

EFFECTS OF PSYCHOLOGICAL AND SOCIAL FACTORS ON ORGANIC DISEASE: A Critical Assessment of Research on Coronary Heart Disease*

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■ **Abstract** An extensive research literature in the behavioral sciences and medicine suggests that psychological and social factors may play a direct role in organic coronary artery disease (CAD) pathology. However, many in the medical and scientific community regard this evidence with skepticism. This chapter critically examines research on the impact of psychological and psychosocial factors on the development and outcome of coronary heart disease, with particular emphasis on studies employing verifiable outcomes of CAD morbidity or mortality. Five key variables identified as possible psychosocial risk factors for CAD are addressed: acute and chronic stress, hostility, depression, social support, and socioeconomic status. Evidence regarding the efficacy of psychosocial interventions is also presented. It is suggested that, taken as a whole, evidence for a psychological and social impact on CAD morbidity and mortality is convincing. However, continued progress in this area requires multidisciplinary research integrating expertise in cardiology and the behavioral sciences, and more effective efforts to communicate research findings to a biomedical audience.

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INTRODUCTION

“... The evidence for mental state as a cause and cure of today’s scourges is not much better than it was for the afflictions of earlier centuries.... In short, the literature contains few scientifically sound studies of the relation, if there is one, between mental state and disease... it is time to acknowledge that our belief in disease as a direct reflection of mental state is largely folklore”¹ (Angell 1985).

These statements from an editorial in the prestigious *New England Journal of Medicine* continue to reflect the skeptical view of some in the medical community regarding the possible effects of stress, emotions, and personality traits on both chronic diseases (e.g., coronary heart disease, cancers, AIDS) and acute disorders (e.g., upper respiratory infections). There is an extensive accumulated behavioral science literature in health psychology and related fields that suggests the opposite conclusions, at least in terms of the influence of psychological factors on disease processes (Baum & Posluszny 1999, Cohen & Herber 1996, Kiecolt-Glaser et al. 2002, Krantz et al. 1985, Schneiderman et al. 2001). Therefore, this editorial assault aroused considerable opposition and displeasure in the behavioral science

¹The editorialist specifically excluded from her discussion and conceded the important health effects of personal habits such as smoking, diet, alcohol consumption, compliance with health regimens, and the effects of psychological processes on these behaviors. Therefore, health habits and their psychological antecedents are not considered in this review.

community and has been the subject of considerable debate that continues today (Am. Psychosom. Soc. 2001).

What conclusions can be drawn from this divergence of views between behavioral scientists and some in the biomedical community? An informed resolution of these opposing views must depend on a careful evaluation of the existing research literature. In this chapter we address these issues with respect to coronary artery disease (CAD)—including atherosclerosis and its clinical manifestations such as myocardial infarction (heart attack) and sudden cardiac death—which is among the most widely researched areas in health psychology. Recent *Annual Review* chapters have considered the relevance of psychological factors to acute infectious disease, cancer, AIDS, and other chronic diseases (Cohen & Herbert 1996, Schneiderman et al. 2001, Kiecolt-Glaser et al. 2002). Given the present emphasis on organic disease, we focus only on studies that assess “hard,” or verifiable, clinical events (e.g., myocardial infarction and sudden cardiac death) rather than “soft” events (e.g., chest pain, symptoms) that may have an organic basis but that also have a subjective element.

Behavioral research on cardiovascular disorders began with epidemiologic studies documenting the numerous environmental and behavioral lifestyle factors that are involved in the etiology and pathogenesis of CAD. More recently, the ability to combine behavioral research methodologies with methods and techniques in cardiology and medicine to study mechanisms of coronary heart disease pathophysiology has led to increased progress in this area. In addition, a body of evidence suggests that recognizing and treating psychosocial stress in CAD patients might reduce subsequent morbidity and mortality. In light of the breadth of research in this field, we present a selective, rather than comprehensive, review of five key variables that have been identified as possible psychological and psychosocial risk factors for the onset and progression of CAD: acute and chronic stress, behavioral traits of hostility and depression, social support, and socioeconomic status. Evidence regarding the efficacy of psychosocial interventions in CAD patients is also presented.

PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE IN RELATION TO BEHAVIOR

The Disease Process

Coronary heart disease (or ischemic heart disease) refers to a set of conditions thought to result from coronary atherosclerosis, the accumulation of plaque in coronary arteries. The atherosclerotic process is insidious and quite complex, occurring over a span of many years. It involves a series of biochemical, immune-inflammatory, and hemodynamic processes in interaction with various risk factors (Ross 1999). The first symptomatic presentations of this process may include anginal chest pain resulting from decreased cardiac blood flow (ischemia), myocardial

infarction (heart attack), and/or sudden death as a result of malignant disturbances of cardiac rhythm (arrhythmias). Recent evidence suggests that these clinical manifestations of CAD may be triggered by various behavioral activities such as exercise, mental stress, sexual activity, and/or during sleep (Verrier & Mittleman 1996, Mittleman et al. 1995). However, it is important to note that because of the complex pathophysiology of coronary disease, various psychosocial and behavioral variables may relate to different aspects of the disease process.

Physiologic Effects of Stress

The concept of stress is central to linking psychosocial factors to coronary disease, because stress is known to produce hemodynamic, endocrine, and/or immunologic changes that might plausibly affect the development or progression of atherosclerosis or clinical CAD. To the extent that these biological processes are influenced by psychological factors, they lend credibility to the biologic plausibility of psychological variables as potential risk factors. It is important to note, however, that many or all of these physiologic changes can also occur in individuals without coronary disease, and these responses by themselves should not necessarily be considered a sign of disease.

