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Confederates in the Attic:

Posttraumatic Stress Disorder, Cardiovascular Disease, and the Return of Soldier's Heart

J. Douglas Bremner, MD[*,†,‡], **Matthew T. Wittbrodt, PhD**[*], **Amit J. Shah, MD**[‡,§], **Bradley D. Pearce, PhD**[‖], **Nil Z. Gurel, MS**[¶], **Omer T. Inan, PhD**[¶,#], **Paolo Raggi, MD**[**], **Tené T. Lewis, PhD**[‖], **Arshed A. Quyyumi, MD**[§], **Viola Vaccarino, MD, PhD**[§,‖]

[*]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Emory University, Atlanta;

[†]Department of Radiology, Emory University School of Medicine, Emory University, Atlanta;

[‡]Atlanta VA Medical Center, Decatur;

[§]Department of Medicine (Cardiology), Emory University School of Medicine, Emory University;

[‖]Department of Epidemiology, Rollins School of Public Health, Emory University;

[¶]School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, Georgia;

[#]Coulter Department of Biomedical Engineering, Georgia Institute of Technology, Atlanta, Georgia;

[**]Mazankowski Alberta Heart Institute and Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.

Abstract

Da Costa originally described Soldier's Heart in the 19th Century as a syndrome that occurred on the battlefield in soldiers of the American Civil War. Soldier's Heart involved symptoms similar to modern day posttraumatic stress disorder (PTSD) as well as exaggerated cardiovascular reactivity felt to be related to an abnormality of the heart. Interventions were appropriately focused on the cardiovascular system. With the advent of modern psychoanalysis, psychiatric symptoms became divorced from the body and were relegated to the unconscious. Later, the physiology of PTSD and other psychiatric disorders was conceived as solely residing in the brain. More recently, advances in psychosomatic medicine led to the recognition of mind-body relationships and the involvement of multiple physiological systems in the etiology of disorders, including stress, depression PTSD, and cardiovascular disease, has moved to the fore, and has renewed interest in the validity of the original model of the Soldier's Heart syndrome.

Send reprint requests to J. Douglas Bremner, MD, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Emory University, Rm 333, 12 Executive Park Dr NE, Atlanta, GA 30329. jdbremn@emory.edu.

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Keywords

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CONFEDERATES IN THE ATTIC: THE RETURN OF SOLDIER'S HEART

The American Civil War (1861–1865) was an epic conflict between the Union Army of the North and the Confederate States of America in the South. Many of the battles prefigured the bloody conflicts of the future First World War, and were associated with thousands of casualties. The Civil War saw the advent of trench warfare; the remains of the trenches where the Confederates dug in against the invading Union Army can be seen on the slopes of Kennesaw Mountain in Georgia, even today. Their failed attempt to halt the advance of the Union Army on Atlanta from the north resulted in Sherman's March to the Sea and the eventual capitulation of the Confederates. Swords were traded for ploughshares with varying degrees of effort to move on from this divisive war. Years later, battle uniforms and mementos were often rediscovered in the attic by later generations, which led to the well-known phrase "Confederates in the Attic." Political history, however, has the potential to shine a light upon the past in a way that illuminates the present. In a similar way, the history of medicine can shed light on modern conceptions of disease. Syndromes described in earlier eras once thought to have become irrelevant can be the subject of renewed interest in the light of new discoveries in a particular field.

