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Brain-heart connections in stress and cardiovascular disease: Implications for the cardiac patient

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Abstract

The influence of psychological stress on the physiology of the cardiovascular system, and on the etiology and outcomes of cardiovascular disease (CVD) has been the object of intense investigation. As a whole, current knowledge points to a “brain-heart axis” that is especially important in individuals with pre-existing CVD. The use of acute psychological stress provocation in the laboratory has been useful to clarify the effects of psychological stress on cardiovascular physiology, immune function, vascular reactivity, myocardial ischemia, neurobiology and cardiovascular outcomes. An emerging paradigm is that dynamic perturbations of physiological and molecular pathways during stress or negative emotions are important in influencing cardiovascular outcomes, and that some patient subgroups, such as women, patients with an early-onset myocardial infarction, and patients with adverse psychosocial exposures, may be at especially high risk for these effects. This review summarizes recent knowledge on mind-body connections in CVD among cardiac patients and highlights important pathways of risk which could become the object of future intervention efforts. As a whole, this research suggests that an integrated study of mind and body is necessary to fully understand the determinants and consequences of CVD.

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Declaration of competing interests

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1. Introduction

Despite extraordinary advances in our understanding of the risk factors and pathophysiology of cardiovascular disease (CVD), this condition remains a major cause of morbidity and mortality in the United States and throughout the world. Dramatic declines in CVD mortality in the United States over the past 40 years represent some enormous progress but have also uncovered troubling disparities as not all segments of the population have benefited equally from such improvements. Young women, Americans who live in rural communities or who are from racial/ethnic minority groups have experienced fewer gains or even a worsening of CVD incidence and case fatality[1–8] and these disparities are growing.[7–12]

One area where knowledge still lags, and which could help us understand population disparities, is the sphere of psychological influences on CVD. For many decades, data from epidemiological studies, clinical research and animal models have pointed to a connection between emotional stress and the likelihood of developing CVD, as well as its progression and adverse outcomes.[13, 14] Chronic mental health conditions closely related to stress, such as depression and posttraumatic stress disorder (PTSD), have also been linked to CVD risk and prognosis in epidemiological research.[15] However, causal evidence in humans has remained insufficient and mechanisms unclear because of difficulties in measuring stress. Research has been limited by the reliance on self-reported measures and the inability to capture fluctuations of emotions and mood over time and in real life. Consequently, this sphere remains inadequately recognized in clinical medicine and prevention.[16] Using modern imaging modalities and controlled testing in the laboratory with experimental mental stress protocols, research from our group and others in the past decade has overcome some of these limitations and has demonstrated that such influences can be powerful.[17–21]

The goal of this review is to highlight recent knowledge on mind-body connections in CVD with emphasis on individuals with pre-existing CVD, a high-risk group who can be disproportionally affected by the effects of psychological stress.[14] We will summarize empirical studies from our laboratory and others that have used mental stress testing in this population, an approach that has proved helpful in the clarification of pathways related to stress and emotions. As a whole, this research suggests that an integrated study of mind and body is necessary to fully understand the determinants and consequences of CVD.

2. Overview of contributions of laboratory research on mental stress

Over the past decade, we centered efforts on the effects of acute psychological stress as measured experimentally in the laboratory on cardiovascular physiology, immune function, myocardial ischemia, neurobiology and cardiovascular outcomes in men and women with CVD.[19–29] Others have also reported that acute mental stress is associated with abnormal coronary reactivity, plaque rupture, as well as cardiac arrhythmias.[23, 30–34] We have developed the concept that stress and mental health are especially important in influencing cardiovascular outcomes in patient subgroups such as women, patients with an early-onset myocardial infarction (MI), and patients with adverse psychosocial exposures.

