Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy

Alan Rozanski, MD; James A. Blumenthal, PhD; Jay Kaplan, PhD

Abstract—Recent studies provide clear and convincing evidence that psychosocial factors contribute significantly to the pathogenesis and expression of coronary artery disease (CAD). This evidence is composed largely of data relating CAD risk to 5 specific psychosocial domains: (1) depression, (2) anxiety, (3) personality factors and character traits, (4) social isolation, and (5) chronic life stress. Pathophysiological mechanisms underlying the relationship between these entities and CAD can be divided into behavioral mechanisms, whereby psychosocial conditions contribute to a higher frequency of adverse health behaviors, such as poor diet and smoking, and direct pathophysiological mechanisms, such as neuroendocrine and platelet activation.

An extensive body of evidence from animal models (especially the cynomolgus monkey, Macaca fascicularis) reveals that chronic psychosocial stress can lead, probably via a mechanism involving excessive sympathetic nervous system activation, to exacerbation of coronary artery atherosclerosis as well as to transient endothelial dysfunction and even necrosis. Evidence from monkeys also indicates that psychosocial stress reliably induces ovarian dysfunction, hypercortisolemia, and excessive adrenergic activation in premenopausal females, leading to accelerated atherosclerosis. Also reviewed are data relating CAD to acute stress and individual differences in sympathetic nervous system responsivity. New technologies and research from animal models demonstrate that acute stress triggers myocardial ischemia, promotes arrhythmogenesis, stimulates platelet function, and increases blood viscosity through hemoconcentration. In the presence of underlying atherosclerosis (eg, in CAD patients), acute stress also causes coronary vasoconstriction. Recent data indicate that the foregoing effects result, at least in part, from the endothelial dysfunction and injury induced by acute stress. Hyperresponsivity of the sympathetic nervous system, manifested by exaggerated heart rate and blood pressure responses to psychological stimuli, is an intrinsic characteristic among some individuals. Current data link sympathetic nervous system hyperresponsivity to accelerated development of carotid atherosclerosis in human subjects and to exacerbated coronary and carotid atherosclerosis in monkeys.

Thus far, intervention trials designed to reduce psychosocial stress have been limited in size and number. Specific suggestions to improve the assessment of behavioral interventions include more complete delineation of the physiological mechanisms by which such interventions might work; increased use of new, more convenient “alternative” end points for behavioral intervention trials; development of specifically targeted behavioral interventions (based on profiling of patient factors); and evaluation of previously developed models of predicting behavioral change. The importance of maximizing the efficacy of behavioral interventions is underscored by the recognition that psychosocial stresses tend to cluster together. When they do so, the resultant risk for cardiac events is often substantially elevated, equaling that associated with previously established risk factors for CAD, such as hypertension and hypercholesterolemia. (Circulation. 1999;99:2192-2217.)

Key Words: coronary disease ■ stress ■ psychology

Although the importance of psychosocial factors in the development and expression of coronary artery disease (CAD) has been debated, an extensive recent literature now establishes that psychosocial factors contribute significantly to the pathogenesis of CAD. Furthermore, by use of new technologies and animal models, elucidation of the basic pathophysiology underlying the relationship between psychosocial factors and CAD is expanding rapidly. However, because the literature relating psychosocial factors to CAD is multidisciplinary, there may be an underappreciation of the strength of some of the epidemiological and pathophysiological observations that have been reported. Accordingly, we will review the relationship between psychosocial stress and CAD development, with emphasis on the following psycho-
social factors: (1) depression, (2) anxiety, (3) personality factors and character traits (eg, hostility), (4) social isolation, and (5) chronic and subacute life stress. Although these domains can overlap, epidemiological data for each domain will be reviewed separately, emphasizing studies that have used the “hard” cardiovascular end points of myocardial infarction and cardiac death as outcome variables (or all-cause mortality in the case of some early studies). In some instances, “alternative” cardiac end points will be considered, such as progression of atherosclerosis during serial carotid ultrasonography. Studies that relate psychosocial factors to “soft” cardiac end points, such as angina and static findings on coronary angiography, will not be reviewed. Information regarding the pathophysiology by which psychosocial factors promote CAD development will be examined for each psychological domain. These will include (1) behavioral mechanisms, whereby the given factor exacerbates lifestyles known to potentiate CAD (eg, smoking), and (2) direct pathophysiological effects, as delineated in experimental animal studies and/or investigations in humans. The pathogenic effects of 2 other phenomena, acute psychological stress and sympathetic nervous system hyperresponsivity, will then be reviewed. Finally, the implications of these findings relative to the prevention and treatment of CAD will be discussed.

Psychosocial Factors and CAD

Depression and Related Syndromes

Episodes of major depression are characterized by the presence of a depressed mood and markedly decreased interest in all activities, persisting for at least 2 weeks and accompanied by at least 4 of the following additional symptoms: changes in appetite, sleep disturbance, fatigue, psychomotor retardation or agitation, feelings of guilt or worthlessness, problems concentrating, and suicidal thoughts. The 1-month community-based prevalence of major depression episodes is \( \approx 5\% \). Among CAD patients, however, the prevalence of major depression is \( \approx 3 \)-fold higher. Also, depressive symptoms that are not sufficient in magnitude to meet the criteria for major depression occur at least as commonly among cardiac patients. Recent epidemiological studies evaluating the relationship between depression and CAD among healthy\(^1\)--\(^11\) and CAD\(^12\)--\(^19\) populations consistently demonstrate a significant prospective relationship between the occurrence of major depression episodes and the incidence of cardiac events (Table 1). Two additional findings are notable. First, the presence of depressive symptoms, in the absence of diagnosed major depression episodes, is also associated with an increased risk for cardiac events. Second, a number of studies support a gradient between the magnitude of depression and future cardiac events. Together, these data suggest that risk for CAD associated with depression exists along a continuum, according to the magnitude of depressive symptoms.

One particular aspect of depression, the absence of hope, has received particular attention. Hopelessness has been linked to sudden death, both in observational studies\(^20\),\(^21\) and in animal models of hopelessness.\(^22\) Recently, prospective epidemiological studies have also reported a relationship between symptoms of hopelessness and the development of CAD.\(^4\),\(^5\) In one study, for example, a positive answer to the question “(During the last month) have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?” more than doubled the risk of CAD.\(^4\) It has also been demonstrated that men experiencing hopelessness develop significantly more carotid atherosclerosis over time.\(^23\) A related phenomenon is “vital exhaustion.” This syndrome, measured by the 37-item Maastricht questionnaire,\(^24\) focuses on a triad of symptoms: fatigue, irritability, and demoralized feelings. The presence of vital exhaustion has also been reported to predict future CAD and/or cardiac events in healthy\(^25\) and CAD\(^26\),\(^27\) populations.

Pathophysiological Mechanisms

Considerable evidence indicates that depression has both behavioral and direct pathophysiological effects. With respect to behavioral mechanisms, depression is associated with both unhealthy lifestyle behaviors, such as smoking, and poor patient compliance.\(^29\),\(^30\) Direct pathophysiological effects of depression involve at least 3 mechanisms. First, depression is accompanied by hypercortisolemia.\(^31\)–\(^33\) Associated findings include attenuation of the adrenocorticotropic hormone response to corticotropin-releasing factor administration,\(^32\) non-suppression of cortisol secretion after dexamethasone administration,\(^34\) and elevated corticotropin-releasing factor concentrations in the cerebrospinal fluid of depressed patients.\(^35\) Second, depressed individuals may develop significant impairments in platelet function, including enhanced platelet reactivity and release of platelet products such as platelet factor 4 and \( \beta \)-thromboglobulin.\(^36\),\(^37\) The combination of hypercortisolemia and enhanced platelet function establishes the theoretical basis for explaining the proatherogenic effects of depression. In addition, reduced heart rate variability\(^38\) and impaired vagal control\(^39\) have been reported among depressed patients. These findings suggest that depressed patients may also be subject to enhanced arrhythmogenic potential.

Anxiety Syndromes

Until recently, evidence linking anxiety to CAD was limited to demonstrations of elevated mortality rates among psychiatric patients with anxiety disorders.\(^40\) Increasing evidence now links anxiety disorders to development of cardiac events in general populations (Table 2). Most notably, 3 large-scale community-based studies, including one involving \( \approx 34 \) 000 men, have now reported a significant relationship between anxiety disorders and cardiac death.\(^41\)–\(^43\) Moreover, a dose-dependent relationship has been noted between anxiety levels and the occurrence of cardiac death.\(^42\),\(^43\) Anxiety has not been associated with myocardial infarction in these studies. Rather, the excess mortality appears to be confined to sudden (versus nonsudden) cardiac death.\(^42\),\(^43\) Notably, these community-based studies did not include women,\(^41\)–\(^43\) even though anxiety disorders are more common among women.\(^44\)

Prospective positive associations between CAD and panic disorder\(^45\) and between CAD and “worry” (a subcategory of generalized anxiety disorder)\(^46\) have also been noted in 2
### TABLE 1. Depression and Coronary Artery Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>F/U, y</th>
<th>Scales</th>
<th>End Points</th>
<th>RR (95% CIs) or Other Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anda et al, 1993</td>
<td>2832</td>
<td>12.4</td>
<td>SS of generalized well-being schedule</td>
<td>CD, non-fatal IHD</td>
<td>RR for depressive sx = 1.5 (1.0–2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR for severe hopelessness = 2.1 (1.1–3.9)</td>
</tr>
<tr>
<td>Arooma et al, 1994</td>
<td>5355</td>
<td>6.6</td>
<td>SS of GHQ</td>
<td>MI</td>
<td>RR for depressive sx = 3.5 (1.9–6.8)</td>
</tr>
<tr>
<td>Vogt et al, 1994</td>
<td>2573</td>
<td>15</td>
<td>Investigator-tailored scale</td>
<td>ACM</td>
<td>P = NS for depressive sx</td>
</tr>
<tr>
<td>Everson et al, 1996</td>
<td>2428</td>
<td>6</td>
<td>SS of MMPI</td>
<td>CD; ACM</td>
<td>RR for severe hopelessness = 2.3 (1.1–3.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>RR for moderate hopelessness = 1.6 (1.0–2.5)</td>
</tr>
<tr>
<td>Wasserthal-Smoller et al, 1996</td>
<td>4736</td>
<td>4.5</td>
<td>CES-D scale</td>
<td>ACM, CD, MI; CVA</td>
<td>P = NS for baseline depressive sx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR for increasing depressive sx = 1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>Pratt et al, 1996</td>
<td>1551</td>
<td>13</td>
<td>DIS</td>
<td>MI</td>
<td>RR for MDE = 4.5 (1.7–12.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>RR for dysphoria = 2.1 (1.2–3.7)</td>
</tr>
<tr>
<td>Barefoot et al, 1996</td>
<td>730</td>
<td></td>
<td>OBD SS of MMPI</td>
<td>CD; MI</td>
<td>RR for depressive sx = 1.7 (1.2–2.3) (for MI)*</td>
</tr>
<tr>
<td>Ford et al, 1998</td>
<td>1190</td>
<td>37</td>
<td>Tailored scale</td>
<td>MI</td>
<td>RR for depressive sx = 2.1 (1.2–4.1)</td>
</tr>
<tr>
<td><strong>Known disease</strong></td>
<td></td>
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<tr>
<td>Kennedy et al, 1987</td>
<td>88 pts; syncope or arrhythmia</td>
<td>1.5</td>
<td>Tailored scale</td>
<td>CD</td>
<td>P = 0.01 for depressive sx</td>
</tr>
<tr>
<td>Carney et al, 1988</td>
<td>52; CAD on cath</td>
<td>1.0</td>
<td>DIS</td>
<td>CD, MI, PTCA; CABG</td>
<td>RR for MDE = 2.5, P &lt; 0.02†</td>
</tr>
<tr>
<td>Ahern et al, 1990</td>
<td>502, s/p MI and arrhythmia</td>
<td>1.0</td>
<td>BDI</td>
<td>ACM; CD</td>
<td>P &lt; 0.05 for depressive sx</td>
</tr>
<tr>
<td>Frasure-Smith et al, 1995</td>
<td>222, s/p MI</td>
<td>1.5</td>
<td>DIS; BDI</td>
<td>CD</td>
<td>RR for MDE = 3.6 (1.3–10.1)</td>
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<td></td>
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<td></td>
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<td></td>
<td>RR for depressive sx = 7.8 (2.4–25.3)</td>
</tr>
<tr>
<td>Barefoot et al, 1996</td>
<td>1250; s/p MI</td>
<td>15.2</td>
<td>Zung Self-Rating Depression scale</td>
<td>CD</td>
<td>P = 0.002 for depressive sx</td>
</tr>
<tr>
<td>Denoillet et al, 1998</td>
<td>87; s/p MI &amp; EF&lt;50%</td>
<td>7.9</td>
<td>Million Behavioral Health Inventory and BDI</td>
<td>CD; MI</td>
<td>RR for depressive sx = 4.3 (1.4–13.3)</td>
</tr>
<tr>
<td>Hermann et al, 1998</td>
<td>273, cardiopulmonary</td>
<td>1.9</td>
<td>HADS</td>
<td>ACM</td>
<td>RR for depressive sx = 2.6 (1.1–6.3)</td>
</tr>
<tr>
<td>Frasure-Smith et al, 1999</td>
<td>896, s/p MI</td>
<td>1.0</td>
<td>BDI</td>
<td>CD</td>
<td>RR for depressive sx = 3.2 (1.7–6.3)</td>
</tr>
</tbody>
</table>

