The interaction between psychologic distress and biobehavioral processes in cardiovascular disease

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Introduction

Myocardial infarction and sudden cardiac death can be triggered by emotional distress \cite{1,2}. The vulnerability for these acute coronary syndromes is primarily determined by the presence of coronary artery disease (CAD) and/or structural myocardial damage. Chronic psychiatric, psychologic and social conditions can influence the gradual progression of cardiovascular disease and may further enhance the likelihood or magnitude of emotion-related triggers of acute coronary syndromes, primarily in patients with underlying cardiovascular disease \cite{3,4}. The progression of early stages of cardiovascular disease to its clinical manifestation as acute coronary syndromes can in most cases be described in three phases: gradual subclinical disease progression, the vulnerable disease stage, and the presentation of acute coronary syndromes. Cardiac symptoms such as chest pain and other angina equivalents commonly, but not necessarily, emerge later in the disease process. We have previously proposed a three-category classification framework of cardiovascular psychologic risk factors based on the duration and temporal proximity to the occurrence of coronary syndromes (Fig. 1.1): (1) acute psychologic risk factors (e.g. outbursts of anger, mental activity, and acute distress) that may act as triggers of cardiac events within one hour; (2) episodic psychologic risk factors with a duration lasting from several weeks to two years (e.g. depression, exhaustion and episodes of distress related to job loss, divorce and exposure to extreme physical or mental adversity); and (3) chronic psychologic risk factors that promote the gradual progression of coronary artery disease (e.g. personality traits and adverse socioenvironmental circumstances). Chronic psychologic factors are associated with increased reactivity to acute stressors and also promote the risk of the development of episodic psychologic risk factors. Recent evidence also suggests that episodic risk factors such as depression are associated with an increased emotional and biologic response to acute stressors. As outlined in Fig. 1.1, these types of psychologic risk factors are associated with characteristic biologic and physiologic processes that play distinct roles at different disease stages. These psychologic risk factors often coincide and also need to be understood.
in the context of genetic background factors and traditional cardiovascular risk factors such as hypertension, dyslipidemia and diabetes mellitus.

In this chapter, we provide a selective review of research on measures of psychologic distress in terms of acute, episodic and chronic risk factors for adverse clinical outcomes related to heart disease (Fig 1.1). Our strategy has been to summarize existing literature reviews in this area and provide supplemental research and case reports published over the past five years. Cardiovascular diseases other than those related to cardiac pathologies such as stroke, transient ischemic attack, and peripheral artery disease are beyond the scope of this review. Distress and other psychologic risk factors may have direct physiologic and biologic effects relevant to CAD progression. In addition, risk associated with psychologic distress may be mediated by adverse health behaviors such as smoking [5] and traditional CVD (cardiovascular disease) risk factors (e.g., hypertension, dyslipidemia, and metabolic syndrome) [6,7].

The majority of patients at risk of adverse cardiac outcomes based on psychologic factors do not have clinical psychiatric disorders. We postulate that assessment of psychologic distress is a tool to optimally detect the largest group of patients at risk of adverse cardiac events. As many patients will not meet traditional classification criteria for psychiatric diagnosis such as the DSM-based categories, innovative psychiatric and psychologic strategies will need to be developed to address distress-related psychologic risk factors. This chapter concludes with suggestions for further research in this area.

**Definition of psychologic distress**

Psychologic distress can be broadly defined as a negative internal state of the individual that is dependent on interpretation or appraisal of threat, harm, or demand [8]. The term “stress” is associated with definitional problems and the use of alternative terminology has been suggested [9]. However, there is substantial heuristic validity in the “stress” construct, and we will therefore use the term “distress” to indicate the psychologic reaction to environmental challenges (stressors) [8]. Figure 1.2 depicts a conceptual model of the primary factors involved in psychologic distress.

Multiple methods exist to assess psychologic distress (e.g. self-report questionnaires, interviews, behavioral observations, report from significant others, and ambulatory monitoring
measures). It is important to evaluate psychologic distress in terms of its environmental precipitants (i.e. life events) and factors that may increase vulnerability to these events (i.e. low socioeconomic status, discrimination, and adverse early life experiences) as well as psychologic and social factors that can act as buffers (social support, coping style and resources, and optimism) [8].

