Psychosocial factors in coronary and cerebral vascular disease

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INTRODUCTION

Although recent attention has focused on the role of psychosocial factors in the acute precipitation of myocardial infarction and sudden cardiac death, psychosocial factors may also contribute to the early development of atherosclerosis [1]. The link between psychologic stress and atherosclerosis may be both direct, via damage of the endothelium, and indirect, via aggravation of traditional risk factors such as smoking, hypertension, and lipid metabolism.

Unfortunately, human studies of stress and coronary atherosclerosis have been limited in scope, due primarily to the difficulty in quantifying the degree of atherosclerosis in asymptomatic subjects. Thus, although angiographic data suggest that more extensive atherosclerosis is seen in patients with type A personality [2], confounding issues limit the interpretation. Stronger epidemiologic studies have linked psychosocial factors such as bereavement, loss of job, and depression with hard end points such as myocardial infarction and sudden death [3]. One study which followed 1592 men and women for five years reported that the personality trait of submissiveness, a marker for type B behavior, was protective against nonfatal and total myocardial infarction, particularly in women (relative risk 0.59 and 0.69, respectively) [4].

Depression screening — Depression is associated with increased morbidity and mortality in patients with established coronary heart disease. We agree with the 2008 American Heart Association scientific advisory on Depression and Coronary Heart Disease which recommends

screening for depressive symptoms in such patients [5]. (See "Screening for depression in adults".)

STUDIES IN ANIMALS

The best insights into the role of psychological stress in atherosclerosis come from animal studies, in particular a series of experiments using cynomolgus monkeys [6]. When fed a diet sufficiently rich in saturated fat and cholesterol, these monkeys develop atherosclerosis very rapidly with lesions similar to those seen in humans. Also similar to humans, premenopausal female monkeys are relatively protected from atherosclerosis.

These animals display complex patterns of social interaction characterized by hierarchies of dominant (aggressive) and subordinate (submissive) animals. Since the monkeys respond aggressively to new animals attempting to join their social groupings, the placement of strangers within groups forms the basis for a stressful challenge.

As an initial experiment, 30 animals consumed an atherogenic diet for 22 months [7]. Half of the animals were placed in a stable environment while the other half were moved to new animal groups at one to three month intervals. Animals placed in the latter unstable environment displayed more extreme versions of their behavior. When the coronary arteries were examined at the end of the study, the aggressive animals in the unstable group had more extensive atherosclerosis than did any of the other groups. The development of atherosclerosis was independent of differences in serum cholesterol or triglycerides or blood pressure. Even in normolipemic animals, there was more atherosclerosis in the aggressive animals that were placed in the disrupted social environment. In addition, the arteries of animals housed in an unstable social environment displayed more coronary vasoconstriction than those in a stable environment [8].

The investigators next evaluated the effect of heart rate reactivity to a standardized stress: displaying a large monkey catch-glove in a prominent and threatening manner [9]. Based on heart rate response, the animals were divided into high and low reactors. The high heart reactors had intimal lesions that were twice as extensive as those seen in low-reactors. In a later report, the administration of propranolol, in doses that produced a 20 percent reduction in heart rate, resulted in significantly less atherosclerosis [10].

Another series of studies in rabbits with a genetic defect that results in spontaneous atherosclerosis also found that the social environment affected the progression of atherosclerosis [11].

STUDIES IN HUMANS

Human studies demonstrate an association between type A personality and exaggerated cardiovascular responses when the subjects are exposed to frustrating laboratory tasks [12]. While studies have suggested a larger pressor response to stress among patients with cardiovascular disease [12-14], the link between hyperreactivity and cardiovascular disease has not yet been convincingly made. One prospective study of reactivity and disease prediction found that diastolic blood pressure responses to a cold pressor test were significantly related to the development of coronary heart disease 23 years later [15].

