Autonomic and inflammatory consequences of posttraumatic stress disorder and the link to cardiovascular disease

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POSTTRAUMATIC STRESS DISORDER (PTSD) is a psychiatric illness characterized by persistent emotional and mental stress following a traumatic event. Symptoms of PTSD include hyperarousal, flashbacks, intrusive thoughts, or nightmares, and avoidance of activities that trigger memories of the traumatic event. The health consequences of PTSD are substantial, affecting multiple organ systems, with evidence linking PTSD to diseases such as cancer, arthritis, digestive disease, and cardiovascular disease (CVD) (13, 14, 112). The evidence demonstrating increased risk for CVD in PTSD (9, 15, 19, 49, 57, 58) is compelling, and several excellent recent review articles have highlighted this association (20, 23, 52, 63, 112). While this association could certainly be due, in part, to related unhealthy behaviors, such as increased prevalence of smoking, poor diet, and physical inactivity (46, 119). Yet even after adjustments for lifestyle, comorbid conditions, and combat engagements in multivariate models, PTSD remains a significant and independent risk factor for the development of CVD and CVD-related mortality (15).

Increased CVD risk in PTSD has been demonstrated in both military (21) and civilian populations (44, 82). A co-twin study design (monozygotic and dizygotic), which controlled for genetic and familial confounders, demonstrated that the incidence of coronary heart disease was more than double in Vietnam War veteran twins with PTSD (22.6%) compared with those without PTSD (8.9%) (106). Most recently, one of the largest longitudinal studies examining the association between PTSD and heart failure was completed, and veterans with PTSD were shown to be nearly 50% more likely to develop heart failure than veterans without PTSD (91). This remained significant after adjustments for age, sex, diabetes, hyperlipidemia, hypertension, body mass index, combat, and military service. Civilian PTSD populations are also at greater risk for CVD. Following life-threatening traumatic events such as earthquakes (82), the 9–11 World Trade Center attack (45), and living in urban distressed neighborhoods (111), those diagnosed with PTSD have a higher incidence of CVD and related metabolic syndrome. Moreover, in the Framingham Coronary Heart Disease study, patients with PTSD were found to have increased Framingham risk scores for CVD (40). To date, there have been six PTSD-CVD prospective studies completed, following participants from 1 to 30 years, which have demonstrated consistent associations between PTSD and CVD after adjusting for demographic, clinical, and psychosocial factors, including depression (15, 44, 57, 58, 89, 96). There are multiple risk factors (stroke, hypertension, atherosclerosis, and obesity metabolic syndrome) for the development of CVD, and increases in the incidence of these risk factors are often associated with PTSD (1, 22, 30, 51, 111). Data from the U.S. National Comorbidity Survey showed that...
people with PTSD had a 2.9-fold greater risk for developing hypertension (51). In a sample of more than 300,000 veterans of the Iraq and Afghanistan wars, those with PTSD had a 59% higher chance of developing hypertension compared with those without PTSD (19). In addition to hypertension, there is evidence of increased atherosclerosis in PTSD. Comparing Veterans with PTSD to those without, Ahmadi et al. (3) showed that the PTSD group had increased coronary calcium scores. Similarly, a nonmilitary PTSD population had greater arterial stiffness and vascular dysfunction (109), indicating increased atherosclerosis compared with a non-PTSD population. Furthermore, studies have demonstrated that CVD risk increases incrementally with worsening of PTSD symptoms. In a 14-year prospective study of more than 1,900 patients, men had an increased risk for both nonfatal myocardial infarction and fatal coronary heart disease with every SD increase in symptom level; similarly, women with five or more PTSD symptoms had over three times the risk of incidence of CVD (57, 58). It is also worth noting that clinically significant PTSD symptoms can be induced by cardiovascular related events, and these individuals are more likely to have recurrent major adverse coronary events (24, 59).

In summary, these studies provide compelling evidence for the association between PTSD and increased CVD risk and mortality, with some evidence pointing to a causal relationship. The mechanisms underlying these clinical findings are clearly complex and as pointed out in other reviews (52), the etiology is multifactorial, likely involving autonomic, immune, and neuroendocrine disturbances, resulting from the traumatic event(s). Subsequent sections will expand on these mechanisms and discuss the relevance of the renin-angiotensin system (RAS) in PTSD and its potential role in the link to CVD.