[20, 24, 25, 27, 29, 35–37] A general conceptual framework is that chronic or cumulative stress causes dysregulation of adaptive stress response systems which, in turn, affect CVD risk though downstream effects on autonomic, vascular, immune, metabolic, injury and repair physiology; these effects are exacerbated by dynamic perturbations in response to everyday stressors or recurrent negative emotions (Figure 1).[38]

Both enhanced and blunted cardiovascular reactivity to mental stress have previously been implicated in CVD risk,[39–41] but until recently almost no objective data existed for a possible link with clinical outcomes. A major recent finding from our laboratory is that dynamic changes of vascular and immune function measures with mental stress are related to adverse patient outcomes independent of respective baseline (resting) levels and are often better predictors of adverse outcomes than resting levels. We have observed this pattern with transient endothelial dysfunction with mental stress measured by flow-mediated vasodilation (FMD),[21] with stress-induced peripheral vasoconstriction,[26] and with the inflammatory response to mental stress (especially in women).[29] Using positron emission tomography (PET) imaging of the brain, we have shown that mental stress-induced myocardial ischemia and peripheral vasoconstrictive responses to mental stress are related to activation in brain areas involved in the stress response, emotion and autonomic regulation of the cardiovascular system,[28, 42] and that activation of these areas is associated with cardiovascular outcomes,[19] as well as with angina symptoms[43] and obesity[44] in patients with CVD. These data directly support brain-heart connections and suggest that variations in individuals' responses to acute stress represent mechanisms through which stress leads to increased risk of CVD-related morbidity and mortality.

3. Neurobiology of stress in relation to CVD

Stressful exposures and symptoms of psychiatric disorders related to stress, like PTSD and depression, and even stressful environmental exposures such as ambient noise,[45] are processed in the brain and affect heart function through output pathways to the heart. A network of brain areas involved in memory and fear, including the hippocampus, medial prefrontal cortex, and amygdala, are involved in the brain's response to stress.[46] The hippocampus plays a critical role in memory and is also sensitive to stress. Studies in animals demonstrated that stress results in damage to neurons in the CA3 region of the hippocampus,[47] and stress-related disorders like PTSD and depression are associated with a smaller hippocampal volume and deficits in hippocampal-based declarative memory.[48–50] The medial prefrontal cortex also plays an important role in the stress response. This brain structure includes the anterior cingulate, the orbitofrontal cortex, and adjacent areas. These regions regulate neuroendocrine responses to stress via complex pathways involving the brainstem, the hypothalamus and the amygdala. The hippocampus and the medial prefrontal cortex have inhibitory pathways to the amygdala, which in turn activates neuroendocrine responses to stress.[51, 52] The amygdala also participates in the stress response to noise.[45, 53]

Given these known pathways, it is conceivable that psychological stress acts through brain areas involved in stress response regulation (amygdala, insula, medial prefrontal cortex, and hippocampus) to influence CVD risk. Using the paradigm of inducing mental stress in the laboratory in conjunction with simultaneous heart and brain imaging,[54] we studied heart and

brain correlates of stress in CVD patients. Patients with CVD underwent the stress of performing mental arithmetic or giving a speech with negative feedback in conjunction with PET imaging of brain blood flow and myocardial perfusion imaging using single-photon emission computed tomography (SPECT) of the heart. Using these techniques, we found that patients with a history of traumatic stress and depression where more likely to develop myocardial ischemia with mental stress, typically without chest pain.[37, 55] We also found that CVD patients with mental stress-induced myocardial ischemia had increased anterior cingulate function with mental stress compared to CVD patients without ischemia,[42] and brain activation in these regions correlated with increased stress-induced peripheral vasoconstriction.[28] Furthermore, in a series of studies, we observed that CVD patients have differing brain activation patterns to mental stress based on gender,[56] obesity,[57] symptoms of angina,[43, 58] history of early trauma,[59] and co-occurring depression.[60, 61]

Emphasizing the central role of the brain in these mechanisms, mental stress-induced activation of the rostro-medial prefrontal cortex was prospectively associated with adverse outcomes in CVD patients.[19] This is an area that is key in the regulation of emotion and is also involved in immune and autonomic function. As opposed to other regulatory areas of the medial prefrontal cortex, this region is specifically activated during social stressors that include embarrassment and social rejection.[19] Notably, we found that decreased heart rate variability and increased secretion of inflammatory markers [interleukin 6 (IL-6)] during mental stress mediated the relationship between brain activation and adverse cardiac outcomes, accounting for 33% and 16% of the association, respectively.[19]

In summary, multiple lines of evidence show that stress acts through key brain areas to activate peripheral sympathetic and neurohormonal responses that may increase the risk for CVD. The pathways involved are complex and encompass brain, inflammatory, and autonomic responses with stress, suggesting multiple potential future targets for treatment.

