Depression, psychological stress, vascular dysfunction, and cardiovascular disease: thinking outside the barrel

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THE STRESS RESPONSE is present not only in humans and other mammals but also in more primitive species such as fish (5). It is often said that the accomplishment of some tasks is “easier than shooting fish in a barrel.” However, the potential outcomes of this scenario are not so optimistic from the viewpoint of the fish. In humans, psychological stress, hopelessness, and depression can be risk factors for disastrous cardiovascular events such as stroke, coronary ischemia, and myocardial infarction (8). These conditions can be silent killers, as evidenced by cases where extremely fit individuals without known risk factors suffer sudden catastrophic events such as heart attacks under conditions of sustained stress, either external or self-imposed. The study by d’Audiffret and coworkers in this issue of the Journal of Applied Physiology (2) employs a variety of cardiovascular measurements in a comprehensive study to identify specific vascular changes occurring in an established rodent model of stress and depressive behavior—the unpredictable chronic mild stress (UCMS) model. Using this approach, the authors seek to gain insight into an extremely complex problem, namely how do conditions of psychological stress and/or depression lead to the vascular dysfunction widely reported in human depression?

It is well known that psychological stress and depression are associated with cardiovascular disease (1, 4–6). However, the relationship between stress and/or depression and cardiovascular disease defies easy analysis because there is also good evidence that the presence of cardiovascular disease itself can lead to depression (4). These complex relationships raise three possibilities: 1) depression is a risk factor for cardiovascular disease; 2) cardiovascular disease is a risk factor for depression; or 3) a common underlying pathology related to the effects of chronic stress manifests itself both as depression and as cardiovascular disease, leading to the familiar association between these conditions (4). Superimposed on these complex relationships are potential genetic risk factors and a wide array of societal stressors, including socioeconomic status, employment situations, and interpersonal relationships that can lead to physiological changes favoring the development of vascular dysfunction (1, 5).

Psychological stress can contribute to a number of pathological changes in the vasculature, including intimal-medial thickening (12) and atherosclerotic changes in the blood vessels (1, 11, 12). Controlled mental stress tests have been widely used to identify vascular dysfunction and to gain insight into the factors leading to the development of vascular diseases such as hypertension and atherosclerosis in humans. These approaches have shown that even a brief exposure to mental stress can lead to a fairly sustained reduction in endothelium-dependent vasodilation in humans (3, 7, 9). In women, intimal-medial thickening and subclinical atherosclerosis have been reported to have a significant association with indexes of hopelessness, independent of other factors such as age, race, income, depressive symptoms, and known risk factors for cardiovascular disease (12). Other studies have shown that indicators of endothelial dysfunction are present and associated with anxiety and depression in patients with posttraumatic stress disorder (11) and in cynomolgus monkeys (Macaca fascicularis) subjected to social stress (10, 13).

Studies in monkeys indicate that deficits in endothelial function are closely related to recent stress exposure and do not persist after stressful conditions have been removed (13). Other reports suggest that yoga and meditation to relieve stress lead to improved endothelial function in patients with coronary artery disease (8). Overall, these findings and others indicate that stress and depression can have a dramatic negative impact on vascular function, but vascular dysfunction in these conditions is amenable to therapeutic approaches that reduce stress and depression.

Despite the extensive evidence linking stress and depression with impaired cardiovascular function, the underlying mechanisms for the association between stress, depression, and cardiovascular disease are difficult to decipher. The potential physiological links between stress, depression, and cardiovascular disease are multiple and extremely complex. These include the sympathetic nervous system (1, 5, 10), neuropeptides (1), inflammatory cytokines (1, 5, 11), endothelin-1 (9), oxidant stress and free radical formation (1, 5), humoral factors, (1, 5, 6, 11), elevated homocysteine (1), and dyslipidemia (1), all of which can potentially contribute to altered vascular function, especially reduced endothelium-dependent vasodilatation, which is an important predictor of adverse cardiovascular events in humans.

A major strength of the study by d’Audiffret and coworkers (2) is its novelty, because two disciplines (behavioral sciences and cardiovascular research) team up to evaluate vascular alterations in an established rodent model of stress and depression. The investigators perform a comprehensive evaluation of multiple parameters of vascular function and couple these measurements with an extensive quantitative documentation of depressive behavior in the animals following the stress protocol. Consistent with studies of psychological stress and depression in humans (3, 7, 9), the investigators demonstrate that endothelium-dependent vasodilatation is compromised in aortas of mice subjected to UCMS. The authors also demonstrate that methacholine leads to a large increase in NO release with little H2O2 release in aortas of control mice while the same agonist causes a substantial H2O2 release coupled with a severely reduced NO release in aortas of UCMS mice. Consistent with these observations, L-NAME nearly abolishes methacholine-induced dilation in arteries of control mice.

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while catalase (but not L-NAME) causes a significant inhibition of methacholine-induced dilation in arteries of UCMS mice.

In this study (2), the authors use regression analysis to assess the value of a wide variety of established indicators in predicting vascular dysfunction in the UCMS mice. In their experiments, plasma levels of TNF-α, insulin concentration, and plasma nitrotyrosine levels were well correlated with vascular reactivity in the control mice while other indicators (IL-1β, C-reactive protein, and arterial pressure) were less predictive. Surprisingly, none of the risk factors were strongly predictive of vascular outcomes in the UCMS mice when they were analyzed across the board. Only when the vascular outcomes were divided into tertiles did any of the indicators predict the degree of vascular dysfunction. Specifically, moderate reductions in vascular reactivity to methacholine were predicted when the stress protocol resulted in an elevation of arterial blood pressure alone, and the most severe vascular dysfunction occurred when the stress protocol resulted in a more insulin-resistant hypertensive state.

One intriguing finding of the study is that the same stress protocol led to substantial differences in the degree of vascular dysfunction and in potential indicators of vascular dysfunction in an inbred mouse strain previously shown to be highly susceptible to stress. This occurred even though the mice are genetically homogeneous, in contrast to human populations with their widely diverse genetic background. The authors conclude that common parameters such as inflammation, hypertension, and insulin resistance are not robust predictors of stress-induced vascular dysfunction, and other unidentified mechanisms likely contribute to vascular dysfunction in animals subjected to UCMS. That conclusion is entirely consistent with the complexity of the physiological changes occurring with stress and depression and emphasizes the need for further studies to gain an improved understanding of the mechanisms of vascular dysfunction with stress and depression. The findings of the study suggest that physiological genomic approaches, analysis of gene expression utilizing microarray technology, and pathway analysis using bioinformatic approaches may prove valuable in elucidating the mechanisms of stress-induced vascular changes. In the end, the novelty of the present study by d’Audiffret and coworkers (2) also highlights the complexity of the problem.

REFERENCES