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Psychological Stress and Heart Disease: Fact or Folklore?

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ABSTRACT

For at least a few centuries, if not millennia, psychological stress has been popularly believed to contribute to heart disease. Does psychological stress really contribute to heart disease? Are anecdotal, patient, and lay press reports that angina, heart attack, and even cardiac death are caused by stress based on fact, or are they just folklore? In this review, the study data supporting associations between stress and cardiovascular risk, as well as potential mechanisms by which psychological stress might contribute to heart disease and precipitate myocardial ischemia and infarction, are critically reviewed and summarized.

KEYWORDS: Angina; Heart disease; Myocardial infarction; Myocardial ischemia; Psychological stress

INTRODUCTION

For at least a few centuries,[1-3] if not millennia,[4,5] psychological stress has been popularly believed to contribute to heart disease. More than two centuries ago, William Heberden noted that angina "is increased by disturbance of the mind."[3,6] A prominent news article attributed the, at the time, rising death rates from heart disease to "great mental strain and hurried excitement." What is notable is that this passage is not from any modern investigation, but from an 1872 article in the British newspaper, *The Times*.[7] In 1956, Hans Selye, the father of stress theory,[8] concluded that "at the end of a life under stress . . . was a kind of premature aging due to wear and tear."[9] More recently, *The New York Times* headlined that "Stress May be Your Heart's Worst Enemy."[10] A Google search of "stress and heart disease" produces an astounding 1,320,000 results.

Does psychological stress really contribute to heart disease? Are anecdotal, patient, and lay press reports that angina, heart attack, and even cardiac death are caused by stress based on fact, or are they just folklore? In this review, the study data supporting associations between stress and cardiovascular risk, as well as potential mechanisms by which psychological stress might contribute to heart disease and precipitate myocardial ischemia and infarction is critically reviewed and summarized.

WHAT IS PSYCHOLOGICAL STRESS?

The most widely used and accepted definition of psychological stress is along the lines that "psychological stress occurs when an individual perceives that environmental demands tax or exceed his or her psychological resources or adaptive capacity, endangering his or her well-being."[11-13] Mechanistically, one can view stress in terms of the perceived *stressor* and the body and mind's *stress response*.[14,15] In the modern transactional model of stress, it is an individual's cognitive appraisal of a situation that determines whether the situation is perceived as a stressor that consequently evokes a stress response.[12,15]

Important time immemorial stressors include work, marital discord, social isolation, financial crises, socioeconomic status, the burden of caregiving for a chronically diseased or demented family member, and death of a spouse or loved one.[1,16,17] Additional modern day stressors, including social media, 24/7/365 connectivity, and the COVID pandemic, have likely only added to current levels of stress.

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THE ASSOCIATION OF PSYCHOLOGICAL STRESS AND HEART DISEASE

It is useful when evaluating studies on psychological stress to separately discuss acute psychological stress and chronic psychological stress.

Acute Psychological Stress

There are multiple reports in which natural disasters or man-made tragedies are associated with an increased incidence of acute cardiac events.[18-22] For example, a report on daily mortality around the time of the Northridge (California) earthquake in 1994, which struck at 4:31 AM, found that while during the week prior to the earthquake the average coroner-determined number of sudden deaths related to atherosclerotic cardiovascular disease was 4.6 ± 2.1, the day of the earthquake, the number spiked to 24, a fivefold increase (Figure 1).[18] In a second similar report, it was determined that in the several days after the 1981 Athens earthquake there was an approximate 100% increase in the short-term probability of death from underlying atherosclerotic heart disease.[19]

CLINICAL SIGNIFICANCE

- Acute psychological stress precipitating angina seems biologically plausible, mediated by a combination of coronary vasoconstriction and increased myocardial oxygen demand.
- Multiple reports seem to support the belief that severe acute psychological stress can precipitate myocardial dysfunction, infarction, arrhythmia, and cardiac death.
- A reasonable amount of good quality study data seems to support the belief that chronic psychological stress is associated with some increased risk of heart disease.