4. Autonomic nervous system mechanisms and stress regulation

The autonomic nervous system is an integral component of stress physiology. Sympathetic hyperactivity and parasympathetic withdrawal are core aspects of the acute stress response; these lead to increased heart rates and blood pressure in most individuals undergoing laboratory stress challenges.[23, 62] These changes, and the cascade of inflammatory and prothrombotic effects that are instigated by autonomic activation during acute mental stress, could increase the likelihood of plaque rupture.[14, 63]

Chronic stress, on the other hand, can result in dysregulation of the autonomic nervous system, likely stemming from the brain mechanisms highlighted above.[35, 41, 64] Dysregulation can manifest as hyper-reactivity or blunted activity.[41] Because autonomic activation is essential for activities that include cognitive and physical tasks, a blunting of autonomic regulatory activity can lead to impaired quality of life in domains that require adequate blood circulation during everyday function. This can lead to fatigue and worse cognitive function.[65] Both enhanced and blunted cardiovascular reactivity to mental stress have been related to CVD risk factors.[39–41]

Biomarkers of autonomic activity may help evaluate the physiologic effects of mental stress, risk stratify individuals, and help evaluate certain treatments. One candidate electrocardiographic biomarker is heart rate variability, which describes the variation in heart rate that occurs in response to various physiologic responses, ranging from respiration (high-frequency heart rate variability) to circadian variation (ultra-low frequency heart rate variability). Heart rate variability has been extensively studied as a noninvasive measure of autonomic modulation that predicts adverse CVD outcomes.[66, 67] Heart rate variability and other measures of autonomic dysfunction such as pre-ejection period, galvanic skin response, and T-wave amplitude have promise as quantifiable, unbiased measures of stress physiology that can be measured with ambulatory electrocardiography, track treatment progress, and predict future CVD risk as well.[67, 68] Studies have consistently shown a robust dose-response relationship between reduced heart rate variability and both PTSD and depression.[64] More recently, research has also suggested that low heart rate variability can predict the development of worsening depressive symptoms and future PTSD development in trauma exposed individuals.[69, 70] Unlike psychiatric conditions, the lack of stigma for metrics of autonomic dysfunction make them more likely to be useful in engaging patients and motivating them towards behavioral interventions.

5. Vascular function

In the largest and most comprehensive study investigating the effects of mental stress in patients with CVD, the Mental Stress Ischemia Prognosis Study (MIPS),[22] we found that laboratory induction of mental stress was associated with autonomic activation together with coronary and peripheral microvascular constriction, protracted increase in arterial stiffness, and endothelial dysfunction.[23, 62, 71] These findings are similar to those reported in previous smaller studies of individuals without CVD.[72–74]

Adverse environmental exposures can also cause psychological stress and affect vascular function. Ambient noise, for example, is a recognized environmental stressor.[75] In human experimental models nighttime aircraft noise induced a decrease in endothelial function, a marked increase in sympathetic activation and increase in systolic blood pressure, particularly in patients with established coronary artery disease.[76, 77] Traffic noise has also been linked to arterial inflammation.[53]

Whereas normal coronary arteries dilate in response to mental stress, atherosclerotic epicardial coronary arteries tend to constrict, at least partly due to alpha-adrenergic activation.[78] By measuring peripheral vasomotion using pulsatile digital arterial tonometry in patients with CVD, we found that men tended to have greater peripheral vasoconstriction compared to women,[24, 79] potentially due to the vasodilatory effect of estrogen and sex-based differences in the sensitivity of adrenergic receptors.[80] By testing coronary vascular responses during acute mental stress, we also found a significant correlation between coronary *microvascular* changes with mental stress and the coronary endothelium-dependent, but not endothelium-independent function.[23] Thus, patients with worse coronary endothelial function had reduced microvascular vasodilation in response to mental stress. Moreover, there was a strong correlation between the magnitude of coronary microvascular vasodilation and digital peripheral microvascular constriction during mental stress,

demonstrating that vasoreactivity to mental stress is a generalized phenomenon. It is likely that inflammatory and oxidative pathways play a role in the link between psychological stress and vascular function, as discussed in section 8.