One example of this is a medical diagnosis that came directly from the Civil War, namely, Soldier's Heart or Da Costa's syndrome. The syndrome was originally described by Jacob Mendes Da Costa, a physician in the Union Army (1833–1900) (Fig. 1). Da Costa, born into a small Sephardic Jewish community in St. Thomas, the US Virgin Islands (at that time a Danish colony), attended medical school at Jefferson University in Philadelphia, and was later on the faculty there (Clarke, 1903; Kobrin and Kobrin, 1999). During the Civil War, Da Costa worked at the Satterlee Hospital in Philadelphia, Pennsylvania, the largest hospital in the country serving the Union Army. There he observed over 400 patients with nonspecific cardiac complaints after exposure to the stress of combat. Da Costa published his observations on the syndrome in 1871 in the *American Journal of Medical Sciences* under the title "On Irritable Heart: A Clinical Study of a Form of Functional Cardiac Disorder and Its Consequences," describing how soldiers following exposure to combat developed an array of symptoms including fatigue, shortness of breath, sighing respirations, palpitations, rapid heart rate, and sweating, with no observable cardiological abnormality (Da Costa, 1871).

Soldier's Heart was one of several syndromes found in the history books that identified somatic symptoms after exposure to psychological trauma (Bremner, 2006; Kirmayer et al., 1995; Micale and Lerner, 2001). These syndromes predated the current era, which is dominated by the *Diagnostic and Statistical Manual* (*DSM*) and its establishment of the posttraumatic stress disorder (PTSD) diagnosis in 1980 (American Psychiatric Association, 1981; Saigh and Bremner, 1999). For instance, in 1830, a syndrome called "railway spine"

or “railway injuries” was first described in victims of train accidents in England. Many of the symptoms looked like PTSD, including exaggerated fear reactions, amnesia for aspects of the traumatic event, and anxiety, as well as symptoms of memory disturbance, confusion, and back pain (Micale and Lerner, 2001). The etiology was felt to be contusions of the spinal cord below the level of physical detection, and was described in a book by Erichsen called “On Railway and Other Injuries of the Nervous System” (Erichsen, 1867). About this time in Germany, a psychiatrist named Oppenheim described traumatic neurosis as a psychological stress or extreme shock that could lead to long-term changes in physiology in the absence of physical injury. World War I saw the development of the concept of “shell-shock,” which was originally thought to be a physical disorder caused by exploding shells, but later it was realized that it could develop in locations far from the blast (Micale and Lerner, 2001). Symptoms included confusion on the battlefield and forgetting one’s name or identity. After the war, Freud’s ideas about unconscious conflicts as the source of psychiatric symptoms became dominant. Combat-related reactions were called “combat neurosis” and thought to be caused by a suppressed urge to run from the battlefield (Crocq and Crocq, 2000). In other words, the environment was not the cause and there was no physical disorder, rather symptoms created by unconscious conflicts, similar to anxiety neurosis.

Recent advances in medicine have increased our knowledge of the effects of traumatic stress on the body (Mayer and Bushnell, 2009). This has led to a reappraisal of stress-related psychiatric disorders as more than just “above the neck” disorders and renewed appreciation for earlier concepts of the effects of stress on the individual as involving multiple physiological systems (Anda et al., 2006; Mayer and Bushnell, 2009; Vaccarino et al., 2016a). Stress has lasting effects on a number of physical systems, including the cardiovascular system (Vaccarino et al., 2016b). Accumulating evidence shows a strong relationship between stress-related psychiatric disorders, including both PTSD and depression, and cardiovascular disease (CVD) (Vaccarino and Bremner, 2013, 2015; Vaccarino et al., 2018).

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) affects 8% of people in the United States at some point in their lives, with women affected twice as often as men (Kessler et al., 1995). PTSD is most commonly related to childhood sexual abuse in women and physical assault in men (Kessler et al., 1995), and is more common in civilians in the United States than in combat veterans (MacMillan et al., 1997). PTSD requires exposure to a traumatic event defined as a threat to life or self with associated symptoms of intrusive memories of the event, increased arousal with reminders, avoidance of reminders, negative cognitions, feeling cut off and emotionally numb, disturbed sleep and concentration, hyperarousal, and hypervigilance.