From a clinical perspective, it could be argued that the detection of debilitating distress is the primary gateway to psychiatric referral and intervention in medical settings. Underlying clinical psychiatric conditions can vary from uncomplicated adjustment disorders to major depression and very complex personality disorders. A general factor of “psychologic distress” incorporates a large portion of the predictive values of various specific psychologic cardiovascular risk factors including depression, anxiety, hostility, and low perceived social support [10]. Severe and prolonged uncontrollable distress may result in clinical and subclinical states characterized by negative affect that commonly occur in psychiatric practice (e.g. depression) [8] and conditions that commonly fall outside the range of clinical psychiatry such as burn-out and vital exhaustion. The increased cardiovascular disease risk associated with depression emerges at levels well below clinical diagnostic criteria (i.e. sub-syndromal) for Major Depressive Disorder [11]. This chapter addresses the role of psychologic distress as a “normal adaptive response” to environmental challenges, which may or may not exist parallel to or superimposed on clinical psychiatric disorders (described elsewhere in this book).

**Psychologic distress and cardiovascular disease**

Clinical epidemiologic studies have shown that psychologic distress [12] and related psychologic factors such as depressive symptoms, anxiety, and hostility contribute to cardiovascular disease progression (for reviews see [1,3,4]). Psychologic distress will be reviewed in terms of acute, episodic and chronic distress. As outlined in Fig. 1.1, acute distress is of critical importance as a potential trigger of acute coronary syndromes and cardiac arrhythmias in vulnerable individuals (i.e. among individuals with underlying coronary artery disease and

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**Fig. 1.2** Conceptual model of multi-factorial components of psychologic distress
arrhythmogenic myocardial substrates). In addition, prolonged and repeated exposures to short-term stressors and resulting acute distress responses may result in cumulative effects relevant to gradual cardiac and vascular disease progression. Psychologic distress is a continuous variable and evidence suggests a dose-response relationship between the severity of psychologic distress with biobehavioral correlates as well as cardiovascular disease risk [12].

**Acute distress as trigger of cardiac events**

Approximately 1 in 5 acute coronary syndromes are preceded by an acute trigger. We will use the term acute psychologic distress here for what is often referred to as “mental stress” in the cardiovascular literature. Substantial increases in central and autonomic nervous system activity are a common phenomenon that link acute psychologic, psychiatric and neurologic events to major cardiac pathologies [13]. Among the acute syndromes in cardiology, we will first review triggers of acute coronary syndromes (sudden cardiac death, myocardial infarction, and unstable angina reflecting severe myocardial ischemia) and arrhythmic events, followed by other outcomes (acute heart failure, takotsubo syndrome). Acute psychologic distress also plays a contributing role in clinical syndromes in the absence of well-defined anatomical or structural disease. For example, Prinzmetal’s angina (also referred to as “variant” angina), involves a transient increase in coronary vascular tone and substantial focal constriction (vasospasm). This disorder is more common in patients with vasospastic disorders such as migraine and Raynaud’s disease. Emotional distress may play a role in Prinzmetal’s angina, but few studies have systematically addressed this condition. Another clinical setting in which acute distress and especially panic plays a role is “non-cardiac chest pain”. Research indicates that the differential diagnosis of panic disorder and non-cardiac chest pain can be complicated, particularly considering angina can occur as a result of abnormal tone of the microvascular (resistance) vessels with normal or near normal epicardial (conductance) coronary arteries. Although myocardial infarction (MI) virtually always occurs in the presence of underlying coronary artery disease, the coronary disease severity prior to infarction is often not obstructive (i.e. less than 50% coronary stenosis). Myocardial infarctions that are triggered by acute physical or emotional stressors are not necessarily associated with more severe underlying coronary disease and also not with a worse one-year prognosis [14].

**Acute coronary syndromes**

A few selected recent case reports underscore the importance of environmental factors (“stressors”) that result in psychologic distress as trigger of acute coronary syndromes. One case involves the development of acute and reversible left ventricular dysfunction following an attempt of suicidal hanging. This cardiac abnormality likely resulted from intense emotions combined with physical challenge [15]. Another interesting report describes two cases of unrelated couples in caregiving situations in which the two pairs of spouses were found dead together [16]. In both cases the husband was the caregiver who died of cardiac causes shortly before the husband’s wife expired (one woman died of heart failure, the other of gastrointestinal bleeding-related hypovolemic shock). It cannot be concluded whether the distress related to the spouse’s impending death was the triggering factor for the husband’s death in these cases or vice versa. These cases are consistent with a case report from our group, showing acute coronary occlusion in response to a structured mental challenge task during coronary angiography [2].

Epidemiologic studies are consistent with these case reports and indicate that disasters and other environmental stressors can create acute psychologic distress that increases the risk of acute coronary syndromes, including earthquakes, floods.
and major storms, missile attacks and other acts of war or terrorism, and major sports events (for review see 4). For example, viewing a stressful soccer world cup match doubled the risk of an acute cardiovascular event [17]. Specifically, on days of matches involving the patients’ national team, the incidence of cardiac emergencies was 2.7 times (95%CI = 2.3–3.0; p < 0.001) higher than during the control period, with larger effects for men and those with pre-existing CAD. However, interpretation of these epidemiologic studies is complicated by the lack of control for confounding factors as well as referral and observational biases.