To further illustrate the interplay of brain and CVD, we showed that stress-induced vasoreactivity is associated with activation of brain areas involved in emotion and autonomic regulation. Specifically, we found that CVD patients with stress-induced peripheral vasoconstriction have differential patterns of brain activation with mental stress in areas involved in emotional regulation, including the insula, the parietal cortex and the medial prefrontal cortex.[28]

6. Vascular regenerative pathways

Chronic stress and its associated neurobiological changes also result in activation of the bone marrow.[17, 18] Exposure to cardiovascular risk factors and injury promotes progenitor cell mobilization from the bone marrow and ultimately may lead to depletion of progenitor cells.[81] Progenitor cell counts are considered to be an index of endogenous regenerative capacity and are independent predictors of adverse cardiovascular outcomes.[82, 83] Progenitor cells expressing the CD34 epitope have the potential to differentiate into hematopoietic, endothelial, and other lineages. These progenitor cells are mobilized after acute mental stress, an effect that is mediated through activation of the beta-adrenergic receptor activation in the bone marrow and the production of cytokines.[84, 85] Levels of stromal cell-derived factor-1 (SDF1) or CXCL12, a chemokine that plays a central role in the recruitment of progenitor cells in response to ischemia, are also stimulated by acute mental stress and increase more in patients who develop ischemia with mental stress.[86]

7. Prognostic value of mental stress-induced vascular perturbations

Whether mental stress-induced vascular alterations have a prognostic implication has not been extensively studied. In the MIPS study, we demonstrated that greater digital vasoconstriction during mental stress, measured using digital tonometry, was an independent predictor of adverse events during follow-up.[26] In MIPS, we also demonstrated that the transient decline in endothelial function, measured as flow-mediated vasodilation of the brachial artery in response to mental stress, was an independent predictor of adverse CVD events.[21] Both the magnitude of PC mobilization with mental stress and the change in SDF1 level induced by mental stress were independent predictors of adverse incident cardiovascular events. Finally, we found that activation of specific brain areas during mental stress involved in executive function, stress activation and the limbic system were associated with greater mobilization of progenitor cells.[87]

These results are consistent with the model that activation of specific brain areas with mental stress leads to hemodynamic and vascular responses that, in turn, alter regenerative pathways, and these responses have pathogenic implications on the long-term prognosis of patients with CAD (Figure 2).

8. Inflammatory/immune and oxidative mechanisms

Inflammatory mechanisms play a well-established role in atherosclerosis and coronary artery disease, and acute psychological stress is associated with an increase in inflammatory markers and certain chemokines.[88, 89] Therefore, the immune system is clearly at the intersection between psychological stress and adverse cardiac events. Nevertheless, the mechanistic connections between dysregulated immune responses, psychological stress and CVD are not fully understood.

An important goal of our studies has been to elucidate the pathways connecting psychological stress with CVD through immune mechanisms and interrelated endothelial and microvascular function.[25, 29, 35, 37, 89] Using a well-established stress protocol, we examined changes in cytokines and other immune molecules in response to a controlled laboratory stressor. We collected blood sequentially at 45 and 90 minutes after the mental stress and employed a highly-sensitive electrochemiluminescence assay system. The working hypothesis was that individual differences in the sensitivity to daily stressors have pathophysiological correlates in neurocircuitry and autonomic reactivity, as well as in the provocation of inflammatory responses.[42, 90] In support of these mechanisms, we recently reported that individuals with higher activation of the rostromedial prefrontal cortex in response to a psychological stress challenge had greater increases in stress-induced IL-6 levels.[19]

