Posttraumatic Stress Disorder and Risk of Cardiovascular Disease

Viola Vaccarino and J. Douglas Bremner

Contents

Abstract

PTSD is a disabling mental disorder with health consequences that reach far beyond the neuropsychiatric domain. Growing evidence links PTSD to increased risk of cardiovascular conditions including ischemic heart disease and

V. Vaccarino (✉)
Department of Epidemiology, Rollins School of Public Health, Department of Medicine, School of Medicine, Emory University, Atlanta, GA, USA
e-mail: viola.vaccarino@emory.edu

J.D. Bremner
Emory University School of Medicine, Atlanta, GA, USA

Mental Health Research, Atlanta VAMC, Decatur, GA, USA

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
e-mail: jdbremn@emory.edu

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thromboembolic stroke. Emerging data also suggest that PTSD may be a consequence, in addition to a cause, of acute, life-threatening cardiovascular events. Individuals with PTSD are more likely to engage in adverse lifestyle behaviors, which may predispose to cardiovascular risk factors such as obesity, diabetes, and hypertension. PTSD is also frequently comorbid with other psychiatric conditions which may affect cardiovascular risk, such as depression and substance abuse. However, additional plausible mechanisms exist that go beyond these associated conditions and risk factors. An emerging model of cardiovascular risk in PTSD is that neurobiology plays a role. Specifically, mechanisms such as repeated and heightened physiological activation in association with intrusive memories in PTSD could lead to cumulative long-term damaging effects on the cardiovascular system. This could be mediated through vascular, immune, or other mechanisms. This chapter will review the existing evidence linking PTSD to major cardiovascular disorders, discuss potential underlying pathophysiology, and provide suggestions for future research.

Keywords

Posttraumatic stress disorder • Cardiovascular disease • Stress • Myocardial ischemia • Stroke • Acute coronary syndromes

Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disorder characterized by a persistent maladaptive reaction to a traumatic event (Dohrenwend et al. 2006). It is a common condition, occurring in about 10–12 % of women and 5–6 % of men in the general population (Kessler et al. 1994), and is especially prevalent in military personnel exposed to combat. Among veterans serving in Southeast Asia during the Vietnam War, 15–19 % have developed PTSD; the estimated prevalence of PTSD is even higher in service members from the recent Iraq and Afghanistan conflicts (Hoge et al. 2007). However, in absolute terms, combat trauma is not the most frequent cause of PTSD, since in the general population, noncombat trauma is much more common than combat trauma. In many patients the disorder continues to manifest many years after the initial trauma exposure (Dohrenwend et al. 2006).

PTSD has well-known devastating effects on the mental health and functioning of affected individuals; however, the health consequences of PTSD reach far beyond the neuropsychiatric domain (Glaesmer et al. 2011; Hoge et al. 2007; Qureshi et al. 2009). Particular attention has been given to a possible link between PTSD and major forms of cardiovascular disease (CVD), including ischemic heart disease (IHD) and thromboembolic stroke (Boscarino 2012; Coughlin 2011; Wentworth et al. 2013). It is well established that PTSD increases the risk for many adverse health behaviors, such as smoking, alcohol abuse, and sedentary lifestyle, which in turn predispose to chronic conditions such as obesity, diabetes, hypertension, and hyperlipidemia (Coughlin 2011). PTSD is also often comorbid with other psychiatric conditions that have been related to CVD, especially depression.

While these associated conditions and risk factors are likely to play a significant role in the observed link between PTSD and CVD, other plausible mechanisms exist, mostly related to the peculiar neurobiological features of this psychiatric disorder. There are also emerging data to suggest that PTSD may be a consequence, in addition to a cause, of acute coronary syndromes or acute stroke events, due to the intense stress associated with these life-threatening episodes (Edmondson et al. 2012, 2013).