F/U indicates follow-up; RR, risk ratio; pts, patients; cath, catheterization; s/p, status post; MI, myocardial infarction; EF, ejection fraction; SS, subscale; GHQ, General Health Questionnaire; PSE, Present State Examination; MMPI, Minnesota Multiphasic Personality Inventory; CES-D, Center for Epidemiological Studies Depression; DIS, Mental Health Diagnostic Interview Schedule (DSM-III diagnosis of depression); OBD, obvious depression; BDI, Beck Diagnostic Interview (measures depressive symptoms); HADS, Hospital Anxiety and Depression Scale; CD, cardiac death; IHD, ischemic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; ACM, all-cause mortality; Sx, symptom; and MDE, major depression episode.

*RR for cardiac death = 1.62, P < 0.03; †no CI reported.
recent studies; however, more studies are needed to establish whether these findings are indeed valid. The epidemiological investigation of anxiety disorders among CAD patients has also been quite sparse. Because 4 small studies have each noted a relationship between anxiety and a constellation of hard and soft cardiac events among CAD patients (Table 2),17,18,47,48 more large-scale epidemiological studies among CAD patients now appear to be warranted.

### Pathophysiological Mechanism

The association between anxiety and sudden death, but not myocardial infarction, suggests that ventricular arrhythmias may be the mechanism for cardiac death among individuals with anxiety disorders. In support of this hypothesis, it has been observed that individuals with anxiety disorders have reduced heart rate variability.49 Hence, there may be a pathological alteration in cardiac autonomic tone. This alteration could involve either increased sympathetic stimulation, which has been linked to the occurrence of arrhythmias and sudden death,50 or impaired vagal control, which has also been linked to increased cardiac mortality.51,52 With respect to the latter possibility, reduced vagal control has been linked to impaired, vagally mediated baroreflex control of the heart.53 Such impairment appears to be a particularly important risk factor for sudden death.54,55 Along these lines, a recent study reported reduced baroreflex cardiac control in patients with anxiety,56 but prospective work is needed to determine whether this is a common operative mechanism for sudden deaths among patients with anxiety syndromes.

Individuals with anxiety disorders are prone to more unhealthy lifestyle behaviors42,43; however, the lack of correlation between anxiety syndromes and myocardial infarction (a sign of underlying atherosclerosis) suggests that, at least among initially healthy individuals, this behavioral association is not a significant pathogenic mechanism. It is conceivable, nonetheless, that this behavioral association could be of importance among CAD patients manifesting anxiety.

### Personality and Character Traits

After the identification of the type A behavior pattern by Friedman and Rosenman in the late 1950s,57 a syndrome characterized by competition, hostility, and exaggerated commitment to work, many studies have investigated whether personality patterns or individual character traits promote the development of CAD. Other personality types have included “type D” personality,17 “social dominance,”58 and a “hardy personality” construct59; these latter personality types have not been widely studied as potential risk factors for CAD. Interest in type A behavior accelerated after the Western

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**TABLE 2. Anxiety Disorders**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>No. of Subjects</th>
<th>F/U, y</th>
<th>Condition Studied</th>
<th>Scale</th>
<th>End Points</th>
<th>RRss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy subjects</strong></td>
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<tr>
<td>Phobic anxiety</td>
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<tr>
<td>Haines et al, 1987</td>
<td>1457</td>
<td>6</td>
<td>Phobic anxiety</td>
<td>Crowne-Crisp CD</td>
<td>CD</td>
<td>3.8 (1.6–8.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
<td>1.3 (0.6–2.5)</td>
</tr>
<tr>
<td>Kawachi et al, 1994</td>
<td>33,999</td>
<td>2</td>
<td>Phobic anxiety</td>
<td>Crowne-Crisp CD</td>
<td>CD</td>
<td>2.5 (1.0–6.0)*</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>MI</td>
<td>0.9 (0.5–1.8)</td>
</tr>
<tr>
<td>Kawachi et al, 1994</td>
<td>2271</td>
<td>32</td>
<td>Anxiety</td>
<td>Anxiety SS of the Cornell Medical Index</td>
<td>CD</td>
<td>1.9 (0.7–5.4)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
<td>1.0 (0.3–3.6)</td>
</tr>
<tr>
<td>Other syndromes</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weissman, 1990</td>
<td>60 with panic; 3778 healthy</td>
<td>NR</td>
<td>Panic disorder</td>
<td>DIS CD</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CD</td>
<td>4.5 (1.7–12.3)</td>
</tr>
<tr>
<td>Kubzansky et al, 1997</td>
<td>1759</td>
<td>20</td>
<td>Worry</td>
<td>Worries Scale CD</td>
<td>CD</td>
<td>0.8 (0.5–1.4)‡</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
<td>2.4 (1.4–4.1)‡</td>
</tr>
<tr>
<td><strong>CAD patients</strong></td>
<td></td>
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</tr>
<tr>
<td>Frasure-Smith et al, 1995</td>
<td>222 pts, s/p MI</td>
<td>1</td>
<td>Anxiety</td>
<td>State Trait Anxiety Inventory</td>
<td>Combined 1</td>
<td>2.5 (1.6–5.6)</td>
</tr>
<tr>
<td>Moser et al, 1996</td>
<td>86 pts, s/p MI</td>
<td>IHS</td>
<td>Anxiety</td>
<td>Brief Symptom Inventory</td>
<td>Combined 2</td>
<td>4.9 (2.1–12.2)</td>
</tr>
<tr>
<td>Denuillet et al, 1998</td>
<td>87 pts, s/p MI</td>
<td>7.9</td>
<td>Anxiety</td>
<td>State Anxiety Scale</td>
<td>Combined 3</td>
<td>3.9 (1.2–9.6)§</td>
</tr>
<tr>
<td>Herrman et al, 1998</td>
<td>454 pts; 273 with cardiopulmonary disease</td>
<td>1.9</td>
<td>Anxiety</td>
<td>HADS ACM</td>
<td>2.5 (1.4–4.4)</td>
<td></td>
</tr>
</tbody>
</table>

NR indicates not reported; IHS, in-hospital study of cardiac events; 1, events include CD, MI and unstable angina. 2, events include CD, MI, acute ischemia; sustained VT or VF. 3, CD; MI; unstable angina; cardiac arrest survival. Other abbreviations as in Table 1.

*RR for sudden CD = 6.1 (2.4–15.7); RR compares highest- vs lowest-risk quartiles.
†RR for sudden CD = 4.7 (0.9–21.6).
‡RR for highest vs lowest terciles.
§Crude RR. Adjusted RR not reported.
¶Other patients had other medical conditions.
Collaborative Group Study, which reported that type A behavior was associated with a 2-fold increased risk of CAD and 5-fold increased risk of recurrent MI over an 8.5-year follow-up.60 Although type A behavior continues to receive attention,61 a series of studies have reported no correlation between type A behavior and CAD risk.62–66 This lack of consistency has cast doubt on the potential robustness of the type A behavior as a clinical syndrome. Potential confounders have been suggested. For instance, animal model studies67 and some human studies68,69 suggest that social support is a potential confounding variable. Furthermore, suspecting that not all components of type A behavior are pathogenic, investigators have examined the components of this behavior pattern.

Hostility, a major attribute of the type A behavior pattern, has received considerable attention as a potential “toxic” element in this personality construct. Hostility is a broad psychological construct, encompassing negative orientations toward interpersonal relationships, and includes such traits as anger, cynicism, and mistrust. Table 3 lists 10 studies assessing the relationship between hostility and CAD in healthy subjects.70–79 The results of these prognostic studies are mixed, with both positive and negative studies. However, the studies are of uneven quality. For instance, in one negative study, 57% of the individuals were lost to follow-up,75 whereas the follow-up of healthy individuals in another study was only 3 years.76 Of note, 2 large studies that used tailored scales to focus on cynical mistrust77 and anger79 have yielded positive associations with cardiac events. In the anger study, a gradient was noted between anger levels and the frequency of subsequent cardiac events.79 Thus, it is possible that certain components of the hostility construct are more pathogenic.