Other reports of adverse cardiac events due to acute stress are also notable. A several-fold increase in the number of patients with acute myocardial infarction (MI) and sudden cardiac death was observed in an Israeli medical center in the days after initial Iraqi missile attacks during the Gulf War.[20] In an analysis of 200 consecutive patients who underwent implanted cardioverter-defibrillator interrogation in the greater New York area around the time of the World Trade Center terrorist attack, it was found that the frequency of detected tachyarrhythmias resulting in defibrillation or anti-tachycardia pacing increased more than twofold (8.0% vs 3.5%) during the 30 days immediately after the attack, when compared with the 1-month periods encompassing the 3 months prior or 12 months afterwards.[21] And a case-crossover analysis from the Stockholm Heart Epidemiology Program in which participants served as their own controls found that having ''had a high pressure deadline at work'' was associated with a sixfold increase in risk of MI during the 24 hours subsequent to that deadline.[22] Such "natural" and "man-made" experiments do seem to suggest that severe acute stressors can indeed precipitate cardiac ischemia, infarction, and arrhythmia. Additional study data have linked triggers such as the death of someone close, very stressful work changes, emotional upset, and even sporting competitions such as the 2006 FIFA World Cup with increased cardiovascular event rates,[6] further supporting this seeming temporal relationship between stressful occurrences and adverse cardiac events.

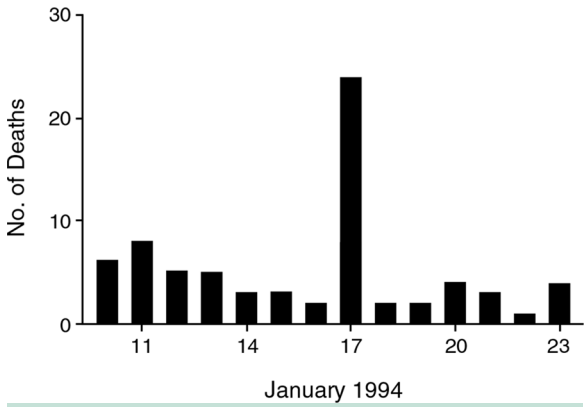

Figure 1 Daily sudden deaths related to atherosclerotic cardiovascular disease around the time of the Northridge (California) earthquake in 1994. While during the week prior to the earthquake, the average coroner-determined number of daily deaths was 4.6 ± 2.1, the day of the earthquake, the number spiked to 24 (reproduced from Leor et al, 1996.[18])

Another notable manifestation of acute psychological stress is that of stress cardiomyopathy or "broken heart syndrome." Stress cardiomyopathy represents a form of neurocardiogenic myocardial stunning,[23] in which patients who have undergone a recent intense psychological stress develop characteristic non-coronary artery distribution wall motion abnormalities (Figure 2)[24] and left ventricular dysfunction, as well as electrocardiographic abnormalities and troponin elevation that can mimic acute MI. The most common psychological stressors include death of a loved one, violent confrontation or attack, extreme anger, profound financial loss, and natural disasters, experienced 1-5 days prior to presentation.[23,25]

Chronic Psychological Stress

There is a growing body of study data that seems to establish an association between chronic psychological stress and incident heart disease. Using a case-control design, the worldwide INTERHEART study, with approximately 25,000 participants analyzed, found that work stress was consistently associated with statistically significant increased risk of MI, and that there was a "dose response" relationship, with periodic stress conferring some risk (adjusted odds ratio 1.45) and permanent stress conferring higher risk (adjusted odds ratio 2.17). Similar "dose response" findings were determined for financial stress and

