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Traumatic Stress Is Heartbreaking

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There is growing recognition that the consequences of posttraumatic stress disorder (PTSD) on health may reach far beyond the neuropsychiatric sphere. For many years, studies have documented numerous physical health problems in PTSD (1), and a possible connection between PTSD and risk of coronary heart disease (CHD) has received special attention.

Despite this growing interest, evidence of a link between PTSD and CHD has remained elusive, mainly because of weaknesses in the existing literature. Until recently, much of the research in the area of PTSD and CHD has been hindered by methodologic limitations, including the use of cross-sectional designs, assessments of cardiac symptoms or diagnoses based on self-reports, or unvalidated administrative data. Research reports have often failed to adjust for potential confounding factors, such as smoking, drug and alcohol abuse, and depression.

Cross-sectional designs based on self-report are especially problematic in this context because of potential recall bias and possible reverse causation, with inability to demonstrate a temporal relationship between PTSD and CHD. For instance, PTSD patients tend to report a wide range of symptoms and medical conditions related to almost all body systems, in addition to symptoms of CHD (1). The implications for reverse causation are that PTSD can be a consequence, in addition to a cause, of a heart attack (2). Although recent longitudinal studies have lent support to a relationship between PTSD and CHD (3–5), most have examined PTSD symptoms in communities with a low prevalence of PTSD and usually relied on clinical events or causes of death that were often not clinically confirmed.

It is only recently that data are beginning to emerge on a link between a PTSD diagnosis and CHD using more objective measures of CHD. These measures have included coronary artery calcium scores as markers for plaque burden (6), accurate measurement of the incidence of clinical CHD events, and myocardial perfusion imaging data (7). These studies have typically found substantial elevations of risk of CHD in persons with PTSD, approximately a twofold increase. For example, in a study of Vietnam-era twins, we found that twins with PTSD were twice as likely to undergo hospitalizations or revascularization procedures for CHD over a median follow-up of 13 years compared with twins without

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PTSD, even after adjusting for traditional CHD risk factors, health behaviors, depression, and other psychiatric diagnoses (7). The increased risk of CHD events was confirmed by quantitative measures of coronary perfusion and myocardial blood flow assessed with positron emission tomography. The results showed that twins with PTSD had almost twice as much compromised coronary perfusion than those without PTSD. These differences were only modestly reduced when comparing twins discordant for PTSD, who are naturally matched for sociodemographic factors, early environment and, for the monozygotic twins, also for genetic factors. These withinpair results lent further validity to the association of PTSD with CHD.

The study by Turner *et al.*, in this issue of *Biological Psychiatry* (8), confirms these previous findings in a sample of patients from outpatient clinics of two Veteran Affairs Medical Centers. In this study, ischemia was assessed by exercise electrocardiography (ECG). Exercise ECG testing is considered less accurate for the assessment of ischemia than stress testing in conjunction with myocardial perfusion imaging, especially because of low specificity and because ST-segment changes during treadmill ECG testing are weak markers of prevalent or incident ischemic heart disease (9). Despite these limitations, the results are impressively similar to the twin study mentioned earlier, showing about twice the prevalence of ischemia in patients with PTSD compared with those without the disease. Non-ECG measures of exercise treadmill testing—in particular, exercise capacity—have emerged as stronger predictors of cardiovascular risk than ECG measures (9). It is unfortunate that exercise capacity data from the treadmill tests were not presented in this article because they would have been useful complementary information.

As in previous studies (6), the report by Turner *et al.* is based on a clinical sample from Veteran Affairs outpatient clinics. There is a potential for selection bias when study participants are identified through medical encounters because patients with PTSD may differ in their likelihood to undergo, or be referred for, medical evaluation or treatments compared with those without PTSD. That this might be true is suggested by the fact that, in this study, patients with and without PTSD did not vary in smoking behavior or socioeconomic factors, which is surprising and inconsistent with previous studies. Thus, the need remains for more studies based on community samples or other nonselected populations.