The hemodynamic and neuroendocrine responses to stress are characterized by release of catecholamines and corticosteroids, increases in heart rate, cardiac output, and blood pressure (Krantz & Manuck 1984), and changes in processes relevant to clotting processes (hemostasis and thrombosis), such as coronary vasoconstriction, platelet aggregation, or plaque rupture (Muller et al. 1989, Patterson et al. 1995). In patients with atherosclerosis these physiological changes may increase vulnerability to clinical events. In this regard, studies making use of current techniques for assessing cardiac function provide evidence for the effects of stress as an acute trigger of myocardial ischemia (Deanfield et al. 1984, Gottdiener et al. 1994, Rozanski et al. 1988). Stress-induced autonomic nervous system activation might also predispose to clinical cardiovascular events by promoting the development of atherosclerosis over time and/or dysfunction of cells in the coronary artery lining (endothelium), or by directly triggering lethal arrhythmias through alterations of neural transmission to the heart (Muller et al. 1989, Kamarck & Jennings 1991). More recent models of the stress process provide plausible mechanisms by which chronic stress might affect endocrine and metabolic risk factors (e.g., insulin resistance) for atherosclerosis (e.g., McEwen 1998).

Acute Versus Chronic Risk Factors

In understanding the possible role of behavioral factors in CAD, it is useful to make the temporal distinction between chronic and acute risk factors (Muller et al. 1994). Chronic risk factors—which can be both biological and behavioral—are longstanding and exert their influences over a period of time. Thus, the extent of atherosclerosis can change over time under the influence of longstanding or chronic risk factors such as elevated LDL cholesterol, smoking, hypertension, etc. An acute risk factor is a transient pathophysiological change that results from exposure to

external physical (exercise) or psychological (e.g., acute stress) factors that can trigger clinical events such as ischemia, infarction, or sudden death. Related to the notion of acute risk factors is the concept of psychophysiological reactivity, referring to changes in response to stress (e.g., Krantz & Manuck 1984, Matthews et al. 1995). Together, chronic and acute risk factors are hypothesized to combine to increase risk of clinical events (see Figure 1). A third category, episodic risk factors, refers to behavioral characteristics (e.g., depression) that are neither acute nor chronic, but range in duration from several months to years (Kop 1999). This framework helps explain the heretofore unpredictable timing of coronary events by identifying the importance of behavioral triggers of clinical events. Individuals with elevated chronic or episodic risk factors and/or known coronary disease are at the greatest risk of clinical events when acute risk factors become elevated (see Muller et al. 1994).

Animal Model Studies

Appropriate animal models enable the controlled application of stress manipulations not possible in humans, and the careful assessment of causal pathogenetic mechanisms in disease. Their shortcoming, of course, is that they cannot identically reproduce the human condition in terms of either behavior or physiology. With regard to animal behavioral models of CAD, recent progress has been made in two areas (McCabe et al. 2000): behavioral influences on the development of atherosclerosis and behavioral influences on the pathophysiology of the heart.

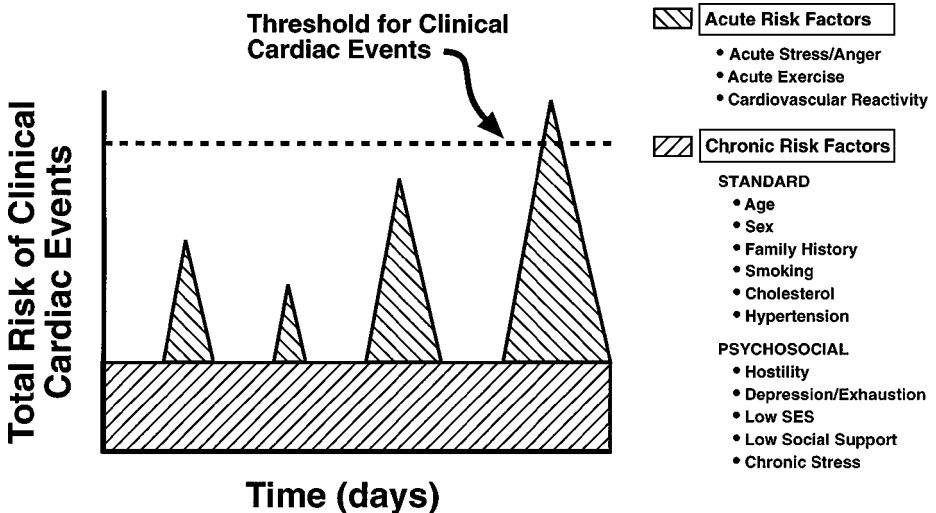


Figure 1 Acute and chronic risk factors combine to reach threshold for clinical cardiac events (myocardial ischemia, myocardial infarction, arrhythmia). Standard risk factors and putative psychosocial risk factors considered in this chapter are listed to the right of the figure. (Adapted with permission from James E. Muller, personal communication.)

With regard to the atherosclerotic process, an important series of studies has been conducted by Kaplan, Manuck and colleagues (see Kaplan & Manuck 1999, McCabe et al. 2000 for reviews). They used cynomolgus monkeys, whose coronary disease pathology closely resembles that of humans. Many of their social behaviors, such as forming a social hierarchy, competition, and aggression, are analogous to those implicated as potential contributors to coronary disease in humans. In addition, premenopausal females of this species are relatively protected from atherosclerosis. For female monkeys, they demonstrated that impaired ovarian function can be induced by the stress of social subordination. This social condition, in turn, eliminates the usual “protection” from atherosclerosis usually demonstrated in females. Furthermore, subordinate premenopausal female animals typically display elevated cortisol levels and exaggerated heart rate responses to stress and display abnormal coronary vasoconstriction (Kaplan & Manuck 1999)—characteristics that have been identified as possible risk factors for CAD in humans.

Other animal models have been utilized to study the effects of stress on hearts with preexisting disease. In this regard, a series of studies (Natelson et al. 1991, McCabe et al. 2000) demonstrated that stress could worsen the effects of heart failure and cardiac death in a hamster model with inherited heart disease. With regard to cardiac arrhythmias and sudden death, studies by Verrier and colleagues (Verrier & Lown 1984) have shown that stress can lower the threshold for malignant arrhythmias in dogs with induced coronary artery blockage. It has also been shown in canines that an acute, socially induced conflict (anger) situation can cause delayed coronary constriction (Verrier et al. 1987) and increase risk markers for arrhythmias (Kovach et al. 2001).