Bremner described a trauma-spectrum group of psychiatric disorders that held in common exposure to a traumatic event (Bremner, 1999a, 2002a). Trauma-spectrum disorders shared a common neurobiological mechanism with slight variations based on the interaction of stress with genetics, environment, and other factors (Bremner, 1999a, 2002a). A series of studies showed that the trauma-spectrum disorders share important neurobiological fingerprints that differentiate them from the non-PTSD anxiety disorders. Trauma-spectrum disorders of

PTSD, major depression related to childhood abuse, borderline personality disorder, and dissociative identity disorder share in common smaller hippocampal volume (a brain area sensitive to stress that plays an important role in short term memory) as measured with magnetic resonance imaging, a finding not seen in other anxiety disorders (Bremner, 2004a, 2005a; Schmahl et al., 2003; Vermetten et al., 2006; Vythilingam et al., 2002). In fact, a number of the symptoms of trauma-spectrum disorders are overlapping or can be seen as a rephrasing of symptoms that are essentially identical (Bremner, 1999b, 2002a, 2004b). Grouping of psychiatric disorders by common biological or etiological framework was a departure from the pure descriptive format that underlay the development of the original versions of the *DSM* (Bremner, 2006). The descriptive approach was itself a conscious departure from the previous system, which was built around the theoretical formulation of repressed, unconscious conflicts as the root basis of psychiatric disorders (Bremner, 2006). The synthetic framework of the trauma-spectrum disorders involved a shift in perspective of psychiatric disorders as more than just what was happening “from the neck up” and instead incorporating whole-body etiologies. Stress-related psychiatric disorders in fact involve lasting alterations in peripheral autonomic, cardiovascular, and inflammatory systems, and are in fact much more than pure brain-based disorders (Bremner and Vaccarino, 2015; Vaccarino and Bremner, 2013; Vaccarino et al., 2018). It is alterations in these systems that are largely responsible for the symptoms of Soldier’s Heart.

THE ORIGINS OF SOLDIER’S HEART

Lasting disruptions of peripheral autonomic and cardiovascular function after exposure to extreme traumas such as the stress of war are best thought of from larger developmental and evolutionary perspectives (Bracha et al., 2005). Behaviors such as hypervigilance, hyperarousal, and light sleep that had survival value for primitive hunter gatherers thousands of years ago are no longer useful for humans who live in buildings with security systems and no longer have natural predators (Teicher et al., 2003). Symptoms of anxiety probably served specific purposes, for instance, if there was a pack of lions in the area where a band of hunter-gatherers was camped, this could lead to an increase in fear and vigilance, which may have made the difference between life and death. These symptoms would persist for long periods, possibly after the threat had been removed. The fight-or-flight response that was formerly critical to survival holds less importance in the modern age when we are rarely under actual physical threat. Activation of the fight-or-flight response involves the peripheral autonomic and cardiovascular systems, with the resultant symptoms of rapid heart rate and respiratory changes looking like Da Costa’s syndrome. If these responses become chronic, they can in fact lead to the development of CVD or acceleration of the disease process (Shively et al., 2009). Similarly, in combat arenas, soldiers develop behaviors such as being jumpy or easily startled that may have survival value, especially if there is an ongoing threat of unexpected attack by insurgents. It is only when the soldier returns from the battlefield and is unable to turn off the “combat mind” that he or she runs into trouble. Behaviors that were adaptive in one environment suddenly become not so in another. Chronic stress not adaptive in modern contexts can therefore lead to psychiatric symptoms in some individuals, in addition to progression of CVD (Shively et al., 2009).

NEUROBIOLOGY OF POSTTRAUMATIC STRESS DISORDER

Recent studies showed that PTSD and other stress-related psychiatric disorders are associated with an increase in CVD (Vaccarino et al., 2007, 2013). PTSD is also associated with a range of other medical disorders, including infectious diseases, diabetes, and asthma (Anda et al., 2008; Sareen et al., 2007; Zatzick et al., 2010). Childhood abuse is also linked to increase risk factors for CVD, including obesity, smoking, alcohol abuse, and drug abuse (Anda et al., 2006; Dube et al., 2003; Williamson et al., 2002).