Despite these issues, the study by Turner *et al.* provides welcome new evidence of a link between PTSD and CHD. The mechanisms behind this relationship, however, still need to be understood. Clearly, maladaptive behaviors, such as smoking and substance abuse, which are almost invariably more common in persons with PTSD, may be implicated. Lower propensity to seek medical care and poor functioning could translate to reduced self-care or reduced access to health care. In addition to behavioral and lifestyle factors, however, it has long been suggested that neurobiological features characteristic of PTSD could have potential damaging effects on the cardiovascular system (Figure 1).

PTSD is characterized by chronic dysregulation of neurohormonal systems involved in the stress response. Dysregulation of the hypothalamic-pituitary-adrenal axis in PTSD is evidenced by increased corticotrophin releasing factor levels and decreased peripheral

cortisol concentrations at rest, in addition to increased cortisol release with psychological stressors, particularly reminders of the trauma. In addition, there is increased activation of the sympathetic nervous system during psychological stressors, again particularly with trauma-reminiscent events (10). Indeed, combat veterans with PTSD, compared with control subjects, exhibit an increase in heart rate and other physiologic parameters in response to auditory reminders of trauma (such as tapes of the sound of gunfire), combat slides, or scripts of the individual's traumatic experiences. They also evidence an increase in heart rate, blood pressure, and PTSD symptoms with pharmacologic stimulation of the noradrenergic system, as well as altered brain function (decreased frontal lobe function) compared with subjects without PTSD (10). No similar responses are observed in conjunction with neutral stressors such as mental arithmetic.

Hemodynamic and neuroendocrine hyperreactivity during psychological stress have been linked to future adverse cardiovascular health status. However, the specific mechanisms for such effects are not clear. A commonly endorsed risk pathway is chronic disruption of neuroendocrine and immune function systems involved in physiologic homeostasis, leading to repeated and eventually sustained elevations in blood pressure, heart rate, plasma glucose, insulin resistance, and dyslipidemia. However, it seems unlikely that these risk factors entirely account for the relationship between PTSD and CHD risk because when they were adjusted for statistically in previous studies, the relationship remained. In addition, although some studies found an association between PTSD and these metabolic risk factors, many others did not. In our twin study, PTSD was unrelated to metabolic risk factors measured at follow-up, such as glucose levels, blood pressure, dyslipidemia, and obesity (7). Thus, pathways other than traditional cardiovascular risk factors must be involved in the relationship between PTSD and CHD.

Elevated catecholamine response to trauma-reminiscent cues may have direct effects on the myocardium, the vascular endothelium, plaque stability, inflammation, and platelet function, which could affect cardiovascular risk independent of traditional risk factors and even independent of coronary plaque burden. For example, catecholamine-induced peripheral vasoconstriction during psychologic stress may increase cardiac afterload, which could predispose to myocardial ischemia. In addition, neuroendocrine and hemodynamic hyperreactivity could have long-term effects on vessel function, including coronary microvascular function, an established early marker of ischemic heart disease. Repeated sympathetic system responses to trauma reminders could also affect myocardial electrical stability and the risk for cardiac arrhythmias, as suggested by the observation that heart rate variability and baroreflex function, important risk factors for cardiac events, arrhythmias and mortality, are reduced in subjects with PTSD. Finally, epigenetic processes are emerging as a potential connection between psychosocial stress, psychiatric disorders including PTSD, and cardiovascular disease, and provide a biological mechanism through which environmental exposures, such as psychological trauma, can modulate gene expression.

Much has been learned about the connection between PTSD and CHD, but much more needs to be discovered, particularly in relation to underlying mechanisms. Furthermore, more needs to be learned about PTSD-related factors that may modulate CHD risk. These include, for example, the time course of PTSD (i.e., age of onset, duration, treatment

response, and remission); the type and severity of PTSD symptoms; the role of psychiatric comorbidity, such as depression and substance abuse; the type of trauma and developmental epoch in which it occurs; the potential effects of treatment drugs, such as antipsychotics; and the role of buffering factors such as social connections and emotional support. These data would provide important information related to vulnerability or resilience toward CHD risk in persons with PTSD. In addition to being a debilitating and prevalent psychiatric condition, PTSD represents a useful model for how psychological stress can get “under the skin,” and thus the implications of this research will be broad.

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Figure 1.

Schematic representation of potential mechanisms linking posttraumatic stress disorder to coronary heart disease. HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system.