One of the major systematic studies determining the relative risk of MI after acute triggers included measures of psychologic distress as well as a range of other activities and exposures [18]. Using a case-crossover design, 1623 MI patients were interviewed at an average of 4 days after MI admission and asked about a wide range of activities such as physical exercise, drug use, and emotions in the hours prior to the event and also about the estimated usual frequency of these activities. Anger occurred in 39 patients in the 2 hours preceding the MI, and the relative risk associated with anger was 2.3 (95%CI = 1.7–3.2) [18]. The strength of the case-crossover methodology is that patients serve as their own control, but results may be influenced by retrospective bias (i.e. patients reporting emotional triggers as part of “seeking meaning” for their cardiac event). In addition, although about 20% of infarctions are triggered by exogenous activities [14], less than 3% (39/1623 interviewed patients) were triggered by anger [18]. Studies on mental stress-induced ischemia are not complicated by these practical limitations and further demonstrate the triggering potential of acute mental stress.

Myocardial ischemia

Myocardial ischemia develops when cardiac demand exceeds oxygen requirements of heart muscle, usually due to inadequate coronary blood flow at rest or in response to stressors (e.g. physical exertion, mental distress, tachyarrhythmias) to the heart muscle. Severe and sustained myocardial ischemia causes infarctions (see above) precluding experimentally controlled studies, whereas transient stress-induced ischemia can be used to investigate the effects of acute emotional states on cardiac function [4]. Acute challenges, including exercise and psychologic distress, can induce transient myocardial ischemia by increasing cardiac demand (increased heart rate and other factors that increase cardiac workload such as blood pressure-related afterload and cardiac contractility) [4]. In addition, acute psychologic distress may cause decreased coronary supply as a result of coronary constriction, which is related to the magnitude of stress-induced blood pressure reactivity and possibly emotional arousal [19]. However, marked coronary constriction occurs in approximately 1/5 of patients with CAD [19] and impaired vasodilatory responses in the cardiac resistance vessels may in part contribute to stress-induced reduced myocardial supply. Ischemia induced by acute psychologic distress is characterized by the following: (a) occurs in 40%–70% of CAD patients with exercise-inducible ischemia, (b) is generally not detectable by ECG ST-segment changes and thus requires measurement of cardiac function (SPECT, echocardiography, or radionuclide ventriculography), (c) generally asymptomatic (silent), (d) occurs at lower heart rates and similar blood pressure compared to exercise-induced ischemia, (e) is associated with lower ischemic thresholds during exercise testing and ambulatory monitoring, and (f) is associated with a greater than two-fold risk of adverse CVD outcomes [4]. Investigations using mental stress-induced myocardial ischemia therefore provide unique opportunities for the investigation of triggers of cardiac events.

Cardiac arrhythmias

Acute psychologic distress can act as a trigger for life threatening arrhythmias and sudden cardiac death [20]. Distress-related arrhythmic
vulnerability is potentiated by myocardial ischemia, but also occurs in the absence of ischemia in vulnerable patients [21]. Psychologic distress can precipitate ventricular ectopy within one hour in post-MI patients. Some evidence indicates that psychologic distress may also trigger idiopathic ventricular fibrillation [22]. In this study 9 out of 25 patients experienced moderate to severe distress in the 24 hours prior to ventricular fibrillation, compared to 2/25 in a comparison group admitted for acute coronary syndrome (p = 0.04). During the preceding 6 months, these numbers were 22/25 vs. 10/25, respectively (p = 0.008). Other evidence for the effects of acute stress on arrhythmic vulnerability is derived from patients with defibrillators and patterns of device discharges following the 9/11 destruction of the World Trade Center in New York City [23]. However, closer inspection of these data indicates that these arrhythmic events emerged hours to days after the event and elevated risks remained until one month later. This suggests that other processes may have played a role, such as repeated exposure to graphic scenes by the media and possibly rumination and other psychologic processes that elevate chronic distress levels (see below) [24].