Among patients with coronary artery disease, myocardial ischemia that occurs in response to mental stress is associated with subsequent adverse events. A meta-analysis pooled results from five observational studies in which patients with stable coronary artery disease (n = 555) were tested in a laboratory for mental stress induced myocardial ischemia and then followed prospectively [16]. The risk of subsequent coronary artery disease events (eg, myocardial infarction or unstable angina) or mortality was two times greater in patients with mental stress induced myocardial ischemia.

Multiple prospective studies indicate that adverse psychosocial working conditions, including job strain (n >100,000 individuals), effort-reward imbalance (n >90,000 individuals), and bullying (n >79,000 individuals) are associated with a higher risk of cardiovascular disease [17-21]. In addition, one study in 28 European countries found that job strain, long working hours, effort-reward imbalance, and job insecurity accounted for 8 percent of the overall burden of coronary heart disease [22].

Development of coronary disease — The association between psychosocial factors and the presence of asymptomatic coronary heart disease is uncertain. One study evaluated 630 active-duty army personnel, age 38 to 45, without known coronary disease who underwent electron beam computed tomography; there was no correlation between the presence of coronary artery calcification and prior or current psychiatric disorders, such as anxiety, hostility, and stress [23]. (See "Coronary artery calcium scoring (CAC): Overview and clinical utilization".)

In contrast, another study of 1305 men with a mean age of 62 found that symptomatic depression, as measured by the Minnesota Multiphasic Personality Inventory, was associated with an increased risk of coronary heart disease and angina pectoris [24].

Other personality traits and affective disorders may be associated with the development of coronary heart disease [25]. The Normative Aging Study followed 1305 men of a mean age of 62 who were free of coronary heart disease and completed the Minnesota Multiphasic Personality

Inventory [24]. After a mean follow-up of 7 to 8 years, those with the highest level of depression, anger, or social competitiveness (dominance) had an increased risk of coronary heart disease, including nonfatal infarction and coronary death, compared to those with the lowest levels of these traits (multivariate adjusted relative risk of 1.46, 3.15, and 1.8, respectively) [24,26,27].

Anger in response to stress may be important for the development of premature cardiovascular disease in young men. This issue was addressed in a longitudinal study of 1055 male medical students that documented anger reactions to stress by self-reporting on a questionnaire administered in medical school [28]. After a median follow-up of 36 years, those with the highest level of anger, compared to those with lower levels, had a significant increased risk of premature cardiovascular disease developing before the age of 55 (adjusted relative risk 3.1), coronary heart disease (adjusted relative risk 3.5), and myocardial infarction (relative risk 6.4). (See "Coronary artery disease and myocardial infarction in young people".)

Type D (distressed) personality, which is characterized by social inhibition plus negative affectivity such as anxiety and sadness, is associated with a poor prognosis in cardiovascular disease [29]. A meta-analysis of 11 prospective studies in patients with cardiovascular disease (n >5000) found that after adjusting for potential confounding factors (eg, age and cardiac disease severity), the probability of mortality and nonfatal myocardial infarction was more than two times greater in patients with type D personality than those with non-type D personality (hazard ratio 2.2, 95% CI 1.4-3.7) [30].

The association of psychosocial factors and coronary heart disease may be prominent in individuals at high risk for the development of coronary disease. As an example, the Family Heart study of 2300 subjects at high risk, based upon the age of onset of coronary heart disease in biologically related family members, found that, after controlling for other risk factors, hostility was associated with a history of revascularization in high risk men (odds ratio 1.21) and a history of myocardial infarction in high risk women (odds ratio 1.39) [31]. A high degree of social support reduced the odds of a myocardial infarction in high risk women (odds ratio 0.76), but not in high risk men. There was no association between these outcome and hostility or social support in a random sample of 2447 individuals.