Definition and Diagnosis of PTSD

A PTSD diagnosis requires, as a fundamental criterion, exposure to severe psychological stress or trauma. A traumatic event has been traditionally defined as a threat to one's life or self- integrity, accompanied by intense fear, horror, or helplessness. It may include, for example, rape, assault, motor vehicle accidents, or childhood abuse, in addition to combat trauma (Reed et al. 2012). More than half of Americans will experience a traumatic event at some time in their lives; for women the most common type of trauma is sexual abuse or assault, and for men it is physical assault (Reese et al. 2012). In about half of cases, PTSD becomes a chronic condition that can last for years. Persons with PTSD may suffer severe functional impairment, including difficulties with employment and relationships and increased rates of depression and substance abuse.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, which have been used in clinical practice and research for almost two decades, PTSD is characterized by three major symptom clusters, intrusions, avoidance, and hypervigilance, lasting for at least 1 month and resulting in significant impairment in work and/or social function. *Intrusion symptoms* include recurrent memories of the traumatic event that the patient cannot control or nightmares about the event. *Avoidance symptoms* include avoiding situations that would remind the person of the trauma and avoiding thinking of the trauma, for example, having trouble remembering an important aspect of the traumatic event, feeling detached or cutoff from others, or feeling emotionally numb. As part of their avoidance, PTSD patients might feel uncomfortable in crowds and may have trouble just getting out of the house. *Hypervigilance* symptoms include trouble falling or staying asleep, irritability, outbursts of anger, and difficulty concentrating. An increased startle response, for instance, being jumpy with loud noises, is another symptom of hypervigilance. In the recently released DSM-5, symptoms of PTSD have remained mostly the same, but the trauma definition no longer requires feelings of fear, helplessness, or horror in conjunction with the trauma (American Psychiatric Association 2013). In addition, new qualifying symptoms were added. These include a new criterion of *negative alterations in cognition and mood* which comprises many different symptoms, including new ones such as a persistent and distorted blame of self or others and a persistent negative emotional state. A new symptom of reckless or destructive behavior was also added as part of the hyperarousal symptom cluster. The DSM-5 has overall loosened the criteria for

PTSD, so that a much larger proportion of the population is expected to meet criteria for PTSD under the new definition.

PTSD and Incidence of Ischemic Heart Disease

In the past several decades, a wealth of studies have documented many physical health problems in PTSD, especially cardiac symptoms (Wentworth et al. 2012). However, until recently most of these studies have used a cross-sectional design, which has limited the ability to infer a temporal relationship between PTSD and cardiac conditions such as IHD (Qureshi et al. 2009; Vaccarino and Bremner 2013). Studies that have used self-report assessments of cardiac symptoms are especially problematic. There could be recall bias, and in fact PTSD patients tend to report more symptoms and medical problems in general, not just IHD, compared with persons without PTSD (Qureshi et al. 2009). There could be reverse causation, since PTSD can be a consequence, in addition to a cause, of a heart attack (Edmondson et al. 2012). Selection bias is also a potential problem, since many studies have relied on clinical samples of self-referred patients who may have a higher prevalence of medical problems compared with PTSD cases from the general population.

In the past 10 years, a number of longitudinal studies have been published linking PTSD symptoms or a PTSD diagnosis to IHD incidence (Boscarino 2006, 2008; Dirkzwager et al. 2007; Kang et al. 2006; Kubzansky et al. 2007, 2009; Scherrer et al. 2010). All these studies have shown significant associations, although many have lacked validated measures of IHD outcomes and have relied, in several instances, on death certificate codes or administrative records. More recent investigations that used objective measures of coronary atherosclerosis or myocardial ischemia, however, have confirmed these observations (Ahmadi et al. 2011; Turner et al. 2013; Vaccarino et al. 2013). These recent studies have found substantial evidence of increased coronary artery disease or myocardial perfusion abnormalities in individuals with PTSD compared to those without PTSD. Ahmadi et al. studied veterans who underwent clinically indicated computed tomography for evaluation of coronary artery calcification, a marker of coronary atherosclerosis, and found that PTSD patients had twice the odds of coronary artery calcification than those without PTSD (Ahmadi et al. 2011). In another veteran sample from the Veteran Health Administration outpatient clinics, Turner et al. found about twice the prevalence of myocardial ischemia assessed by exercise electrocardiography (ECG) in patients with PTSD than those without PTSD (Turner et al. 2013). These studies provide important new evidence for a link between PTSD and IHD, but a remaining concern is possible selection bias because they were based on clinical samples from medical encounters. Compared with persons without PTSD, those with PTSD may differ in their likelihood to seek care, or to be referred for, medical evaluation, or treatments for CVD, since they tend to report more symptoms and health problems in general (Qureshi et al. 2009). Thus, PTSD patients selected from hospitals or clinics may have an increased likelihood to be

diagnosed with IHD than it would be found in individuals with PTSD from the community or patients without PTSD.

