A New Mechanism Linking Stress to Coronary Pathophysiology?

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The report by Williams et al1 in this issue of Circulation joins a long list of studies exploring the relation between stress and coronary artery pathophysiology. It is interesting to reflect on the different threads of research underlying this complex tapestry.

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For generations, physicians have been struck by the powerful impact of stressors on the heart. Who has not seen cases of angina, myocardial infarction, arrhythmia, or sudden death in settings of emotional travail? Such phenomena are difficult to study, and it is so easy to find stress post hoc. After all, most of us could relate numerous significant stressors per week (and perhaps per day). How often or under what circumstances do stressors relate to cardiac disease?

Investigators are still grappling with this problem of defining stress consistently. In the 1960s and 1970s, research flourished, generating a glossary of life events that could be reliably rated (for a recent review, see Reference 2). Unfortunately, it may be inadequate to define stress without considering the subjective impact, for “...there is nothing either good or bad, but thinking makes it so.”3 Sometimes even the most stark stressors affect people differently; loss of a spouse may be an occasion for one person’s bereavement and another’s relief. Because of this, in evaluating stressfulness, investigators are increasingly considering both the stressful event and the subjective assessment of the patient.4

Aside from these basic issues in defining stressors, it is important to recognize that there are substantial differences in host vulnerabilities to stressors. Activation of the sympathetic nervous system may produce little more than an increase in heart rate, blood pressure, and free fatty acids in normal subjects; whereas, in those with serious coronary atherosclerosis, it can precipitate angina, cardiac arrhythmia, or pulmonary edema.5–10 Certain psychosocial factors such as social isolation,11 personality,12 and possibly depression13,14 may also increase cardiac vulnerability to stress.

Given the complexity of assessing such host vulnerabilities, investigators have turned increasingly to experiments that deliberately impose a stressor so that they can scrutinize the physiological consequences. Animal studies are highly valued because they lend themselves to tight experimental control of confounders such as diet and genetic background. In addition, such animal studies allow direct inspection of the coronary arteries. Human studies, on the other hand, typically are limited to examining heart rate and blood pressure reactivity to stressors imposed in the laboratory and, occasionally, in the field.15

Early studies in lipid physiology devoted considerable attention to the effects of sympathetic nervous system activation on lipid physiology and atherosclerosis. The first volume of Journal Lipid Research, for instance, includes classic articles on this topic.16,17 The field then bifurcated, with researchers interested in psychosomatic medicine publishing extensively on the effects of stressors on free fatty acid and cholesterol levels in humans18; lipid physiologists, on the other hand, focused attention on diet, genetics, and the complexities of lipoprotein physiology. Only recently have these two streams of research begun to reconverge.

The Williams study1 offers several unique perspectives on this important, complex research field. 1) By studying cynomolgus macaques, Williams et al used an animal model that has much in common with human lipoprotein physiology.19,20) Building on careful psychobiological studies of stress, Williams et al studied the effect of repeated chronic social disruption. 3) Instead of examining the effects of a single massive stressful event, the investigators used a model of continuous social disruption (akin to working in a university with rapid changes in deans, departmental chairmen, and hospital administrators).

The Williams study did not emphasize changes in fixed coronary artery disease. Instead, it focused on dynamic physiology: the ability of the coronary artery to vasodilate in response to the muscarinic agonist acetylcholine. The coronary arteries of monkeys housed in stable living groups and consuming low cholesterol diets dilated in response to acetylcholine.
The coronary arteries of monkeys housed in unstable social groups vasoconstricted with acetylcholine whether the diet was high or low in cholesterol (i.e., dietary cholesterol explained less vasoemotion than did social stability; see Figure 1 in the Williams article).

Where does this leave us? Recent studies of coronary vasoemotion have taught us that the coronary arteries are in constant motion, dilating and constringing to stimuli that we are only beginning to understand. Kaplan et al previously reported that chronic social disruption led to increased heart rate and atherosclerosis in these macaques.21 With the article in this issue of Circulation, they demonstrate that such disruption also alters vasoemotion in response to neurotransmitter stimulation. They found that a social manipulation was enough to reverse the coronary artery dilation in response to the common neurotransmitter acetylcholine. Even a prudent low-cholesterol diet did not shield the coronary artery from the effect of this social disruption. The physiological mechanism for the effect of social disruption remains a black box, an enticing puzzle for other investigators. Future research might also examine the dosing of the stressor imposition (e.g., intensity and duration) as well as the generalizability to other species. This study is an interesting thread that contributes to our understanding of the complex physiological links weaving together psychosocial factors and coronary pathophysiology.

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References

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