In summary, controlled animal experiments have convincingly demonstrated important effects of social stress and social status on organic disease—the development of atherosclerosis. These studies have investigated mediating mechanisms and have implicated the effects of the sympathetic nervous system in males and disruption of reproductive hormones in females. Research has also convincingly shown that in animals with manifest disease, acute and/or chronic stress may influence cardiac pathology that predisposes to arrhythmias and sudden cardiac death. These data provide strong evidence that social and behavioral factors can affect organic pathology. However, because animal models can only approximate the human condition in terms of either physiology and/or behavior, their relevance to human disease requires additional investigation.

EFFECTS OF CHRONIC AND ACUTE STRESS IN HUMANS

Chronic Stress

The diverse epidemiologic literature on psychosocial stress and coronary heart disease encompasses the effects of chronic stressors including psychological and social conditions at work and in other life domains (e.g., home and family). Some reviewers subsume issues such as social isolation and lack of social support, the

effects of emotional distress and depression on prognosis in post-myocardial infarction (MI) patients under the topic of "stress," but these issues are treated in separate sections in this chapter. In this section we briefly consider the effects of occupational stress and of family demands in women.

OCCUPATIONAL STRESS Research on occupational stress and health has sought to determine which occupations are most stressful and the particular characteristics of occupations that lead to elevated risk of coronary disease (cf. Karasek & Theorell 1990). Working conditions that have been associated with coronary heart disease risk include the psychological demands of the job, autonomy on the job (how much input workers have in making decisions), and satisfaction on the job. Job demands refer to job conditions that tax or interfere with the worker's performance abilities, such as workload and work responsibilities. Level of job autonomy or control refers to the ability of the worker to control the speed, nature, and conditions of work. Job satisfaction includes gratification of the worker's needs and aspirations derived from employment.

Karasek and colleagues (e.g., Karasek & Theorell 1990) proposed that high work demands combined with low decision latitude, resulting in high levels of job strain, are associated with increased risk of coronary disease. Job strain has been shown to predict cardiovascular disease and mortality in several studies of European and American populations (Karasek & Theorell 1990, Karasek et al. 1988, Schnall et al. 1990). However, at least one prospective study of patients who underwent diagnostic testing for coronary disease did not find that occupational stress was related to extent of disease or to subsequent cardiac morbidity or mortality (Hlatky et al. 1995). These negative findings might be attributable to the fact that the study group consisted of a select group of patients, and the effects of job strain may be obscured in such a population. Recent longitudinal studies of male and female civil servants demonstrate that self-reports of low control at work predict CAD in a dose-response gradient (Bosma et al. 1997). Low control is also associated with high concentrations of fibrinogen, a blood clotting factor that predicts cardiovascular disease (Brunner et al. 1996).

FAMILY DEMANDS AND MARITAL STRAIN It is also of interest that occupational stress interacts with family demands, such that mothers who work outside the home may be at greater risk of developing CAD than mothers who do not work outside the home. An analysis from the Framingham Study reported that this risk increases linearly with the number of children a working mother has (LaCroix & Haynes 1987). Other recent studies helped to confirm that working women, particularly those with children, experience stress owing to work overload and role conflicts both at work and at home. For example, Lundberg & Frankenhaeuser (1999) demonstrated that women in their study experienced more work stress and higher norepinephrine levels than men, owing to greater unpaid workload and greater responsibilities for home and family. Moreover, norepinephrine levels were lower at home than at work for men and women who had no children, but not for working mothers.

Acute Stress and Anger as Cardiac Disease Triggers

Recent research has focused on the role of acute stress and emotions as triggers of the onset of CAD manifestations in individuals with preexisting disease. Epidemiologic evidence suggests that in susceptible patients, clinically important cardiac events (e.g., myocardial infarction, cardiac ischemia) are frequently triggered by activities such as physical or mental stress, rather than occurring spontaneously (Muller et al. 1987; see Krantz et al. 1996 for review). In addition, studies making use of a variety of current techniques for assessing cardiac function in the laboratory and in the field provide evidence for pathophysiological mechanisms and effects of behavioral factors as triggers of myocardial ischemia (Deanfield et al. 1984, Gottdiener et al. 1994, Rozanski et al. 1988).

EPIDEMIOLOGIC STUDIES Earlier epidemiologic studies observed that there was an increase in cardiovascular mortality among widowers. Other studies have noted that stressful life events, such as death of a spouse and/or other loss events, occurred with increased frequency in the 24 hours preceding sudden cardiac death (e.g., Myers & Dewar 1975, Cottington et al. 1980). However, these and related studies are subject to the criticism of biased recall of stressful events by relatives or friends of sudden death victims, who served as informants in these studies. The occurrence of natural disasters and/or man-made traumas have also been related to increased rates of heart attacks and sudden cardiac deaths. For example, during the Iraqi missile attacks on Israel during the initial days of the 1991 Gulf War, there was a significant increase in fatal and nonfatal cardiac events among the population living close to Tel Aviv (Meisel et al. 1991). Israeli mortality statistics during this period showed that on the day of the first missile strike, excess mortality observed was greater among women than among men (Kark et al. 1995).

Mittleman et al. (1995) used a novel epidemiologic methodology that compares each patient's pre-MI activities to his/her usual levels of activities to assess the immediate physical and mental triggers of onset of heart attack. In a study of patients interviewed a median of 4 days post-MI, there were elevated reports of episodes of anger within the 2 hours prior to myocardial infarction onset. The presence of anger episodes resulted in a doubling of heart attack risk compared with control periods. Other studies by this group established increased infarction rates triggered by acute exercise, an effect that was more pronounced among less fit individuals (Mittleman et al. 1993). However, by its nature, the case-crossover design uses a methodology that relies on retrospective recall of activities. It is important to note that the vast majority of heart attacks occur in individuals with preexisting coronary artery disease, and it is to this population that these studies of acute triggers are most relevant.

STRESS AND CARDIAC ISCHEMIA Myocardial ischemia is the inadequate supply of blood to the heart that is a clinical manifestation of CAD. The majority of

episodes of cardiac ischemia occur during normal daily activities (e.g., Gabbay et al. 1996). Mental stress and emotion also appear to be potent triggers of daily life ischemia in coronary patients (Barry et al. 1988, Gullette et al. 1997, Gabbay et al. 1996). For example, Gabbay et al. observed that the likelihood of ischemia was greatest during intense physical and during stressful mental activities. Strenuous physical activity (e.g., walking) and the experience of intense anger were also triggers of ischemia. Gullette and colleagues (1997) demonstrated that, among cardiac patients during daily life, the relative risk of ischemia was 2.2 during periods when patients reported feeling tension, sadness, and frustration (i.e., about half).