A recent twin study of PTSD and IHD was able to address this concern since it was based on a registry of twins (Vaccarino et al. 2013). The study followed a sample of 562 military veteran twins from the Vietnam Era who did not report a previous history of IHD at baseline, when PTSD was measured with the Diagnostic Interview Schedule (Robins et al. 1981) and when the mean age of the twins was 43 years. After an average follow-up of 13 years, IHD was measured. Assessment included the occurrence of clinical events (myocardial infarction, other hospitalizations for IHD, and coronary revascularization) by self-report, in conjunction with objective measures of IHD using myocardial perfusion imaging with N-13 ammonia positron emission tomography (PET). Twins with PTSD were greater than twofold more likely to report hospitalizations or revascularization procedures for IHD over the follow-up compared with twins without PTSD (23 % vs. 9 %). The association was robust to adjustment for lifestyle factors, IHD risk factors, and even depression (adjusted odds ratio, 2.2, 95 % CI, 1.2–4.1). PET measures of coronary perfusion and myocardial blood flow supported the self-reported results. A quantitative measure of perfusion defects, the stress total severity score (STSS), was significantly higher (+95 %, $p = 0.001$) in twins with PTSD than those without, denoting almost twice as many myocardial perfusion abnormalities. PET-measured coronary flow reserve was also lower in twins with PTSD compared to those without PTSD ($-0.21, p = 0.02$), denoting worse coronary microvascular function. In addition, there was a graded association with increasing PTSD symptom quartiles for both IHD events and STSS. Associations were only mildly attenuated within 117 twin pairs discordant for PTSD, even after adjusting for traditional IHD risk factors, health behaviors, depression, and other psychiatric diagnoses. Figure 1 shows a representative twin pair discordant for PTSD. The co-twin design that compares brothers within twin pairs controls for unmeasured genetic and familial confounders that could be shared between PTSD and cardiovascular diseases and lends further support to a possible causal relationship between PTSD and IHD (McGue et al. 2010).

PTSD and Incidence of Stroke

In addition to IHD, there is also evidence that severe stress increases the risk of stroke even after many years from the original exposure (Thurston et al. 2014; Wilson et al. 2012), but data related specific to PTSD are limited. In a study of former World War II prisoners of war (POWs), those with PTSD had an almost twofold, albeit not statistically significant, increased risk of stroke, 13 % (20 of 158) vs. 8 % (24 of 317), relative risk = 1.7, and 95 % confidence interval 0.95–2.9 (Brass and Page 1996). The small number of stroke events and the similarity of exposures between POWs with and without PTSD are limitations of this study. This study did find a sevenfold difference in stroke between POW and non-POW veterans. In a cross-sectional survey of female veterans who received care at the

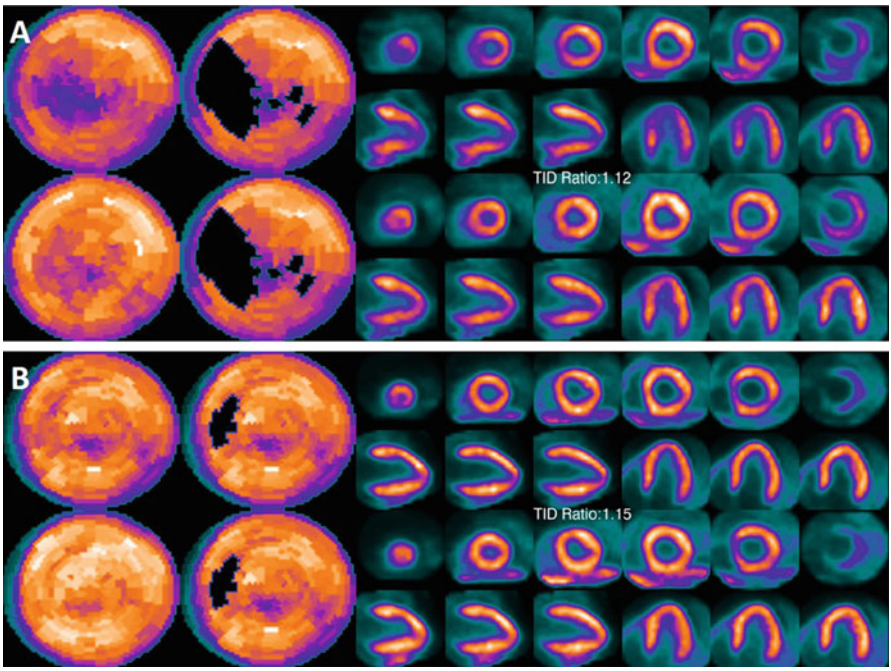

Fig. 1 Positron emission tomography myocardial perfusion scan in a representative twin pair. (**a**) Twin with PTSD. (**b**) Twin without PTSD. In the polar maps on the left, the extent of hypoperfusion is shown as *blackout*. The severity of hypoperfusion was quantified by a stress total severity score (*STSS*) that measured the total number of standard deviations below the mean for the entire extent of the abnormality compared to a normal database

