Blood Pressure Reactivity to Psychological Stress
A New Risk Factor for Coronary Disease?

Redford B. Williams

The report by Matthews et al in this issue of Hypertension that increased systolic blood pressure reactivity while playing a video game predicts increased incidence of having some coronary calcification 13 years later is consistent with prior research they cite showing associations between cardiovascular reactivity to acute stress and various indices of atherosclerotic disease in human and animal studies. What sets this report apart from the prior research, however, is (1) the prediction of increased coronary artery calcification by blood pressure (BP) reactivity in a large, diverse sample of healthy young adults; (2) the demonstration that this prediction is independent of resting blood pressure and other established coronary heart disease (CHD) risk factors measured at the same time; and (3) the demonstration that the prediction is not mediated by interim development of hypertension or the metabolic syndrome.

The authors are appropriately cautious in noting that final appraisal of the full implications of their findings will depend on results obtained when “BP reactivity protocols are added to future epidemiological protocols.” As one who has previously joined with other behavioral and social science advocates in what seemed, in many cases, to be an uphill battle to convince those in charge of designing large-scale prospective epidemiological studies of CHD risk factors (including the Coronary Artery Risk Development In young Adults [CARDIA] study) to include assessment of cardiovascular reactivity (CVR) to psychological stress, I cannot suppress a strong “I told you so!” on encountering these findings by Matthews et al. Yes, let us see what further evidence shows before we conclude that CVR to psychological stress is truly involved in the pathogenesis of coronary atherosclerosis, but let us take the evidence now in hand, thanks to inclusion of the reactivity protocol in CARDIA, and use it as a basis for design of future epidemiological studies.

There are several biologically plausible mechanisms whereby CVR to acute psychological stress could contribute to the development of the atherosclerotic lesions. Endothelial injury has been identified as one of the initial steps in atherogenesis, and blood pressure surges occurring in the injury has been identified as one of the initial steps in atherogenesis.2 and blood pressure surges occurring in the setting of acute psychological stress could contribute, via increased flow turbulence at arterial branch points, to endothelial damage. One consequence of such endothelial injury is the release of inflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF) or that then stimulate (eg, via hepatic release of CRP) an inflammatory cascade that plays a critical role in atherogenesis. Evidence that CVR to psychological stress contributes to endothelial injury and subsequent cytokine release comes from research showing that persons with increased CVR to acute mental stress show larger increases in circulating IL-6 and TNFα following the same stressor.3 Increased CVR to mental stress is also associated with increased insulin resistance4 and lipid levels5 in healthy young men. Even though Matthews et al found no evidence for mediation of effects of CVR on coronary calcification by metabolic syndrome, it is possible that the combined effects of CVR on both metabolic syndrome and increased levels of inflammatory cytokines will be shown in subsequent, larger-scale epidemiological studies to account for a CVR effect on atherogenesis.

Increased CVR to psychological stress has been reported in persons who carry the long allele of a functional promoter polymorphism of the serotonin transporter gene (5HTTLPR). The 5HTTLPR long allele was also associated with increased risk of myocardial infarction in 2 case-control studies, suggesting that it will be possible to identify variation in candidate genes that underlies the tendency of some individuals to express increased CVR to stress and the consequent increased risk of developing CHD. It will be important, therefore, in the future epidemiological studies that include the BP reactivity protocols that Matthews et al call for, to also include collection of DNA, so that the genetic variants that predispose to increased CVR to psychological stress can be identified. Much work remains to be done before such assessments can be incorporated into risk factor batteries, but if successful this work will lead to a time when instead of having to argue for inclusion of BP reactivity protocols, it will be possible to specify a panel of polymorphisms in candidate genes that will enable us to identify with even greater precision those who are risk of developing CHD because of increased CVR to psychological stress.

The ultimate application of such knowledge will be, of course, to identify persons who will benefit from interventions that target increased CVR to psychological stress with the goal of reducing incidence of CHD and other medical problems (eg, type 2 diabetes, given the association between CVR and insulin resistance) associated with increased CVR to stress. Such interventions could be either pharmacological, behavioral, or both. Matthews et al cite a study that found treatment with the β-blocker propranolol—which would be expected to reduce CVR reactivity to stress—inhibited the development of coronary atherosclerosis in behaviorally stressed monkeys fed an atherogenic diet.9 In a randomized
trial of psychosocial skills training in patients following coronary artery bypass graft surgery, Bishop et al.\textsuperscript{10} found that the training resulted in reduced levels not only of psychosocial factors like anger and depression but also of systolic BP and heart rate, both at rest and in reaction to an anger recall task.

Results from intervention studies like these combine with the findings from the current Matthews et al.\textsuperscript{1} study to make the case for evaluating CVR to stress in future epidemiological studies even stronger, not only to understand better the mechanisms that put some people at increased risk for developing CHD, but because when we are able to identify them with some accuracy (perhaps using genetic profiling), there will be means available to reduce CVR to stress.

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**References**


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