Review Article

Stress, Cardiovascular Diseases and Exercise – A Narrative Review

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Abstract

The assuredness that adverse life stressors can lead to major negative impacts on an individual's health has been held since antiquity. Stress is considered a state of homeostasis being challenged, with biological consequences that can cause cardiovascular diseases (CVD). Stressors may be diverse and include a variety of psychological stressors, such as family stress, job strain, effort-award imbalance, long working hours, insecurity, social isolation, and lack of purpose in life. However, stressors may also be physical, immunological, metabolic, or environmental. Type of personality, anxiety, depression, pessimism or hostility, previous experience, genomics, body composition, nutritive and training status modulate stress responses and are important co-stressors. Chronic stress is linked with altered neurohormonal activity, which increases apoptotic pathways in cardiomyocytes. These pathways contribute to impaired myocardial contractility, increased risk of myocardial ischemia, infarction, heart failure, and arrhythmias. While stress is a vital risk factor for CVD, it has not been a major focus of preventive strategies. The purpose of this article is to review the impact of stress on CVD risk with an emphasis on approaches for stress reduction. Strength and endurance exercise, although being stress itself, leads to better adaptiveness to other types of stress, and by far has played an inevitable role in CVD risk reduction. Innovative strategies to combat CVD are strongly needed and exercise may be the best population-level cost-effective approach.

Keywords: Cardiovascular diseases, exercise, stress

Introduction

Stress is considered to be a threat to the physical, mental, or social integrity of the individual by the external environment or internal body milieu.[1-3] In other words, the statement that stress is a homeostasis is challenged, uncertain, or a lack of control.[1-3] While traditionally stress heralds an acute activation or chronic modulation of the hypothalamic–pituitary–adrenal (HPA) axis and a series of sympatho-adrenomedullary (SAM) reactions, it is evident that even lower organisms, isolated tissues or cells may have stress responses.[2,3] For example, oxidative stress and endoplasmic stress gained scientific attention in the past several years, first, being specifically referred to as a disruption of redox signaling and control,[4] and second, the accumulation of unfolded proteins in the endoplasmic reticulum.[5] Conceptually, there are three stress types: eustress (positive stress), sustress (inadequate stress), and distress (negative stress).[6] While eustress might benefit health through optimization of homeostasis, producing enhanced attention, readiness and performance, both sustress and distress might lead to pathological conditions, including cardiovascular (CV) diseases (CVD).[7] While acute stress (i.e., stress that lasts from minutes to hours) represents an immediate threat to the psychophysical integrity, chronic stress (e.g., stress that persists for several hours a day for weeks/months) implies the loss of control in the situation that lasts.[1,2] Bouts of acute stress with adequate time for system recovery are thought to be associated with salubrious adaptive effects. However, in contrast, chronic stress can lead to maladaptation of neuroendocrine regulatory mechanisms.[6,7]

Stress may be both an agent and a result, and this confusion can be avoided by the distinction between "stress" and "stressor".[6]

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Stressors may be diverse and include a variety of psychological stressors (PS), such as family stress, bereavement, job strain, effort-award imbalance, long working hours, insecurity, social isolation, lack of purpose in life, personal or work-related goals and deadlines, however, stressors may also be physical, immunological, metabolic, environmental, or man-induced events, such as war or sports events.[6,7] Type of personality, pessimism, hostility, previous experience, genomics, early life stress, body composition, nutritive and training status, substance abuse, sleep quality, smoking, socioeconomic status, and education level modulate stress responses, and are important co-stressors.[6,7] Anxiety and depression represent stress effects; however, they act as co-stressors and contribute to the development of other stress-related diseases.[8]

In this review, we will analyze the impact of stress on CV health, stress-related mechanisms that promote CVD, as well as approaches for stress reduction with emphasis on the role of exercise and improvements in cardiorespiratory fitness (CRF).