The Renin-Angiotensin System: Beyond Blood Pressure Control

It is well known that the RAS plays a fundamental role in blood pressure and fluid and electrolyte homeostasis. This neurohormonal system also promotes cardiovascular injury (i.e., vasoconstriction, inflammation, hypertrophy, and fibrosis) and is activated in response to psychological stress (42, 94). In response to increased psychological stress, sympathetic activation leads to renin release from the juxtaglomerular cells of the kidney through noradrenergic activation of β1 receptors, increasing ANG II synthesis through downstream processes (42, 56). In turn, ANG II causes its effects by binding to its two receptor subtypes: the angiotensin type 1 receptor (AT1R) and the angiotensin type 2 receptor (AT2R). The des Asp1 ANG II metabolite (ANG III) is also a full agonist of the AT1R and AT2R. Other metabolites of ANG II; des-Asp1,des-Arg2 ANG II (ANG III) and des Phe8 ANG II (ANG 1–7) are also physiologically active, binding to the angiotensin type 4 receptor (AT4R) and mas, respectively, [see review (102)]. The AT1R is expressed across many organs, including the heart, kidney, vasculature, and brain (71, 116). The major cardiovascular effects, including elevation in blood pressure, increased sympathetic activity, and altered electrolyte balance, as well as proliferative, hypertrophic, and proinflammatory effects, are mediated by AT1R signaling. Inhibition of the RAS with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), which selectively block the AT1R, are, therefore, widely used for the treatment of hypertension and CVD. There is a growing body of evidence, however, demonstrating that the therapeutic actions of both ACE-Is and ARBs extend beyond blood pressure reduction (11, 92, 108) and may have beneficial effects on stress-related pathologies, such as PTSD and panic disorder (43, 50).

Chronic stress, as manifested with PTSD, induces activation of the RAS, leading to increased ANG II synthesis (86). Experimental studies have shown that immobilization stress in rats increases circulating levels of ANG II (18) and binding of brain AT1R. Inhibition of the RAS using ACE-Is and ARBs can reverse these effects (6, 17, 62, 94). Additional studies provide evidence that blockade of the RAS has protective effects against stress, anxiety, brain inflammation, and neurodegeneration (5, 10, 93, 95). Other studies have shown that increased circulating and brain components of RAS correlate with increased hypothalamic-pituitary-adrenal axis (HPA) stimulation and increased corticotrophin-releasing hormone (CRH), a critical stress hormone (2, 6, 84). Supporting these data, Krause et al. (55) demonstrated that knockdown of AT1R with siRNA (synthetic RNA) within the brain (hypothalamic region), attenuates the HPA neuroendocrine and anxiety stress response in rats. Chronic stress can lead to a breakdown of the negative feedback systems of the HPA axis, promoting reduced CRH and cortisol, which profoundly affect the long-term psychological state of affected individuals. This is endorsed by a meta-analysis showing decreased CRH and cortisol levels in individuals with psychiatric illness, including PTSD (76). Although it is clear that long-term elevations in HPA activity contribute to psychopathology, the associated increases in ANG II production and the influence of ANG II on psychiatric disorders, such as PTSD, are unknown. Further understanding the role of ANG II and the RAS in psychiatric disease is important, as current treatment strategies are limited. Recent clinical and preclinical data presented in the next section support a major role of the RAS in PTSD.

In a highly traumatized inner-city population, Khoury et al. (50), reported that individuals taking ARBs and ACE-Is had fewer PTSD symptoms. Notably, this reduction in PTSD symptoms was not observed with other classes of blood pressure medications, including β-blockers, calcium channel blockers, and diuretics. These clinical data support a role for the RAS in the regulation of stress response in individuals exposed to traumatic stress, and this finding was recently replicated (80). In this same study, genetic evidence for a single nucleotide polymorphism (SNP) in the ACE gene in this PTSD cohort was determined. Differential responses to ACE-Is and ARBs were found in those with the ACE intronic SNP (rs4311), as well as greater symptom improvements in PTSD among those with the CC genotype (80). Although speculative, it is possible that ACE genetic polymorphisms such as SNP (rs4311) may explain the varying individual propensities to develop CVD in this PTSD population.

