stimuli, individual perceptions or evaluations, and physiologic responses, indicators of each of these three factors have been used to assess stress. However, most studies only measure stress in one of these domains (eg, self report only or physiologic responses only). Assessment of stress can be complicated by the fact that all of these stress markers may not be present in an individual at any particular time. A useful analogy might be differences between various markers of ischemia (eg, myocardial perfusion, LV wall motion, electrocardiographic changes) or differences between structural and functional measures of CAD. Of these multiple indicators, just as there is no single “gold standard” for the presence of myocardial ischemia, there is no single consensus measure of stress. Relying on the presence of a single potentially stressful environmental event, without measuring self-reported distress, is often problematic because there are differences in interpretations of potentially threatening events and in individual coping abilities.

**Self-Report**

Perhaps the most common general methodologic approach in stress research is to use self-report instruments. Self-report measures of stress, including checklists and interviews, are relatively simple and economical to use, and they especially lend themselves to epidemiologic studies in which a premium is necessarily placed on brevity. These measures may include assessments of the accumulation of life events that are believed to cause stress; the amount of stress that is associated with work; level of perceived stress irrespective of its source; and somatic and emotional components of the stress response.

Measures of life events include checklists for quantifying cumulative exposure to various negative events such as job or family difficulties, death in the family, change in residence, loss of a job, and the like, over a defined period such as the past 6 months.\textsuperscript{42} Other methods include self-report diaries of stressful experiences on a daily basis.\textsuperscript{138} Instruments also have been constructed to measure stress specifically stemming from work.\textsuperscript{139} Another questionnaire that shows considerable use and promise is the Perceived Stress Scale,\textsuperscript{140} which measures generalized perceived stress due to multiple causes.\textsuperscript{141} This instrument has proven to be predictive of a variety of biological end points important in the pathophysiology of disease.

The experience of stress can also include somatic symptoms and emotions such as anxiety,
sadness, anger, and fear. Several standardized instruments are available to assess these symptoms.\textsuperscript{142} Other questionnaires focus more specifically on mood states.\textsuperscript{131} Still others measure a range of symptoms including a variety of somatic, psychological, and behavioral reactions.\textsuperscript{143}

The advantages of these instruments include ease of measurement and the fact that they tap into individual experiences of distress. Limitations of self-report measures include biases in self-report and inaccuracies in remembering events. Another issue is that in some cases, especially when only a few questions or items are asked, the reliability and validity of these self-report instruments are not known. Unvalidated or truncated instruments are also frequently used in epidemiologic studies. Self-reported distress may reflect exposure to a prior environmental stressor in some individuals, whereas for others, self-reported distress may reflect personality or psychopathology rather than a response to a particular stressor. Assessing stress using only a measure of self-perceived distress or psychological perceptions has the shortcoming that individuals may not be able or willing to accurately report inner experiences. Analogous problems arise also when a single measure is used to evaluate stress physiology because of individual biologic differences and also because all physiologic systems are not always similarly influenced in extent or direction by central nervous system and autonomic activation.

Physiologic Measurement of Stress

\textit{Corticosteroids}

Cortisol is the primary human glucocorticoid, a type of corticosteroid. Circulating cortisol in the plasma, cortisol in the saliva, and small amounts of free (unmetabolized) cortisol and its metabolite tetrahydrocortisol in urine can be identified via radioimmunoassay techniques. These techniques are relatively easy to use, reliable, and extensively validated.\textsuperscript{41} Saliva samples that can be obtained noninvasively and frequently throughout the day are particularly advantageous to psychophysiologists studying the stress response, especially because of their ease of use in ambulatory subjects.

\textit{Catecholamines}

Another hormonal measure of stress is the assessment of circulating or excreted epinephrine or norepinephrine. Circulating catecholamines in plasma and small amounts of free (unmetabolized) catecholamines and their metabolites (eg, metanephrine and normetanephrine) in urine can be measured using radioenzymatic assay or high-performance liquid chromatography. Both techniques are reliable and have been extensively validated. Turnover and decay of circulating levels occur very quickly, and measures from blood reflect an acute SNS response. Moreover, catecholamines are very sensitive to movement or activity and are affected by diet or drugs. Urinary measures are slower to respond and less sensitive to transient stimuli, thus providing longer, more cumulative indices of SNS activity.\textsuperscript{41}

\textit{Behavioral/Performance Measures of Stress}

Stress responses can also be measured in the form of behavioral and performance assessments. These types of measures provide less subjective assessments of stress in an individual by relying on objective performance outcomes and observer ratings of overt behavior. The rationale for including behavioral measures (eg, decrements in performance) in stress research is that they capture consequences of the stress response that cannot be accessed through self-report or physiology. Although behavioral and performance measures are more objective than self-report, bias can be introduced through subject motivation and ability.\textsuperscript{41}

\textit{Task Demands and Psychophysiologic Response Patterning}

We noted earlier that animal stress studies\textsuperscript{98,99} demonstrated evidence of specificity in which different types of stressors were associated with distinct patterns of neuroendocrine adjustment. These findings have their counterparts in the psychophysiology of human stress. For example, structured tasks used in the laboratory, such as mental arithmetic and the induction of anger, elicit different patterns of responses, that is, increases in myocardial performance reflected in systolic blood pressure and heart rate increases...
and attenuation of the pre-ejection period.\textsuperscript{144-146} By contrast, tasks that require the subject to attend passively to aversive stimuli (eg, watching a stressful film) result in a hemodynamic response characterized by vasoconstriction and more pronounced effects on total systemic resistance.\textsuperscript{145} Still other laboratory tasks (eg, cold pressor) induce a pattern represented by cardiovascular adjustments including small heart rate elevations and large vascular responses. These phenomena further demonstrate how the nature of a stressor determines the pattern of cardiovascular consequences of exposure to stress.

**Concluding Comments and Observations**

In evaluating research on the impact of stress on cardiovascular outcomes, it is important to emphasize several general issues. Most important of these is the fact that stress is a multifactorial process reflecting environmental factors and numerous individual attributes, experiences, and coping behaviors. Stress can result in multiple physiologic response patterns. It is therefore difficult to identify one single consensus marker of stress that is applicable in all situations. Use of a single biologic measure in the assessment of stress can be complicated by individual differences in physiologic stress responses because patterns of physiologic responses depend on the nature and demands of the stressful situation and also because individuals differ in the awareness and reporting of stress and distress.

Standardized, reliable, and valid measures have been developed to assess subjective\textsuperscript{140} and environmental components of stress. Reliable methods have also been developed for assessment of daily life experiences of stress, emotion, and activities.\textsuperscript{129,130} Short-term emotional states and chronic traits such as anxiety and hostility also can be measured by several reliable and valid instruments.\textsuperscript{117,132,133} Unfortunately, because investigators are constrained by limited subject testing time, many epidemiologic studies use shortened or unreliable versions of measurement scales. Reliable and valid instruments should be used where possible.

There are important associations between clinically relevant cardiovascular end points and acute and chronic stressors. These relationships provide a promising direction for further interdisciplinary and multidisciplinary research. As research in this continues, a major goal is better integration of psychosocial concepts and measures into cardiology research and practice.

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