To date, there have been no large-scale epidemiological studies evaluating hostility among CAD patients. Four small epidemiological studies among CAD patients, however, have been positive, as noted in Table 3.76,80–82 In addition, studies have reported that CAD patients with high levels of hostility have a greater rate of restenosis after angioplasty,83 experience more rapid atherosclerosis progression during serial carotid ultrasonography,84,85 and manifest more ischemia during stress testing than other CAD patients.86

Pathophysiological Mechanisms
Hostility may affect atherogenic activity by behavioral mechanisms. Hostility is associated with a higher concentration of unhealthy lifestyle behaviors, including smoking, poor diet, obesity, and alcoholism.77,79,87 Hostile individuals are also more likely to manifest other psychosocial factors associated

### Psychological Factors and CAD

#### TABLE 3. Hostility and the Pathogenesis of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>F/U, y</th>
<th>Scales</th>
<th>End Points</th>
<th>RRs or Other Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy subjects</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Shekelle et al, 1983</td>
<td>118 lawyers</td>
<td>28</td>
<td>MMPI Ho SS</td>
<td>ACM</td>
<td>Ho score associated with mortality (P&lt;0.01)</td>
</tr>
<tr>
<td>Barefoot et al, 1983</td>
<td>255 MDs</td>
<td>25</td>
<td>MMPI Ho SS</td>
<td>CD; Mi; AP</td>
<td>Ho score predicted both ACM and CAD (P&lt;0.005)</td>
</tr>
<tr>
<td>McCranie et al, 1986</td>
<td>478 MDs</td>
<td>25</td>
<td>MMPI Ho SS</td>
<td>CD; Mi; angina</td>
<td>No association</td>
</tr>
<tr>
<td>Leon et al, 1988</td>
<td>280</td>
<td></td>
<td>MMPI Ho SS</td>
<td>CD; Mi</td>
<td>No association</td>
</tr>
<tr>
<td>Barefoot et al, 1989</td>
<td>118 lawyers</td>
<td>28</td>
<td>MMPI Ho SS</td>
<td>ACM</td>
<td>Ho score associated with mortality (P&lt;0.01)</td>
</tr>
<tr>
<td>Hearn et al, 1989</td>
<td>1399</td>
<td>33</td>
<td>MMPI Ho SS</td>
<td>CD; ACM</td>
<td>No association</td>
</tr>
<tr>
<td>Maruta et al, 1993</td>
<td>620</td>
<td>20</td>
<td>MMPI Ho SS</td>
<td>ACM; CD</td>
<td>No association</td>
</tr>
<tr>
<td>Koskenvuo et al, 1993</td>
<td>2885</td>
<td>3</td>
<td>Self-rating SS</td>
<td>CD; CAD diagnosis</td>
<td>No association (but P=0.08 for ACM)</td>
</tr>
<tr>
<td>Everson et al, 1994</td>
<td>2125</td>
<td>9</td>
<td>Cynical Distrust scale</td>
<td>CD; Mi; ACM</td>
<td>1.5 (0.7–3.25)</td>
</tr>
<tr>
<td>Barefoot et al, 1995</td>
<td>730</td>
<td>27</td>
<td>Abbr MMPI Ho SS</td>
<td>ACM; Mi</td>
<td>RR for MI=1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>Kawachi et al, 1996</td>
<td>1305</td>
<td>7</td>
<td>MMPI-2 anger SS</td>
<td>CD; Mi; angina</td>
<td>RR for chronic anger=2.7 (1.3–5.6). Gradient of risk with increasing anger (P=0.008)</td>
</tr>
<tr>
<td><strong>Patients with CAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hecker et al, 1988</td>
<td>250†</td>
<td>8.5</td>
<td>SI</td>
<td>CD; Mi; AP</td>
<td>RR=1.9 (1.3–2.8)</td>
</tr>
<tr>
<td>Dembroski et al, 1989</td>
<td>192*</td>
<td>7.1</td>
<td>SI</td>
<td>CD; Mi</td>
<td>RR for total potential for hostility=1.7 (P=0.005)</td>
</tr>
<tr>
<td>Koskenvuo et al, 1993</td>
<td>104, CAD and HBP</td>
<td>3</td>
<td>Self-ratings§</td>
<td>Restenosis</td>
<td>RR=14.6 (1.4–110), for highest vs lowest quartile</td>
</tr>
<tr>
<td>DeLeon et al, 1996</td>
<td>149, s/p PTCA</td>
<td>1.5</td>
<td>State-Trait Anger Scale</td>
<td>CD; Mi; CABG; PTCA; new lesions</td>
<td>RR=2.1 (1.1–4.0)</td>
</tr>
</tbody>
</table>

HBP indicates high blood pressure; Ho, hostility; Abbr, abbreviated; and AP, angina pectoris. Other abbreviations as in previous tables.

*Matched case-control design; patients compared with 384 controls; §500 matched controls.

**Self-rating of irritability; ease of anger-arousal; and argumentativeness.

§Assessed “potential for hostility,” derived from the structured interview.

†Adjusted RR for CD after adjustment for both biological and behavioral risk factors, but the crude RR was 2.7 (1.3–5.6); similar RR for MI.

‡Derived from the Cook-Medley Hostility Scale.
with CAD, such as social isolation. An accumulating body of evidence also suggests multiple pathophysiological mechanisms by which hostility may be linked to CAD. For example, compared with nonhostile individuals, hostile subjects manifest higher heart rate and blood pressure responses to physiological stimuli, such as mental tasks, as well as higher ambulatory blood pressure levels during daily-life activity. Also, evidence suggests that hostile individuals are more likely to exhibit hypercortisolemia and high levels of circulating catecholamines, as well as diminished mononuclear leukocyte β-adrenergic receptor function. Preliminary data suggest that hostile individuals may also manifest diminished vagal modulation of heart function and increased platelet reactivity.

Social Isolation and Lack of Social Support

Since the late 1970s, a series of prospective community-based studies have examined the influence of social factors on the development of CAD. Initial studies focused on quantitative aspects of social support, such as the presence of family affiliations, number of friends, and the extent of one’s participation in group and organizational activities. This domain of measurement has been called one’s “social network.” Within this domain, some studies evaluated the influence of partner status (living alone, marital status, and/or marital disruption), and others have assessed aspects of “instrumental” (ie, tangible) support, such as access to guidance and practical community services. Over time, however, the qualitative nature of one’s social support system (eg, amount of perceived emotional support) has also been increasingly subject to study. Fifteen studies examining the impact of social factors on the future incidence of CAD in initially healthy populations are summarized in Table 4. A relatively small network has been found, on average, to be associated with a 2- to 3-fold increase in the incidence of CAD over time. Similarly, low levels of perceived emotional support confer an even greater increased risk for future cardiac events. Table 5 lists 11 studies evaluating the relationship between social factors and prognosis in patients with preexisting CAD. Significant prognostic relationships are present in most of these studies, and the risk ratios are substantial. For instance, Berkman et al observed a nearly 3-fold increase in subsequent cardiac events in post-MI patients reporting a low level of emotional support, and Williams et al observed a similar 3-fold increase in mortality over 5 years among CAD patients who were unmarried or had no significant confidant in their life.

In addition to the consistency and magnitude of these findings, the cause-and-effect relationship between social factors and CAD development is also supported by other evidence. First, an inverse gradient has been reported between the magnitude of social support and the incidence of CAD and/or future cardiac events, as summarized in Table 6. Moreover, acculturation independently influences CAD development. For instance, in one study, 3809 Japanese-Americans in California were classified according to the degree to which they retained a traditional Japanese culture. The most traditional group of Japanese-Americans had a CAD prevalence as low as that observed in Japan, whereas the group that was most acculturated had a 3- to 5-fold excess in CAD prevalence. Major CAD risk factors did not account for these differences. In another study, temporal rates of CAD development were assessed in Roseto, Pa, and an adjacent town. Initially, CAD incidence was significantly lower in Roseto, despite shared medical resources. At that time, Roseto was a cohesive and homogeneous community of generation households, descendants of Italian immigrants. As the distinguishing social characteristics of the Roseto community disappeared over time, its lower incidence of CAD vanished. Finally, animal studies have also implicated social factors in the promotion of atherogenesis. For instance, Ratcliffe and Cronin described the potential importance of social disruption among animals, noting that crowding and social disruption were the apparent causal factors for a 10-fold increase in atherosclerotic lesions that occurred among birds and mammals over a 20-year period at the Philadelphia Zoo. Ratcliffe et al also studied social support experimentally by deliberately assigning swine to various social situations (alone, pairs, groups). At postmortem examination, coronary arteriosclerosis was most advanced in isolated females, intermediate in isolated males, and least advanced in animals sustained in groups. More recently, the extent of atherosclerosis was compared among 39 cynomolgus female monkeys exposed to different housing conditions: 15 monkeys housed in single cages and 24 housed in groups. The extent of arteriosclerosis was 4 times greater, on average, in the females that were housed alone than in those housed in social groups. This difference occurred in the absence of significant differences in plasma lipids. In combination, these data provide strong evidence that social factors relating to grouping and isolation can promote atherogenesis.

Socioeconomic Status

Aside from social factors, low socioeconomic status is a significant contributor to increased risk in healthy persons and a contributor toward poor prognosis in patients with established CAD, in graded fashion. The gradient between socioeconomic status and cardiac outcome is observable whether measured by education, income, or occupation. Low socioeconomic status is associated with increased levels of high-risk behaviors and psychosocial risk factors. Interestingly, some evidence also suggests that low socioeconomic status may be an independent risk factor in its own right, but this possibility requires prospective validation and, if true, delineation of the operative pathophysiological mechanism(s). In any case, when low socioeconomic status is clustered together with other psychosocial risk factors, the risk of cardiac events is often magnified.

Pathophysiological Mechanisms

Like other psychosocial factors, social support influences the extent to which individuals engage in such high-risk behaviors as smoking, fatty diet intake, and excessive alcohol consumption. In addition, social factors may exert direct pathophysiological effects, including hypercortisolism. Animal studies have reported an association between social isolation and hypercortisolism and reversible increases in resting heart rates among cynomolgus monkeys, depending...
on the presence or absence of social separation. Similarly, human studies have demonstrated an inverse relationship between the quality of social relationships and urinary levels of epinephrine and between the degree of social support and resting heart rates. Elevated resting heart rates may constitute a sign of altered autonomic arousal. The presence of social support may also attenuate blood pressure and heart rate responses to stressful stimuli in humans. In summary, these data suggest that social factors promote atherosclerosis through activation of the autonomic nervous system.

**Chronic and Subacute Life Stress**

Work-related stress is the most widely studied chronic life stress relative to CAD. Although many aspects of one’s work environment relative to the development of CAD have been studied, much interest has focused on models of inherent “tension” at work. One such model has been the “job strain” model, defined by Karasek et al as jobs with high demand but low decision latitude. In one prospective study of 1928 male workers followed up for 6 years, job strain was associated with a 4-fold increase in the risk of cardiovascular system–related death. Subsequent studies have supported the relationship between job strain and CAD risk, but negative studies have also been reported.