Coronary heart disease symptoms — There is an association between psychosocial factors and the presence of symptomatic coronary disease. Mental stress-induced angina results from an increase in heart rate and blood pressure, which increases cardiac demand, and coronary vasoconstriction, which reduces coronary blood flow and myocardial oxygen supply [32]. Several clinical studies illustrate the effects on cardiac symptoms and quality of life. Two

approaches have been used: the frequency of stress in patients who have angina and the frequency of angina in patients with depression.

- One prospective study compared psychosocial variables in 767 patients who had chronic stable angina with 50 healthy subjects [33]. The patients with angina experienced more stressful events, more frequently suffered from disturbed and psychosomatic symptoms, and had higher scores for hostility and lower levels of overall wellbeing. These psychosocial findings were more common among women than men, although women had less type A behavior and hostility.

- In a review of 1024 patients with stable CHD, 201 had depressive symptoms [34]. Patients with depressive symptoms were more likely than those without such symptoms to report monthly or more frequent angina, physical activity limitation, diminished quality of life, and fair to poor overall health. In contrast to the correlation of depression with these symptom indices, there was no correlation of either ejection fraction or stress echocardiographic evidence of ischemia with reported symptom status.

- Similar findings were noted in a series of 1282 patients with coronary heart disease who completed a Mental Health Inventory and the Seattle Angina Questionnaire [35,36]. Depression was associated with more frequent angina, physical limitation, less treatment satisfaction, and a lower perceived quality of life [35,36].

Progression of coronary heart disease — Adverse psychosocial factors may be associated with progression of atherosclerosis in patients with documented coronary disease. As an example:

- One study of 162 patients who underwent angiography at baseline and again after two years found that only those who had low emotional social support and also expressed anger outwardly were at an increased risk for the progression of coronary heart disease (odds ratio 30); this association was independent of medication or other risk factors [37].

- Among 292 middle-aged women hospitalized for an acute coronary event and followed for five years, the presence of two or more depressive symptoms and the lack of social integration were each associated with approximately twice as many recurrent cardiac events (including death, myocardial infarction, and revascularization), compared to patients without these features [38].

- In 312 women followed more than two years, psychosocial well-being was associated with less progression of coronary artery calcium [39].

Cardiovascular mortality — Psychosocial factors can contribute to cardiovascular mortality. The potential magnitude of this effect is illustrated by the following observations:

- The Cardiovascular Health Study of 5201 men and women ≥65 years of age who were followed for six years found that a high level of depression was associated with a significant increase in mortality (24 versus 18 percent for low level of depression, adjusted relative risk 1.24) [40].

- Using data from the EPIC-Norfolk United Kingdom Prospective cohort study, the relationship between death from ischemic heart disease and major depressive disorder was evaluated in over 19,000 men and women initially free of coronary heart disease [41]. After a median follow-up period of 8.5 years, participants who had major depression in the year prior to enrollment were 2.7 times more likely to die from ischemic heart disease after adjustment for traditional and other sociodemographic risk factors.

Outcome after CABG — The prevalence of depression after coronary artery bypass graft (CABG) surgery is 20 to 40 percent and its presence is associated with a poorer outcome after CABG [42-45]. (See "Coronary artery bypass graft surgery: Graft choices".)

The following reports illustrate the range of findings:

- A prospective study of 309 patients, followed for one year after CABG, found that cardiac events (angina, heart failure, myocardial infarction, cardiac arrest, need for repeat revascularization, and cardiac mortality) were more common in those with a major depressive disorder (27 versus 10 percent without depression, adjusted risk ratio 2.3) [43].

- A larger prospective analysis of 817 patients followed for a longer interval (five years) demonstrated an effect of depression on survival [44]. There were 122 deaths (15 percent). The all-cause mortality rate was higher for patients with moderate to severe depression at baseline (adjusted hazard ratio 2.4) and for patients with depression of any degree that persisted for six months (adjusted hazard ratio 2.2).