Stress Effects and the Link with Cardiovascular Disease

During acute stress, the brain takes action to remove the threat or uncertainty as soon as possible.[9] The estimation of uncertainty presence is registered by the anterior cingulate cortex,[10,11] while the amygdala recognizes the threat to wellbeing.[12] These two interreact and activate two pathways: locus coeruleus norepinephrine system, and the ventromedial hypothalamus and the paraventricular nucleus, activating the sympathetic nervous system and HPA axis.[9] The activation of the HPA and the SAM axis provokes the release of hormones such as growth hormone, adrenocorticotropic hormone, cortisol, prolactin, epinephrine, and norepinephrine, as well as parasympathetic withdrawal. Both systems enable a hypervigilant "solving problem" state of the body, which includes enhancing blood flow, glucose supply, and cerebral ketone supply, but all these at the cost of high-flow-speed arterial turbulences, and central redistribution of adiposity.[9,13] These stress effects lead to the development of many somatic effects, such as precipitation of insulin resistance, activation of renin–angiotensin–aldosterone system and increased blood pressure, metabolic syndrome, diabetes, impaired immune response, and increase in sinus node firing rate and atrioventricular conduction velocity.[9,13-15] Systemic inflammation caused by stress is coupled by elevating the production of inflammatory cytokines (proinflammatory cytokine interleukin-6, intercellular adhesion molecule-1, and acute phase reactant C-reactive protein) and by altering the type 1/type 2 cytokine balance, thereby inducing suppression the function of immunoprotective cells, mononuclear cell aggregation, and lymphocyte adhesion.[16] Furthermore, mitogen-activated protein kinases and tumor necrosis factor-alpha play a potential role in the inflammatory process, and the adrenergic receptors and CXCL12 chemokine are involved with hematopoiesis and the development of atherosclerosis.[17] Endothelial dysfunction occurs associated with reduced nitrogen-monoxide production or bioavailability, and hence, the development of CVD.[17] Stress-related CVD includes ventricular tachycardia and ventricular fibrillation, atrial fibrillation, stroke, myocardial infarction, and other acute coronary syndromes (i.e., unstable angina and stress cardiomyopathy). Stress not only causes the progression of atherosclerosis but also allows triggering events among people with an already high atherosclerotic plaque burden.[18,19] Excessive levels of circulating catecholamines contribute to the disruption of the fibrous cap of atherosclerotic plaque, which is, besides active inflammation, coupled with platelet activation, hypercoagulability, and followed by electric instability.[18,19] As such, stress-related CVD includes ventricular tachycardia and ventricular fibrillation, atrial fibrillation, stroke, myocardial infarction, and other forms of acute coronary syndromes (i.e., unstable angina and stress cardiomyopathy). Indeed, large studies, such as the INTERHEART study (29,972 participants from 52 countries) and the INTERSTROKE study (26,919 participants from 32 countries), identified chronic stress as one of the major factors for CVD onset.[20,21]

A picturesque example of CV stress effect is stress-induced cardiomyopathy, which is recognized as "broken heart syndrome" or "Takotsubo cardiomyopathy." This is a transient left ventricular dysfunction phenomenon with wall-motion abnormalities that mimic ischemic heart disease and is considered an acute heart failure syndrome.[22-24] Emotional or physical stressors, mostly in postmenopausal women, precede this reversible acute heart failure syndrome and lead to cardiac dysfunction through catecholamine-mediated microvascular dysfunction or direct toxicity.[25]

The link between the brain and heart can be elaborated by analyzing posttraumatic stress disorder, which has long been associated with a heightened risk of CVD.[26] Neural deficits in posttraumatic stress disorder suggest that the brain–heart axis, a pathway connecting frontal and limbic brain regions to the brainstem and periphery through the autonomic nervous system, is altered and coupled by increased systemic inflammation, platelet activation, and endothelial dysfunction.[26] These alterations manifest as high resting heart rate and low heart rate variability, low diurnal cortisol levels, a significant reduction in flow-mediated dilatation, and significantly high levels of interleukin-1 β, interleukin-6, and interferon γ.[27,28]

Additional burdens for CVD development are behavioral changes that may accompany stressful events, including smoking, binge drinking, drug abuse, sleep disorder, inactivity, obesity, and medication nonadherence.[29-33]

"Garden" Variety of Stressors and Co-Stressors Linked to Cardiovascular Disease

Stress in the narrow sense is usually considered to be PS or psychosocial stress.[6,7] There is a growing body of evidence demonstrating the link between PS and CVD, but also an increased understanding that positive psychological well-being

can protect against adverse physical health outcomes, including CVD.[34]