More recently, research has begun to focus on other forms of work-related stress. For example, one model views work stress as the outcome of high work demand and low reward. This model both predicts cardiac events and has been correlated with progression of carotid atherosclerosis. Also, low job control, per se, predicts future cardiac

### Table 4. Social Influences and the Pathogenesis of CAD in Healthy Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th># of Subjects</th>
<th>F/U, Y</th>
<th>Social Parameter(s) Studied</th>
<th>End Points</th>
<th>RR/Other</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkman &amp; Syme, 1979</td>
<td>Alameda County</td>
<td>6928</td>
<td>9</td>
<td>Network index</td>
<td>ACM; CD</td>
<td>2.3†</td>
<td></td>
</tr>
<tr>
<td>Blazer et al, 1982</td>
<td>Durham, NC</td>
<td>339*</td>
<td>2.5</td>
<td>Roles and attachments</td>
<td>ACM</td>
<td>2.0 (1.2–3.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Perceived social support</td>
<td>ACM</td>
<td>3.4 (1.9–6.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Frequency of interactions</td>
<td>1.9 (1.1–3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>House, et al, 1982</td>
<td>Tecumseh</td>
<td>2754</td>
<td>12</td>
<td>Social network variables</td>
<td>ACM</td>
<td>1.9–2.8‡</td>
<td></td>
</tr>
<tr>
<td>Reed et al, 1983</td>
<td>Japanese in Hawaii</td>
<td>4653</td>
<td>6</td>
<td>Network scope</td>
<td>CD; MI; AP</td>
<td></td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>Welin et al, 1985</td>
<td>Gothenberg, Sweden</td>
<td>989</td>
<td>9</td>
<td>Number of social activities</td>
<td>ACM</td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of people living at home</td>
<td>P&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schoenbach et al, 1986</td>
<td>Evans County, Ga</td>
<td>2059</td>
<td>13</td>
<td>Network index</td>
<td>ACM</td>
<td>1.5 (0.8–2.6)§</td>
<td></td>
</tr>
<tr>
<td>Orth-Gomer et al, 1987</td>
<td>Swedish Registry</td>
<td>17 433</td>
<td>6</td>
<td>Network scope/frequency</td>
<td>ACM; CD</td>
<td>1.4 (1.1–1.7) (ACM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marital status</td>
<td></td>
<td>0.4 (0.97–2 (MI))</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.97–2 (MI))</td>
<td></td>
</tr>
<tr>
<td>Seeman, et al, 1987</td>
<td>Alameda County</td>
<td>564**</td>
<td>17</td>
<td>Social network index</td>
<td>ACM</td>
<td>1.5 (1–2.5)</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al, 1988</td>
<td>Finland</td>
<td>13 301</td>
<td>5</td>
<td>Social network</td>
<td>ACM; CD</td>
<td>1.5 (1.2–2.0)</td>
<td></td>
</tr>
<tr>
<td>Hansen et al, 1989</td>
<td>Malmo, Sweden</td>
<td>500</td>
<td>5</td>
<td>Amount of emotional support</td>
<td>ACM</td>
<td>2.2 (2.1–4.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amount of social participation</td>
<td>ACM</td>
<td>2.5 (1.2–5.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Marital status</td>
<td></td>
<td>2.0 (1.0–3.8)</td>
<td></td>
</tr>
<tr>
<td>Pennix et al, 1992</td>
<td>Amsterdam</td>
<td>2829</td>
<td>2.4</td>
<td>Requiring instrumental support</td>
<td>ACM</td>
<td>1.7 (1.1–2.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive emotional support</td>
<td></td>
<td>0.5 (0.3–0.7)</td>
<td></td>
</tr>
<tr>
<td>Vogt et al, 1992</td>
<td>HMO Members, California</td>
<td>2603</td>
<td>15</td>
<td>Network scope</td>
<td>ACM</td>
<td>2.7 (1.8–4.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Network frequency</td>
<td>ACM</td>
<td>1.5 (1.1–2.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Network size</td>
<td>ACM</td>
<td>1.4 (1.1–1.8)</td>
<td></td>
</tr>
<tr>
<td>Orth-Gomer et al, 1993</td>
<td>Gothenberg, Sweden</td>
<td>736</td>
<td>6</td>
<td>Social integration</td>
<td>CD; MI</td>
<td>3.8 (1.1–13.9)¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Social attachment</td>
<td></td>
<td>3.8 (1.3–7.8)¶</td>
<td></td>
</tr>
<tr>
<td>Seeman et al, 1993</td>
<td>New Haven (NH)</td>
<td>2812*</td>
<td>5</td>
<td>Social ties, NH</td>
<td>ACM</td>
<td>2.4 (1.4–3.1)¶</td>
<td></td>
</tr>
<tr>
<td>(3 samples)</td>
<td>Iowa (I), East Boston (EB)</td>
<td>3673*</td>
<td>1</td>
<td>Social ties, I</td>
<td>ACM</td>
<td>1.4 (0.9–2.3)¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Social ties, EB</td>
<td>ACM</td>
<td>1.0 (0.7–1.5)¶</td>
<td></td>
</tr>
<tr>
<td>Kaplan et al, 1994</td>
<td>Kuopio, Finland</td>
<td>2503</td>
<td>5.9</td>
<td>Participation in organizations</td>
<td>ACM</td>
<td>2.1 (1.3–3.7)#</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quality of relationships</td>
<td>ACM</td>
<td>1.8 (1.1–3.2)#</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Divorced or separated</td>
<td>ACM</td>
<td>2.0 (1.2–3.3)</td>
<td></td>
</tr>
</tbody>
</table>

*= >65 years old.
†This is the RR in males; RR = 2.8 in females. No CIs provided.
‡Range of values for different variables in men. RR range = 1.1–1.9 in women. §Values for men only. P = NS for women.
¶For lowest vs upper 3 quartiles; # for highest vs lowest values.
**>= 70 years old.

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**Psychological Factors and CAD**

by guest on April 22, 2017 http://circ.ahajournals.org/ Downloaded from
events.149 Taken together, the studies regarding presence of stress at work and subsequent CAD development have been largely positive, suggesting a strong causal relationship between this form of chronic stress and development of atherosclerosis.

Because many observational studies have reported psychological prodromata in the months preceding development of acute MI,150 interest has also been focused on the potential pathogenicity of “subacute” life stress (defined as an accumulation of stressful life events over a duration of months). In one of the earliest attempts to quantify the relationship between subacute psychological stress and CAD, Holmes and Rahe151 developed a “Recent Life Change Questionnaire,” with a predetermined weighting assigned to different life events, ranging from high numbers for such events as the death of a spouse, divorce, or loss of a job to low weightings for vacations and holidays. In one study, marked elevations in Recent Life Change scores were seen for most cases of MI or sudden cardiac death during the 6-month period preceding these events.152 Similar confirmations of increased life stress before cardiac events can be extended to specific cohorts, ranging from healthy middle-aged men153 to patients presenting with acute myocardial infarction.154

**Pathophysiological Mechanisms**

Like other psychosocial factors, chronic stress appears to exert direct pathophysiological effects, including elevation of arterial blood pressure155,156 and neurohumoral arousal.157 Evidence of neurohumoral arousal has also been noted in situations associated with subacute stress.158,159

**“Clustering” of Psychosocial Variables**

Although psychosocial stresses have been reviewed here as individual entities, generally, these stresses tend to cluster

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>No. of Patients</th>
<th>F/U, y</th>
<th>Social Parameters Studied</th>
<th>End Points</th>
<th>RR or Other Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chandra et al, 1983</td>
<td>Baltimore</td>
<td>888, s/p MI</td>
<td>10.0</td>
<td>Marital status</td>
<td>ACM</td>
<td>$P&lt;0.025$</td>
</tr>
<tr>
<td>Ruberand et al, 1984</td>
<td>BHAT trial</td>
<td>2320, s/p MI</td>
<td>3.0</td>
<td>Social isolation</td>
<td>CD; ACM</td>
<td>$P&lt;0.001^*$</td>
</tr>
<tr>
<td>Wiklund et al, 1988</td>
<td>Gothenburg</td>
<td>201, s/p MI</td>
<td>5.0</td>
<td>Marital status</td>
<td>ACM; MI</td>
<td>$P&lt;0.001$</td>
</tr>
<tr>
<td>Ahern et al, 1990</td>
<td>CAPS‡</td>
<td>324, s/p MI</td>
<td>1.0</td>
<td>Marital status; No. of people at home</td>
<td>CD</td>
<td>No association</td>
</tr>
<tr>
<td>Case et al, 1992</td>
<td>New York</td>
<td>1234 s/p MI</td>
<td>2.1</td>
<td>Living alone</td>
<td>CD; MI</td>
<td>$RR=1.5$ ($1.0–2.3)$</td>
</tr>
<tr>
<td>Williams et al, 1992</td>
<td>Duke U.</td>
<td>1368, CAD</td>
<td>9</td>
<td>Unmarried without confidant</td>
<td>CD</td>
<td>$RR=3.3$ ($1.8–6.2)$</td>
</tr>
<tr>
<td>Berkman et al, 1992</td>
<td>New Haven</td>
<td>194, s/p MI</td>
<td>0.5</td>
<td>Magnitude of emotional support</td>
<td>CD</td>
<td>$RR=2.9$ ($1.2–6.9)$</td>
</tr>
<tr>
<td>Gorkin et al, 1993</td>
<td>CAST-1‡</td>
<td>1332, s/p MI</td>
<td>0.8</td>
<td>Magnitude of emotional support and social functioning index</td>
<td>CD</td>
<td>$RR=1.5$, $P=0.01$</td>
</tr>
<tr>
<td>Jenkinson et al, 1993</td>
<td>England</td>
<td>1376 s/p MI</td>
<td>3</td>
<td>Social isolation</td>
<td>ACM</td>
<td>$RR=1.5$ ($1.0–2.2)$</td>
</tr>
<tr>
<td>Weloshin et al, 1997</td>
<td>Manitoba</td>
<td>734, s/p MI</td>
<td>1</td>
<td>Diminished perceived tangible support (3 grades)</td>
<td>ACM</td>
<td>$RR=6.5$ ($2.0–25.6)$†</td>
</tr>
<tr>
<td>Krumholz et al, 1998</td>
<td>New Haven</td>
<td>292, CHF</td>
<td>1</td>
<td>Magnitude of emotional support</td>
<td>CD</td>
<td>$RR=2.6$ ($1.0–6.6)$</td>
</tr>
</tbody>
</table>

*Approximate RR of a 2-fold increase; 95% CIs not available.
†For highest of 3 grades of increasingly diminished support; mild and intermediate grade RRs = 1.8 (0.6–5.8) and 3.2 (1.1–9.4).
‡Multicenter arrhythmia trials.

**TABLE 6. Social Support and Clinical Outcome: Evidence of a Gradient Effect**

<table>
<thead>
<tr>
<th>Variable Assessed (Reference)</th>
<th>End Point</th>
<th>Subjects</th>
<th>No. of Divisions</th>
<th>% Experiencing End Point From Least to Most Socially Supportive Division (1 = least supportive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional support (119)</td>
<td>Death</td>
<td>Men (n = 100)†</td>
<td>3</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Social integration (100)</td>
<td>6-year CAD incidence</td>
<td>All patients (n = 749)</td>
<td>3</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Social network (98)</td>
<td>Death</td>
<td>Men (n = 2229)</td>
<td>4</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Social activity score (103)</td>
<td>Death</td>
<td>Men, 1913 (n = 787)</td>
<td>5</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Social relationships (101)</td>
<td>Death</td>
<td>Men, 1923 (n = 292)</td>
<td>5</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td></td>
<td>Women (n = 1251)</td>
<td>6</td>
<td>1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women (n = 1284)</td>
<td>6</td>
<td>1 2 3 4 5 6</td>
<td></td>
</tr>
</tbody>
</table>

N/A indicates not applicable.
*Based on studies reporting percentages for each end point observed per division.
†s/p MI.
TABLE 7. Bayesian Probability of CAD in a 47-Year-Old Man With NACP According to Risk Factors and Depressive Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>CAD Probability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACP</td>
<td>20</td>
</tr>
<tr>
<td>NACP + currently smoking and HBP (systolic BP = 165 mm Hg)</td>
<td>30</td>
</tr>
<tr>
<td>NACP + smoking/HBP + depressive symptoms</td>
<td>46</td>
</tr>
<tr>
<td>NACP + smoking/HBP + major depression</td>
<td>66</td>
</tr>
</tbody>
</table>

NACP indicates nonanginal chest pain; HBP, high blood pressure.

Assumptions: For the purpose of this schematic example, we used the data of Pratt et al., which reported RR data for both depressive symptoms in the absence of major depression (RR = 2.1) and RR data for the presence of major depression (RR = 4.5). Change in initial probability (P) is calculated as follows:

1. \( P/(1 - P) \times \text{odds ratio} = \text{odds} \).
2. New probability = odds/(1 + odds).