Carotid artery atherosclerosis — Psychosocial stress may also be associated with the development of carotid artery atherosclerosis. This issue was examined in the Family Health study of 3617 subjects judged to be high risk, based upon the age of onset of coronary heart disease in biologically related family members [46]. After adjusting for other risk factors, hostility alone or associated with low social support increased the odds of carotid lesions in high risk women (odds ratio 1.18 and 1.47, respectively), but not high risk men or 1026 subjects at low to medium coronary heart disease risk.

Stroke — Multiple studies indicate that depression and psychosocial stress are risk factors for stroke [47], but the magnitude of the association is often small:

- After adjusting for potential confounding factors such as smoking and hypertension, a meta-analysis of 17 prospective community or population studies (206,641 participants, including 6086 cases of stroke) found that stroke occurred in significantly more participants who were depressed than those not depressed (relative risk 1.3, 95% CI 1.2-1.5) [48].

- A subsequent prospective study included more than 400,000 individuals with no prior history of cardiovascular disease who were assessed for depression at baseline with a self-report screening instrument, the two-item Patient Health Questionnaire (PHQ-2) (table 1) [49]. The median length of follow-up was eight years, during which time over 3000 fatal and nonfatal strokes occurred. After adjusting for potential confounding factors (eg, age, smoking, and history of diabetes), the analyses showed that each one-point increase in PHQ-2 scores was modestly associated with an increased risk of stroke, including symptom levels below the threshold that indicate potential depressive disorders (hazard ratio 1.10, 95% CI 1.06-1.14). The corresponding incidence of stroke per 10,000 person-years of follow-up was greater among individuals with a PHQ-2 score of 4 or more, compared with a score of 0 (15 versus 10).

  The same paper included a pooled analysis of participant-level data from 21 prospective studies of individuals with no prior history of cardiovascular disease (n >160,000); the results again showed a clinically small association between depressive symptoms at baseline and subsequent risk of stroke (1.05, 95% CI 1.01-1.10) [49].

- A retrospective study in 32 countries included patients with first acute stroke (n >13,000) and controls matched for age and sex (n >13,000) [50]. After adjusting for potential confounding factors (education, occupation, and wealth), the probability of stroke was greater in those with increased stress at home (odds ratio 1.95, 95% CI 1.77-2.15) and at work (2.70, 95% CI 2.25-3.23), and in those with recent stressful life events (1.31, 95% CI, 1.19-1.43) [50]. By contrast, the likelihood of stroke was less in those with higher locus of control at home and work.

PATHOPHYSIOLOGY

A brief period of mental stress, similar to that occurring in everyday life, can cause transient endothelial dysfunction in young healthy individuals without evidence of vascular disease or

risk factors for cardiovascular disease [51,52]. The endothelial dysfunction appears to be mediated by endothelin, since it can be prevented by a selective endothelin-A receptor antagonist [52], and lasts for as long as one to four hours [51,52].

Psychological stress, perhaps via activation of the hypothalamic, pituitary and adrenocortical axis, also produces endothelial injury in animals, an important first step in the generation of atherosclerosis [53-55]. As an example, an increase in hemodynamic turbulence promotes endothelial injury in the coronary arteries, particularly at branch points. Damage to the endothelium will promote the movement of lipoproteins from the circulation to the artery wall, platelet aggregation, and the release of growth factors that further stimulate atherogenesis.

In addition to the hemodynamic effects of increased sympathetic tone, other factors may contribute to the endothelial injury associated with stress:

- Cortisol may play a potentiating role on vasoconstriction induced by catecholamines [56]
- The serotoninergic system may modulate sympathetic activity [57]
- Mental stress and increased exposure to epinephrine can lead to platelet activation and deposition [58-60]
- Psychologic stress can modify macrophage activity and the inflammatory response [61]
- Hypertensive, but not hypercholesterolemic patients, have impaired nitric oxide-dependent vasodilation during mental stress [62]

Effect on risk factors — Psychosocial factors may also promote atherosclerosis via an effect on traditional risk factors. As examples, cigarette smokers typically increase their consumption in response to stress, and serum cholesterol levels have been shown to rise in stressful situations [63-65]. The increases range from 8 to 65 percent in situations such as the preparation of tax returns in April by accountants, the taking of examinations by students, and following job loss or significant life events [65].These data suggest an interaction between diet and the stressor. The cholesterol increase may result from free fatty acid mobilization induced by epinephrine [66].