Stress-related disorders are robustly associated with multiple types of CVD, independent of the history of somatic/psychiatric diseases, psychiatric comorbidity, or familial background.[35] Song *et al*. demonstrated that during up to 27 years of follow-up of exposed individuals, their unaffected full siblings, and the matched unexposed individuals, the hazard ratio (HR) for any CVD was 1.64 during the 1st year after the diagnosis of any stress-related disorder, with the highest specific HR observed for heart failure. Beyond 1 year, HR for CVD became lower (on average 1.29). Stress-related disorders were more strongly associated with early onset CVD for attained age <50 (HR 1.4) than for later onset ones (HR 1.24). Only fatal CVD was modified by the presence of psychiatric comorbidity.[35]

Family stress is directly linked to increased blood pressure, atherosclerosis progression, and coronary artery disease (CAD).[36-38] Work stress, effort-award imbalance, long working hours, insecurity, personal or work-related goals, and deadlines are ubiquitarian stressors leading to impairment of mental well-being and CVD burden.[38,39] In the study of 600,000 workers from 27 cohort studies, it was reported that pressures relating to success, job strain and more than 50 working hours per week increase the incidence of developing stroke and CAD by up to ~40% compared with those free of such stressors.[39]

Type A personality, anger and hostility, as well as pessimism, are typically associated with CVD.[40-43] Altered adrenocorticotropic responses,[44] excessive vasoconstriction mediated by endothelial dysfunction,[41] and increased intima-media thickness,[45] are some of the mechanisms linking these traits with potential CVD. In patients with stable CAD, the tendency to suppress angry and hostile feelings, and particularly openly aggressive behavior, was associated with daily life ischemia.[42] Anger and hostility are associated with CVD outcomes in healthy and diseased populations.[40] Intriguingly, the harmful effect of anger and hostility on CVD events in healthy people was greater in men than women.[46] However, younger women who got divorced or split, have an increased prevalence of obesity, smoking, diabetes, depression, and anxiety, and had higher levels of cumulative stress and CVD burden.[40,47]

Early life stress is an additional independent contributor to the biological responsiveness to future stress and heralds increased incidence of developing a broad range of chronic conditions such as CVD later in life.[48] Exposure to stress in early life modifies the biological programming of the CV system, inducing long-lasting effects on the responsiveness to stress stimuli.[47]

A sense of purpose, driven by valued life goals, is associated with reduced CVD risk in the meta-analysis of 10 prospective studies.[49]

Socioeconomic status is an additional important determinant of health.[50,51] For example, a recent study demonstrated that there was an increased prevalence of myocardial infarction in cancer survivors compared with noncancer patients, however, it seems that an even stronger stimulus for CVD occurs in subjects with increased financial worry, food insecurity, and financial burden of medical bills.[52] Furthermore, patients with low income have a significantly higher risk for readmission due to myocardial infarction and CV death after 1 year.[53]

Depression and anxiety are additional strong contributors to CVD burden.[54-56] They are double actors, being the consequence of PS on one side, and the stress itself on the other. Almost one-third of patients with CVD also have depression, and individuals exhibiting depressive symptoms and anxiety are 2.7 times more likely to die from CVD.[55,56]

In addition to all these stressors, there are stress-modifying conditions, such as genomics, body composition, nutritional and training status, substance abuse, sleep quality, smoking, and education level, and they are important co-stressors.[6,7] For example, diet quality plays mediating role in common mental health problems, and it was shown to be reduced in stressed and neurotic individuals.[57] Poor sleep quality is associated with stress, worse glycemic management, and CVD.[58] Finally, training status hugely modulates stress reaction and CV reactivity, enabling powerful tool to combat CVD.[59,60] Summary of stressors, co-stressors and stress responses is listed at Figure 1.

The Role of Physical Activity and Exercise in Mitigating Stress Effects

Target stress nonpharmacologic therapies include relaxation techniques, mental training, cognitive behavioral therapies, meditation, graded adaptation to stressors, and physical activity (PA).[61]

It was previously shown that elite athletes demonstrated markedly reduced PS and physiological responsiveness compared to untrained subjects. They are generally calmer and less anxious or depressive.[59] Highly trained individuals have altered SAM and HPA responses to a PS compared to untrained individuals.[60,62-64] Both aerobic and resistance training lower CV reactivity to PS[62] and have beneficial effects on mental and physical health, protecting against the detrimental consequences of chronic stress and stress-related CVD.