VA Puget Sound Health Care System, there was an association between PTSD and self-reported history of stroke, although, again, the number of stroke events was small. Of the female veterans with PTSD, 5 % (13 of 256) reported a history of stroke as compared with 3 % (28 of 905) of those without PTSD (age-adjusted odds ratio = 2.9, 95 % confidence interval 1.4–6.0) (Dobie et al. 2004). A study of trauma and PTSD among 3,171 men and women from a German community sample found that those with a history of trauma or PTSD had higher odds of self-reported stroke, as well as of other cardiovascular diseases, compared with those without trauma, after adjusting for demographic factors, CVD risk factors, and lifestyle factors (Spitzer et al. 2009). Thus, although more data are needed, the overall evidence points to a possible increase in stroke risk associated with PTSD.

PTSD as a Consequence of Acute Cardiovascular Events

Some patients may develop PTSD as a consequence of acute, life-threatening cardiovascular events such as a heart attack or stroke. According to a recent meta-analysis, clinically significant PTSD symptoms occur on average in

approximately 12 % of patients hospitalized for acute coronary syndromes, or one in every eight patients, but there is substantial heterogeneity in various studies, with prevalence rates ranging from 0 % to 32 % (Edmondson et al. 2012). Although few studies assessed a psychiatric diagnosis of PTSD using a clinical interview, 4 % of the patients on average met full diagnostic criteria for the disorder. Younger patient age is associated with greater likelihood of developing PTSD following an acute cardiac event; in some studies, female sex, ethnic minority status, low socioeconomic status, and previous history of psychiatric disorders were related to the development of PTSD (Roberge et al. 2010; Wikman et al. 2008). Additionally, experiencing intense fear, lack of control or helplessness, and perceived life threat during the acute cardiac event have all been reported as predictors of PTSD. However, clinical severity of the cardiac event appears to be unrelated to PTSD.

PTSD secondary to acute coronary syndromes is associated with approximately doubled risk for recurrent cardiac events and mortality (Edmondson et al. 2012). No study to date has been sufficiently large to assess potential mechanisms for the relationship between PTSD induced by acute coronary syndromes and adverse clinical outcomes. However, since both acute coronary syndromes and PTSD are associated with noradrenergic activation and elevated proinflammatory cytokines (as discussed below), there could be synergistic adverse effects on inflammatory and procoagulant processes that may increase the risk of recurrent cardiac events or mortality.

PTSD may also be a consequence of acute cerebrovascular accidents such as stroke or transient ischemic attacks (TIA). In a recent meta-analysis, the prevalence of PTSD among stroke survivors was estimated at 23 % (95 % confidence interval, 16–33 %) within 1 year of the stroke or TIA and 11 % (95 % confidence interval, 8–14 %) after 1 year (Edmondson et al. 2013). Thus, stroke-induced PTSD is relatively common, with approximately one in four stroke patients experiencing PTSD in the first year after the event and one in nine experiencing chronic PTSD over a year later. It is currently unknown whether PTSD after stroke is associated with poorer survival.

PTSD is even more common among survivors of an out-of-hospital cardiac arrest, with a prevalence ranging from 27 % to 38 % (Gamper et al. 2004; Ladwig et al. 2008). In a study of patients with an implantable cardioverter defibrillator, a significant proportion of whom survived a cardiac arrest or a myocardial infarction, PTSD was associated with a threefold increased risk of subsequent mortality (Ladwig et al. 2008).

Potential Mechanisms

The mechanisms behind the relationship between PTSD and CVD incidence or recurrence are not entirely clear and are likely to be multifactorial. It is believed that acute CVD events are triggered by a confluence of several factors including biological, environmental, and emotional factors, like a “perfect storm” (Arbab-Zadeh et al. 2012). Maladaptive behaviors are likely to be important contributors,

such as smoking, substance abuse, sedentary lifestyle, medication nonadherence, and sleep disturbances, which are all prevalent in persons with PTSD (Breslau et al. 2003). In most studies, however, adjusting for these factors did not explain away the relationship between PTSD and CVD, suggesting that they are not sufficient mechanisms in themselves. Similarly, comorbidity of PTSD with other psychiatric disorders, such as depression, did not explain the association with CVD (Ahmadi et al. 2011; Kubzansky et al. 2009; Turner et al. 2013; Vaccarino et al. 2013).