There is also a correlation between high blood pressure and psychosocial variables of a stressful nature, such as job loss and demanding occupations. However, the increase in blood pressure tends to return to normal following removal of the stress [67].

A more prolonged response to stress may be seen in those with a genetic predisposition to hypertension. As an example, individuals with a family history of hypertension show

exaggerated cardiovascular responsiveness to stressors when compared to those with normotensive parents. Furthermore, hyperreactivity may be a marker for individuals at increased risk for developing hypertension. The mechanism of the rise in pressure may be related to the increased plasma catecholamines that have been shown in some hypertensives.

The effect of work stress on traditional risk factors for cardiovascular disease may vary according to the specific stressor and traditional risk factor:

- A meta-analysis of participant-level data from four prospective observational studies included individuals with no history of type 2 diabetes mellitus (n >18,000), who were assessed at baseline for workplace bullying [68]. Mean length of follow-up was 12 years. After adjusting for potential confounding factors (eg, age, marital status, and body mass index), the analyses showed that the risk of type 2 diabetes mellitus was greater among individuals who were bullied than those who were not (hazard ratio 1.4, 95% CI 1.1-1.7).

- A prospective observational study assessed decision latitude in the workplace at baseline and followed individuals (n >3800) for 20 years [69]. After adjusting for potential confounding factors (eg, age, diet quality, and social support), the analyses found that low decision latitude was associated with weight gain ≥10 percent of baseline weight (odds ratio 1.3, 95% CI 1.1-1.5).

- However, job strain does not appear to be associated with obesity. A meta-analysis of four prospective observational studies, with individuals (n >42,000) who were followed for 3.5 to 6.5 years, found that after adjusting for age, sex, and socioeconomic status, the risk of becoming obese was comparable for those with job strain or no job strain (odds ratio 1.0, 95% CI 0.9-1.1) [70]. In addition, job strain was not associated with weight gain.

Although genetic factors influence the effect of stress on heart rate and blood pressure [71], one prospective observational study found that stress did not interact with genetic risk scores in predicting coronary artery disease, fatal myocardial infarction, and nonfatal myocardial infarction [72].

Association with inflammation — The association between inflammatory markers associated with CHD, such as serum C-reactive protein and interleukin (IL)-6, was evaluated in a report from the PRIME study of healthy, middle-aged men [73]. The 335 men who subsequently developed CHD were compared to matched controls. The odds ratio of depressive mood for CHD was 1.35 on univariate analysis. The depressed men had higher levels of inflammatory markers; however, after adjustment for these markers, depression was still associated with CHD.

INTERVENTIONS

Although medications such as beta blockers and psychosocial interventions can reduce the physiologic response to some forms of stress, there are no convincing data on their ability alone to prevent or regress atherosclerosis in humans. Therefore it would be difficult to justify these interventions for purposes of prevention of atherosclerosis. However, in patients with known coronary disease, the cardioprotective effect of beta blockers with regard to myocardial infarction and sudden cardiac death may be due in part to a diminution of catecholamine and hemodynamic-induced endothelial damage and a raising of the threshold for ventricular fibrillation. (See "Psychosocial factors in acute coronary syndrome".)