*Risk ratios may be used instead of odds ratios when probabilities are low, as in this example. Odds ratios should be employed when probabilities are high.

Together. When they do so, risk ratios for cardiac events often rise substantially. For example, in one study of post-MI patients, the presence of high levels of life stress and social isolation were each associated with an \( =2 \)-fold increase in subsequent events. But when the 2 factors occurred together, the rate of subsequent events was 4-fold higher. A similar synergy between these 2 factors has also been reported among healthy individuals. Similarly, the combination of anxiety and depression compounds cardiac risk in post-MI patients, and many other examples can be found within the psychosocial literature. These data indicate that psychological factors occurring in combination substantially magnify risk associated with individual psychological factors, resulting in risk elevations that are comparable to those associated with hypercholesterolemia, hypertension, and other major risk factors for CAD. Furthermore, psychosocial factors also interact synergistically with conventional CAD risk factors to heighten the risk for cardiac events. For example, depressed patients who smoke have a substantially higher risk of cardiac events than depressed patients who do not smoke. These findings could provide impetus for developing algorithms that integrate psychosocial factors and conventional risk factors into the Bayesian analysis of CAD, as schematized for a patient with nonanginal chest pain in Table 7.

Pathophysiological Mechanisms

From a pathophysiological point of view, the increase in cardiac events associated with clustering of psychosocial stresses suggests that this clustering compounds the health-damaging effects of individual psychosocial stresses. However, because psychosocial stresses and behavioral risk factors in humans change over time and cluster together in variable fashion, it is difficult to study the potential mechanisms by which they exert their pathophysiological effects. In contrast, adequate experimental control can be achieved in animal models, especially monkeys. In this regard, cynomolgus monkeys (Macaca fascicularis) provide a potentially relevant model for studying the interaction of multiple psychological factors in a controlled setting. Like humans, cynomolgus monkeys develop coronary atherosclerosis when fed fatty diets and manifest similarities to people in the development of coronary lesions and coronary vasodilator abnormalities. Notably, cynomolgus monkeys resemble human beings in both the organization and expression of their social behavior. For example, dominance and nurturance are sometimes considered to be the 2 major dimensions that define the content of interpersonal human behavior. Cynomolgus monkeys are characterized by well-defined social status hierarchies in which some animals (dominants) reliably defeat others (subordinates) in competitive interactions, as well as by elaborate, generation-spanning, networks of affiliation, alliance, and mutual support. Humans and monkeys also use similar facial expressions and postures to communicate an antagonistic or combative mood, and both rely extensively on visual cues to signal moods quickly and unambiguously in complex social settings. These behavioral similarities suggest that monkeys might be especially useful for modeling the human expression of anger or hostility.

In a set of investigations designed to evaluate the interaction between personality factors and a stressful social environment, 30 male monkeys were fed a moderately atherogenic diet while housed in 5-member social groups and assigned to 1 of 2 social conditions: (1) an “unstable” environment in which animals were switched among groups on a regular basis so that animals periodically had to reestablish their dominance and affiliative relationships or (2) a “stable” environment in which initial group memberships were maintained without disruption throughout a 22-month period. Repeated behavioral observations permitted identification of individuals as relatively more dominant or subordinate in their social groups. The index of coronary artery atherosclerosis in this and all other cited monkey experiments was the average lesion extent as measured in 15 cross sections of pressure-perfused coronary arteries. Five sections each were taken from the left circumflex, left anterior descending, and right coronary arteries for these determinations. At the end of this study, quantitative evaluation of the coronary arteries of these animals revealed that dominant male monkeys in an unstable environment had significantly more coronary artery atherosclerosis than the other 3 subgroups (Figure 1, top). These results were independent of variations in serum lipid concentrations and blood pressure. Thus, this animal model revealed that it was the interaction between 2 psychosocial factors that proved pathogenic in cynomolgus monkeys: the trait of “dominance,” coupled with environmental stress.

Subsequently, to test the causal role of sympathetic activation in promoting atherogenesis in these predisposed animals, a number of male monkeys were housed in unstable social groups and fed an atherogenic diet for 26 months; however, half of the monkeys also received a \( \beta \)-adrenergic antagonist, propranolol, throughout the study. As shown in Figure 1, bottom, untreated dominant monkeys again developed substantial atherosclerosis; however, pretreatment with propranolol abolished the excess atherosclerosis that develops among dominants housed in an unstable environment.
These data provide strong confirmatory evidence that the atherogenic effect of chronic psychological stress in these monkeys is dependent on concomitant sympathetic activation.

Cynomolgus monkeys have also been used to study the influence of chronic psychosocial stress on coronary endothelial integrity. First, it was demonstrated that the stress model cited above induces atherosclerosis in dominant male monkeys in the absence of hypercholesteremia, albeit with smaller lesions than those noted for monkeys concomitantly fed a high-cholesterol diet. Thus, under conditions of chronic psychological stress, endothelial injury can occur even without dietary provocation. Subsequently, quantitative coronary angiography was used to demonstrate that psychosocial stress in cynomolgus monkeys can also lead to impairment of endothelial function in the presence of underlying coronary atherosclerosis. Specifically, arterial responses in nonatherosclerotic controls (which always consumed a low-cholesterol diet and were housed in stable groups) were compared with those in monkeys that consumed a high-cholesterol diet for 1 year and were subsequently assigned to 1 of 3 experimental conditions: (1) continued consumption of a high-cholesterol diet plus exposure to periodic social disruption, (2) consumption of a low-cholesterol diet plus exposure to periodic social disruption, and (3) consumption of a low-cholesterol diet and housed in stable social groups. As shown in Figure 2, coronary vascular responses to acetylcholine differed across groups in a manner consistent with the exposure to psychosocial stress. Thus, chronic psychosocial stress can impair endothelium-dependent vascular responses in a manner that is not necessarily dependent on extent of underlying atherosclerosis or diet.

**Sex Differences**

The relative sparing of premenopausal women in relation to men of similar age is a prominent feature of CAD, ischemic stroke, and atherosclerosis. Although this phenomenon is sometimes referred to as “female protection,” it is more accurately characterized as a delay in disease onset, with the incidence curve for women lagging behind that of men by ≈10 years. The various effects of estrogen are believed to account for most of this sex difference, at least with respect to CAD incidence and atherosclerosis. Not only are premenopausal women “protected” from atherosclerosis, but the provision of estrogen replacement to initially healthy postmenopausal women is associated with a significant reduction in CAD risk. Nevertheless, because atherosclerosis progresses over decades, it is likely that the clinical events occurring in postmenopausal women have their beginnings in the premenopausal years. This conclusion is supported by a recent study showing the presence of relatively extensive focal atherosclerosis in premenopausal women. Ovarian abnormalities or failure, by reducing the amount of endogenous estrogen, could accelerate atherogenesis in premenopausal women, thereby predisposing these individuals to CAD (and possibly ischemic stroke) in later years.

Notably, studies in premenopausal monkeys suggest that psychosocial stress reliably induces ovarian impairment in the half of socially housed females that occupy subordinate status in their social groups. Subordinate monkeys have estradiol concentrations of ≈60 pg/mL, contrasting significantly with dominants at ≈130 pg/mL. Furthermore, these subordinate, ovary-impaired females, compared with their dominant counterparts, develop exacerbated atherosclerosis and abnormalities in coronary reactivity. Such females are also typically hypercortisolemic and have exaggerated heart responses to stress, characteristics that are themselves risk factors for atherosclerosis in both humans and monkeys.

These animal findings establish the possibility that behavioral stressors influence the development of CAD in women during the premenopausal period, through effects on estrogenic and neuroendocrine activity. In fact, several lines of evidence are consistent with the suggestion that ovarian impairment, possibly stress-induced, potentiates atherogenesis before menopause in women. First, 2 studies have linked a lifelong history of menstrual irregularity with a significantly increased risk for acute myocardial infarction. A third study has shown that irregularly menstruating women, in comparison with normally cycling control women, have...
elevated plasma fibrinogen concentrations (a risk factor for CAD) and a thickened arterial intima. The possibility that these observations might reflect the reduced concentrations of endogenous estrogen characteristic of ovary-impaired women is supported by the finding that premenopausal women with angiographically confirmed CAD have significantly lower plasma estradiol concentrations than do control subjects and that such levels resemble those observed in subordinate female monkeys. Notably, many premenopausal women may experience ovarian compromise at some time during their reproductive years. The general term for this compromise is functional hypothalamic hypogonadism, the manifestations of which range from subclinical luteal-phase defects with regular menstrual intervals to irregular cycles to amenorrhea. Psychogenic stress is often linked to functional hypothalamic hypogonadism in women. One particular expression of this syndrome, functional hypothalamic amenorrhea, is associated with abnormal luteinizing hormone pulse generator activity and is accompanied by hypercortisolism and other neuroendocrine and behavioral indicators of stress. Furthermore, recent data suggest that subclinical ovarian abnormalities sufficient to cause premenopausal bone loss may affect a substantial number of women. For example, disturbed luteal phase function characterized 29% of the menstrual cycles recorded from a sample of 66 premenopausal women thought to be cycling normally; decreases in spinal density at both 1 and 5 years after measurement were significantly associated with this degree of abnormality. If ovarian hormones are indeed cardioprotective, women with functional hypothalamic hypogonadism and subclinical ovarian dysfunction could share with subordinate monkeys a predilection for accelerated atherosclerosis and an increased risk of CAD, especially because a relatively modest impairment of ovarian function is sufficient to cause marked exacerbation of atherosclerosis in monkeys.

Ovarian impairment probably has eluded detection as a risk factor for CAD because it is often occult and because premenopausal women have a low incidence of CAD. Nonetheless, surrogate measures (eg, a history of menstrual irregularity) are associated with premature CAD or elevated CAD risk factors. Hence, the percentage of premenopausal women who experience accelerated atherosclerosis may be much larger than the number diagnosed as amenorrheic or otherwise ovary-impaired. At present, however, atherosclerosis progression has not been studied prospectively in premenopausal women in conjunction with ovarian function.

Acute Life Stress

Anecdotal reports and case studies have long reported a relationship between acute stress and the development of cardiac disease. In addition, the effects of acute stress on heart disease are well supported by epidemiological studies regarding natural life stressors. An acute stressor associated with increased rates of cardiac events is bereavement. Physiological and behavioral responses to bereavement are well characterized, but the long-term effects of bereavement on coronary artery disease (CAD) are not well understood. The relationship between acute life stress and CAD is complex and multifactorial, involving both physiological and psychological factors. This relationship is bidirectional, with chronic stress increasing the risk of CAD and acute stress exacerbating the effects of CAD. The mechanisms by which acute stress may contribute to CAD include increased sympathetic activity, higher circulating levels of stress hormones, and changes in cardiac function. The effects of acute stress on CAD are likely to be influenced by individual differences in stress response, coping strategies, and personality traits.
example, in one study of 95,647 individuals followed up for 4 to 5 years, the highest relative mortality occurred immediately after bereavement, with a >2-fold higher risk for men and 3-fold higher risk for women. After the first month, mortality rates returned to normal population levels. Cardiac event rates also increased in the immediate aftermath of other acute life stressors, such as earthquakes and terrorist activities. For instance, during the massive Los Angeles earthquake of 1994, the number of sudden cardiac deaths due to CAD rose sharply, from a daily average of 4.6 in the preceding week to 24 on the day of the earthquake. Similarly, there was also a sharp increase in the number of deaths on the first day of missile strikes on Israeli cities during the Gulf War of 1991. Finally, a retrospective interview format has been used to examine the effect of anger as an acute trigger of myocardial infarction among 1,623 post-MI patients. A 7-point self-report anger scale (1 = calm, 7 = enraged) was used, with anger episodes defined as scores ≥5. After an episode of anger, the relative risk of myocardial infarction was increased >2-fold.

