Cardiovascular Responses to Stress and Disease Outcomes

A Test of the Reactivity Hypothesis

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The idea that stress can contribute to disease has been a part of the lore of medicine since the ancient Greeks. In the field of psychosomatic medicine, Alexander argued that emotional dispositions could lead to persistent bodily response biases that could contribute to organic disease. In hypertension research, Hines and Brown proposed that an increased risk for hypertension could be revealed by an exaggerated blood pressure response to the stress of immersing a hand or foot in ice water (the cold pressor test). These proposals contributed to the more recent “stress reactivity hypothesis” that a highly reactive psychological disposition or physiological constitution could increase risk for disease. Despite the intuitive appeal of this idea, proof of a reactivity connection to cardiovascular disease has been very difficult to produce.

Barriers to such proof include the gradual development of hypertension and heart disease, resulting in the need for long follow-up periods on large numbers of persons; the presence of confounding variables, such as higher rates of smoking in persons experiencing stress in life; and the lack of standardized psychological stress paradigms analogous to the exercise protocols used in cardiology. Additional difficulty arises from uncertainty over the stability of emotional and stress responses in a given individual. Not surprisingly, these obstacles all tend to work against finding effects of stress reactivity on disease, and they result in variability in results across studies.

In this issue of Hypertension, Chida and Steptoe have published an outstanding meta-analysis of studies on cardiovascular reactivity and its impact on clinical outcomes. The results are drawn from 31 separate cohorts composed of 169 associations between a reactivity score and future outcomes, such as elevated blood pressure. The overall analysis resulted in an association of $r = 0.091$. Most consistent was the set of relationships predicting future elevated blood pressure or outright hypertension ($r = 0.101$). These $r$ values indicate that, in general, reactivity tendencies account for $\approx 1\%$ of the variance in outcomes and, therefore, represent very small effect sizes.

Using hypertension as an outcome, the authors report that persons with higher reactivity scores would have a $23\%$ increase in risk of hypertension, and most would agree that a 20-mm Hg blood pressure difference was clinically meaningful.

Although these relationships are statistically significant, the strength of association is low. However, the assembled tests of association presented in the Table of the article by Chida and Steptoe suggest that useful inferences can be drawn about the information contained in reactivity analyses. Before we can conclude that the association is of no consequence for disease outcomes, we might ask how this strength of association compares with associations between standard risk factors and outcomes in cardiovascular disease epidemiology. In the Framingham Study, after a follow-up of 34 years, an increase of 20 mm Hg in resting systolic blood pressure was associated with a $25\%$ increase in carotid stenosis, with an odds ratio of 2.11 in men and 1.98 in women. This $25\%$ increase in clinical outcome compares favorably with the $23\%$ increase in future hypertension reported in the article by Chida and Steptoe.

In considering the predictive value of cardiovascular reactivity measures, the Table in the article by Chida and Steptoe provides the specific effect size estimates for all 169 of the associations included in the meta-analysis. We note that the 2 largest effect sizes came from studies using blood pressure responses as predictors of myocardial infarction and stroke. Manuck et al. reported an effect size of 0.85 between systolic blood pressure reactivity and myocardial infarction and stroke over 3.3 to 3.5 years of follow-up in persons with previous myocardial infarction. Similarly, diastolic blood pressure responses to stress predicted myocardial infarction over a 14-year follow-up in hypertensive patients with an effect size of 0.89. Certainly, under some circumstances high levels of reactivity can be strongly predictive of future outcomes. However, it may be significant that, in these 2 studies with the largest effect sizes, the patients already had known coronary artery disease.

This leads to the question of the relationship between high levels of reactivity and disease pathophysiology. Does a high level of reactivity cause disease in an otherwise healthy or low-risk individual, or does a high level of reactivity reflect underlying disease pathophysiology? Because the largest effect sizes in the meta-analysis were found in studies of patients with existing cardiac disease, the data suggest that high reactivity may have a greater impact on disease progression than on its initiation. This view is complimentary with our own work in which the largest blood pressure reactivity scores occurred in persons with 2 risk factors, a family history hypertension and modestly elevated resting pressures (systolic blood pressure: $\approx 125$ mm Hg), indicative of a preclinical tendency toward elevated blood pressure.

The analysis by Chida and Steptoe provides the strongest support for the reactivity hypothesis to date. This information is...
of use to persons doing basic research on the etiology and pathophysiology of hypertension. However, the clinical applicability of these findings is circumscribed by 3 considerations. First, reactivity scores were relatively good predictors of outcomes in men but not in women. Second, the range of associations across studies was rather wide, suggesting that the predictive value varies across specific subgroups and individuals, making it more difficult to use reactivity scores in clinical decisions. Third, an essential element in the reactivity hypothesis is that reactivity reflects stable individual differences, either psychological or physiological. To the extent that reactivity is an ingrained tendency, the range of possible prevention strategies available to the health community is limited. Reducing salt intake is a difficult but manageable behavioral intervention. Teaching patients to be less reactive to stress may prove more challenging. Those considerations notwithstanding, the data assembled by Chida and Steptoe support the idea that persons who are highly reactive to stress are at higher risk of poorer cardiovascular outcomes, including hypertension.

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None.

**References**

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