Although both PS and exercise stress are mediated by the SAM and HPA axis co-activity, the responsiveness of these systems is still stressor-specific and includes a multitude of autonomic pathways and brain regions.[65-67] Some animal studies demonstrate that the consequences of physical stress appear early after exposure but are relatively moderate, whereas the effects of psychological stress appear late but are more severe.[68]

The stress response is primarily adaptive and serves to protect an organism from the threat. However, the magnitude of the stress response is also determinant: intermediate, not too high

or low is the most resilient and adaptive.[67,69] According to the cross-stressor hypothesis, repeated continuously planned and adequately dosed PA stress leads to serial adaptive changes that mitigate reactions to PS stress.[70] It seems that there is a specific alteration of HPA and SAM pathways during exercise. Both nervous and endocrine arms of the stress machinery are challenged, positively impacting overall health, since both augmented and blunted reactivity of those systems are associated with CVD.[69] According to the results of previous prospective studies, stress reactivity is a predictor for future health and disease outcomes. Dysregulation of stress reactivity coupled with exercise may represent a mechanism by which exercise contributes to the development of future health and disease outcomes related to PS.[70]

The analysis of 98 studies published between 1988 and 2015 with a sample size of 648,726 demonstrated that leisure-time PA and transport PA had a positive association with mental health, however, work-related PA and household PA had no positive association.[71]

Moreover, the 2018 Federal Physical Activity Guidelines Advisory Committee's Scientific Report suggested exercise for treating stress-related disorders due to its anxiolytic effects in adults and older adults.[72-74] So far, continuous aerobic exercise of moderate volumes (i.e., 3–5 days/week, 70% of peak oxygen uptake [peak VO_2], ~30 min/session) is recommended, since its effects are confirmed by most randomized-controlled studies.[74,75] To date, there is no applicable knowledge about the potential effect of higher intensities or volumes of aerobic exercise on stress, however, recent studies suggest high-intensity interval training (HIIT) as superior for CRF improvement, which represents a strong correlate of mental health.[76,77] For example, HIIT was shown to improve stress responses and CRF in breast cancer survivors and gave promising results as a time-efficient intensity to improve physical health and stress, reducing CVD risk.[78]

Regular resistance exercise training (i.e., at least 2 days per week) is a vital component of the PA guidelines and is shown to improve markers of stress as well as aerobic exercise.[73,79] Recent studies demonstrated that exercise training has stress-reducing benefits regardless of the type of exercise.[80] Both resistance and endurance PA may be effectively used to improve stress regulation competence while having less impact on changing specific coping strategies.[80] The intensity of resistance training that should be applied in stress reduction is still a subject of debate, as it is known that there is greater strength gain in those completing vigorous resistance exercise training (8–10 repetitions at 75%–85% of maximum) than in those randomized to moderate intensity, however, the later accomplishes a greater decrease in anxiety.[79]

On the other side, some meta-analyses show that excessive doses of exercise can be counterproductive and cause unintended harm by chronically exposing the body to stress hormones.[81] Unaccustomed strenuous exercise in habitually sedentary persons with underlying CVD is associated with a disproportionate incidence of acute CVD events.[82] Moreover, extreme exercise regimens appear to increase coronary calcification and the likelihood of developing atrial fibrillation.[82] These data suggest that low-to-moderate