Pathophysiological Mechanisms
In contrast to chronic stress, acute stress is easier to model and can be studied under controlled laboratory conditions in both humans and animals. In recent years, as increasingly sophisticated techniques, such as radionuclide imaging techniques and the measurement of coronary endothelial function, have been applied to the laboratory study of acute stress, an understanding has emerged as to how such acute stress causes deleterious effects in CAD patients, as schematized in Figure 3 and elucidated below.

**Induction of Myocardial Ischemia**
The ability of acute psychological stress to induce myocardial ischemia has been assessed in the laboratory with modeled forms of stress (e.g., mental arithmetic and speaking tasks) and sensitive imaging techniques able to detect the extent and severity of mental stress–induced myocardial ischemia. These techniques include those used to measure left ventricular function (radionuclide ventriculography [Figure 4], echocardiography, assessment of left ventricular changes by either stationary probe and ambulatory VEST) and

![Figure 3. Schematic of pathophysiological effects of acute psychosocial stress. Sympathetic nervous system (SNS) stimulation emanating from acute stress leads to a variety of effects, ranging from heart rate and blood pressure stimulation to direct effects on coronary vascular endothelium. Clinical consequences of these effects include development of myocardial ischemia, cardiac arrhythmias, and fostering of more vulnerable coronary plaques and hemostatic changes. These changes form substrate for development of acute myocardial infarction and sudden cardiac death.](image)

![Figure 4. Comparative still-images of left anterior oblique scintigrams in patient who underwent radionuclide ventriculography at rest and then during a mental stress task involving a speech task given in an imaging laboratory. Patient had worsening of left ventricular segmental wall motion while speaking about feelings of personal stress concerning his problems in caring for his family. Images shown for rest are on top and those for the speaking task on bottom. Shown are end-diastolic (ED) images (left), end-systolic (ES) images (middle), and superimposed ED and ES edges (right). During speech, frank dyskinesia (abnormal outward motion during systole) developed in septum.](image)
those used to assess myocardial perfusion (positron emission tomography\textsuperscript{203} and \textsuperscript{99m}Tc-sestamibi myocardial perfusion tomography\textsuperscript{204}). Approximately half of CAD patients with exercise-induced myocardial ischemia also manifest inducible ischemia during mental stress testing in the laboratory, as identified by these techniques. Mental stress--induced ischemia, however, is not common among CAD patients without exercise-induced ischemia. Mental stress--induced ischemia is usually electrocardiographically and clinically “silent” and generally occurs at relatively low heart rate elevations compared with exercise testing. In addition, the frequency and magnitude of mental stress--induced ischemia varies according to the type of mental stressor. Specifically, stress that is more emotionally laden and/or personally relevant, such as a speaking assignment concerning personal faults, results in a significantly greater frequency and magnitude of inducible left ventricular wall motion abnormalities than does more nonspecific mental stress, such as the performance of mental arithmetic or the Stroop Color-Word task.\textsuperscript{195} Because the mean heart rate increases of \textasciitilde15 to 20 bpm during laboratory-modeled public speaking\textsuperscript{201} are far less than those of real-life speaking experiences,\textsuperscript{205,206} this and similar tasks may underestimate the potential potency of mental stress in certain real-life situations. Recall of angry events is also a laboratory trigger of myocardial ischemia,\textsuperscript{196} which supports the epidemiological study of anger by Mittleman et al.\textsuperscript{194}

These laboratory studies are complemented by ambulatory ECG studies that demonstrate an association between psychological stress and/or negative emotions and the occurrence of myocardial ischemia during daily-life circumstances (Figure 5).\textsuperscript{207–209} Like ischemia induced during mental stress testing in the laboratory, transient ischemic episodes out of hospital are overwhelmingly silent and occur at relatively low heart rate elevations.\textsuperscript{210} Furthermore, patients who manifest myocardial ischemia during laboratory mental stress are also more likely to manifest myocardial ischemia during ambulatory ECG monitoring of daily-life activity.\textsuperscript{208,209,211} Just as CAD patients who demonstrate myocardial ischemia during daily-life activity manifest a significantly increased likelihood of subsequent cardiac events,\textsuperscript{212} recent studies also suggest that mental stress--induced ischemia in the laboratory setting also predicts cardiac events (Figure 6).\textsuperscript{197,198}

Mechanisms for mental stress--induced myocardial ischemia. Even though heart rate elevations during laboratory-induced mental stress are relatively small, blood pressure elevations during mental stress are substantial, paralleling those noted with exercise.\textsuperscript{195,200} Thus, oxygen demand is increased during mental stress testing. However, because the double product threshold for the induction of ischemia during mental stress testing is substantially lower than that associated with exercise testing, other mechanisms must also be involved. One mechanism is mental stress--induced coronary vasoconstriction.\textsuperscript{213,214} During mental stress, significant coronary vasoconstriction may occur in CAD patients at sites manifesting vasoconstriction during acetylcholine infusion.\textsuperscript{213} Because acetylcholine is used to test for endothelium-dependent coronary vasoconstriction, these findings sug-
mental stress.20 By contrast, laboratory exercise is always abnormal during laboratory abnormalities are induced relatively rapidly during laboratory
Maximal heart rate and blood pressure responses are gener-
tally observed at the near onset of mental stress, and ischemic thresholds for ischemia. One potential factor may relate to why mental stress ischemia is induced at relatively low
Exercise-induced ST-segment depression of $1 \text{ mm}$ was induced in a healthy individuals were exercised to a high workload with-
antaly observed at the near onset of mental stress, and ischemic
During mental stress–induced EF change plotted at 2 prototypical values, 1 SD below (EF change $= -12.40\%$) and 1 SD above (EF change $= +1.05\%$) mean of entire sample (EF change $= -6.73\%$). Curves are adjusted for baseline EF, history of myo-
cardial infarction, and age. Relative risk associated with lower curve compared with higher curve is $2.40$ ($P=0.024$). From Reference 197.

Figure 6. After performance of mental tasks during radionuclide ventriculography, patients were followed up over time ($x$-axis). Probability of event-free survival is plotted as a function of mental stress–induced EF change plotted at 2 prototypical values, 1 SD below (EF change $= -12.40\%$) and 1 SD above (EF change $= +1.05\%$) mean of entire sample (EF change $= -6.73\%$). Curves are adjusted for baseline EF, history of myo-
cardial infarction, and age. Relative risk associated with lower curve compared with higher curve is $2.40$ ($P=0.024$). From Reference 197.

gest that neurohumoral stimulation during mental stress induces coronary vasoconstriction through an endothelium-
dependent mechanism. In addition, it has been reported that the coronary microcirculation fails to dilate during mental stress,215 However, significant coronary vasoconstriction also occurs during exercise in CAD patients216 through the same endothelium-dependent mechanism as noted for mental stress. Thus, other mechanisms must be considered to explain why mental stress ischemia is induced at relatively low double-product thresholds compared with exercise test thresholds for ischemia. One potential factor may relate to the presentation of stress. Mental stress testing in the labora-
tory is a “sudden” stressor, presenting without warm-up. Maximal heart rate and blood pressure responses are gener-
ally observed at the near onset of mental stress, and ischemic abnormalities are induced relatively rapidly during laboratory mental stress.201 By contrast, laboratory exercise is always presented to patients in a graded fashion. However, when healthy individuals were exercised to a high workload with-
out warm-up, ST-segment depression was induced in a significant number of subjects.217 Similarly, Eschar et al218 compared 6 CAD patients during graded versus sudden exercise stress; during the graded stress protocol, 3 patients had the indication of chest pain, and only 1 patient developed exercise-induced ST-segment depression of $\geq 1 \text{ mm}$. By contrast, during sudden stress, all 6 patients both had the induction of chest pain and developed $> 2 \text{ mm}$ of ST-segment depression. Because CAD patients may commonly experience short bursts of strenuous physical and mental stress without warm-up during daily life, further study of this issue is warranted.

Autonomic factors may also be operative in regulating myocardial ischemia. For instance, myocardial ischemia dur-
ing daily life shows a characteristic circadian rhythm.219 Even though exogenous factors (ie, the amount of physical and mental activity) trigger episodes of myocardial ischemia,206,209,219 Krantz et al219 demonstrated that the circadian rhythm of myocardial ischemia also appears to have an endogenous component, as demonstrated in Figure 7. Understanding the factors driving this apparent endogenous component could help further elucidate the pathophysiology of mental stress–induced ischemia.

Other factors that may potentially help regulate myocardial ischemia may be elucidated by the evolving study of factors that modify hemodynamic responses to exercise and mental stress. This includes the study of systems modulating systemic vascular tone, such as the endothelial system. In the Psychophysiological Investigations of Myocardial Ischemia (PIMI) Study, systemic vascular resistance increased during mental stress and decreased during exercise testing among CAD patients.199 In that study, increased systemic vascular resistance during mental stress testing was reported to be the most significant hemodynamic feature associated with mental stress–induced myocardial ischemia. Interestingly, in a subsequent recent study, increases in systemic vascular resistance during mental stress were directly related to compromised peripheral endothelial function in a group of 40 healthy men and women.220 These data raise the possibility that excessive systemic vascular resistance responses to mental stress may be a potential marker of peripheral endothelial dysfunction. However, prospective work is clearly indicated to determine the reproducibility and validity of these new observations and their potential pathophysiological import.

Promotion of Arrhythmogenesis
Investigators have consistently noted an interrelationship between behavioral factors and arrhythmogenesis in humans.50,221–224 According to Lown et al,221 3 sets of condi-
tions contribute to the occurrence of such arrhythmias: (1) myocardial electrical instability, most often due to CAD; (2) an acute triggering event, frequently related to mental stress; and (3) a chronic, pervasive, and intense psychological state, often including depression and hopelessness. To study the pathophysiological interrelationship between behavioral factors and ventricular fibrillation, Verrier et al225 assessed myocardial electrical instability in conscious, freely moving dogs by placing a catheter in the right ventricular apex, scanning the ECG, and delivering repeated electrical stimu-
lumination during the vulnerable part of the cardiac cycle. The amount of electrical stimulation required to produce repetitive extrasystoles (REs) was used to define the ventricular fibrillatory threshold. Inasmuch as the animal does not perceive this stimulation, investigators can more directly study the effects of experimentally produced behavioral states on the ventricular fibrillatory threshold. In an initial series of studies, dogs were exposed to either an undisturbed environ-
ment or one in which the animal was held in a sling and given periodic transthoracic shocks over 3 successive days.50 Be-
haviorally, the animals seemed relaxed in the undisturbed environment and agitated and autonomically aroused in the sling. The RE threshold was reduced by $> 40\%$ when animals were moved from the benign to the stressed environment.
Similarly, a natural emotion, an anger-like state provoked by denial of access to food, similarly reduced the RE threshold.225

Taken together, these studies show that behavioral stress, whether produced by aversive conditioning or a more naturalistic conflict, significantly decreases the electrical stability of the heart. Furthermore, β-adrenergic blockade prevents the effects of either aversive conditioning or induced anger on the RE threshold, suggesting that these effects are mediated, in part, by sympathetic arousal.226 Other work demonstrated that when dogs were first predisposed to arrhythmia by acute myocardial ischemia (a 10-minute period of coronary artery occlusion followed by reperfusion), exposure to the stress of an aversive environment significantly increased the incidence of ventricular fibrillation.225 In general, stimuli that elicit anger-like responses are especially likely to provoke abnormalities in rhythm.225 Researchers have also related behavioral factors to arrhythmia in other experimental animals.227 Thus, the data relating behavioral factors to arrhythmias are impressive in reliability of the effects and in the identification of excessive sympathetic activation as a major precipitating factor.