Measures of cardiac electrical instability, such as T-wave alternans and QT variability, also increase with acute psychologic distress in vulnerable patients. Our group has demonstrated that acute mental stress induced by anger recall and mental arithmetic with mild harassment was associated with increases in T-wave alternans in patients with an implantable defibrillator (rest = 15.8 ± 0.8 μV, anger recall 21.3 ± 1.6 μV, mental arithmetic 24.7 ± 1.7 μV, p values from baseline < 0.01) and that these increases were higher than in controls without arrhythmic vulnerability, independent of inducible ischemia, left ventricular ejection fraction and co-morbidities, but lower than exercise-induced T-wave alternans [21]. Mental arousal-induced T-wave alternans is also potentially predictive of future arrhythmias as shown in a study of 62 defibrillator patients during one year follow-up (event incidence = 33% vs. 4%, p < 0.01 for patients in highest vs. lower three quartiles of T-wave alternans during anger recall) [25]. Mental arithmetic may induce prolongation of QT interval and other ECG-derived indices of arrhythmic vulnerability. Current investigations are being conducted to evaluate the role of acute distress-induced cardiac electrical instability in high-risk patient groups such as heart failure and atrial fibrillation.

**Acute heart failure and the takotsubo syndrome**

Triggers of acute heart failure overlap in part with triggers of myocardial ischemia, but the evidence for acute distress-induced heart failure exacerbations is sparse. There are substantially more studies on the association between sustained psychologic distress, and especially depression, than acute precipitants of the clinical progression of heart failure (see below).

The takotsubo syndrome or stress cardiomyopathy was first described in 1991 and is a relatively rare cardiomyopathy with signs and symptoms suggestive of acute myocardial infarction [26]. Clinical characteristics involve substantial left ventricular dysfunction (ejection fractions ranging from 10%–30%), apical ballooning, and generally minimal underlying coronary artery disease and no or minimal cardiac damage as measured by troponin levels. This syndrome typically develops in post-menopausal women. Extensive sympathetic stimulation as reflected by pronounced catecholamine increases is probably a critical component [26], but the etiology and management of takotsubo syndrome requires further investigation. In Fig. 1.3, an echocardiogram of one of our patients with takotsubo syndrome is shown. The patient was a 59 year old woman who was very distressed when visiting one of her family members admitted to the shock trauma clinic following a lethal motor vehicle accident. She experienced typical angina chest pain radiating to the jaw and was admitted to the
emergency department with ventricular fibrillation. Left ventriculography revealed an ejection fraction of 10%–20% (anterolateral, apical, inferior, and posterobasal akinesia) but only moderate non-obstructive disease in the left anterior descending artery on coronary angiography. Echocardiography was consistent (see Fig. 1.3) with moderately severe left ventricular (LV) dysfunction with elevated left atrial pressure and mild left atrial dilation. Relative to the large degree of LV segmental wall motion abnormality there was only a moderate increase in troponin levels (peak 29.9) followed by a downward trend. The patient had a prior history

Fig. 1.3 A case of apical ballooning in a patient with takotsubo syndrome
of a myocardial infarction, atrial fibrillation, and mitral valve repair, and echocardiography three months earlier documented a normal ejection fraction of approximately 65%. The non-cardiac medical history included joint disease (unspecified) and restless leg syndrome. The patient recovered well and was discharged after three days in stable condition with ACE inhibition and other cardiovascular medications combined with a referral for defibrillator implantation. This case illustrates the substantial cardiac responses to acute emotional distress, including severely compromised left ventricular function, life threatening arrhythmias, in the absence of severe coronary disease and with a fast and uncomplicated recovery. A high percentage of patients with stress cardiomyopathy return to normal or near normal LV function. Treatment includes patient education, psychologic counseling, and pharmacologic therapy may include beta adrenergic receptor blockers.

**Episodic factors: periods of distress, depression, and exhaustion**

Episodic psychologic risk factors are transient and recurring, and the duration ranges from several weeks to two years [2]. Depression is the most extensively investigated episodic risk factor in the area where psychiatry and cardiology overlap. Although the primary focus of this chapter is on distress, depression is one of the potential end-points of prolonged distress and depressive episodes can also be triggered by emotionally distressing life events [27]. In this section we will first summarize research on episodes of psychologic distress, followed by other episodic constructs related to distress (depression) and vital exhaustion.