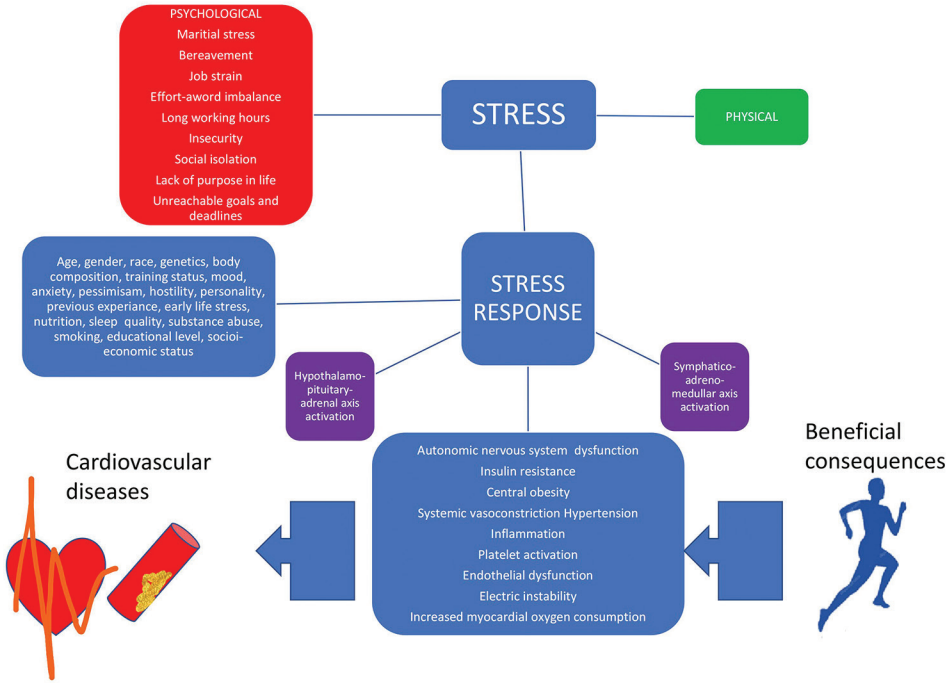

Figure 1: Both physical and psychological stress trigger stress responses. While psychological stress leads to multiple disorders, physical allows adaptation to stress, ameliorating the effects of psychological stress

exercises have more beneficial effects on stress reduction and that professional assessment and consultation may be optimal approaches to combat stress-related disorders.[83]

Mindfulness yoga programs and tai chi are examples of mind-body stress therapies incorporating both physical and cognitive-behavioral approaches.[84,85] For example, among patients with mild-to-moderate Parkinson's disease, the yoga program was found to be as effective as resistance training in improving motor performance, with the additional benefits of a reduction in depressive symptoms, anxiety, and overall well-being.[86]

Antistress Value of Cardiac Rehabilitation Programs

More and more, cardiorespiratory (CR) programs incorporate evaluation of PS status, and exercise strategies to cope with it.[87] PS, including depression, anxiety, and hostility, is an independent risk factor for mortality in patients with CAD, and substantial data have demonstrated the role of exercise training in reducing it.[88] Marked reductions in PS and all-cause mortality, around 70%, are demonstrated following CR programs in depressed patients diagnosed with CAD.[89,90] Group exercise and collaborative PA seems to provide additional benefit, as well as enhanced CR, including stress management techniques combined with education, group support, and cognitive-behavior therapy.[89,91] In the postpandemic era, the need for CR emerges, due to a large span of global CV disorders and symptoms.[92] COVID-19 has resulted in profound PS, reduced cognitive efficiency, and altered circadian rhythm, which inevitably worsens the obesity and physical activity habits.[93] Exercise as a compound of structured CR programs has shown to have beneficial effects in coping with postpandemic stress disorders.[94]

Indisputably, regular exercise is associated with a reduced risk of CVD and mortality, and as such plays an important role in primary and secondary prevention of CVD. This is enabled by cardiac, vascular, mitochondrial adaptations, and by reductions of both traditional and nontraditional risk factors, including PS. Although a precise dosage of training load is desirable, every physical activity is useful and accumulates positive effects during lifespan.

Conclusion

Every individual faces diverse stress exposure during lifespan. The most challenging of all is PS stress, in various forms, largely coupled with CVD. Both physical and PS trigger stress responses. While PS leads to multiple disorders, physical allows adaptation to the stress effects of PS. Due to the huge underestimation of PS in clinical practice, there is a lack of uniform recommended coping strategies that may reduce stress-related diseases. However, evidence is strong that regular exercise of moderate intensity and volume, both aerobic and anaerobic, leads to better adaptiveness to stress. Exercise in combination with other mind-body stress therapies, such as yoga, or cognitive-behavioral strategies, gives even better results in stress reduction and combating CVD burden and mortality.

Ethical statement

The ethical statement is not applicable for this article.

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Conflicts of interest

Dr. Carl J. Lavie is an Associate Editor-in-Chief of Heart and Mind. The article was subject to the journal's standard procedures, with peer review handled independently of Dr. Carl J. Lavie and their research groups. There are no conflicts of interest.

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