Laboratory mental stressors can provoke ischemia in a substantial subset of CAD patients (e.g., Rozanski et al. 1988, Gottdiener et al. 1994, Goldberg et al. 1996, Blumenthal et al. 1995). Ischemia provides a good model for studying CAD pathophysiology because it is easily provokable and reversible, clinically important, and can be ethically induced in the laboratory in humans. Ironson et al. (1992) further reported that an anger-inducing stressor was a particularly potent psychological stressor in its ability to trigger ischemia.

MENTAL STRESS ISCHEMIA AND PROGNOSIS IN CARDIAC PATIENTS At least three published studies have shown that the presence of mental stress-induced ischemia has been shown to predict subsequent clinical events in patients with CAD (Jain et al. 1995, Krantz et al. 1999, Jaing et al. 1996). So-called soft events (e.g., referral for revascularization procedures) in these studies that may be influenced by either patient or physician perceptions were included as morbidity endpoints. There is a need for further predictive studies that rely on "hard" outcomes such as myocardial infarction or sudden cardiac death. In this regard, one recent study reported that patients with mental stress ischemia were more likely to die over a 3-year follow-up period (Sheps et al. 2000).

STRESS REACTIVITY Stress reactivity involves the assessment of physiological changes in response to stress, as opposed to the sole assessment of resting levels of physiologic variables (see Krantz & Manuck 1984, Manuck 1994). Research has examined the possibility that excessive reactivity to stress may itself be a risk factor for coronary disease. In one study of initially healthy men followed for 23 years (Keys et al. 1971), the magnitude of their diastolic blood pressure reactions to a cold pressor test (which involves immersing the hand in cold water) predicted later heart disease. In fact, this physiologic response was a stronger predictor than many of the standard risk factors assessed in the study. However, a later study (Coresh et al. 1992) failed to replicate these findings.

In addition, studies of cynomolgus monkeys fed on a cholesterol-rich diet reveal 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 (Kaplan & Manuck 1999). Studies of cardiac patients also indicate that high blood pressure reactors to acute stress are also more likely to evidence

mental stress-induced ischemia and to show worsened clinical outcomes over time (Blumenthal et al. 1995, Krantz et al. 2000).

COMMENT Animal studies of acute and chronic stress (e.g., Kaplan & Manuck 1999, Verrier & Lown 1984), and human epidemiological and clinical studies provide significant evidence for the effects of acute and chronic stress on aspects of organic coronary artery disease pathology (e.g., atherogenesis, ischemia, and arrhythmia). However, there remain persistent doubts about the scientific validity and/or clinical relevance of this evidence because of difficulties and inconsistencies in defining and measuring stress in various studies, the multifactorial nature of coronary disease and its onset, and negative results in some studies (e.g., Hlatky et al. 1995). The recent attention to acute triggering events and the effects of stress on infarction, ischemia, and arrhythmia may solidify the connection between acutely stressful events and organic coronary disease endpoints.

SOCIOECONOMIC STATUS: THE GRADIENT WITH CORONARY ARTERY DISEASE

Socioeconomic status (SES), defined as an individual's occupation, economic resources, social standing, and education (Kaplan & Lynch 1997), is a powerful predictor of cardiovascular risk. SES can also refer to the standing of a household, rather than an individual. Evidence is clear that there is a social gradient affecting CAD risk factors and cardiovascular disease (Adler & Ostrove 1999). Much of this research has been done in countries that record social class in some form on death certificates or medical records, such as England (e.g., Smith et al. 1990, Kunst & Mackenbach 1994). However, it has also been demonstrated in the United States that cardiovascular disease is related to SES (e.g., McDonough et al. 1997).

Before the mid-1980s, the study of socioeconomic status and health largely focused on individuals living below the poverty line. Scientists generally held a threshold view of income that held that once household income was above the poverty line, family members no longer suffered ill effects as a result of their SES. However, in the mid-1980s a longitudinal study of British civil servants (the Whitehall study) revealed a "social gradient" in which health improved and mortality decreased at each higher socioeconomic level (Marmot et al. 1984, Adler & Ostrove 1999). This SES-CAD "gradient" has been found in many industrialized countries, although the strength of the association is not necessarily uniform (Adler & Ostrove 1999).

Possible Mechanisms for the Gradient

Numerous pathways have been proposed for the effects of SES on disease, including access to medical care, nutrition, living conditions, and risk-related behaviors,

such as low levels of physical activity (e.g., Kuczmarski et al. 1994). In spite of strong relationships, these traditional risk factors explain only about one-quarter of the SES-CAD gradient. More recently, psychological variables have also come under scrutiny as possible mechanisms.

PSYCHOSOCIAL VARIABLES An analysis of data from more than 2000 Finnish men determined that those in the lower socioeconomic strata (as determined by income) were nearly 2.66 times more likely to die of cardiovascular disease than those in the highest strata (Lynch et al. 1996). The risk ratio was decreased to 1.24 when biologic risk factors (such as blood pressure and serum cholesterol) were controlled, to 1.83 when behavioral factors (such as smoking and physical activity) were controlled, and to 1.71 when psychosocial factors (such as depression and social support) were controlled. However, when all 23 risk factors in the study were controlled, the social gradient was eliminated, suggesting that psychosocial variables do play an important role in the association between SES and CAD.

These psychosocial factors may include lack of social support, job strain, and chronic stress (see below). Because factors such as death and divorce can also result in economic hardship, individuals with fewer economic resources to begin with may not have adequate means for social support. As described later in this chapter, low levels of social support appear to be related to CAD risk. In the Whitehall study, measures of social support in the workplace did not substantially change the SES-CAD gradient (Marmot et al. 1997). However, as discussed in the section on social support, family support may be considerably more predictive of CAD than workplace support.