Even the link between PTSD and traditional CVD risk factors such as hypertension, obesity, and diabetes is not entirely clear. Although several studies have described such associations, others have not (Ahmadi et al. 2011; Kubzansky et al. 2007, 2009; Vaccarino et al. 2013, 2014). Some reports have even found a paradoxically *lower* total cholesterol or LDL cholesterol level in persons with PTSD than those without PTSD (Ahmadi et al. 2011; Vaccarino et al. 2013). Furthermore, when these risk factors were adjusted for in the analysis, the relationship between PTSD and CVD usually persisted. Thus, pathways other than traditional CVD risk factors are likely to be involved in the link between PTSD and CVD.

A current conceptual model is that neurobiological features characteristic of PTSD could play a role in increasing the risk of CVD in this population. Specifically, heightened and repeated physiological activation with reexperiencing symptoms and intrusive memories in PTSD could result in cumulative long-term damaging cardiovascular effects through vascular and immune mechanisms (Fig. 2) (Vaccarino and Bremner 2013).

Neurobiology of PTSD

PTSD is characterized by chronic dysregulation of neurohormonal systems involved in the two main arms of the physiological stress response, namely, the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis (Bremner and Charney 2010; Yehuda 2002). Disturbances in the SNS and other aspects of the autonomic nervous system are evidenced by the fact that heart rate variability (HRV) and baroreflex function, both established markers of autonomic imbalance and inflexibility, tend to be abnormal in individuals with PTSD compared with controls (Hughes et al. 2007; Shah et al. 2013). Autonomic inflexibility measured by these and other indices is a well-known indicator of increased CVD risk and an adverse prognostic factor. In a study where 24-h HRV was measured in 459 middle-aged male twins who served in the military during the Vietnam Era, current PTSD was inversely associated with very-low-frequency HRV and low-frequency HRV both in individual twins and within 20 twin pairs discordant for current PTSD. Twins with current PTSD had a 49 % lower