Extending these clinical observations, recent studies using an animal model of PTSD have examined the acute and chronic effects of AT1R inhibition on fear memory (68). Patients with PTSD and other anxiety disorders are thought to have deficits in extinction of aversive memories (12, 113). Similarly, rodents with anxiety-like behavior or trauma exposure demonstrate a deficit in extinction of conditioned fear (4, 41). Using Pavlovian fear conditioning (pairing of auditory cues with
footshocks), we examined the acute and chronic effects of the ARB losartan on extinction. While no effect of losartan was observed on extinction training, there was a marked reduction in fear, as measured by freezing behavior to an auditory cue when tested the following day (extinction retention). Similarly, when losartan was given chronically, animals exhibited reduced freezing during extinction. Importantly, losartan had no significant effects on locomotion, baseline anxiety, or blood pressure measures. Gene expression changes in the brain were also altered in mice with chronic ARB treatment, in particular, reduced mRNA levels of AT$_1$R in the amygdala and c-Fos in the bed nucleus of the stria terminalis (68).

The amygdala is an integral part of the fear circuitry (47, 60), and key inputs to the amygdala from the medial prefrontal cortex are thought to be required for the extinction of fear (64, 65). It is, therefore, plausible that brain AT$_1$R signaling may be an important factor in the fear circuit pathway contributing to extinction and fear-related behaviors. A recent study by Marínzalda et al. (67), showing that AT$_1$R in the central amygdala modulates fear-potentiated behavior, provides further support for this hypothesis. Currently, the mechanisms for ANG II-mediated effects on fear memory are unknown; however, it is possible that brain ANG II modulates local excitatory and inhibitory neurons and CRF production (2, 6, 39), influencing the neural networks involved in fear memory formation (97). Aside from its unknown role in amygdala/fear-dependent neural pathways, the autonomic and proinflammatory effects of ANG II may also play a direct or indirect role in promoting CVD in the setting of PTSD (Fig. 1).

### Autonomic Dysfunction in PTSD

The sympathoexcitatory effects of ANG II are well recognized (69, 87), and previous studies in both animals and humans with a variety of chronic diseases, such as obesity, heart failure, and chronic kidney disease, have shown that blockade of the RAS reduces sympathetic nervous system (SNS) activity and improves baroreceptor sensitivity (BRS) (25, 34, 53, 105, 110, 118). One of the hallmark symptoms of PTSD is hyperarousal, and therefore, it is not surprising that basal overactivation of the SNS is present. For example, studies investigating indirect markers of sympathetic activity show that PTSD patients have higher resting heart rates and blood pressure, decreased heart rate variability, and increased plasma and urine catecholamine levels, suggesting a state of SNS overactivity (9, 16). In addition, failure of blood pressure (BP) to decrease by $\geq 10\%$ nocturnally (nondipping), which is thought to be mediated by SNS overactivity, is associated with increased CVD risk and is more prevalent in young African-Americans with PTSD (72).

One potential mechanism underlying SNS overactivity in PTSD is decreased baroreceptor sensitivity (BRS). Arterial baroreceptors, located in the carotid arteries and aortic arch, are sensory nerve endings that function as arterial pressure sensors that connect to sympathetic control centers in the brain. The baroreceptors are important in the moment-to-moment control of BP and buffering of acute fluctuations in arterial BP during postural and volume changes, as well as physiological or mental stress, thereby minimizing BP variability. Decreased BRS contributes to the pathogenesis of many conditions characterized by SNS overactivity, including chronic heart failure (32), obesity (33), and hypertension (70, 79). In PTSD, there is evidence for dysfunctional baroreflexes as well. For example, Gulf War veterans with comorbid PTSD and chronic fatigue syndrome have greater hypotensive responses to orthostatic stress (85), and female PTSD patients have blunted changes in heart rate interbeat interval in relation to BP at rest (38). Further evidence of autonomic dysfunction in PTSD has emerged from studies examining disrupted sleep patterns (trauma-related night-
matters, insomnia) in PTSD (81, 90). In particular, blunted day-to-night reduction (8, 72, 73) and elevation of nocturnal SNS arousal or SNS dominance over parasympathetic nervous system (PNS) function have been observed in PTSD (77, 115). Moreover, young adult African-Americans with PTSD had a lower PNS activation indexed by heart rate variability during sleep at home compared with those who were resilient to trauma (i.e., individuals who had never experienced significant PTSD symptoms despite exposure to a high-impact trauma) (54). Interestingly, diminished SNS activation with increased sleep duration was observed in resilient individuals, but not those with PTSD (54). These observations of elevated nocturnal SNS arousal and dissociations between sleep duration and SNS activity suggest the possibility that sleep disturbance in PTSD is a likely contributor to decreased BRS, autonomic dysfunction, and increased CVD risk. Despite these data, the mechanisms contributing to SNS overactivity, BRS dysfunction, and associated consequences in PTSD are unclear.