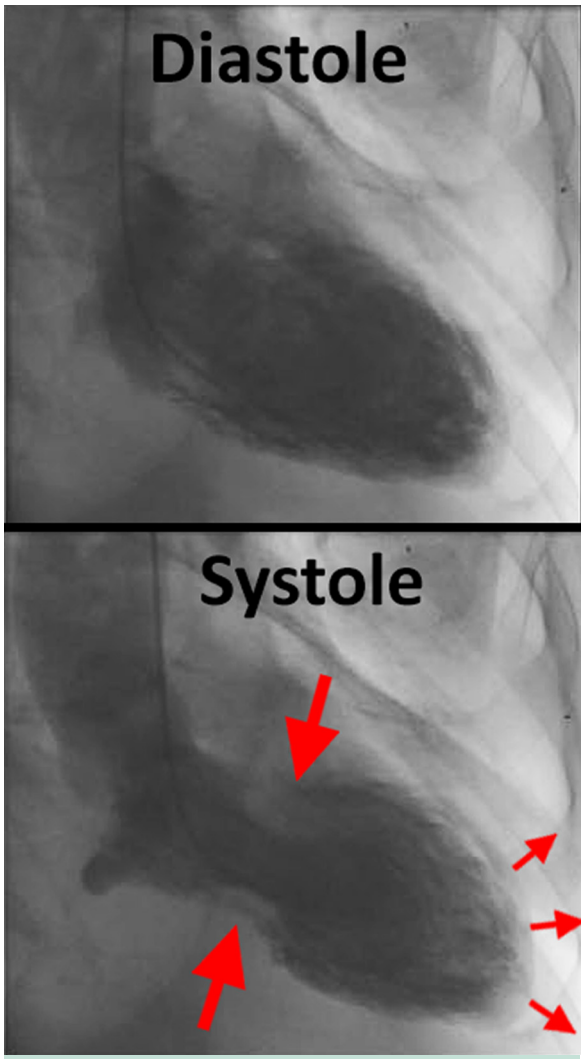

Figure 2 The typical pattern of apical ballooning (small arrows) seen in stress cardiomyopathy. There is normal contraction of the basal left ventricle (large arrows). Adapted with permission from Suzuki et al, 2014..[24]

stressful life events. The findings were statistically adjusted for age, sex, geographic region, and smoking.[26] A second example comes from a population-based cohort study using data from the international PURE study with over 100,000 participants, in which psychological stress was assessed at study entry. After a mean follow-up of 10.2 years, it was found that those with high stress, compared with no stress, were associated with a significantly increased risk of cardiovascular disease (hazard ratio [HR] 1.22) after adjustment for traditional cardiac risk factors.[27] A meta-analysis of prospective cohort studies that measured self-reported perceived stress and subsequent incident coronary heart disease, which included a total of 6 studies and 119,696 participants, determined an aggregate risk ratio of 1.27 (95% confidence interval, 1.12-1.45) for those with high perceived stress compared with those with low perceived stress.[28]

Many adults spend half their waking life at work,[29] and numerous studies have examined the relationship between work-related stress and cardiovascular disease. In the prospective Whitehall II study of 10,308 British civil servants 35-55 years of age, participants filled out a detailed questionnaire and were followed for an average of 5.3 years.[30] Participants with high work-related stress had more than double the risk of developing new coronary heart disease after adjusting for classical coronary risk factors. Nine-year follow-up in those who had completed the MRFIT trial found that the greater the number of work stressors, the greater the risk of subsequent cardiovascular death. In those with 3 or more work stressors, the statistically significant adjusted relative risk when compared with those with no work stressors was 1.34.[31] In a multi-cohort report from the Individual Participant Data Meta-analysis in Working Populations (IPD-Work) consortium, it was found that in those with cardiometabolic disease, job stress was associated with significantly increased rates of total mortality (adjusted HR 1.68) and mortality from cardiovascular disease (adjusted HR 1.71).[32] One recent comprehensive review of studies of work stress and cardiovascular disease found that relative risk ranged from no statistically significant increased risk to a relative risk of 4.53.[33] An extensive review that examined both individual studies and numerous meta-analyses concluded that work stress increased the risk of incident coronary heart disease and stroke by 10%-40%.[29]

Marital stress is commonly accepted as an important type of psychological stress. Alas, there is more research on marital *status* and heart disease than marital *stress* and heart disease per se. Perhaps the best data on marital stress and heart disease come from a report from the Stockholm Female Coronary Risk Study, in which 292 women with acute MI were assessed for marital stress using the Stockholm Marital Stress Scale and followed for a median of 4.8 years. Moderate or severe marital stress was associated with an almost threefold increased risk of recurrent cardiac events, compared with mild or absent marital stress after adjustment for numerous cardiac risk and prognostic factors.[34]