PTSD is characterized by lasting changes in stress circuits and systems that can also underlie both the development of CVD and symptoms of PTSD (Bremner, 2002a, 2002b; Bremner and Charney, 2010; Bremner and Pearce, 2016; Bremner and Vermetten, 2001). The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the stress response. Early-life stress leads to long-term sensitization of the HPA axis (Coplan et al., 1996; Levine et al., 1993; Makino et al., 1995; Plotsky and Meaney, 1993; Stanton et al., 1988), and lasting alterations in this system are associated with PTSD. Stress also leads to overactivation of the norepinephrine system, which plays a critical role in the fight-or-flight response (Bremner et al., 1996a, 1996b).

A network of brain areas involved in memory and fear, including the hippocampus, medial prefrontal cortex, insula, and amygdala, is involved in the brain's response to stress (Bremner, 2005b, 2011; Campanella and Bremner, 2016; Rauch et al., 2006). The hippocampus plays a critical role in memory and is also sensitive to stress. Studies in animals showed that stress resulted in damage to neurons in the CA3 region of the hippocampus (Gould et al., 1998; Magarinos et al., 1996; McEwen et al., 1992; Nibuya et al., 1995; Sapolsky, 1996; Sapolsky et al., 1990). High levels of glucocorticoids seen with stress were also associated with deficits in new learning (Diamond et al., 1996; Luine et al., 1994). The medial prefrontal cortex mediates extinction through inhibition of fear memories in the amygdala (Milad and Quirk, 2002; Quirk et al., 2006). Peripheral cardiovascular and neurohormonal responses to stress are also regulated by the medial prefrontal cortex (Diorio et al., 1993; Feldman et al., 1995; Frysztak and Neafsey, 1994). This brain area is also sensitive to early stress, which leads to decreased branching of neurons (Radley et al., 2004).

PTSD is associated with lasting alterations in HPA axis function (Yehuda, 2002). For instance, it is related to normal or low cortisol in 24-hour urine collections (Yehuda et al., 1995b, 1996b) and decreased baseline cortisol based on 24-hour diurnal assessments of plasma with 10-minute sampling periods, a flattening of the normal diurnal cortisol curve, and increased pulsatility of cortisol reflecting dysregulation of corticotropin-releasing factor (CRF) release (Bremner et al., 2007; Yehuda et al., 1994, 1996b). Other findings in PTSD include increased cortisol response to personalized scripts of traumatic events (Elzinga et al., 2003) and "neutral" mental stress tasks including mental arithmetic (Bremner et al., 2003), increased suppression of cortisol in response to low doses of dexamethasone (Goenjian et al., 1996; Stein et al., 1997; Yehuda et al., 1993, 1995a, 2002), increased glucocorticoid receptors (GRs) in peripheral lymphocytes (van Zuiden et al., 2011; Yehuda et al., 1991), hypersensitivity of pituitary response to metyrapone (Yehuda et al., 1996a) consistent with increased feedback sensitivity in PTSD, a blunted effect of glucocorticoids (dexamethasone)

on declarative memory function, suggesting decreased sensitivity of GRs in the hippocampus (Bremner et al., 2004), blunted suppression response of T-cell proliferation in leukocytes to dexamethasone (de Kloet et al., 2007), and increased CRF in cerebrospinal fluid (CSF) (Baker et al., 1999, 2005; Bremner et al., 1997b; Sautter et al., 2003) and plasma (de Kloet et al., 2008). Dysregulation of the HPA axis likely contributes to immune system alterations in PTSD, including chronic low-grade inflammation, which is particularly relevant to cardiovascular pathophysiology (Bremner and Pearce, 2016; Michopoulos et al., 2016; Neigh and Ali, 2016; Speer et al., 2018). In summary, these findings are consistent with lasting alterations in HPA function in PTSD that may contribute to an increased risk of cardiovascular disorders.