Psychologic distress may be the common factor involved in both depression and exhaustion as cardiovascular risk factors. Various domains of psychologic distress have been identified (e.g. marital distress, prolonged distress following natural disasters, job loss, and job strain) and caregiving of a chronically ill family member. A large international study (INTERHEART) used a case-control design of 11,119 patients hospitalized for myocardial infarction versus 13,648 age- and sex-matched controls. Participants were enrolled in Africa, Asia, Australia, Europe, the Middle East, and North and South America. Psychologic distress was assessed by four 1-item questions about stress at work, stress at home, financial stress, and major life events in the past year. Assessments were also made for locus of control and depressive symptoms. Myocardial infarction was associated with a higher prevalence of all four stress factors, lower locus of control, and more depression (p values all <0.0001). General distress (at work and/or home) was associated with an odds ratio of 1.45 (99%CI = 1.30–1.61) for several periods and 2.17 (CI = 1.84–2.55) for permanent stress. Depression was also more prevalent in MI patients than controls (OR = 1.55, 99%CI = 1.42–1.69). These associations were consistent across international regions and ethnic groups, and remained significant when adjusting for cardiovascular risk factors. Evidence of a dose-response relationship was found for psychologic distress but not for depression. Despite the multiple strengths of the INTERHEART Study, retrospective report bias may have partially accounted for the observed associations; patients with acute hospitalizations may have affirmed the psychologic questions in order to find an explanation for their cardiac event. The effects are nonetheless remarkably strong and also consistent with controlled laboratory studies in which psychologic distress is manipulated in a structured manner and myocardial ischemia documented with various cardiac imaging techniques. In addition, prospective studies further support the predictive value of distress for adverse cardiovascular outcomes, including marital conflict [28], caregiving of an ill family member and high job demand combined with low job control.

The onset of depressive episodes in cardiac patients can be precipitated by environmental challenges associated with distress that are
unrelated to cardiac disease per se, psychologic reactions to having a life threatening disease that is often accompanied by symptoms and/or functional limitations, and cardiovascular disease-related biologic and physiologic changes that may affect the central nervous system. Some evidence suggests that mild to moderately severe depressive episodes are precipitated by adverse life events whereas severe depressive episodes may not be associated with such factors [29]. Among the psychologic disease-related antecedents of depression are dysfunctional cognitions and/or a maladaptive response to loss of an important person, health or other valued aspects of life that may be threatened as a consequence of cardiac disease [30]. The functional severity of cardiac disease (e.g. exercise intolerance and severity of shortness of breath) is also related to depressive symptoms. For example, the severity of depression is highest at the time of acute exacerbations of heart failure and related to functional heart failure severity [31]. Social factors may also promote the onset of depression, including living alone, alcohol abuse, and economic burden. The etiology of depression is also influenced by the biologic factors specifically related to the atherosclerotic disease process (e.g. inflammation), whereas the anatomical and structural disease severity does not seem to play a primary role in depression (see below).

Depression is predictive of first and recurrent myocardial infarction and sudden cardiac death (for review see for example 11). Prevalence estimates of DSM-IV-based depressive mood disorder range from 15% to 40% in patients with coronary artery disease [2]. Depression is even more prevalent in clinical heart failure, and predictive of heart failure rehospitalization and mortality [32]. Depression is under-diagnosed and hence frequently untreated [33]. Untreated depression is a major concern because it adversely affects quality of life and significantly increases risk of subsequent cardiac events, which may at least in part be related to non compliance with evidence-based lifestyle and drug treatments.

The American Heart Association published a Scientific Advisory in 2008 documenting the need for a coordinated detection and treatment plan for depression, including: screening, subsequent referral for comprehensive evaluation and management, as well as monitoring for adherence, treatment safety and efficacy [34]. There are some practical and theoretical concerns related to this approach, but this statement underscores the importance of depression in the management of patients with cardiovascular disease.

The clinical presentation of depression in cardiac patients is often very different from what is commonly observed in psychiatric patients. Fatigue or lack of energy, and irritability are more frequently observed in cardiac patients than typical depression symptoms, such as sad or depressed mood states or feelings of guilt and low self-esteem (for reviews see 37). Some evidence based on administrative data suggests that a diagnosis of psychiatric disorders as documented during admission for acute coronary syndromes is less prevalent than psychiatric diagnoses obtained during admission for acute coronary syndromes is less prevalent than psychiatric diagnosis prior to admission (24% vs. 10%) and that such prior diagnoses are a stronger predictor of post-MI mortality than psychiatric diagnoses obtained during admission for MI [35]. There are similarities between the clinical features of depression that develop in otherwise healthy individuals aged 55 and above and the features of depression in cardiac patients, which may in part overlap with the phenotype of vascular depression (i.e. depression resulting from cerebrovascular disease). Earlier research indicated that the predictive value of depression for recurrent cardiac events was stronger than for new-onset events in healthy individuals without previous coronary disease, but recent evidence based on large-scale meta analyses indicates that the risks for incident and recurrent events are comparable and approximately two-fold [11]. The originally postulated higher risk for recurrent events appears to be accounted for by stronger confounding of cardiovascular risk factors in patients with coronary disease. It is not
clear whether depression reflects one single underlying pathologic process, or whether a group of distinct disorders with overlapping characteristics is characteristic of patients with cardiovascular disease risk [27], and there may be common genetic predisposing factors [36].