Posttraumatic stress disorder (PTSD) is the sentinel stress-related mental disorder that occurs after exposure to a potentially traumatic life event.[17] While commonly associated with military conflict, PTSD can result from physical or sexual assault, childhood or domestic abuse, and exposure to traumatic events (eg, mass gun shooting, natural disaster). A meta-analysis of 9 prospective studies comprising 151,144 total participants assessing the association between PTSD and incident coronary heart disease calculated a hazard ratio of 1.61 (HR 1.46 after controlling for concurrent depression).[35]

Overall, psychological stress has been estimated to be associated with an ≈40%-60% excess risk of coronary heart disease,[1,13] with extreme stress in childhood perhaps having a greater associated HR than stress in adulthood.[6] The absolute magnitude of increased cardiovascular risk with stress

may be greater in those at high risk for, or with established, coronary heart disease than in healthier individuals.[6]

POTENTIAL MECHANISMS

A key question as to whether psychological stress truly contributes to heart disease and acute cardiac events is whether the relationship between stress and heart disease is merely a statistical association, hopelessly confounded despite best efforts by other unmeasured or unaccounted for variables that lead to heart disease, or rather an independent causative or contributory factor. In other words, is there reasonable biological plausibility, and actual study data, that stress is etiologically and mechanistically contributory to heart disease?

Acute Psychological Stress

The acute neurocardiovascular response to stress represents a complex series of activations of, and increased blood flow to, cortical and subcortical areas of the brain, including the neomammalian brain and the limbic system (which includes the hippocampus, amygdala, and hypothalamus), followed by a heightened state of sympathetic nervous system and neuroendocrine activity,[13,14,23,36,37] and represents the end product of the *flight or fight* response, an evolutionarily adaptive process enabling an organism to survive a life-threatening event.

Two important systems that mediate the neurocardiovascular response to acute stress are the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenal-medullary system.[13,36] Downstream effects of these processes include increased sympathetic nervous system activity, parasympathetic withdrawal, increased circulating catecholamines (eg, epinephrine, norepinephrine), increased cortisol levels, increased plasma pro-inflammatory cytokines, and immune system activation.[13-15,36] In addition to these systemic processes, stress perception also results in activation of preganglionic sympathetic neurons in the spinal cord, which via prevertebral or paravertebral ganglia directly innervate end organs, including the heart.[13] Resultant hemodynamic changes with mental stress include increased heart rate, blood pressure, systemic vascular resistance, and cardiac output, though not usually to the extent seen with physical activity.[38]

In patients with coronary artery disease, 2 seminal studies in the 1980s demonstrated that experimentally induced mental stress could induce myocardial ischemia. In one study, 2 minutes of serial 7 subtraction led to positron emission tomography scanning measuring myocardial regional perfusion abnormalities.[39] In the second study, mental stress, particularly personally relevant mental stress, induced left ventricular wall-motion abnormalities, as assessed by radionuclide ventriculography.[40] Hemodynamic changes (eg, heart rate and blood pressure) alone did not explain the findings of stress-induced ischemia. These findings of psychological stress-induced myocardial ischemia or dysfunction have been replicated in several dozen other studies assessing mental stress-induced myocardial ischemia utilizing various methodologies.[38] Overall, in patients with coronary artery disease, myocardial ischemia is detected in 30% of patients when using electrocardiographic criteria, 37%-41% of patients based on decreased ejection fraction or wall motion abnormalities, and >75% of patients based upon perfusion abnormalities.[38]

One mechanism that can contribute to mental stress-induced ischemia in patients with coronary artery disease is coronary vasoconstriction. In one seminal study, patients who were referred for diagnostic cardiac catheterization for the evaluation of chest pain were, during the catheterization, subjected to mental stress.[41] During mental stress, quantitative coronary angiography demonstrated an average 24% ± 4% constriction in stenosed arterial segments. The combination of coronary vasoconstriction at the site of existing coronary lesions, reducing myocardial oxygen supply, and increases in heart rate and blood pressure, increasing myocardial oxygen demand, seems to provide a plausible explanation for the oft-reported phenomena by many patients that acute stressful events lead to the development of angina.