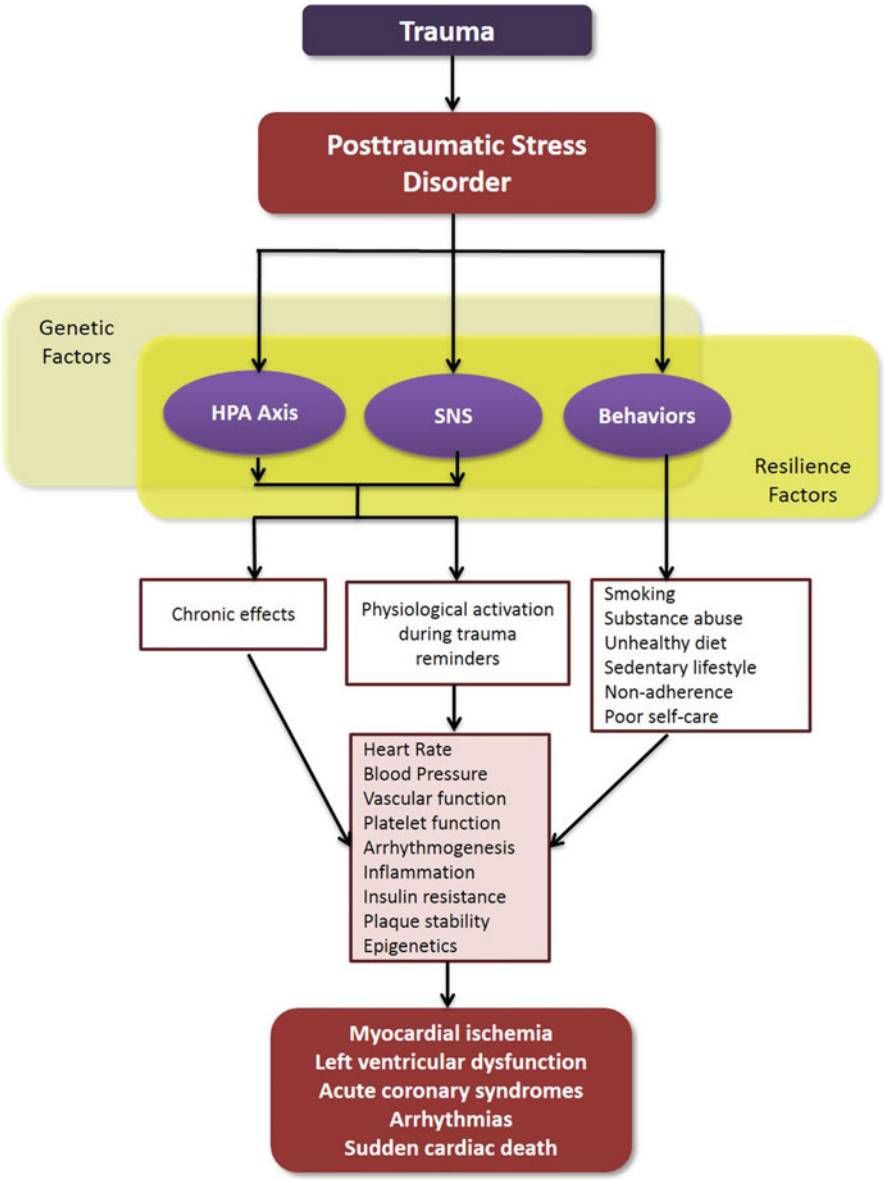

Fig. 2 Schematic representation diagram illustrating potential mechanisms linking PTSD to coronary heart disease. HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system (From Vaccarino V, & Bremner JD. Biol Psychiatry 2013;74:790-792. Reproduced with publisher's permission)

low-frequency HRV than their brothers without PTSD ($p < 0.001$). Remitted PTSD was not associated with HRV. Results were robust to adjustment for depression and other risk factors. These data suggest that PTSD, especially current PTSD, is associated with autonomic inflexibility indices previously shown to be prognostic and that this effect might reverse with remission of PTSD (Shah et al. 2013).

One of the biological hallmarks of PTSD is enhanced sensitivity of the noradrenergic system resulting in heightened SNS activity, particularly during trauma reminders (Bremner and Charney 2010; Yehuda 2002; Zoladz and Diamond 2013). For example, combat veterans with PTSD, compared with controls, exhibit an increase in catecholamines, heart rate, and other physiological parameters in response to reminders of trauma such as sound of gunfire, combat slides, or scripts of their traumatic experiences (Blanchard et al. 1982; Pitman et al. 1987). They also show altered brain function (especially decreased frontal lobe function) compared to non-PTSD subjects in response to traumatic reminders (Bremner and Charney 2010). Most of these responses are not observed when using neutral stressors such as mental arithmetic (Blanchard et al. 1982).

In addition to dysfunction of the autonomic nervous system, PTSD is characterized by dysregulation of the HPA axis. Overall, individuals with PTSD show enhanced negative feedback sensitivity of the glucocorticoid receptors, as evidenced by increased corticotrophin-releasing factor and decreased peripheral cortisol concentrations at rest, suggesting that the HPA system may be downregulated (Bremner and Charney 2010; Yehuda 2002; Zoladz and Diamond 2013). However, there is enhanced cortisol release with reminders of the trauma in PTSD compared with controls. For example, women with abuse-related PTSD listening to traumatic scripts had a fourfold salivary cortisol response than women with abuse without PTSD (Elzinga et al. 2003). PTSD patients also show increased cortisol response to the type of cognitive mental stress challenge used in studies of patients with CVD (Bremner et al. 2003). Patients with PTSD, however, have lower serial cortisol levels throughout the day and a blunted effect of dexamethasone on declarative memory function.

Stress Reactivity in PTSD and IHD

A commonly endorsed pathway for the increased CVD risk in PTSD is neuroendocrine, hemodynamic, and immune hyperreactivity during psychological stress, which has been related to cardiovascular risk factors such as hypertension and to CVD events (Chida and Steptoe 2010; Treiber et al. 2003). PTSD patients subjected to a stress challenge in the laboratory involving personalized trauma scripts show higher increases in blood pressure, heart rate, and other indicators of activated SNS compared with controls (Bremner et al. 1999). Patients with depression and CVD and a history of childhood abuse (many of whom had comorbid PTSD) showed an increase in myocardial ischemia in response to mental stress relative to patients with CVD without depression or abuse (Bremner et al. 2009). This suggests that early abuse may play a role in sensitizing patients to stress-induced myocardial

ischemia in adulthood. It is plausible that these responses result in a cumulative long-term increase in cardiovascular risk, but whether this is true needs further investigation.