Among young women with CVD, we found higher levels of circulating IL-6 at rest, and an enhanced IL-6 response to stress, compared to men of a similar age and CVD status.[25] This suggests that accentuated IL-6 responses to mental stress among women may be associated with a greater risk for major adverse cardiac events. Indeed, among women with stable CVD, there was a significant positive relationship between stress-induced IL-6 and adverse cardiovascular events, while there was no such association among men.[29] A similar female-specific relationship was found for the chemokine monocyte chemoattractant protein-1 (MCP-1, also referred to as CCL2). The mechanism connecting this sex specific enhanced inflammatory response to adverse cardiac outcomes has not been elucidated. However, studies in animal models, and to a lesser extent in humans, suggest that sex differences in neuronal circuitry and bidirectional brain-immune interactions may explain some aspects of the over-activation of inflammatory responses to stress in women compared with men.[91] Considering the specific role of the rostromedial prefrontal cortex in processing and reacting to social stressors, and our finding that post-mental stress IL-6 levels correlated with activation of this brain region, a future direction of our studies is to examine sex and gender differences in brain immune interactions in relation to adverse cardiac outcomes. Overall, as the mind-body connections in CVD continue to be revealed, individual differences in immune responses to psychological stress will undoubtedly be discovered to play an important role.

It is well established that there is extensive intercommunication between the sympathetic nervous system and the innate immune system.[92] Accordingly, transient inflammatory responses to mental stress may result in part from activation of the sympathetic nervous system, perhaps by mobilization of monocytes. Oxidative pathways are likewise

interconnected with the immune and sympathetic nervous systems, which presents additional mechanisms by which mental stress can influence cardiovascular disease risk.[93, 94] There is a large literature showing that psychological stress can increase reactive oxygen species and cause lipid peroxidation and DNA damage.[94] These stress-associated alterations of reactive oxygen species occur in both the periphery and the brain (especially through activation of microglia).[94] Oxidative damage, in turn, plays a well-established role in endothelial dysfunction.[93] Considering the importance of endothelial dysfunction in the microvascular response to mental stress (described above), reactive oxygen species are likely important intermediates in the connection between psychological stress and cardiovascular disease.

9. Mental stress-induced myocardial ischemia

In approximately 1 in 6 patients with clinically stable CHD, acute mental stress in the laboratory can trigger myocardial ischemia, a phenomenon that can be detected with myocardial perfusion imaging.[20, 95] Mental stress-induced myocardial ischemia is analogous to ischemia provoked by exercise (e.g., treadmill testing), except that the stimulus is psychological rather than physical.[96, 97]

While the prognostic significance of ischemia with mental stress was suspected for many years based on a limited number of small studies that measured mental stress-induced changes in left ventricular dysfunction,[97] recent studies show that mental stress ischemia measured with myocardial perfusion imaging (the gold standard for ischemia detection) is also prospectively associated with an elevated risk of adverse cardiovascular events.[98] The excess risk associated with mental stress ischemia is approximately two-fold after multivariable adjustment. Cardiovascular risk factors, other clinical characteristics, and even psychological disturbances do not explain the excess risk associated with mental stress ischemia, suggesting that this phenomenon has clinical significance beyond the assessment of other known risk factors.

Myocardial ischemia provoked by mental stress has distinct characteristics compared with exercise stress ischemia. It is usually silent, occurs at a lower hemodynamic workload has not been consistently related with coronary atherosclerosis, and can occur in patients who do not have a positive conventional stress test or have been successfully revascularized.[71, 95, 99] These characteristics suggest that ischemia with mental stress is subtended by unique mechanisms. Many factors have been associated with mental stress ischemia, including abnormal peripheral vasomotion, psychological conditions, platelet reactivity, inflammation, and metabolic risk factors,[23, 24, 96, 100, 101] but the exact mechanisms remain unclear.

While systemic vascular resistance falls in response to exercise, it rises with mental stress, due to peripheral vasoconstriction and increasing left ventricular afterload.[96] Patients who develop mental stress ischemia have a more pronounced peripheral vasoconstriction with mental stress.[62, 71, 102] In the MIPS study of patients with stable CVD, the major independent vascular predictors of mental stress ischemia were a greater hemodynamic response during mental stress, measured as the rate-pressure product change, and a greater magnitude of peripheral vasoconstriction, measured as digital vasoconstriction during

mental stress [62] (Figure 3), suggesting that a combination of reduced coronary perfusion due to generalized vasoconstriction and higher myocardial demand, increase the likelihood of myocardial ischemia with mental stress, findings suggested also by some previous studies.[96]