Fatigue is among the most common premonitory symptoms of acute coronary syndromes. This state of extreme fatigue is characteristically part of a construct referred to as “vital exhaustion” which consists of lack of energy, increased irritability, and feelings of demoralization. The term “vital” is used in this construct to emphasize the far-reaching consequences of this condition on daily life functioning (similar to vital depression) and will be omitted in the remainder of this chapter. The predictive value of exhaustion for adverse cardiovascular events has been demonstrated in prospective studies examining healthy populations and patients with cardiovascular disease [2,37]. Whether exhaustion reflects the same construct as depression is not fully understood, but some evidence suggests that depression and exhaustion are not entirely overlapping conditions and have different biologic concomitants [2,37]. In addition, increasing evidence suggests that somatic depressive symptoms (fatigability, sleep problems, appetite changes, and psychomotor agitation/retardation) are associated with better predictive value of post-MI mortality and hospitalization than cognitive-affective depressive symptoms (depressed mood, lack of interest/anhedonia, negative feelings about self, concentration problems and suicidal ideation) [38]. Exhaustion may reflect the end-stage of prolonged uncontrollable psychologic distress and is best understood in terms of Selye’s General Adaptation Syndrome.

The adverse risks of depression, exhaustion and psychologic distress for clinical cardiac events are well established (see above). However, no consistent associations have been found between episodic risk factors (depression and exhaustion) and the severity of underlying coronary artery disease or cardiac function [2]. In selected cases, however, complaints of exhaustion may reflect severe underlying cardiac pathology which require immediate cardiologic attention. The association between depression with non-invasive evidence for vascular disease indices, such as carotid intima-media thickness and coronary calcification, is also inconsistent. Recent evidence suggests that there is an association between depressive symptoms and endothelial dysfunction in peripheral arteries [39], but not in coronary arteries [40], findings that may be related to methodology or differential effects on various vascular beds. These are important observations because such lack of association indicates that depression and exhaustion in cardiac patients is not merely an artifact of underlying disease. In addition, the predictive value of episodic risk factors decreases when the follow-up exceeds two years [11]. It has therefore been hypothesized that the duration of episodic risk factors may not be long enough to initiate and sustain an atherosclerotic process, and that plaque activation, rather than gradual disease progression, may be primarily involved in the adverse risk associated with episodic psychologic risk factors [2,41]. Because of the recurring nature of episodic risk factors, longitudinal studies are needed to clarify whether the “active phase” of these episodes is disproportionately related to the vulnerability for acute coronary syndromes. The relationship between post-MI depression and non-compliance to medical regimen is covered elsewhere in other chapters in this book.

Chronic distress; personality traits, adverse socioenvironmental factors and re-experiencing prior distressing events

Chronic psychologic factors include personality traits such as hostility and the Type A behavior pattern, Type D personality, and trait anxiety. These personality traits may have genetic underpinnings. Chronic psychologic risk factors may promote the onset of initial stages of
atherosclerosis by various biobehavioral pathways starting in young adulthood, including sympathetic nervous system-mediated processes (e.g. lipid deposition and inflammation), adverse health behaviors (e.g. smoking, poor dietary habits) and their association with known CAD risk factors (e.g. hypertension, smoking, lipids, and obesity). At advanced disease stages, these chronic psychologic factors may increase the effects of acute psychologic risk factors thereby triggering acute coronary syndromes (Fig. 1.1).

Hostility and the Type A behavior pattern have been extensively investigated as cardiovascular risk factors since pivotal work by Friedman and Rosenman in the late 1950s (e.g. [42]). Later studies have indicated that hostility is probably the toxic component of Type A behavior. Hostility is a trait characterized by cynical mistrust, aggressive responding, and an overall antagonistic attitude [43]. Most studies report cross-sectional associations between hostility/Type A behavior and severity of underlying coronary disease as well as a longitudinal association with incident myocardial infarction [43]. The association between hostility and MI is stronger in younger (< 55 years of age) than older men. In contrast, evidence for the predictive value of hostility/Type A behavior for recurrent coronary events is less consistent. In addition to hostility, other psychologic traits such as trait anxiety as well as sociologic factors – particularly low socioeconomic status – may act as additional sources of persistent exposure to psychologic distress.

It has been argued that there is a general underlying trait factor that predisposes individuals to chronic distress [1,44]. Such a personality factor may capture a general psychologic vulnerability factor that accounts for the predictive value of depression, anxiety, and trait anger as risk indicators for acute coronary syndromes. The “distressed” or Type D personality refers to a chronic form of distress characterized by an individual’s inclination to experience negative emotions (negative affectivity) combined with the inhibition of self-expression in social interaction (social inhibition) [44]. Several studies have shown that Type D personality reflects a general propensity to psychologic distress that adversely affects cardiovascular outcomes, but negative effects have been documented was well (for review see [44]). More research is needed to establish the content as well as divergent validity of the Type D construct, but a general vulnerability factor seems plausible and the stability over time [45] as well as independent predictive value of Type D personality from depression[44] have been documented.