Increased noradrenergic and peripheral sympathetic function is linked to PTSD (Bremner et al., 1996a, 1996b). Symptoms characteristic of increased noradrenergic function include irritability, increased startle, hyperarousal, and sleep disturbance (Bremner et al., 1996b). Baseline concentrations of norepinephrine and its metabolites were found to be elevated in plasma of PTSD patients (De Bellis et al., 1994, 1999; Lemieux and Coe, 1995; Mason et al., 1988; Yehuda et al., 1998) or normal (Blanchard et al., 1991; McFall et al., 1992; Mellman et al., 1995; Pitman and Orr, 1990; Southwick et al., 1993), while CSF concentrations were increased (Geracioti et al., 2001). Reminders of the original trauma in the form of pictures and sounds or scripts resulted in increased noradrenergic reactivity, shown by an increase in heart rate, blood pressure, and skin conductance, all markers of sympathetic function (Blanchard et al., 1982, 1986; Bremner et al., 1996b; Malloy et al., 1983; McFall et al., 1990; Orr et al., 1993, 1995, 1998; Orr and Roth, 2000), as well as increased norepinephrine and epinephrine in plasma (Blanchard et al., 1991; McFall et al., 1992). Increased baseline heart rate after trauma exposure predicted subsequent development of chronic PTSD (Shalev et al., 1998). Other findings include decreased binding to platelet $alpha_2$ receptors (Perry et al., 1991), decreased activity of the second messenger, cyclic adenosine monophosphate (Lerer et al., 1990; Lerer et al., 1987), and decreased platelet monoamine oxidase activity (Davidson et al., 1985), all consistent with downregulation due to chronic elevations of norepinephrine. The administration of the $alpha_2$ adrenergic receptor yohimbine, which increases firing of noradrenergic neurons in the locus coeruleus, increased PTSD symptoms and anxiety and concentrations of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol in plasma (Southwick et al., 1993, 1997). PTSD patients had a decrease in brain function in the medial prefrontal cortex with yohimbine not seen in healthy controls (decreased frontal lobe function occurs with excessive release of norepinephrine in that brain area) (Bremner et al., 1997a). Based on this study, clinical trials of the alpha-1 antagonist prazosin were conducted, with findings of efficacy for nightmares in PTSD (Raskind et al., 2000). These findings support increased noradrenergic function in PTSD.

Alterations in brain areas involved in the stress response are associated with PTSD (Bremner, 2010). Studies have shown smaller volume and/or altered function in anterior cingulate/medial prefrontal cortex, hippocampus, insula, and amygdala (Andersen et al., 2008; Campanella and Bremner, 2016; Kitayama et al., 2005; Shin et al., 2009; Smith, 2005). These brain areas have projections that regulate peripheral neurohormonal and

autonomic nervous system (ANS) responses to stress that can promote the development of CVD (Soufer et al., 2009; Vaccarino and Bremner, 2015).

POSTTRAUMATIC STRESS DISORDER AND CARDIOVASCULAR DISEASE

PTSD is associated with an increased risk for CVD (Vaccarino et al., 2013), probably through multiple pathways including activation of neurohormonal or brain circuit pathways (Vaccarino, 2018) (Fig. 2). Stress-induced activation of norepinephrine and cortisol or neuroendocrine dysregulation associated with chronic PTSD may lead to an increase in atherosclerosis or vulnerability to cardiac arrhythmias or other consequences that increase the risk for CVD and/or adverse cardiac outcomes. PTSD may lead to adverse CVD outcomes directly or through an increase in risk factors for CVD or unhealthy behaviors including smoking, substance abuse, lack of exercise, or obesity (Beckham, 1999; Butterfield et al., 2000; Dube et al., 2003; Williamson et al., 2002). All of these factors contribute to the fact that an increased risk for CVD is seen in both depression (Carney and Freedland, 2003; Evans et al., 2005) and PTSD (Vaccarino and Bremner, 2013). Behaviors such as stress-induced anger were also associated with increased CVD risk (Boltwood et al., 1993; Burg et al., 1993; Gabbay et al., 1996; Mittleman et al., 1995; Strike et al., 2006; Strike and Steptoe, 2005). Anger and irritability, symptoms of PTSD, could therefore contribute to increased risk of CVD. PTSD is also associated with a decrease in heart rate variability (the normal increase and decrease in heart rate that occurs with respiration) (Shah et al., 2013), which increases the risk of sudden death from arrhythmia. Stress and emotion also have effects on myocardial electrical stability, increasing the risk for cardiac arrhythmias (Kop et al., 2004; Lampert et al., 2002; Lane et al., 2005).