Another pathway by which acute mental stress can lead to myocardial ischemia and infarction is via prothrombotic and pre-inflammatory effects. Some, although clearly not all, published studies have demonstrated that acute mental stress can acutely increase measured thrombotic factors including platelet activation, platelet aggregability, circulating platelet aggregates, and platelet proinflammatory activity.[42-47] Acute mental stress has also been shown to increase blood viscosity, fibrinogen levels, and D-dimer levels.[48] Several studies of the effects of psychological stress and pro-inflammatory cytokines found acute mental stress-related increases in cytokines interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha.[49,50] These factors are believed to contribute to vascular inflammation and may contribute to atheromatous plaque destabilization.[6,51]

These findings taken as a whole provide some reasonable biologically plausible pathophysiologic mechanisms by which acute psychological stress results in myocardial ischemia, left ventricular dysfunction, and MI. In many cases, there is likely a synergistic effect of these different pathways and processes.

Chronic Psychological Stress

One suggested possible mechanism by which chronic psychological stress might contribute to heart disease is by contributing to the development or at least progression of atherosclerosis.[5,6] Chronic stress may plausibly lead to detrimental lifestyle factors, including smoking (and decreased smoking cessation success), unhealthy eating habits, decreased exercise and sleep, poorer adherence to cardioprotective medications (eg, antihypertensive agents, lipid-lowering therapies), and lesser medical follow-up and screening.[14,36,52-56] Poor lifestyle related to stress might also contribute to obesity, hyperglycemia, and diabetes.[6,57]