Post-traumatic stress disorder (PTDD) can be viewed as a chronic risk factor and is predictive of increased healthcare use, adverse cardiovascular risk factors and increased cardiovascular morbidity and mortality [46]. It is possible that part of the association between PTSD and adverse cardiac outcomes is related to underlying psychologic vulnerability factors, but more likely to rumination about the adverse event or other biobehavioral processes associated with continued central and autonomic nervous system activity that may promote atherosclerosis [24].

**Biologic pathways linking psychologic distress to cardiovascular risk**

There is substantial overlap in the biologic correlates of acute, episodic and chronic distress, although this is a complicated area of research with multiple nuances. In general, biologic responses to acute exogenous stressors are adaptive, whereas prolonged exposure to stressors may lead to an imbalance of normal homeostatic functions. Several theories have been postulated of which the construct of allostatic load may be of relevance to the relationship between episodic and chronic distress as related to cardiovascular disease [47]. In the paragraphs below we will therefore focus on neurohormonal and immune system-related correlates of prolonged (episodic and chronic) psychologic distress.
Neurohormonal activation and autonomic nervous system dysregulation

A large literature suggests that psychologic distress is associated with sympathetic adrenomedullary (SAM) activation, including circulating catecholamine levels and hypothalamic-pituitary-adrenal hormones. Psychologic distress is also associated with a shift toward increased sympathetic nervous system activity and decreased parasympathetic (vagal) activity. The pattern of results is complex such that exhaustion and atypical forms of depression (i.e. hyperphagia and hypersomnia and mood reactivity), are generally characterized by inactivation of the CRH system and reduced norepinephrine levels [27] as well as dampened hemodynamic reactivity to challenge tasks. Neurohormonal and autonomic nervous system dysregulation contribute to a disruption of homeostasis and influence cardiovascular disease progression either by direct effects on the cardiovascular system or via other biologic processes, such as the immune and coagulation systems.

Inflammation and psychologic distress

The inflammation response is contained within the general “stress response” [48], but associations between psychologic distress and the immune system are complex. The immunosuppressive correlates of prolonged psychologic distress are similar to those observed in depression [49]. Our group and others have consistently found elevated CRP levels among individuals with depressive symptoms (e.g. [50]). These associations may be mediated, in part, by being overweight and other adverse health behaviors. Patients with depression and/or exhaustion also have increased levels of antibody to several herpes viruses, including CMV [51]. The association between psychologic distress and inflammatory markers is characterized by bi-directional relationships.

The immune system correlates of prolonged psychologic distress (e.g. increased levels of leukocytes, cytokines and antibodies to viruses) are also associated with elevated risk for acute coronary syndromes. These pro-inflammatory markers may promote cardiovascular disease progression by enhancing macrophage and lipid deposition processes at early stages of atherosclerosis. More importantly, low-grade inflammation may alter the stability of atherosclerotic plaques and increase the risk of plaque rupture leading to acute coronary syndromes. It has been shown that approximately 10–15% of the association between depression and cardiovascular disease progression can be explained by inflammation-related processes [52].

Conclusions and future directions

This review indicates that the role of psychologic distress in cardiovascular disease varies with the stage of the disease. Acute stressors are primarily of importance as triggers of acute coronary syndromes in the presence of relatively advanced coronary artery disease, whereas episodes of sustained elevated distress are associated with increased vulnerability for acute coronary syndromes, and chronic distress related to traits and/or stable adverse socio-environmental factors is associated with the gradual progression of coronary artery disease (Fig. 1.1) Multiple factors are involved in the onset and maintenance of psychologic distress, including environmental and personal vulnerability factors that increase the likelihood of developing acute or prolonged distress as well as factors that may buffer or attenuate the distress response (Fig. 1.2). There appears to be a dose-response relationship between the severity of psychologic distress and the risk of cardiovascular disease, but more research is needed to determine whether general psychologic distress per se or clinical conditions such as major depressive and anxiety disorders are better predictors of adverse cardiovascular health outcomes. The importance of the symptomatic presentation (e.g. somatic versus...
cognitive-affective depressive symptoms) also requires more research. It is important to consider the environment in which these questions are addressed. For example, in clinical cardiology samples, reactive distress-related disorders to an acute cardiac event are observed in approximately 50% of patients with depression [53] which may not be relevant in large-scale epidemiologic studies of community-dwelling individuals.