**Autonomic-Immune Dysfunction in PTSD**

The autonomic nervous system has extensive communication with the immune system (78). Thus, dysregulation of the immune system leading to inflammation is a likely consequence of autonomic dysfunction in PTSD. Chronic elevations in catecholamines increases cytokine production via stimulation of β2-adrenergic receptors on immune cells (78), which may contribute to the numerous lines of evidence showing increased levels of inflammatory markers in PTSD (48). For example, PTSD patients exhibit increases in blood levels of proinflammatory cytokines including IL-1β, IL-2, IL-6, the IL-6 receptor, and TNF-α (26–28, 35, 37, 66, 104) and decreases in anti-inflammatory cytokines such as IL-4 (48, 98). Moreover, peripheral blood mononuclear cells produced more IL-1β, IL-6, and TNF-α in those with PTSD than in healthy controls (31). Overall, these studies demonstrate a shift to an increase in proinflammatory cytokines and a decrease in anti-inflammatory cytokines, which increases inflammation in PTSD. C-reactive protein (CRP), a biomarker of inflammation that is also predictive of cardiovascular disease (88), is also increased and frequently associated with PTSD in many (36, 74, 103), but not all studies (7, 101).

It is likely that dysregulation of the HPA axis, as discussed above, contribute to heightened immune responses and inflammation in PTSD. Further evidence of altered immune function in PTSD has been demonstrated in studies showing that the numbers of leukocytes and lymphocytes, as well as early activation markers of T lymphocytes such as CD45RA, are elevated in PTSD (29, 61, 107). Moreover, numbers of T regulatory cells, which are involved in suppressing inflammatory T lymphocyte responses, are significantly reduced (99). Taken together, these alterations in T lymphocytes can cause immunodysfunction, thus contributing to CVD progression and/or other inflammatory diseases. Overall, studies of inflammatory markers in PTSD have generally been cross-sectional and included a small sample size and failed to correct for potential confounding factors (such as depression, known cardiovascular disease, or cardiovascular risk factors) that increase levels of peripheral inflammatory cytokines. Despite these limitations and inconsistencies, the majority of evidence supports an association between PTSD and heightened immune function and inflammation.

When considering inflammation as a contributing factor or consequence of PTSD, it is important to keep in mind that inflammation and cytokines may have secondary effects on neurotransmitters, which could contribute to the impairments in fear memory and extinction processes found in PTSD patients and other psychiatric diseases (75). For example, under stress, microglia, endothelial cells, and macrophages release IL-1β, and many IL-1β receptors are concentrated near the hippocampus and amygdala. These may alter fear memory (100, 114) by influencing synaptic strength and signaling between neurons. Both IL-1β and nitric oxide are thought to play a role in long-term potentiation (increased postsynaptic response to a fixed stimulus), which can serve to enhance learning and memory (83, 100). Interestingly, IL-1β has been found to promote fear memory and the conditioned fear response. Following footshock, rats receiving an intracerebroventricular infusion of IL-1β showed a heightened fear memory (100), while blocking the IL-1 receptor in mice decreased perceived anxiety-type behavior, thus emphasizing the importance of this cytokine in fear memory (114). These and other data suggest that the development of PTSD may involve a failure of immune system homeostasis, such that inflammation and cytokines can disrupt neuronal signaling, promote injury, and impair circuits involved in fear memory extinction. Moreover, as described earlier in The Renin-Angiotensin System: Beyond Blood Pressure Control, ANG II is an important mediator of brain inflammation and activates microglia (117, 123). Therefore, it is possible that ANG II may directly or indirectly affect central signals involved in fear memory formation. Overall, we hypothesize that following a traumatic event, increases in peripheral and central ANG II lead to enhanced autonomic and proinflammatory effects that alter fear extinction mechanisms, and in time, position these individuals at greater risk for CVD-related mortality (Fig. 1). Other factors such as PTSD-associated sleep disturbances may accelerate the development of CVD.

**Summary and Conclusion**

In summary, there are accumulating epidemiological studies demonstrating a link between PTSD and CVD and evidence that the RAS, sympathetic overactivation, and inflammation contribute to compromised cardiovascular health in PTSD. Furthering the understanding of these neurobiological/immunological pathways and the role of the brain and peripheral RAS will be critical to identifying new treatment and prevention strategies and importantly identifying PTSD patients at risk for the development of CVD. Continued multidisciplinary research will be essential to identifying unique biological and genetic markers in these patients with the goal of improved clinical outcomes in PTSD and other stress-related illnesses.

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AUTHOR CONTRIBUTIONS

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