Stress can be standardized in laboratory protocols to understand its effects on CVD (Hammadah et al., 2017a). Mental stress involves the use of public speaking tasks or mental arithmetic (performing problem solving under time pressure with negative feedback) (Bremner et al., 2003; Hammadah et al., 2017a). These “neutral” mental stress tasks used in research on CVD are to be differentiated from trauma-specific stressor such as listening to personalized traumatic scripts often used in PTSD research (Elzinga et al., 2003). Studies have shown that mental stress can induce myocardial ischemia (MSI) in coronary artery disease (CAD) patients using these standardized protocols (Arri et al., 2016; Hammadah et al., 2017b; Ramadan et al., 2013; Vaccarino et al., 2014; Wei et al., 2014a; Wei et al., 2014b). Mental stress-induced MSI often occurs without pain and has been hypothesized to be related to coronary vasospasm (Deanfield et al., 1984; Lacy et al., 1995) and/or peripheral vasoconstriction during stress (Arri et al., 2016; Ramadan et al., 2013; Sullivan et al., 2018; Vaccarino et al., 2018). MSI occurs at lower heart rates than those required for physical stress-induced ischemia, often occurs in patients without physical stress-induced MSI (Krantz et al., 1991; LaVeau et al., 1989; Ramachandruni et al., 2006; Rozanski et al., 1988; Schang and Pepine, 1977), is more common in women than men, and is associated with worse outcomes, especially in younger women (Sullivan et al., 2018; Vaccarino et al., 2009, 2016b). MSI may represent the mechanism by which patients with stress-related mental disorders including PTSD and depression are at increased risk for CAD (Lima et al., 2018; Wei et al., 2014a).

Brain areas involved in memory and the stress response that have been implicated in PTSD, including the medial prefrontal cortex/anterior cingulate/orbitofrontal cortex, likely play a role in MSI (Campanella and Bremner, 2016). This region has been shown to modulate peripheral cardiovascular function, including heart rate variability (Thayer et al., 2009), and peripheral cardiovascular and neurohormonal responses to stress (Campanella and Bremner, 2016; Vaccarino and Bremner, 2017). MSI in CAD patients was associated with increased activation in anterior cingulate, in addition to other brain areas mediating stress, including inferior frontal gyrus, insula, and parietal (Bremner et al., 2018).

As noted previously, PTSD and depression are associated with increased sympathetic function, causing an increase in heart rate and blood pressure, especially with traumatic reminders (Bremner et al., 1996a, 1996b; Delgado and Moreno, 2000). PTSD and depression, as discussed previously, are also associated with increases in stress-induced cortisol release, especially related to specific traumatic reminders (Bremner et al., 2003; Elzinga et al., 2003; Heim et al., 2000). Stress-induced activation of norepinephrine may lead to damage to the endothelium or inner lining of the coronary arteries, as well as accelerated atherosclerosis (Kaplan et al., 1982, 1987; Troxler et al., 1977). An excess in cortisol levels with stress may also increase the risk for CVD by injuring the endothelium (Kemper et al., 1957; Nahas et al., 1958).