Deleterious Endothelial Effects

In animal model studies, acute stress also causes coronary endothelial abnormalities, which range from endothelial dysfunction to frank endothelial injury and necrosis. For example, borderline hypertensive rats exposed to air-jet stress in the face (2 h/d for 10 days) display impaired arterial dilation in response to acetylcholine.228 Furthermore, the stressed animals also have a reduced sensitivity to nitroprusside, indicating an attenuated response to exogenous nitric oxide. The authors concluded that behavioral stress impairs endothelium-independent and nitric oxide–mediated coronary relaxation, but without causing visible endothelial damage (as evaluated by scanning electron microscopy). With respect to endothelial injury, investigators have directly tested the hypothesis that sympathetic stimulation alters endothelial integrity by exposing rabbits to chloralose anesthesia, a manipulation that produces persistent and reproducible increases in heart rate, blood pressure, and plasma norepinephrine concentrations (all indicators of sympathetic activation).229,230 Compared with conscious controls, chloralose-treated animals developed marked endothelial injury (as indicated by IgG incorporation) at both unbranched and circumostial areas of the descending thoracic aorta. In contrast, pretreatment with a β-blocking agent attenuated heart rate and blood pressure increases, and endothelial injury was completely inhibited. Finally, male monkeys exposed to a clear-cut acute psychological stressor, 72 hour introduction to social strangers, had a significantly higher frequency of IgG-positive (injured) endothelial cells in the circumostial areas of the descending thoracic aorta than did control animals not exposed to this stressor.231 Again, pretreatment with β-adrenergic blocking agents prevented this stress-induced arterial damage (Figure 8). Importantly, the animals in this study consumed a low-cholesterol diet, indicating that the endothelial response to behavioral stimulation and adrenergic blockade was independent of dietary stimulation. Studies such as these clearly link

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**Figure 7 A.** Hour-by-hour circadian variation of myocardial ischemia in 63 CAD patients manifesting myocardial ischemia during ambulatory ECG monitoring. Left, Total ischemic time (minutes) in each hour of day; right, number of ischemic episodes in each hour. There was a morning peak in ischemic time/hour between 6 and 11 AM, with a secondary rise between 2 and 6 PM, before tapering of ischemia in evening. ANOVAs revealed a significant overall temporal variation in ischemic time during course of day. A similar pattern was noted for number of ischemic episodes. B, To assess contribution of an endogenous component to diurnal variation of ischemia, hourly duration of ischemia was controlled for concomitant activities, according to a statistical formula that regressed maximal physical and mental activity levels for each hour on corresponding ischemic time. This yielded “activity-adjusted residual scores,” which reflect measurements of ischemia not accounted for by activity. Shown are 3 separate curves for adjusted measurements of predicted ischemic time per hour of day, including those adjusted for (1) physical activity, (2) mental activity, and (3) heart rate. Adjusted ischemic times >0 on y axis indicate ischemic times that were longer than expected on the basis of concurrent activity levels or heart rate. Conversely, values <0 indicate ischemic times that were shorter than expected. Thus, if there had been no ischemic effect independent of activity, flat curves would be present. Rather, analyses showed a significant diurnal variation for all 3 curves (P<0.01), proving presence of a circadian rhythm that is endogenous in nature. Further statistical analysis of hour-by-hour changes in ischemic time revealed that for each curve, there was a significant increase in ischemic time at 6 AM vs 5 AM. Afternoon peak in ischemia noted in A, however, is now abolished, suggesting that this afternoon rise in ischemia is of an exogenous nature, driven by physical and mental activity levels. From Reference 220.
Coagulation Effects

The ability of emotional stress to induce coagulation abnormalities in human beings has been known for many years.\(^2\) More recently, the effects of acute psychological stress on indices of coagulation have been studied during laboratory mental stress tasks\(^3\) and during various naturalistic stressors.\(^4\) In both situations, significant, but not always consistent, platelet abnormalities have been observed. Acute laboratory mental stress also causes hemoconcentration through stress-induced decreases in plasma volume, as observed in various studies.\(^5\) This latter finding is significant in light of recent observations linking blood viscosity to cardiovascular reactivity.\(^6\) Animal studies further confirm the ability of acute stress to induce coagulation abnormalities.\(^7\)

The duration of coagulation abnormalities induced by acute natural stresses is not yet known. However, because blood samples were fortuitously obtained in 42 hypertensive patients before the large Hanshin-Awaji earthquake, investigators obtained repeat blood samples 7 to 14 days afterward to assess the effects of this acute stressor on coagulation parameters.\(^8\) The earthquake induced transient increases in blood pressure; blood viscosity determinants, such as hematocrit and fibrinogen levels; and various hemostatic factors, including fibrin turnover and plasmin-\(\alpha\)-plasmin inhibitor complex, an activation marker of fibrinolysis. These parameters returned to normal levels by 4 to 6 months after the earthquake. These findings suggest that coagulation abnormalities may persist for weeks after a single stressful event. A more chronic hypercoagulable profile has also been reported among individuals subjected to forms of subacute stress.\(^9\)

It is not yet clear whether mental stress--induced hemoconcentration and mental stress--induced platelet activation are the result of the same or different mechanisms. A recent laboratory study, however, suggests that different mechanisms may be operative, because platelet activation in this particular study correlated only with changes in serum catecholamine levels during mental stress, whereas mental stress--induced hemoconcentration correlated only with changes in mean arterial blood pressure, but not serum catecholamine levels, during mental stress.

Sympathetic Nervous System Hyperresponsivity

Sympathetic nervous system hyperreactivity (also called cardiovascular reactivity) has been defined as a dispositional tendency to exhibit exaggerated heart rate and blood pressure responses when encountering behavioral stimuli experienced as engaging, challenging, or aversive. On a theoretical basis, it has been postulated that individuals manifesting more elevated heart rate and blood pressure responses to such physiological challenge (ie, “hot reactors”) may experience more substantial sympathetic nervous system responses over time than “cold reactors” and that this may in turn promote the development of atherosclerosis. The first findings to support this hypothesis were reported by Keys et al.,\(^1\) who evaluated 20 clinical variables in 275 men followed up for 20 years. Among these clinical variables, the diastolic blood pressure response to cold pressor stimulation was the most predictive variable for future CAD development. Subsequently, however, negative prognostic studies were also reported.\(^2\) In a recent development, the potential atherogenic effect of sympathetic hyperresponsivity has been assessed in 4 studies that used serial carotid Doppler measurements.\(^3\) In each study, progression of carotid atherosclerosis was more rapid among individuals manifesting more pronounced heart rate and blood pressure responses to physiological challenge.

Cynomolgus monkeys consistently display significant individual differences in heart rate response during a threat of capture and during exposure to a benign manipulation involving the mere appearance of the experimenter in the monkey housing area. Because these monkeys can thus be reliably identified as hot versus cold reactors, they establish an excellent animal model for the study of sympathetic nervous system hypersensitivity. Moreover, among cynomolgus monkeys fed the same high-fat diet, the atherosclerotic lesions of hot-reactor monkeys are twice as large as those of their low-reactive counterparts.\(^4\) This reactivity-atherosclerosis association is seen in both male and female monkeys and in both the coronary and carotid arteries.\(^5\)

Inasmuch as sympathetic nervous system hyperresponsivity is not concentrated in dominant male monkeys, there appear to be 2 mechanisms by which psychological factors promote atherogenesis in males of this species. First, some monkeys (ie, hot reactors) may be susceptible to development of atherosclerosis because of an intrinsic sympathoadrenal...
hyperresponsivity to behavioral stimuli. Other monkeys (ie, dominant individuals in unstable social environments), conversely, may be at increased risk because of frequent elicitation of heart rate (and presumably blood pressure) responses in stressful environments. Sympathoadrenal activation, provoked in either of 2 ways, could thus provide a common pathway by which atherosclerosis is mediated. Among females, social subordination, ovarian impairment, hypercortisolemia, and exaggerated heart rate responses to stress seem to occur concurrently, dramatically accelerating atherogenesis in affected individuals. Other studies have linked sympathetic hyperresponsivity to the induction of ischemia during exercise and mental stress and to the development of hypertension. Combined, these recent animal and human studies raise the possibility that sympathetic hyperresponsivity may constitute a risk factor for the development or progression of CAD.

Therapeutic Implications

As we have summarized, a confluence of pathophysiological and epidemiological studies establish that both acute and chronic forms of psychosocial stress contribute to the pathogenesis of coronary atherosclerosis. These data establish an imperative for enhancing behavioral interventions among CAD-prone individuals. Because acute forms of psychosocial stress are ubiquitous and frequently unavoidable, it could be argued that the best general protection from their deleterious effects is the underlying prevention and treatment of coronary artery disease. However, because chronic forms of psychosocial stress are subject to clinical modification, their contribution to the underlying development of coronary disease might potentially be reduced by interventions designed to treat these factors. Evidence to support this hypothesis has been limited by a lack of adequate clinical investigation. In our opinion, the issue of studying and integrating psychosocial interventions into clinical practice would benefit from the following measures.

1. Physicians need to emphasize the role of psychosocial risk factors in counseling their patients. Patients often know that their lifestyle and psychosocial problems may affect their health, but when physicians do not take these problems seriously, patients are likely to conclude that such problems are not important. Conversely, when physicians engage patients in the identification of psychosocial issues, alteration of the psychosocial risk factors is more likely. Thus, more physicians need to be made aware of the recent developments that establish key psychosocial variables as risk factors for the development of CAD and as contributing factors to the expression of disease activity.

2. The effectiveness of behavioral interventions for cardiac patients needs to be evaluated and implemented in clinical settings. Among some physicians, there is a perception that psychosocial factors do not merit much attention. Reasons for this may be multifold. First, many physicians are not aware of the strength of association between psychosocial risk factors and CAD development. Second, the lack of consensus regarding the measurement of some psychosocial risk factors may be confusing to clinical practitioners. Third, physicians who regard psychosocial factors as potentially important may nonetheless lack expertise to assist patients in modifying these factors. Perhaps with the exception of risk factors that may be altered pharmacologically (eg, as in the treatment of depression), many physicians lack training in behavioral intervention techniques. Fourth, even when physician motivation and training are present, such interventions are often time-consuming and labor-intensive. Also, reimbursement for such services is often limited. Finally, available evidence showing the effectiveness of psychosocial interventions often suffers from methodological limitations, such as “soft” clinical end points, and inconsistent results. Regarding this last point, a recent meta-analysis, in fact, demonstrates significant health benefits when psychosocial interventions are added to routine medical management of patients with CAD. At the same time, there are discordant results among 14 published behavioral intervention trials that have assessed the impact of psychosocial interventions on the frequency of major cardiac events, such as cardiac death and myocardial infarction (see Table 8). These trials are also notable for their limitations in size and number. Most notably, however, no reduction in psychological distress was observed in most of the negative trials noted in Table 8. This includes the 2 large trials recently conducted by Jones and West and Frasure-Smith et al. Thus, one of the potential reasons for the discordance among these behavioral intervention studies appears to be the use of ineffective behavioral interventions.