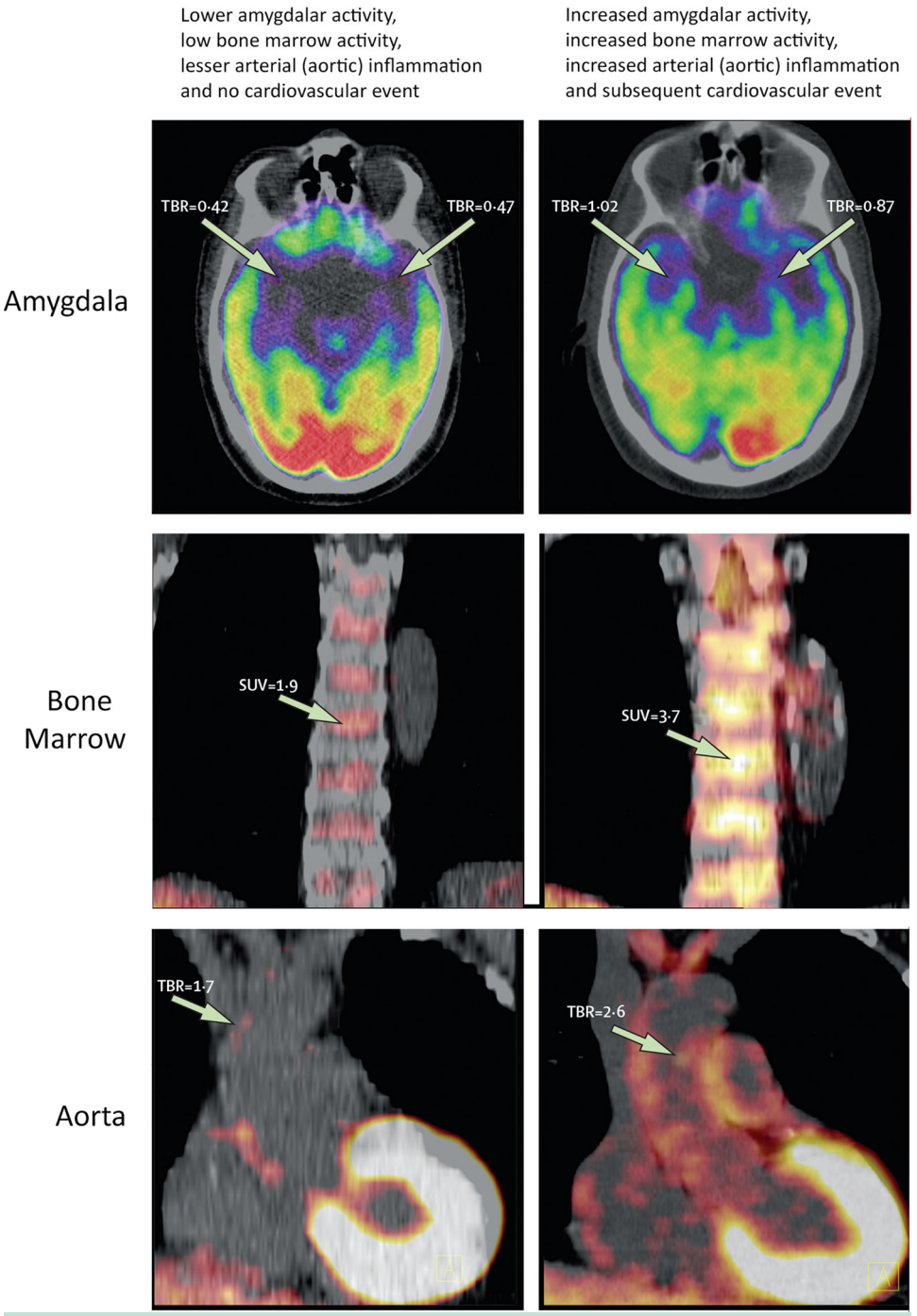

Figure 3 In a series of eloquent studies, perceived stress was shown to be associated with increased amygdalar activity (stress-associated neural activity), increased bone marrow activity, arterial inflammation, and subsequent cardiovascular events. Left images are an illustrative example from a subject with low amygdalar activity and no subsequent cardiovascular event; right panel is from a subject with high amygdalar activity (top row), increased bone-marrow (in the spine) activity (middle row), increased arterial (aortic) inflammation (bottom row), and subsequent cardiovascular event. Adapted from Tawakol et al, 2017.[64]

There are some modest data that support such detrimental effects,[6,14,27,36,52-57] although clearly more study data are desirable.

Chronic sympathetic nervous system stimulation due to stress leads to increased blood pressure,[14] and some (though again, not all) studies have linked chronic psychological stress and elevated stress hormone levels with increased blood pressure levels and overt hypertension,[58-62] a major risk factor contributing to coronary atherogenesis. For example, in the Jackson Heart Study, in those without