10. Special at-risk populations

Women seem to be particularly susceptible to psychological stressors, and women are twice as likely to be diagnosed with conditions such as depression and PTSD.[103, 104] Studies clearly demonstrate that depression is a major contributor to poor CVD outcomes in women diagnosed with a myocardial infarction.[104, 105] Furthermore, women, especially younger women, are more likely to develop mental stress ischemia than men,[20, 106] even in absence of obstructive coronary disease.[99] In the settings of acute and chronic coronary syndromes, women are more likely to have ischemia with no obstructive coronary arteries (INOCA).[20, 24] Comorbid psychological factors and vital exhaustion are highly prevalent in these patients, and psychosocial stress can contribute to and exacerbate angina.[107] In addition to angina during exercise, INOCA patients often report rest angina at low hemodynamic workloads, emotional-stress induced angina, as well as symptoms even after cessation of exercise.[108] In the absence of definitive treatment, INOCA patients with persistent angina make repeated visits to emergency departments and physician offices for chest pain, have reduced health-related quality of life, and high symptom-related disability.[109–111] They undergo repeated cycles of diagnostic testing and hospitalization for general evaluation, but percutaneous coronary interventions or other approaches to revascularization to reduce ischemia are not options for persons with INOCA as there is no culprit lesion(s) to target. Compared to asymptomatic women without INOCA, those with INOCA have more microvascular vasoconstriction in response to mental stress.[112] Among women, microvascular reactivity with stress plays a more pronounced role in mental stress ischemia than in men,[20, 24] and women with ischemia with mental stress, but not men, are more likely to report angina in everyday life.[107] This suggests that, at least among women, mental stress ischemia could be a marker of myocardial ischemia occurring in everyday life.

Myocardial infarction patients with PTSD,[37] depression,[113] and anger,[114] are also more likely to develop mental stress ischemia. Women with CVD and myocardial infarction patients with PTSD, in addition to showing a higher propensity for mental stress ischemia, also exhibit a heightened inflammatory response to acute stress.[25, 27] Furthermore, we have observed that stress-induced IL-6 is a predictor of subsequent CVD events in women with CVD, but not in men.[29] We have also found that patients with CVD who have a phenotype of chronic psychological distress defined as a combination of symptoms of depression, PTSD, anxiety, anger, hostility, and perceived stress, have a higher risk of subsequent cardiovascular events, especially among women.[115] These observations suggest that there are subgroups of CVD patients, including women and patients with psychological distress and mental health conditions, who are disproportionally vulnerable to mental stress ischemia. They also indicate that inflammation and vascular function are key pathways of risk linking psychological stress, mental stress ischemia and adverse outcomes in these at-risk patient populations.

A potentially related condition that is more common in women, where the brain-heart connection is clearly evident, is Takotsubo syndrome. This is a condition where intense emotional or physical stress triggers a catecholamine surge, characteristic ventricular wall motion abnormalities, and acute heart failure.[116]

Certain racial/ethnic groups, such as African Americans, may also be more susceptible to the adverse cardiovascular consequences of psychological risk factors in part through exposure to adverse social determinants of health.[117–121] African American patients report more adverse life events, discrimination, lower income, more chronic stressors, and negative emotions, but whether these psychosocial factors have synergistic effects with traditional risk CVD factors, or directly contribute to pathobiological mechanisms differentially in African Americans vs. other groups is unclear.[122]

11. Management and secondary prevention

Clinical and translational studies designed to modulate the autonomic nervous system and mitigate adverse physiological responses to stress are the next frontier in biobehavioral medicine. While there is growing evidence that psychological stress contributes to CVD, it has not been systematically targeted as a risk factor in clinical care. In the busy clinical care of cardiology and primary care clinics, a thorough history of psychological risk factors and stressful exposures may not be feasible, but brief screening tools for depression and anxiety can alert the clinician to refer to a biobehavioral expert to address these factors (or a mental health specialist in severe cases). The recent ACC/AHA guidelines for prevention of CVD recommend that clinicians address psychological factors as well as social determinants of health when devising an individualized treatment plan for the cardiac patient.[123] Biological responses to stress can be modulated by techniques such as yoga, deep breathing, meditation, biofeedback, and noninvasive vagal nerve stimulation. These modalities may directly modulate autonomic function, have neuroplastic effects on the brain, reduce inflammation, reduce arrhythmia burden, improve quality of life, and reduce the risk of CVD events.[124] Stress management training that includes group support, education, and cognitive behavioral therapy, may also improve perceived stress and reduce the risk of CVD events in patients undergoing cardiac rehabilitation.[125]