In our view, future improvements in this area require work in the following 2 areas:

A. The efficacy of psychosocial interventions may be improved by development of “patient-specific” treatment plans, based on the “profiling” of the major psychosocial risk factors in individual patients.

Because multiple psychosocial factors contribute to the development of CAD, patient-specific targeted interventions may be appropriate. To date, however, few psychosocial intervention trials have tailored their intervention to specific psychosocial risk factors. This approach requires that individual difference characteristics be identified (eg, clinical depression, social isolation, job stress). On the basis of such profiling, patient-specific interventions could target specific psychosocial risk factors. For instance, individuals lacking in social support might be preferentially targeted for therapies incorporating group support or the development of more adequate social skills. Of note, recent trials are beginning to focus on the potential utility of targeting individual psychosocial factors. For instance, in the NHLBI-sponsored Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial, more than 3000 patients with major depressive disorder and/or social isolation are randomized to either a cognitive therapy stress reduction program or usual care. In the industry-sponsored Sertraline and Depression in Heart Attack Study (SADHART), post–acute MI patients with major depressive disorder are randomized to antidepressant therapy (ie, sertraline, a selective serotonin receptor inhibitor) or placebo.

B. Because the problem of lifestyle factors (eg, smoking, alcohol use) and psychosocial stress frequently cluster together, treatment of patients who are noncompliant with
lifestyle changes may benefit from consideration of concomitant psychosocial stresses.

As schematized in Figure 9, in addition to directly promoting the pathogenesis of atherosclerosis, psychosocial factors also promote the pathogenesis of atherosclerosis in 2 other basic ways: (1) the maintenance of lifestyle behaviors that promote atherosclerosis and (2) the discouragement of their modification. Conversely, amelioration of behavioral risk factors may also promote psychosocial well-being. For example, exercise training not only improves functional capacity but also may reduce symptoms of depression. Thus, the problem of psychosocial stress and patient noncompliance with behavioral risk factors should be considered together from the perspective of use of economic resources and development of cost-effective behavioral intervention strategies.

This overall problem is best tackled by further acknowledgment that the modification of lifestyle habits and certain forms of psychosocial stress are often difficult to achieve. For this reason, considerable attention has been given to study of the predictors of successful and unsuccessful behavioral changes among individuals. A variety of models of behavioral change have been introduced and in some instances studied among patients with CAD or CAD risk factors.275,276 Furthermore, psychological theories related to the issue of motivation have increasingly been used to provide incentive to employees and promote productivity in the corporate world. The application of these approaches is also warranted to employees and promote productivity in the corporate world.

### TABLE 8: Impact of Psychosocial Intervention Trials on Cardiac Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Patients</th>
<th>No. of Patients</th>
<th>F/U, y</th>
<th>Type of Intervention</th>
<th>Reduction in Psychosocial Factors?</th>
<th>Cardiac End Points</th>
<th>Reduction in Events?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahe et al, 1979</td>
<td>s/p MI</td>
<td>22/39</td>
<td>3</td>
<td>Group education and support</td>
<td>Yes (for overwork; time urgency)</td>
<td>CD/MI</td>
<td>Yes (P&lt;0.05)</td>
</tr>
<tr>
<td>Stern et al, 1983</td>
<td>s/p MI</td>
<td>20/35</td>
<td>1</td>
<td>Group counseling</td>
<td>Yes (for depression)</td>
<td>ACM/MI</td>
<td>No</td>
</tr>
<tr>
<td>Friedman et al, 1984</td>
<td>s/p MI</td>
<td>270/592</td>
<td>4.5</td>
<td>TABP modification and group counseling</td>
<td>Yes (for TABP)</td>
<td>CD/MI</td>
<td>Yes (P&lt;0.005)</td>
</tr>
<tr>
<td>Horlick et al, 1984</td>
<td>s/p MI</td>
<td>33/83</td>
<td>0.5</td>
<td>Hospital-based education program (6 wk)</td>
<td>No (for anxiety; depression)</td>
<td>CD</td>
<td>No</td>
</tr>
<tr>
<td>Patel et al, 1985</td>
<td>≈2 RF</td>
<td>93/99</td>
<td>4</td>
<td>Breathing, muscle relaxation, meditation</td>
<td>Not assessed</td>
<td>Angina/MI-1; CD</td>
<td>Small sample</td>
</tr>
<tr>
<td>Maeland et al, 1987</td>
<td>s/p MI</td>
<td>1115/137</td>
<td>3.3</td>
<td>Educational program</td>
<td>No (for anxiety; depression)</td>
<td>ACM</td>
<td>No*</td>
</tr>
<tr>
<td>Diacko et al, 1987</td>
<td>s/p MI</td>
<td>46/42</td>
<td>2.5</td>
<td>Physiological relaxation (eg, breathing, exercised)</td>
<td>Not assessed</td>
<td>CD; MI; UAP; CABG</td>
<td>Yes (P=0.05)</td>
</tr>
<tr>
<td>Frasure Smith et al, 1989</td>
<td>s/p MI</td>
<td>229/232</td>
<td>5</td>
<td>Home-based nursing intervention</td>
<td>Yes (for GHQ)</td>
<td>MI; CD</td>
<td>Yes (P=0.04 for MI†)</td>
</tr>
<tr>
<td>Thompson et al, 1990</td>
<td>60 s/p MI</td>
<td>30/30</td>
<td>0.5</td>
<td>Group counseling</td>
<td>Yes (for anxiety and depression)</td>
<td>ACM</td>
<td>Small sample</td>
</tr>
<tr>
<td>Nelson et al, 1994</td>
<td>s/p MI</td>
<td>20/20</td>
<td>0.5</td>
<td>Physiologic stress management (eg, breathing)</td>
<td>Yes (for ability to handle “stress”)</td>
<td>MI; ACM</td>
<td>Small sample</td>
</tr>
<tr>
<td>Burell et al, 1994</td>
<td>s/p MI</td>
<td>24/23</td>
<td>2</td>
<td>TABP modification</td>
<td>Yes (for TABP)</td>
<td>CD/MI</td>
<td>Small sample</td>
</tr>
<tr>
<td>Jones et al, 1996</td>
<td>s/p MI</td>
<td>1155/1159</td>
<td>1</td>
<td>Group sessions × 7 wks for stress management and counseling</td>
<td>No (for anxiety; depression)</td>
<td>ACM; CD</td>
<td>No</td>
</tr>
<tr>
<td>Blumenthal et al, 1997</td>
<td>CAD with EII</td>
<td>40/33</td>
<td>5</td>
<td>Structured group instruction with multiple stress reduction components</td>
<td>Yes (for GHQ scores and hostility)</td>
<td>CD, MI, PTCA, CABG</td>
<td>Yes RR=0.26 (0.07–0.90)</td>
</tr>
<tr>
<td>Frasure Smith et al, 1997</td>
<td>s/p MI</td>
<td>684/692</td>
<td>1</td>
<td>Home-based nursing intervention, to decrease transient increase in distress</td>
<td>No (for anxiety; depression)</td>
<td>CD</td>
<td>No</td>
</tr>
</tbody>
</table>

RF indicates risk factors; EII, exercise-induced ischemia; TABP, type A behavior pattern; MI-1, undocumented myocardial infarction; and UAP, unstable angina pectoris.

*At 6 months of follow-up, short-term lower anxiety and death rate (P<0.05) in intervention group.
†At 1 year (length of intervention), P=0.07 for CD reduction in intervention group.
animals housed in stable social groups; (2) an “early-stress” group of animals, housed in unstable groups for the first half of the experiment and thereafter in stable groups (ie, the equivalent of a stress reduction group); and (3) a “current-stress” group of animals, housed in stable social groups for the first half of the experiment, and thereafter in disrupted groups. In comparison to the current-stress group, the early-stress animals had less endothelial dysfunction, despite ingestion of the same diet (Figure 10). These data indicate that whereas exposure to chronic stress impairs endothelium-mediated dilation of atherosclerotic iliac arteries, its removal tends to reverse this process. On the basis of such data, a prospective trial to test the possibility that stress reduction improves endothelial dysfunction may be indicated in humans.

Although both acute and chronic forms of psychosocial factors may induce coronary endothelial dysfunction,165,228,231,277 the mechanisms by which this occurs are currently unknown. Increasingly, however, the inflammatory nature of coronary disease as it relates to coronary endothelial function is being delineated.278 For instance, both biomechanical factors associated with pulsatile blood flow (eg, shear stress and cyclic strain) and biochemical factors (eg, cytokines and growth factors) appear to promote inflammatory inducers of atherosclerosis, such as vascular cell adhesion molecules.279 Prospective studies are needed to determine whether and how psychosocial factors adversely promote this molecular pathobiology or, in the case of biobehavioral interventions, favorably modify it.

4. The relevance and design of future behavioral intervention trials need to be improved.

In the real world, biobehavioral interventions are not undertaken in the absence of other medical regimens. Thus, a useful practical design for future studies is one that incorporates effective medical treatment (eg, lipid-lowering therapy) and conventional lifestyle modifications (eg, dietary recommendations) in all patients and then looks at the added risk reduction associated with the incorporation of effective psychosocial stress interventions in a subgroup of the patients. However, because large-scale epidemiological studies are costly and require years of evaluation, potential alternative end points are also needed to permit the early and rapid assessment of the efficacy of specific behavioral interventions. Current potential end points might include noninvasive measurements of endothelial function, the magnitude of atherosclerosis progression on carotid ultrasound, and the magnitude of inducible myocardial ischemia during stress testing. For instance, using myocardial ischemic end points, Blumenthal et al272 were able to assess the efficacy of a stress-reduction intervention by using a small sample of ≈100 patients (Figure 11). Once a behavioral intervention looks promising with respect to its effect on such alternative end points, more large-scale epidemiological investigations could then be designed based on the garnered practical experience.

5. Organizational support is needed to spur interdisciplinary scientific collaboration among scientists interested in biobehavioral medicine.
Scientists from a wide variety of backgrounds have contributed to the observations noted in this article. The American Heart Association and American College of Cardiology have tremendous potential for spurring more formal communication and cooperation of an interdisciplinary nature. By encouraging research and collaboration that span across disciplines, the future development of interventions for psychosocial risk factors could derive the synergistic benefit represented by the maxim “the whole is greater than the sum of its parts.”

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References


Figure 11. Assessment of frequency of episodes of transient ST-segment depression during ambulatory ECG monitoring (y axis) both before treatment and after a 4-month behavioral intervention trial. Three groups are assessed among 107 patients: those undergoing exercise training ( ), those undergoing stress management ( ), and those undergoing usual care ( ). High baseline frequency group (n = 28) represents patients in upper quartile ( fissures 4 episodes/h) of ambulatory ischemia at time of initial assessment. Low-frequency group (n = 78) represents patients in lower quartiles. Patients with low baseline frequency of ischemic episodes before treatment exhibited little change in ischemic activity after treatment. However, patients with high baseline frequency of ischemic episodes who participated in stress management showed greater reduction in number of ischemic episodes vs usual care controls ( P = 0.003). From Reference 272.
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Impact of Psychological Factors on the Pathogenesis of Cardiovascular Disease and Implications for Therapy
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