Vascular and Immune Effects

Heightened physiological stress activation during reexperiencing episodes in PTSD, such as it was described above, could have cumulative and enduring effects that directly or indirectly impact the endothelium, the myocardium, immune function, platelet activity, and vascular repair processes. These in turn may affect vascular function and plaque stability and may result in acute cardiac events through pathways that are independent of traditional risk factors and even independent of atherosclerotic plaque burden (Bhattacharyya and Steptoe 2007; Strike et al. 2006). For example, catecholamines have direct adverse effects on the myocardium, the cardiac conduction system, the endothelium, and platelet function and have also been implicated in the development of heart failure and cardiac ischemia (Brotman et al. 2007).

Vascular Function. SNS activation during stress, through the neurohormone epinephrine, can cause peripheral vasoconstriction. This has been demonstrated in acute stress studies in the laboratory (mental stress testing), where peripheral vasoconstriction was measured noninvasively (Hassan et al. 2009b; Ramadan et al. 2013a). In addition, enhanced SNS activation could lead to microvascular and endothelial dysfunction, early precursors of IHD. It has been shown that even a brief period of mental stress induced in the laboratory may result in prolonged peripheral vascular endothelial dysfunction (Ghiadoni et al. 2000).

Peripheral vasoconstriction during mental stress could lead to myocardial ischemia because of a sudden increase in cardiac afterload or because it correlates with coronary vascular dysfunction. Indeed, noninvasively measured peripheral vasoconstriction predicts mental stress-induced myocardial ischemia (Burg et al. 2009; Hassan et al. 2009a, b). In a study of 384 cardiac patients, peripheral vascular tone was measured noninvasively using a device which recorded the pulse wave amplitude of vascular flow in the microvessels of the fingers, deriving a ratio of amplitude during mental stress over the amplitude at rest (Ramadan et al. 2013b). This ratio was lower in those who developed mental stress ischemia during a speech task compared with those who did not, indicating greater digital microvascular constriction. Notably, this measure did not correlate with angiographic severity of coronary artery disease and was a better predictor of mental stress ischemia than angiographically measured coronary disease. It is possible that these vascular effects occur in subjects with PTSD during episodes of intrusive memories associated with marked SNS activation, and thus, they may predispose some individuals to acute myocardial ischemia.

Inflammation and Immunity. There have been many reports that persons with PTSD have higher levels of inflammatory biomarkers and evidence of immune dysregulation (Gill et al. 2009). Recently, PTSD has also been associated with

cellular adhesion molecules and other endothelium-derived circulating proteins, including ICAM-1, VCAM-1, selectins (von Kanel et al. 2010), and some clotting factors (von Kanel et al. 2006, 2008). In a twin study, there was a robust association between PTSD and ICAM-1, within a panel of inflammatory markers including CRP, IL-6, fibrinogen, and white blood cells, in addition to ICAM-1 and VCAM-1 (Plantinga et al. 2013). In within-pair analyses of twin pairs discordant for PTSD, ICAM-1 was the only biomarker that was significantly associated with PTSD.

Circulating adhesion molecules are especially relevant here because they are markers of inflammation but also of endothelial injury and predict IHD risk (Blann et al. 2003; Hope and Meredith 2003a, b). ICAM-1, in particular, increases during acute stress and was found to go up about 12 % more in PTSD subjects than those without PTSD under stress conditions (von Kanel et al. 2010). ICAM-1 is associated with remarkably higher risk of IHD in prospective studies, while VCAM-1 is not as good of a predictor (Hwang et al. 1997; Luc et al. 2003). The endothelial adhesion molecule E-selectin and the platelet adhesion molecule P-selectin have also been associated with IHD (Blann et al. 2003; Hwang et al. 1997).

Although the mechanisms underlying immune dysfunction in PTSD are not clear, they may be related to neurobiological features of PTSD characterized by a hyperactive noradrenergic system and lower basal cortisol levels and/or to protracted activation of stress systems during stressful reexperiencing episodes (Bremner 2010; Bremner and Charney 2010; Garakani et al. 2011). Glucocorticoids and catecholamines affect the immune system in many ways (Elenkov and Chrousos 2002). Psychosocial stress directly triggers inflammation through norepinephrine-dependent activation of the transcription factor NF-κB in circulating monocytes (Bierhaus et al. 2003). During mental stress, the concentration of several circulating inflammatory molecules goes up within 90–120 min, with most consistent increases for interleukin (IL)-6 and IL-1β, and marginal effects for C-reactive protein (CRP) (Steptoe et al. 2007). It is important to remember that inflammatory processes promote a hypercoagulable state and endothelial dysfunction, which are mechanisms of IHD and could lead to plaque instability, plaque disruption, or superimposed thrombus, which could lead to myocardial ischemia.

