Connecting the dots—Establishing causality between chronic stress, depression, and cardiovascular disease

Lola DiVincenzo, Megan Reber, Vidushani Perera, and William M. Chilian

Department of Integrative Medical Sciences, Northeast Ohio Medical University, Rootstown, Ohio

IN THIS ISSUE, Stanley et al. (16a) reported sex differences of unpredictable chronic mild stress (UCMS) on vascular function. They found that BALB/cJ mice subjected to UCMS [reported to induce depression in rodents (9, 10)] demonstrate impairment in endothelium-dependent dilation and that the symptoms of stress/depression were more severe in females than males but that endothelium-dependent dilation to acetylcholine or methacholine was more impaired in males. As to the mechanisms underlying endothelial dysfunction, production of thromboxane A2 was elevated and that of prostacyclin was decreased, which was interpreted as due to scavenging by elevated levels of reactive oxygen species. The authors also associated the blunted endothelium-dependent dilation with the cytokines, tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1). They found that BALB/cJ mice subjected to UCMS unpredictably chronic mild stress (UCMS) on vascular function. Although endothelial dysfunction is not vascular disease, it is the first step in a sequence of pathological developments that can evolve to vascular disease. Importantly, the endothelial dysfunction reported by the authors was not the result of hypertension, because hypertension was not found. Rather it was through unpredictable chronic mild stress itself. This is noteworthy, because if the animals had developed hypertension, endothelial dysfunction would have been expected (14, 16).

What is known about the mechanisms by which stress and depression impact cardiovascular disease? The answer is simple: little! The literature even has evidence supporting the hypothesis that vascular dysfunction can lead to depression and cognitive deficits (1, 2, 5) in addition to depression causing the vascular pathology. A literature analysis concluded that the relationship between vascular disease and depression cannot be explained by current established risk factors and that factors such as endothelial dysfunction and cytokines must be considered (17). Along this line, a recent report suggests that endothelial dysfunction in UCMS is due to the production of TNF-α, because the dysfunction was rescued by administration of the TNF neutralizing antibody infliximab (7). The study of Stanley et al. not only corroborates this particular finding but extends the observation to include a potential role of monocyte chemoattractant protein-1 (MCP-1), reactive oxygen species, thromboxane A2, and decreased production of prostacyclin. However, there remain many gaps in our knowledge. For example, what is the mechanism for increased expression/production of TNFα? Are inflammatory cells involved and if so how are they activated? And, what is the role of MCP-1 in this process? Typically MCP-1 attracts monocytes to areas of injury, but in this case, where is the injury and what tissue(s) is (are) expressing the cytokine? Obviously there are many gaps in our understanding of the links between stress and depression to cardiovascular disease. The contribution by Stanley et al. helps in understanding the connections.

What is the basis for the difference in sex, and does this apply in humans? One of the provocative observations in the study by Stanley et al. was the sex-related difference in response to UCMS: females demonstrated a greater response to UCMS than males in terms of coat status, anhedonia, delayed grooming, cortisol levels, and oxidative stress (nitrotyrosine), but males had a larger deficit in endothelial function. The mechanisms underlying this difference remain unresolved. First, this effect was likely mediated via an effect on or by the endothelium. Supporting these observations that contraction and relaxation of arteries to agonists acting directly on smooth muscle (phenylephrine and nitroprusside) were virtually equivalent among the different groups. Females also produced more NO and prostacyclin and less thromboxane A2 than males. However, it is worth noting that constriction of arterioles to phenylephrine was augmented in male mice (compared with females) subjected to UCMS, so there may be a smooth muscle component, although this effect seems small. Interestingly, the authors also observed that TNFα and MCP-1 concentrations were higher in females than males subjected to UCMS, yet endothelial dysfunction was, as mentioned, greater in males. This provocative observation was not further interrogated, suggesting where further research is needed. Perhaps such a response to stress also provides insight into many of the sex-related differences in the occurrence of depression, in which there is a higher incidence in women than men (15), and even in premenopausal women (4), who are at lower risk for heart and vascular disease than men. An interesting clinical correlate is provided by Hamano et al. (12), in which the effects of depression were more strongly correlated with stroke in men than women. Is this the human clinical counterpart of Stanley et al.—that a more depressed, stressed female mouse would have better endothelial function than a male depressed mouse? Of course this question has not been answered, but it appears that the authors’ model and study may have parallels to the human condition.
Another interesting implication of the results of Stanley et al. was that the female rats were studied at random in their estrous cycle. This would mean that levels of hormones associated with the estrous cycle, e.g., estrogen, would vary considerably in the female rats being subjected to UCMS. Our interpretation of this observation is that the preservation of vascular function during UCMS is more related to sex than to a particular hormonal change associated with the estrous cycle.

*Are there limitations to the present study?* No study is without limitations, and it is important to provide some perspective in this context. Does the unpredictable chronic mild stress protocol in mice mimic any condition in depressed, stressed humans? This question remains unanswered, but we should emphasize that the UCMS protocol used by Stanley [and also by other groups engaged in behavioral studies (9, 10)] is a *model!* Although some may argue that this model does not mimic the human condition (what does delayed grooming equate to in the human condition?), it does produce observable stress and depression in mice such as changes in cortisol and cytokines—inindispensible changes consistent with chronic stress and depression. Although Stanley et al. did not study depressive behavior in the UCMS model, other laboratories have found many symptoms also consistent with depression such as avoidance of sugar water (10). There are other limitations such as measurements of ROS were not made, correlations do not prove causality, and a drug such a fluoxetine (Prozac) to potentially minimize the effects of the UCMS was not used to attempt rescue of vascular dysfunction. These limitations should not be construed as detracting from the message of the paper; rather, they are the type of limitations indicating further work needs to be done to establish potential causality and connect the dots! We also opine that these dots need to be connected—in this underresearched area—by first examining the basic biology to elucidate the mechanistic basis by which sex affects cardiovascular responses to stress and depression. We commend the authors on a provocative and important study.

**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

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**REFERENCES**