Many of the techniques discussed in this review that are performed in the laboratory to study acute mental stress may have future clinical applications for patient monitoring. For example, ambulatory devices for the assessment of heart rate variability, or the assessment of peripheral vasoconstriction, could be useful in tracking everyday stress in individuals undergoing biobehavioral therapies. More work is needed, however, to standardize measurement techniques and algorithms, as well as to identify a clinically relevant magnitude of change achievable with interventions through randomized controlled trials.

12. Conclusions and future directions

Recent research advances, using modern imaging modalities and controlled testing in the laboratory, provide growing evidence that brain-heart influences are powerful contributors of risk in individuals with CVD. These recent discoveries highlight the possibility for objective

evaluation of psychological stress reactivity and its cardiovascular effects through laboratory-based and ambulatory metrics, and will hopefully inspire new randomized controlled trials that may eventually improve our ability to risk stratify patients and enhance the well-being of the heart-brain axis. Despite recent calls,[16, 126, 127] this sphere remains insufficiently recognized in clinical medicine and prevention, as there is a tendency for health care professionals to focus on the physical aspects of the disease and neglect mental health in their evaluation and treatment of cardiac patients. Increased attention to this area should shift the prevailing paradigm of cardiovascular risk assessment to incorporate mental health and psychological factors. It is also hoped that this growing body of knowledge will stimulate future mechanistic research and the development of innovative interventions that could transform CVD prevention and clinical care. Future studies are needed to assess the mechanisms of stress on pathobiology using powerful approaches such as proteomics and metabolomics, as well as using real-time assessments for capturing stress and negative emotions via wearable technologies. Intervention studies in diverse populations are urgently needed, to shed light into treatment modalities that are effective in all segments of the population.

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Highlights

- A “brain-heart axis” exerts influences on the prognosis of individuals with cardiovascular disease.
- Acute psychological stress provocation in the lab has helped clarify stress-related pathophysiological pathways.
- Dynamic perturbations of physiological and molecular systems during stress affect cardiovascular outcomes.
- Some patient subgroups are at especially high risk for these effects.