The interaction of social support with low educational level can also impact on mortality after myocardial infarction. Ruberman et al. (1984) demonstrated that men with low educational levels were more socially isolated and experienced more stress than men with higher educational levels. Men with low educational levels were twice as likely to die from subsequent cardiac events than those with more education and higher levels of social support. Studies like this are important to establish a firm link between social support and SES.

SOCIAL STATUS An individual's status in society and the way in which he interprets that status may also be linked to cardiovascular disease. In the United States, approaches that place people in hierarchical class strata are generally not well accepted. However, animal models of social structure have provided some insight into this area. Sapolsky & Mott (1987) observed that, in wild baboons, high-density lipoprotein ("good cholesterol") levels were higher in dominant males than in subordinate males. Similarly, it has been observed in civil servants that high-density lipoprotein levels rise incrementally with higher social status (Brunner et al. 1993). It is important to note, however, that low social status is not inherently pathological in monkeys (Kaplan & Manuck 1999), whereas it appears to be a uniform risk factor in humans. Further, social status in humans and dominance

status in monkeys are clearly not the same construct (Kaplan & Manuck 1999). However, a measure of social status in humans has been developed and is currently being tested (Bunker et al. 1992, Adler & Ostrove 1999). In addition, other studies are focusing on cardiovascular disease in populations that are believed to struggle with maintaining or improving their social status in this country, such as women and ethnic minorities (e.g., Rogers et al. 1997, Flack et al. 1995).

CHRONIC STRESS AS A MECHANISM It has been suggested that the aforementioned issues in varying degrees result in greater levels of chronic stress in individuals with lower socioeconomic status (e.g., Baum et al. 1999). There is evidence from the Whitehall study (Marmot et al. 1991) that a stepwise relationship exists between SES and the prevalence of perceived financial strain (Ullah 1990), stressful life events (McLeod & Kessler 1990), low self-esteem (Brown 1986), and fatalism (Eaker et al. 1992). Higher income is associated with more happiness and self-confidence (Link et al. 1993). Individuals in lower socioeconomic strata are likely to live in areas with more crowding, more noise pollution, more crime, and more discrimination. Living in low-SES neighborhoods increases the probability of an individual encountering stressors without having support systems sufficient to meet the demand placed on him (Kessler & Cleary 1980). More definitive prospective studies are necessary to confirm the association between low SES and chronic stress, but it appears stress may account for some of the increased risk of cardiovascular disease morbidity and mortality in lower SES populations. Although there is preliminary evidence that individuals in lower socioeconomic strata experience more stress than those in higher strata, it is too early to conclude that differences in chronic stress account for all SES effects (Baum et al. 1999).

Comment

Of the psychological pathways for the development and progression of cardiovascular disease discussed in this chapter, the theories regarding SES are perhaps the least developed. There is even some controversy regarding what constitutes SES. Some studies have measured SES using only income, whereas others use property ownership. Still other studies have used residential characteristics of the individual's neighborhood, which, in turn, have been shown to predict morbidity and mortality beyond individual SES variables (e.g., Haan et al. 1987). It has further been argued that level of education is a more accurate indicator because it is unlikely to change substantially in adulthood, is unlikely to be influenced by cardiac morbidity, and is available for retired or unemployed persons (Winkleby et al. 1992). Education is more highly associated with cardiovascular disease than with other chronic illnesses. However, education may affect health directly via increased knowledge of health behaviors and promotion of health-promoting psychological attributes such as self-efficacy (Smith et al. 1998). In fact, the validity of this view is uncertain because studies that have examined the effects of income on

health while controlling for education's effect on income yield conflicting results (Sorlie et al. 1995, Winkleby et al. 1992).

HOSTILITY AND RELATED TRAITS

Personality characteristics, such as hostility, anger, and mistrust (so-called cynical hostility) (Barefoot et al. 1983) have emerged as correlates of CAD incidence as well as mortality from all causes, although several studies have not found this relationship (see Rozanski et al. 1999, Smith 1992). In support of the notion of hostility as a risk marker, traits of hostility have been related to the development of CAD in high-risk men (Dembroski et al. 1989), to restenosis following coronary angioplasty, and to progression of carotid atherosclerosis (Rozanski et al. 1999). Subsequent research has further suggested that hostility is higher in low SES groups, in men, and in nonwhites in the United States, and also clusters with other risk factors, such as smoking (Siegler 1994).

However, other studies have found no association between hostility and cardiovascular disease. Although several reviews and meta-analyses have reported that hostility is an important risk factor for coronary disease (e.g., Smith 1992), more recent meta-analyses (e.g., Miller et al. 1996, Heminway & Marmot 1999) report that as many as half of the studies of hostility and cardiovascular disease yield null findings. The significant number of negative studies may indicate that the effects of hostility may be difficult to identify and/or do not apply in all populations.

The reasons for these conflicting findings are unclear. One possible issue affecting outcome is that of the possible mediating role of traditional coronary risk factors. Hostility has consistently been associated with age, sex, ethnicity, increased fat and calorie intake, decreased physical activity, and alcohol and tobacco use (Siegler 1994). If these negative behaviors are the mechanism by which hostility impacts cardiovascular disease, then controlling for them in studies may certainly diminish observable associations with hostility.

There are also uncertainties about which populations are at higher CAD risk as a function of hostility. There are few large-scale studies documenting the effects of hostility, chronic anger, and related traits to poorer outcomes in cardiac patients (Rozanski et al. 1999). Demographic characteristics may also affect outcome. For example, evidence also suggests that hostility is more highly associated with cardiovascular outcomes in younger individuals (e.g., Miller et al. 1996). One study of a relatively young sample taken from the general population, with approximately even numbers of men and women, and African-Americans and whites, reported that hostility was significantly associated with extent of coronary calcification, a measure of early subclinical CAD (Iribarren et al. 2000). On the other hand, another recent study reported no association between hostility and calcification (O'Malley et al. 2000). However, the latter study has been criticized for being very selected—i.e., mostly male, mostly white, and consisting entirely of active-duty military personnel.