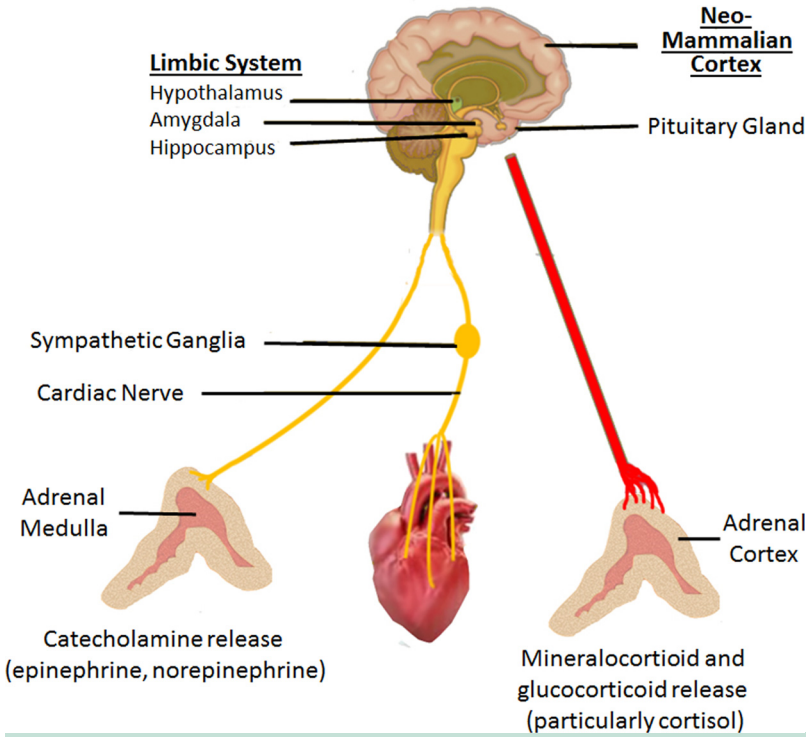

Figure 4 Overview of the neurocardiovascular mechanisms by which psychological stress may contribute to cardiovascular risk. Stress increases 1) sympathetic-adrenal-medullary (SAM) activity (leading to increased catecholamine, particularly epinephrine, release); 2) hypothalamic-pituitary-adrenocortical axis [HPA] activity (leading to increased cortisol release); and 3) peripheral sympathetic nervous system activity (leading to direct local release of norepinephrine). Additionally, data suggest that psychological stress can increase inflammation (though circulating pro-inflammatory cytokines) and has prothrombotic effects (related to platelets and other hemostatic factors). These processes (as well as detrimental lifestyle factors) might chronically contribute to the development of atherosclerosis, and acutely contribute to myocardial ischemia, infarction, and arrhythmia.

hypertension at baseline, high levels of stress (as assessed yearly) conferred a statistically significant adjusted 37% greater risk of developing hypertension over the subsequent 7 years when compared with those with low self-reported levels of stress.[62]

The hypothalamic-pituitary-adrenocortical axis also may contribute to neurocardiovascular-mediated morbidity due to psychological stress. The hypothalamus receives afferent stimuli from various neural structures involved in the perception and response to stress.[5,16] The hypothalamus, via the anterior pituitary gland, activates the adrenal gland, leading to increased circulating cortisol levels. Increased cortisol levels increase insulin resistance, increase blood pressure, and contribute to central redistribution of adiposity.[16,63]

Chronic psychological stress might additionally contribute to cardiovascular disease through increased inflammation. Chronic stress has been in some, though again not all, studies associated with elevated C-reactive protein, inflammatory cytokines, and arterial inflammation.[15,64] Increased bone marrow activation, which has been shown in patients with increased stress, is believed to lead to increased release of pro-inflammatory cytokine producing monocytes, resulting in arterial inflammation.[64-66]

The amygdala is a key component of the brain's salience network involved in stress[64] and has been termed the brain's "alarm bell."[67] In a series of elegant studies, it was shown that 1) perceived stress correlates with increased amygdalar activity (as assessed by positron emission tomography-computed tomography); 2) amygdalar high metabolic activity (an indicator of stress-associated neural activity) was associated with increased bone-marrow activation and arterial inflammation (Figure 3);[64] and 3) during median 3.7 years of follow-up, high amygdalar activity was associated with increased risk of cardiovascular events (HR 1.59), even after multivariate adjustments for cardiovascular risk factors. These and other studies suggest that the amygdala may be a key mechanistic link in any causal relationship between stress and cardiovascular disease.[64]