Clinical Implications

PTSD is a common condition in the general population and in patients with CVD. It is associated with considerable disability and impaired quality of life and is now emerging as an important risk factor and prognostic factor for CVD. Nonetheless, PTSD symptoms are often overlooked in general clinical practice. Clinicians who care for patients in primary care settings or in cardiology clinics should be aware that PTSD may have adverse effects on the cardiovascular system including increased risk of adverse cardiovascular events and mortality.

In the United States alone, about one million patients are discharged each year with a diagnosis of acute coronary syndrome (Go et al. 2014); of these, over 100,000 patients could develop clinically significant PTSD symptoms. In addition,

about 800,000 people experience a new or recurrent stroke each year, which may translate into approximately 180,000 patients with PTSD secondary to stroke. To these numbers, one should add PTSD cases that preexisted the onset of CVD. It follows that PTSD could contribute substantially to repeat hospitalization, mortality, and an increase in healthcare costs associated with acute cardiovascular disease.

Effective pharmacological and psychotherapy approaches for the treatment of PTSD and ameliorating symptomatic distress are available (Bandelow et al. 2012; Sullivan and Neria 2009), but whether such treatments also reduce CVD risk is currently unknown. Similarly untested is whether reducing symptoms of PTSD would improve adherence and other health behaviors in PTSD patients. The advantages and disadvantages of routinely screening for PTSD symptoms in cardiac patients are also unknown. Several primary care centers within the Veterans Health Administration in the United States routinely screen for PTSD using questionnaires such as the four-item Primary Care PTSD Screen (PC-PTSD). Although this approach may be useful to detect undiagnosed PTSD in high-risk populations, its utility for CVD prevention or treatment is unknown, and there are currently no guidelines for screening in the nonveteran population at large.

In order to optimize clinical outcomes of patients with comorbid PTSD and CVD, the cardiologist or primary care physician should seek psychiatric consultation as needed, which may also be helpful if associated problems are present, such as depression and substance abuse. In addition, some medications for the treatment of PTSD, especially the older tricyclic medications, may adversely affect cardiovascular function, and thus drug treatment, if needed, should be carefully evaluated within the overall management of the patient.

Conclusion

Research in the past decade has accumulated compelling evidence to support an association between PTSD and incident CVD and is beginning to show a similar relationship between PTSD and recurrent CVD events. However, more longitudinal studies, using established, objective measures of CVD, are needed to definitely prove this link. Additionally, the underlying mechanisms are unclear and are likely to be complex and multifactorial. Better understanding of the underlying pathophysiology will help identify effective management and preventive modalities. PTSD appears to be a pro-inflammatory, procoagulant condition through hyperactivity of the noradrenergic system and downregulation of the HPA axis. Autonomic imbalance is reflected by an exaggerated catecholamine response to stressful circumstances which may contribute to CVD through a multitude of pathways related to inflammation, coagulation, vascular function, and repair processes. Adverse health behaviors are common in PTSD, such as cigarette smoking and substance abuse related to self-medication. At this time, not one causal pathway has been identified and ultimately multiple pathways may be involved. Thus, future research efforts will require wider approaches with rigorous study designs and sufficiently large sample sizes.

It will also be of interest to identify risk factors for susceptibility to both PTSD and CVD, such as whether there are specific exposures, or genetic backgrounds, that might increase individual predisposition to both disorders. Furthermore, it will be important to clarify predisposing factors that might make patients more vulnerable to develop PTSD after an acute cardiovascular event. Finally, research should be directed toward the identification of effective treatments that may help reduce cardiovascular risk and improve prognosis among persons with PTSD. As the scientific community will continue to discover the most important mechanisms underlying the link between PTSD and CVD, clues can be derived about the most promising targets for reducing CVD risk in PTSD. New trials of pharmacologic and behavioral treatments for PTSD should examine the effects of PTSD symptom reduction on these potential mechanisms and on CVD outcomes.

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