Comment

The inconsistent data linking hostility and cardiovascular disease precludes drawing firm conclusions that hostility is a risk factor in all populations (e.g., Petticrew et al. 1997). However, meta-analyses do report consistent, if small, associations with measures of organic coronary disease, and there remains a substantial body of literature documenting the effects of hostility, particularly in younger subjects (Siegler 1994). Inconsistencies in this literature derive from the differences among measures and constructs that are used in various studies to measure hostility. Components of hostility and related constructs, such as anger expression and cynicism (e.g., Barefoot et al. 1989, Williams et al. 2000, Angerer et al. 2000), are currently under investigation to determine if their relative importance is stronger than more global hostility scores.

DEPRESSION AND DEPRESSIVE SYMPTOMS

Prevalence

Clinical depression is a syndrome that includes depressed mood and other symptoms such as changes in weight, insomnia, fatigue, and markedly diminished interest or pleasure (Am. Psychiatr. Assoc. 1994). The lifetime prevalence rate is reported to be 13% for major depression, and 5% for dysthymia in the general population (Kessler et al. 1994). Depression rates are higher in cardiac patients, especially postmyocardial infarction patients, with studies reporting prevalence rates of 16–23% (e.g., Schleifer et al. 1989, Frasure-Smith et al. 1993, Carney et al. 1988). As many as 30% of cardiac patients may have depressive symptoms (Frasure-Smith et al. 1995). Depression rates do not appear to increase markedly with severity of cardiovascular disease or increased disability (Carney et al. 1987, Frasure-Smith et al. 1995).

Epidemiological Data

Data are consistent and convincing that depression affects organic disease processes and subsequent morbidity and mortality among individuals who already have cardiovascular disease. For example, Carney et al. (1988) found that patients with cardiovascular disease who met the criteria for major depression were 2.5 times more likely to develop a serious cardiac complication over the next 12 months than nondepressed patients. More than a dozen subsequent studies have controlled for other risk factors and yielded similar results (e.g., Ahern et al. 1990, Ladwig et al. 1991, Kennedy et al. 1987, Barefoot et al. 1996, Schulz et al. 2000). For example, Frasure-Smith and colleagues followed 222 patients after their first MI. These patients received structured psychiatric examinations within 15 days of their first MI and were followed for 18 months. After controlling for other independent risk factors, depression was associated with a 3.5-fold risk of mortality.

This risk is comparable to other major risk factors for mortality, such as congestive heart failure and left ventricular function (Frasure-Smith et al. 1993, 1995).

It appears that the risk of cardiovascular disease associated with depression increases in a linear manner (e.g., Anda et al. 1993, Pratt et al. 1996) and that depressive symptoms are sufficient to increase risk in the absence of major depressive disorder (Anda et al. 1993). In addition, components of depression and/or depression-related characteristics may also increase risk of morbidity or mortality. For example, vital exhaustion refers to fatigue, irritability, and demoralized feelings and has been associated with development of CAD and incidence of cardiac events in healthy and CAD samples (Appels & Mulder 1988, Kop et al. 1994). In one study the presence of exhaustion predicted adverse clinical outcomes in CAD patients undergoing coronary angioplasty, a nonsurgical cardiac procedure (Kop et al. 1994). These results could not be attributed to preexisting disease. Similarly, the absence of hope has also been identified as a possible risk factor. Both observational and prospective studies have linked hopelessness with the development and worsening of coronary artery disease (Brunn et al. 1974; Anda et al. 1993; Everson et al. 1996, 1997).

Mechanisms

Behavioral and physiological mechanisms have been proposed for the association between depression and cardiovascular illness. Depressed individuals certainly are more likely to engage in risk-related behaviors such as smoking or lack of physical activity (Carney et al. 1995). However, after control of traditional risk factors and risk-related behaviors, depression is still associated with poor cardiac outcomes, suggesting that other factors are involved (e.g., Glassman & Shapiro 1998).

We have already described the effects of acute stress and its neurohormonal sequelae on cardiovascular function. Several studies have revealed hyperactive hypothalamic-pituitary-adrenal axis responses to acute mental stress in depressed individuals (e.g., Nemeroff et al. 1984, Arato et al. 1986, Banki et al. 1992). Depression is also associated with high levels of norepinephrine and its metabolites in blood and urine (e.g., Wyatt et al. 1971, Roy et al. 1988), and there is evidence that hyperexcretion of norepinephrine decreases after treatment with tricyclic antidepressants (e.g., Charney et al. 1981, Golden et al. 1988).

Depressed individuals tend to have reduced heart rate variability (beat-to-beat fluctuations in heart rate) (Stein et al. 2000), which has been validated as a measure of autonomic regulation of the heart. Low heart rate variability is associated with poor cardiovascular outcomes (Stein & Kleiger 1999). It has been proposed that loss of cardiac parasympathetic control leaves the heart vulnerable to unopposed stimulation by the sympathetic nervous system and more susceptible to malignant cardiac arrhythmias and sudden death (Gorman & Sloan 2000). Because increased mortality in depressed patients is largely attributable

to an increased risk in sudden death, it has been proposed that impaired autonomic regulation of the heart predisposes depressed individuals to lethal arrhythmias (Frasure-Smith et al. 1993, 1995; Gorman & Sloan 2000). There is also evidence that the association between depression and cardiovascular disease is mediated, at least in part, by changes in blood platelet function (Musselman et al. 1996).

Ongoing Intervention Trials

The possible effect on CAD morbidity and mortality of behavioral and/or pharmacologic interventions to treat depression is currently the subject of active investigation (Shapiro et al. 1999; ENRICH Investigators 2000). However, as of the writing of this chapter, there has been little published research on the specific effects on hard cardiac endpoints of interventions to reduce depression in cardiac patients, other than to demonstrate the safety of one antidepressant for these individuals (Shapiro et al. 1999). Because depression seems to be clustered with other psychosocial and biological risk factors (Rozanski et al. 1999), other interventions directed at other target behaviors have had the salutary effect of reducing depression. Mendes de Leon et al. (1991) observed that psychosocial interventions, involving stress management and cognitive restructuring, directed at reducing Type A behavior can also reduce depression and other psychosocial risk factors. Behavioral intervention studies are discussed below.