Traumatic stress may also mediate its effects through brain areas sensitive to stress that are affected by PTSD and depression, including amygdala, medial prefrontal cortex, and hippocampus. These brain circuits have direct or indirect outputs through the hypothalamus and medial prefrontal cortex to neurohormonal systems (cortisol, norepinephrine) that influence heart function. The medial prefrontal cortex and anterior cingulate are unique in directly mediating cortisol and sympathetic responses to stress via the brainstem (Diorio et al., 1993). The hippocampus and medial prefrontal cortex have inhibitory pathways to the amygdala (Milad and Quirk, 2002; Morgan and LeDoux, 1995; Morgan et al., 1993; Phillips and LeDoux, 1992) that activates the stress response (Davis, 1992; Hitchcock, 1986; Hitchcock et al., 1989; LeDoux, 1993; Miserendino et al., 1990; Rosen and Davis, 1988), including activation of the peripheral stress response through pathways through the lateral hypothalamus that activate cortisol and sympathetic pathways in the periphery (Hitchcock and Davis, 1991).

In addition to PTSD-mediating CVD, stress-related autonomic and cardiovascular alterations may influence symptoms of PTSD. For instance, stress-induced increases in blood pressure and/or heart rate correlate with activation in the right insula, cerebellum, and the anterior cingulate (Critchley et al., 2000). Studies have also implicated insula and somatosensory cortex in representation of peripheral autonomic function (Critchley et al., 2001). We found in patients with CAD that mental stress-induced MSI was associated with activation in the insula, anterior cingulate, inferior frontal gyrus, parietal, and somatosensory cortex (Bremner et al., 2018). These findings could be interpreted as stress-induced brain activations that lead to increased cardiovascular reactivity with associated MSI or as the brain’s response to peripheral autonomic changes with stress. We have also found that stress-induced MSI is associated with an increase in morbidity and mortality compared with exercise-induced MSI (Vaccarino et al., 1999, 2009, 2014). Stress-induced MSI is also more

common in women than men, especially younger women (Vaccarino et al., 2016b, 2018), which is interesting given that stress-induced psychiatric disorders including PTSD and depression are twice as common in women as in men (Kessler et al., 1995). Overall the findings indicate that there is a subpopulation of individuals at increased risk for stress-induced MSI that parallels the increased vulnerability to psychiatric disorders, although the exact relationship between these entities requires further study.

Researchers have investigated the relationship between PTSD and depression and MSI. CAD patients with a history of traumatic stress and depression had increased MSI (Bremner et al., 2009). In two separate studies, depressed CAD patients showed altered anterior cingulate response to stress, with decreases in some areas related to nondepressed CAD patients and increases in those with MSI (Bremner et al., 2019a, 2019b). Increased heart disease mortality in patients with PTSD or depression could be mediated through “silent” MSI mediated by these brain pathways.

CONCLUSIONS AND FUTURE DIRECTIONS

Over 100 years after the death of Da Costa, his description of the effects of traumatic stress on behavior and cardiovascular function continue to be relevant. PTSD is associated with lasting effects on peripheral neurohormonal, immune, and ANS function. Changes in cortisol and norepinephrine function could increase the risk of CVD observed in PTSD patients, as well as with other stress-related mental disorders including depression. Alterations in autonomic function likely underlie symptoms of PTSD, including recurrent and intrusive thoughts about traumatic events. Emerging findings show that PTSD is no longer a pure brain-based disease and that alterations in whole-body physiological systems first observed by Da Costa need to be taken into account. This approach suggests that treatments focused on neuropsychopharmacology may have limitations. New approaches are needed, such as neuromodulatory interventions that have effects on peripheral physiology. Electrical stimulation of the vagus nerve, associated with decreased peripheral autonomic and sympathetic function and inflammatory function, as well as enhancement of parasympathetic tone, with modulatory effects on anterior cingulate and other brain regions involved in stress, represent some of the potential approaches (Bremner and Rapaport, 2017). Vagal nerve stimulation has been shown to have these salutary effects when paired with both mental stress and personalized traumatic scripts (Bremner et al., 2019b; Gurel et al., 2018, 2020). Future treatment developments should continue to target these peripheral stress physiological systems.