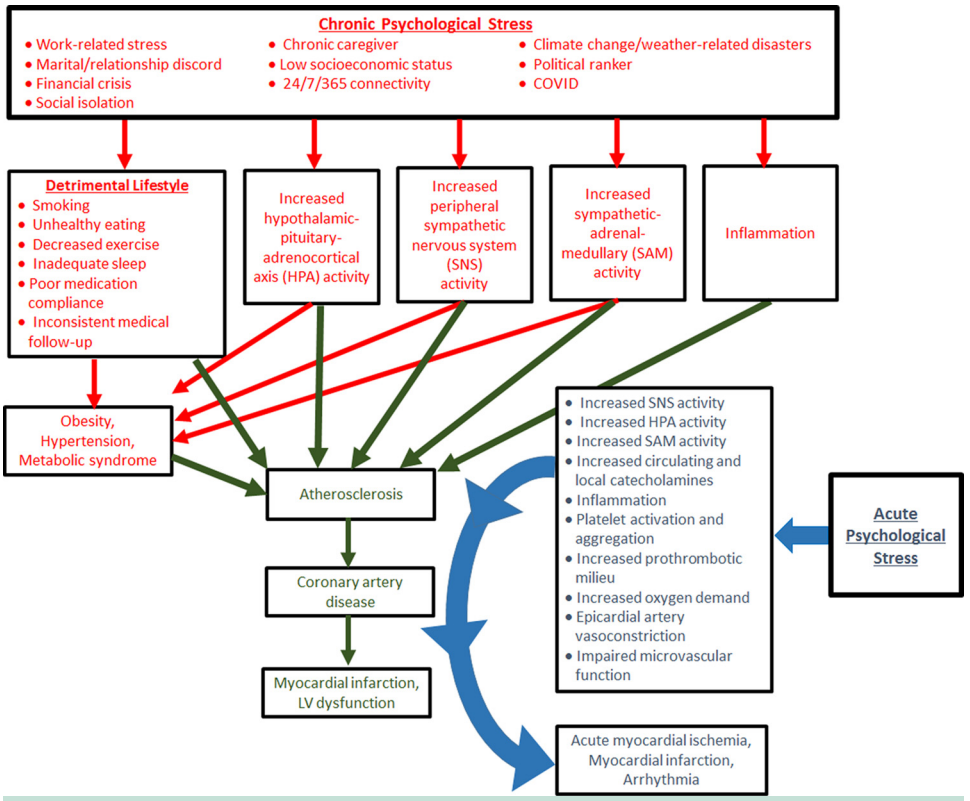

Figure 5 Potential mechanisms and pathways by which psychological stress might contribute to cardiovascular risk and morbidity. Chronic psychological stress might contribute to the development of atherosclerosis via synergic and additive mechanisms, including detrimental lifestyle, increased hypothalamic-pituitary-adrenocortical axis (HPA) activity, increased peripheral sympathetic nervous system (SNS) activity, increased sympathetic-adrenal-medullary (SAM) activity, and inflammation. Acute psychological stress leads to acute increases in sympathetic activity and increased circulating and local levels of catecholamines, prothrombotic effects, epicardial coronary arterial vasoconstriction in areas of pre-existing atherosclerotic disease, and impaired microvascular function, all in the setting of increased myocardial oxygen demand. These acute processes can plausibly lead to myocardial ischemia, myocardial infarction, and (in the setting of acute ischemia, myocardial scar, or left ventricular [LV] dysfunction) ventricular arrhythmia.

The mechanisms by which psychological stress might contribute to atherosclerosis, myocardial ischemia, and acute cardiovascular events are summarized in Figures 4 and 5.

CONCLUSIONS

The oft patient-reported association of acute psychological stress precipitating angina seems biologically plausible, mediated by coronary vasoconstriction at the site of pre-existing coronary stenosis (decreased myocardial oxygen supply) combined with some increase in heart rate and blood pressure (increased myocardial oxygen demand), and is supported by numerous studies documenting experimentally induced acute stress leading to acute myocardial ischemia. Multiple reports of natural and man-made disasters, as well as the now well-accepted phenomenon of stress-induced cardiomyopathy, seem to support the belief that severe acute psychological stress can precipitate myocardial dysfunction, infarction, arrhythmia, and cardiac death. There are multiple, likely synergic, mechanisms by which such stress can predispose to or precipitate such events. A reasonable amount of good quality study data seems to support the belief that chronic psychological stress is associated with an increased risk of heart disease, and there appears to be several mechanisms and pathways by which it might plausibly indirectly or directly contribute to atherosclerosis development and progression. The increased risk does not appear to be on par with risk factors such as diabetes, hypertension, or smoking, but likely exists nonetheless. Thus, the commonly heard and held belief that stress contributes to heart disease does seems to be more fact than just folklore, though clearly further research on this connectivity is desirable.

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