Comment

The evidence linking depression to increased risk of morbidity and mortality in CAD is robust (Hemingway & Marmot 1999, Rozanski et al. 1999, Musselman et al. 1996). These data appear to be more extensive regarding the effects of depression and related symptoms in patients with established CAD, although several studies note an increased risk in population studies of individuals initially free of disease. Nevertheless, further studies of initially healthy populations are needed before depression can be firmly established as a coronary risk factor in otherwise healthy populations.

It is also unclear whether depressive symptoms, in the absence of clinical depression, are sufficient to increase risk for cardiovascular disease. Individuals with depressive symptoms are more likely to develop coronary disease over time (Anda et al. 1993), but we do not know whether or not their symptoms developed into major depression over the time course of the follow-up period. Depression may also be inherently associated with other behavioral or biological risk factors for coronary disease. For example, depression is associated with feelings of fatigue and lack of interest in activities, which may result in a sedentary lifestyle. The mechanisms by which depression is linked with increased coronary risk in cardiac patients are not entirely clear and may involve biological markers such as reduced heart rate variability and parasympathetic function, impaired platelet reactivity, and/or behavioral factors such as associations with other psychosocial risk factors

or reduced compliance with medical regimens. Further studies of these mechanisms might suggest additional useful targets for possible interventions.

SOCIAL SUPPORT

Social support refers to having a variety of social contacts who are available as resources for one's personal benefit (Cohen et al. 2000). Structural support refers to the existence of and interconnections between social ties. Measures of structural support usually include marital status, number of people in one's household, and number of social contacts. These measures are often considered in combination as social integration. Functional support refers to the utility of one's social contacts in providing specific functions, such as emotional support, tangible or instrumental aid, feelings of belonging, and informational support (Cohen et al. 2000, King 1997).

Epidemiological Data

Prospective studies have confirmed the association between low social support and risk of cardiovascular disease. In a 6-year follow-up of residents of South Sweden, Orth-Gomer and colleagues (Orth-Gomer & Johnson 1987) determined that the third of their sample having the lowest number of social contacts were at 50% greater risk of coronary heart disease mortality than those with higher numbers of social ties. At least 4 other studies have yielded similar results (e.g., Kawachi et al. 1996). In a prospective study in the United States, Vogt and colleagues (1992) followed members of a health-maintenance organization for 15 years. Hospital records were then examined to identify incidence of MI. After controlling for standard risk factors, such as hypertension and obesity, they determined that those individuals reporting a wide range of different types of social contacts were less likely to have a heart attack than those who were less socially integrated.

Social support also plays an important role in mortality from preexisting cardiovascular disease. In 1984, Ruberman and colleagues first reported that more socially isolated men were at greater risk of death following an MI. A 4-year follow-up study found that patients who lived alone after a heart attack were at greater risk for recurrent fatal and nonfatal coronary events (Case et al. 1992). Similarly, individuals who were not married and had no confidant have been observed to be more likely to die in the 5 years following an MI (Williams et al. 1992). At least 6 other studies have yielded similar results.

Berkman and colleagues suggest that lack of emotional support may be the reason why social isolation often results in greater post-MI mortality (Berkman et al. 1992). In their longitudinal study, emotional support was measured prospectively, and patients were followed for 6 months. Even after controlling for age, severity of MI, and comorbidity, individuals reporting no sources of emotional

support had a threefold higher risk of mortality than those reporting one or more sources.

Mechanisms

Social support is correlated with SES, medication use, medical compliance, and other factors that are directly related to health. It is not clear whether these variables are potential confounders or mechanisms by which social support affects disease (Uchino et al. 1996). However, the association between social support and health remains even after statistically controlling for coronary risk factors and risky behaviors such as medical noncompliance (Bland et al. 1991).

Although social support has been proposed by some to reduce morbidity and mortality through other factors such as reducing depression, most research focuses on the moderating effects of social support on stress. Lepore (1998) suggests at least three possible pathways through which social support could reduce the pathological effects of stress: direct dampening of neuroendocrine activation, which reduces overall arousal due to stress; facilitated coping through cognitive reappraisal processes; and a combination of direct dampening of arousal and facilitated coping.

Comment

Epidemiological data convincingly suggest that social support plays an important role in the development and progression of coronary disease. The specific aspects of social support that are important and the mechanisms by which social support may affect disease are less clear. Many studies are difficult to compare because each used a different instrument to measure social support. Further, many studies fail to report the psychometric properties of the instrument chosen to measure social support (see Uchino et al. 1996). Research in this area would be strengthened by the use of psychometrically sound, standardized measurement tools.

Another important consideration in social support research is the nature of the study samples used. Many studies of social support are conducted on women, based on the popular assumption that females would be more responsive to social support than males. However, the epidemiological data suggests that, in fact, men may be more responsive to social support than women (e.g., Orth-Gomer & Johnsson 1987). The specific needs of the individual may also mediate the beneficial effects of social support. Epidemiological data suggests that a minimum number of social contacts is necessary for cardiovascular health for women in urban areas (e.g., Orth-Gomer & Johnsson 1987, Berkman & Syme 1979). However, women in rural settings have smaller social networks and do not experience negative cardiovascular effects (e.g., Schoenbach et al. 1986). Orth-Gomer & Johnsson (1987) have speculated that women who live in urban areas lead more unstable lives owing to greater changes and contradictory demands from multiple social roles, and therefore require larger social networks.

Not all social contacts provide support. Social relationships may involve demands for attention or assistance, conflict, and criticism. Further, the number of

supportive relationships an individual has appears to be only weakly correlated with the number of nonsupportive relationships they have (see Seeman 2000 for a review). It has long been suggested that social integration may actually be harmful if it is accompanied by interpersonal conflict or problems (Medalie & Goldbourt 1976). There is now increasing evidence that positive, supportive relationships are associated with lower levels of cardiovascular and neurohormonal reactivity, whereas nonsupportive relationships are associated with heightened physiological stress responses (e.g., Seeman & McEwen 1996). Therefore, the nature of social relationships may be as important as the number, and should be measured as well.