In patients at risk for cardiovascular events who are under increased psychosocial stress, a stress management program can be considered as part of an overall preventive strategy. In general the goal of a stress management program is to reduce the impact in the individual of stressful environmental events and to better regulate the stress response. Interventions may be considered at several levels [74]:

- Removal or alteration of the stressor
- Change in perception of the stressful event
- Reduction in the physiologic sequelae of stress
- Use of alternative coping strategies

Stress management techniques typically include components of muscular relaxation, a quiet environment, passive attitude, and deep breathing with the repetition of a word or phrase. Skills training is also performed, and involves instruction in acquisition of skills to reduce the affective, behavioral, and cognitive components of stress [75]. The physiologic changes produced include a decrease in oxygen consumption, reduced heart rate and respiratory rate and passive attitude and muscular relaxation. Such changes are consistent with a decrease in sympathetic nervous system activity.

The potential efficacy of stress management was illustrated in a randomized trial of 134 patients with stable ischemic heart disease and exercise-induced ischemia [75]. The patients were assigned to usual medical care alone, with exercise training for 35 minutes three times per week, or with 1.5 hours of stress management training for 16 weeks. Compared to usual care, the following significant benefits were noted with active intervention:

- A reduction in depression scores
- A reduction in self-reported measures of general distress

- A smaller reduction in left ventricular ejection fraction during mental stress testing
- A lower mean wall motion abnormality score in patients with significant stress-induced wall motion abnormalities at baseline

Other measures, such as relaxation techniques and biofeedback, can produce a small reduction in blood pressure of 5 to 10 mmHg in some patients [76-78]. Behavior modification programs are also an important adjunct to smoking cessation and have been associated with a reduction in cigarette consumption [79]. Modifications of type A personality have been less well studied, but behavior modification or exercise programs may be of benefit [80,81]. Improvements in compliance with medication regimens may be an additional benefit from stress reduction program [74].

SUMMARY AND RECOMMENDATIONS

- Psychosocial factors may possibly contribute to the early development of atherosclerosis. The link between psychologic stress and atherosclerosis may be both direct, via damage of the endothelium, and indirect, via aggravation of traditional risk factors such as smoking, hypertension, and lipid metabolism. (See 'Introduction' above.)
- Evidence about the association between psychosocial factors and the presence of asymptomatic coronary heart disease is mixed. Some studies suggest a possible link between depression, anger, or social competitiveness (dominance) and an increased risk of coronary heart disease, especially in individuals at high risk for the development of coronary disease by virtue of other factors, such as family history. (See 'Development of coronary disease' above.)
- There is an association between psychosocial factors and the presence of symptomatic coronary disease. Mental stress-induced angina results from an increase in heart rate and blood pressure, which increases cardiac demand, and coronary vasoconstriction, which reduces coronary blood flow and myocardial oxygen, supply. (See 'Coronary heart disease symptoms' above.)
- Psychosocial factors may be associated with the progression of atherosclerosis in patients with documented coronary disease, cardiovascular mortality, poorer outcome after CABG, and the development of carotid artery atherosclerosis. (See 'Progression of coronary heart disease' above and 'Cardiovascular mortality' above and 'Outcome after CABG' above and 'Carotid artery atherosclerosis' above.)

- Psychosocial factors may be involved in coronary and cerebrovascular disease by contributing to endothelial injury, affecting traditional risk factors (cigarette smoking, diet and serum cholesterol levels, and high blood pressure). (See 'Pathophysiology' above.)

- For patients with known coronary disease, the cardioprotective effect of beta blockers with regard to myocardial infarction and sudden cardiac death may be due in part to modifying the effect of psychosocial factors, such as a diminishing catecholamine and hemodynamic-induced endothelial damage and raising the threshold for ventricular fibrillation. (See 'Interventions' above.)

- For patients at risk for cardiovascular events who are under increased psychosocial stress, a stress management program can be considered as part of an overall preventive strategy. The goal of a stress management program is to reduce the impact of stressful environmental events and to better regulate the stress response by removing the stressor, changing the perception of the stressful event, and reducing the physiologic sequelae of stress. Stress management techniques typically include muscular relaxation, a quiet environment, passive attitude, deep breathing with the repetition of a word or phrase, and skills training to reduce the affective, behavioral, and cognitive components of stress. (See 'Interventions' above.)

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