Most research in cardiovascular psychosomatic or behavioral medicine has focused on negative aspects of psychologic distress. The protective effects of optimism, resilience, and related constructs require further study. Epidemiological studies provide strong support for the protective effects of positive traits [54]. Most psychiatric settings will not be optimally situated to address these positive traits and new approaches are needed to derive clinical tools to promote these potentially protective characteristics.

Novel biologic and physiologic cardiovascular disease markers are continuously developed to optimize risk stratification for adverse cardiovascular health outcomes. Such novel biomarkers may not only improve identification of patients who are “at risk”, but may also increase our understanding of the biobehavioral mechanisms by which psychologic distress and related constructs are related to adverse cardiovascular disease. For example, psychologic distress and depression are associated with increased oxidative stress markers, which may have important implications for the distress-cardiovascular disease pathways. In addition, psychologic distress adversely affects health behaviors that increase cardiovascular disease risk, including physical inactivity, poor dietary control, smoking, alcohol consumption, and medication non-adherence [52]. More research is needed on the interplay between biologic and behavioral correlates of psychologic distress. This would potentially lead to multidimensional monitoring of high-risk patients who are treated with psychologic and behavioral interventions.

This chapter has not reviewed the effectiveness of psychologic and psychiatric interventions. Most evidence indicates significant but modest effects of antidepressant medications in reducing depression among cardiac patients, with minimal or no benefits for cardiovascular outcomes with pharmacotherapy [55] or psychologic interventions such as cognitive behavioral therapy [56]. Even in the absence of clinical cardiovascular disease, the effectiveness of antidepressant pharmacotherapy is less if patients have cardiovascular risk factors (e.g. smoking, hypertension, diabetes, hypercholesterolemia, family history of cardiovascular disease). Subgroups of patients who respond well to antidepressant interventions may also display cardiovascular health benefits. Interventions specifically targeting exhaustion revealed similar outcomes, with modest improvements in exhaustion and no effects on cardiac outcomes. It could be that a healthcare system approach, rather than individually-based depression reduction strategies, may be superior in reducing secondary cardiovascular events in clinically depressed patients with cardiovascular disease [57].

In contrast to the variable findings for antidepressant interventions, reduction of psychologic distress seems to have more consistent effects in lowering adverse cardiovascular endpoints [58]. In the review by Linden et al., 43 psychologic intervention studies were examined that targeted distress using various strategies. A reduced risk of all-cause mortality was found within 2 years of intervention (N = 9,856; OR = 0.72, CI = 0.56–0.94), but not with longer follow-up (N = 4,727; OR = 0.89, CI = 0.69–1.14) (the time-related pattern of recurrent cardiac events was reverse). Effects were more beneficial in men than women, and in those that were started later than 2 months versus earlier after a cardiac event. The mortality benefits were achieved with relatively modest improvements in negative affect. The Recurrent Coronary Prevention Project is one of the pivotal trials in this area, reporting reductions in sudden death, but not non-sudden cardiac death [59]. Recent trials
addressing reduction of psychologic distress have also been positive, although most originate from northern European countries [60]. It may be that such interventions more optimally target important behaviors relevant to this population, such as attenuating emotional reactivity to challenging situations, improving patient-healthcare provider interactions, and reducing patient delays in seeking medical care. It is likely, however, that such interventions may not be sufficient in patients with clinical psychiatric disorders. In the latter case, it is probably critical to evaluate the patients’ perceived need for intervention and his/her preferred mode of treatment. We conclude that investigations on interventions targeted at reducing distress will be useful to reduce risk of adverse events in patients with cardiovascular disease, and that important knowledge will be gained about the pathophysiology of cardiovascular disease if such interventions will be combined with multiple assessments of biologic, physiologic and behavioral measures.

**Summary points**

- Acute psychologic distress is a significant trigger of acute coronary syndromes, associated with a greater than two-fold risk and an estimated prevalence of precipitating.
- Assessment of myocardial ischemia and markers of cardiac electrical instability, induced by emotional arousal in controlled clinic or laboratory settings, can be used to develop pathophysiologic models explaining the association between acute psychologic distress and adverse cardiovascular outcomes.
- Clinical psychiatric conditions such as major depressive disorder are significantly associated with poor cardiovascular outcomes and an even wider range of “at-risk” patients can be identified with sub threshold depression and other indicators of increased psychologic distress.
- The predictive value of psychologic distress for adverse cardiovascular disease progression is not an artifact of underlying atherosclerotic disease processes.
- Psychologic distress is associated with adverse cardiovascular outcomes via plausible biologic pathways, including neurohormonal factors, autonomic nervous system dysregulation, elevated inflammation and coagulation factors and reduced response to injury, as well as adverse health behaviors such as smoking, physical inactivity, poor dietary habits and medication non-adherence.

**References**