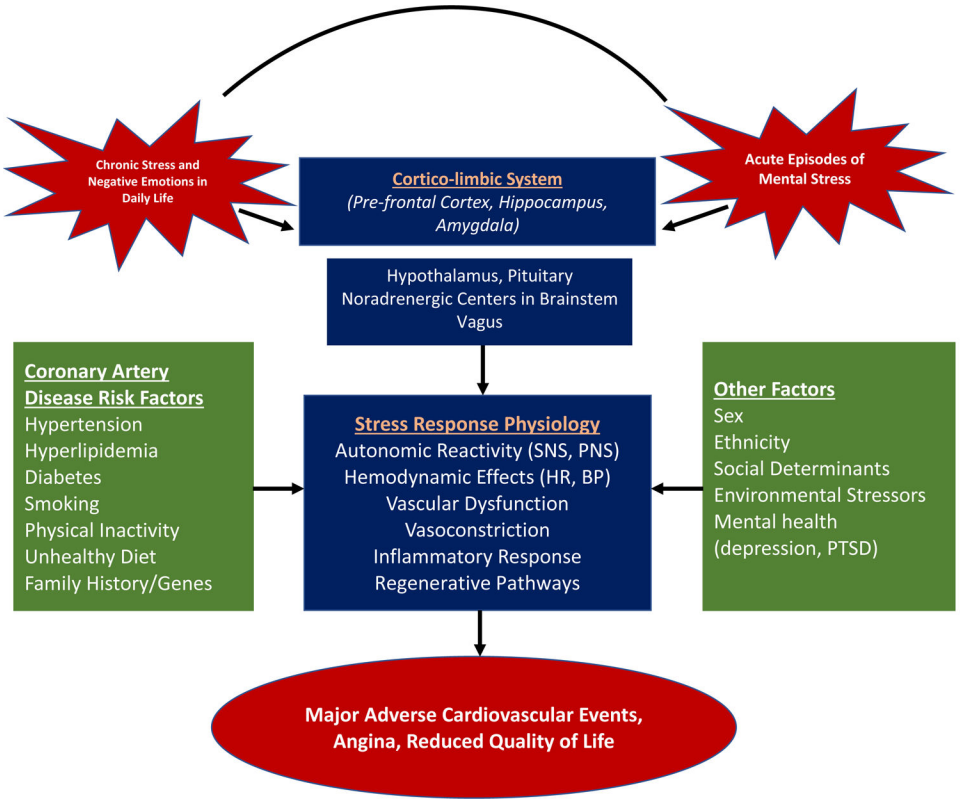

Figure 1. A schematic illustration of the main pathways linking psychological stress with cardiovascular risk.

A chronic background of stress acts together and interacts with acute episodes of stress in everyday life to influence regulatory centers in the brain that control emotional responses, neuroendocrine stress systems and the autonomic nervous system. These, in turn, influence a number of risk pathways for cardiovascular disease that are responsive to stress. These processes are modulated by traditional risk factors, behaviors and genetic background, as well as by concurrent social and environmental exposures and mental health conditions. Abbreviations: SNS: sympathetic nervous system; PNS: parasympathetic nervous system; HR: heart rate; BP: blood pressure; PTSD: posttraumatic stress disorder.

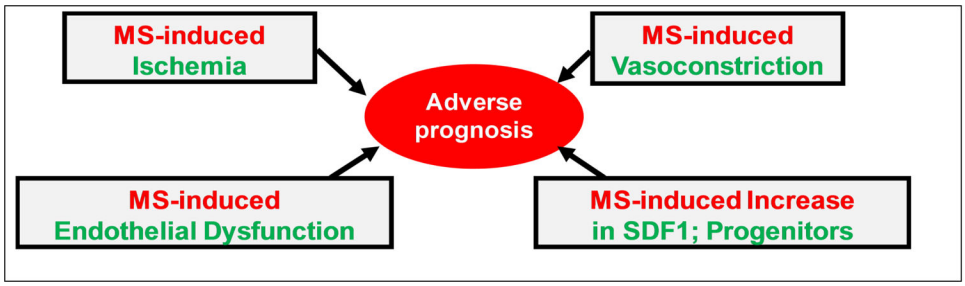

Figure 2. Pathophysiological pathways responsive to acute stress that are postulated to be determinants of adverse prognosis with mental stress.

MS: mental stress; SDF1: stromal cell-derived factor-1.

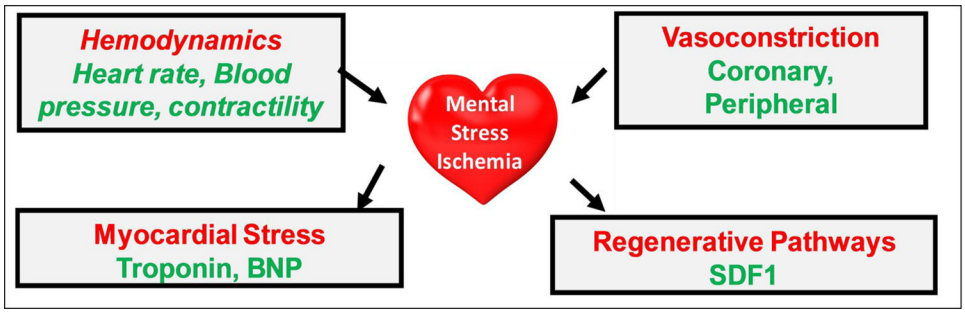

Figure 3. Pathophysiological determinants of mental stress-induced myocardial ischemia and its consequences.

BNP: brain natriuretic peptide; SDF1: stromal cell-derived factor-1.