PSYCHOSOCIAL INTERVENTION TRIALS

Behavioral and psychosocial treatment studies have evaluated the efficacy of reducing stress-related characteristics in cardiac patients morbidity and mortality (see Rozanski et al. 1999, Linden et al. 1996). Patients with CAD are often chosen as targets in these secondary and tertiary prevention studies because of their presumed heightened motivation to change their behavior, as well as the ability to readily assess coronary disease endpoints in this population. Intervention studies have employed a variety of behavioral techniques, including relaxation training, cognitive behavioral stress management, meditation, providing home nurse interventions to reduce stress, group emotional support, and cognitive therapy for depression. This literature has recently been reviewed in depth by Rozanski et al. (1999) and in an *Annual Review* chapter by Schneiderman et al. (2001), and will only be considered briefly here.

A meta-analysis was conducted of more than 20 controlled trials utilizing a variety of hard and soft endpoints that evaluated the impact of psychosocial treatments among cardiac patients (Linden et al. 1996). This analysis indicated that patients receiving psychosocial treatments showed greater reductions compared with control conditions in psychological distress, blood pressure, heart rate, and serum cholesterol levels. Morbidity and mortality data, available in only about half of these studies, indicated that patients not receiving psychosocial treatments showed greater mortality and cardiac recurrence rates during the first 2 years of follow-up (Linden et al. 1996).

However, since the publication of this meta-analysis, several important intervention studies have been published, one yielding positive effects on morbidity (Blumenthal et al. 1997) and two yielding no effects or trends in the opposite direction (Jones & West 1996, Frasure-Smith et al. 1997). In their recent comprehensive review, Rozanski et al. (1999) observed that, at the time of their review, 14 psychosocial intervention trials, both large and small, had assessed the impact of psychosocial interventions on cardiac death and myocardial infarction. These trials yielded both positive and negative evidence for the efficacy of psychosocial interventions on morbidity and mortality. However, some or all of the negative findings on morbidity or mortality could be attributed to the fact that the

intervention methods used in these studies did not reduce reported psychological distress among participants (e.g., Frasure-Smith et al. 1997).

Comment

Those psychosocial intervention trials that have yielded positive results on cardiac morbidity and mortality (e.g., Friedman et al. 1986, Blumenthal et al. 1997, Ornish et al. 1990) have provided encouraging data for the influence of behavioral factors on cardiac endpoints. However, the existence of negative studies in this area highlights the fact that uncertainties exist in terms of (a) the most appropriate and effective types of behavioral and psychosocial interventions and (b) how these should be administered in particular groups of patients (Rozanski et al. 1999, Schneiderman et al. 2001). Another important issue is the fact that some of the published interventions yielding positive results have involved small samples of patients (e.g., Ornish 1998, Ornish et al. 1990), and others have either not yet been replicated or yielded negative results when replications were attempted (Frasure-Smith et al. 1997). It has been noted that these negative studies have failed to document a positive impact of interventions on patients' stress levels, so the studies do not refute a possible role for stress in disease progression. These uncertainties support the conclusion that larger controlled clinical trials are needed to establish the demographic and psychological characteristics of appropriate targets for psychosocial interventions, and the physiological and psychological mechanisms by which effective interventions might operate (Schneiderman et al. 2001).

CONCLUDING COMMENTS

Extensive evidence from multiple sources, including animal model studies, epidemiological studies, and human clinical studies (including laboratory studies and intervention trials), suggests that psychological and psychosocial variables can have a significant impact on organic manifestations of coronary artery disease. In our review we noted that this evidence is more consistent for some putative psychological or social risk factors than for others, and that some of these variables appear to be more (or less) important in certain populations (e.g., healthy individuals vs. coronary disease patients). Nevertheless, taken as a whole, these data provide substantial evidence for the effects of psychosocial variables on organic disease.

In light of these data, why the persistent doubts about the scientific validity and/or clinical relevance of this evidence among some in the biomedical community (see Angell 1985, Scheidt 2000)? It is likely that there are those in the biomedical community who will resist acknowledging a role of psychological and social variables regardless of the evidence. With regard to the state of the research literature, in a thoughtful commentary, Scheidt (2000) describes some of the reasons for such doubts among medical practitioners in the case of coronary artery

disease, for which some of the strongest evidence exists in the health psychology and behavioral medicine field. These reasons include (a) the fact that the literature contains many studies with various design limitations, such as small or selected samples among studies reporting positive (or negative) results, or lack of appropriate control groups; (b) inconsistent results among studies; and (c) doubts about the actual clinical relevance of behavioral variables and interventions. To these issues, we might add several additional points. There are inconsistencies in defining and measuring various psychosocial measures (e.g., stress, hostility, anger), and gaps in knowledge regarding the applicability of various psychological risk factors in different demographic and health groups. Inconsistencies in psychosocial research findings might result from the use of convenience samples or nonvalidated versions of psychological scales in some studies. Studies may also use different measures of putative psychological risk factors (e.g., anger or hostility), perhaps with differing results.

Another important issue that needs to be addressed is the effective communication of research findings. Most biomedical clinicians and biomedical investigators do not read the psychological research literature, and do not have training needed to understand psychological constructs. To gain the attention and (perhaps) the acceptance of the biomedical community, many behavioral researchers elect to publish their findings in medical journals. In order to accomplish this, however, behavioral researchers need to alter the presentation of their work accordingly (e.g., by eliminating psychological jargon and emphasizing the clinical implications of their work). Further, in order to be accepted by biomedical journals, it is necessary that articles be sophisticated with regard to the medical variables and endpoints in question, and it is here that multidisciplinary research teams that are sophisticated in their knowledge of cardiology variables are important.

Some of these issues may be addressed as more large-scale and carefully controlled clinical trials that measure morbidity and mortality outcomes are conducted (Schneiderman et al. 2001). Moreover, laboratory research on behavioral aspects of coronary artery disease is becoming more and more sophisticated and able to avoid the shortcomings of prior work. This progress has been facilitated as behavioral research begins to incorporate the methodologies and increasing knowledge base in cardiology and related fields (Krantz et al. 2000). Communication and dissemination of research findings to other disciplines will be facilitated by the integration of biomedical methodologies with behavioral expertise. Continued progress in this area is dependent on multidisciplinary research that incorporates the knowledge base in both cardiology and in the behavioral sciences.

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