DISCLOSURE

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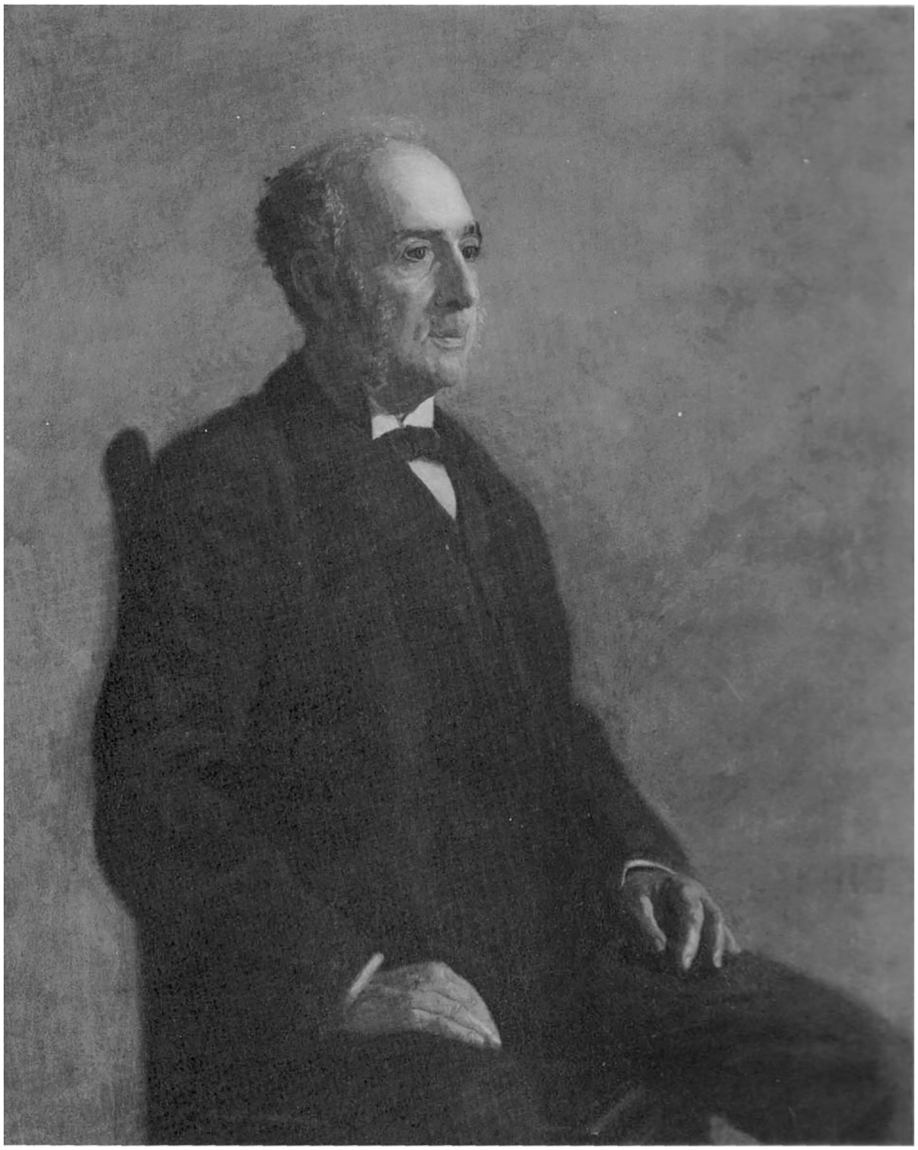

FIGURE 1.

Jacob Mendes Da Costa, American Physician. Portrait by Thomas Eakins, Scanned from "*Thomas Eakins: Volume II*" by Lloyd Goodrich. Harvard University Press, 1982. ISBN 0674884906, Public Domain. Available at: https://commons.wikimedia.org/w/index.php?curid=6821493. Accessed February 12, 2019.

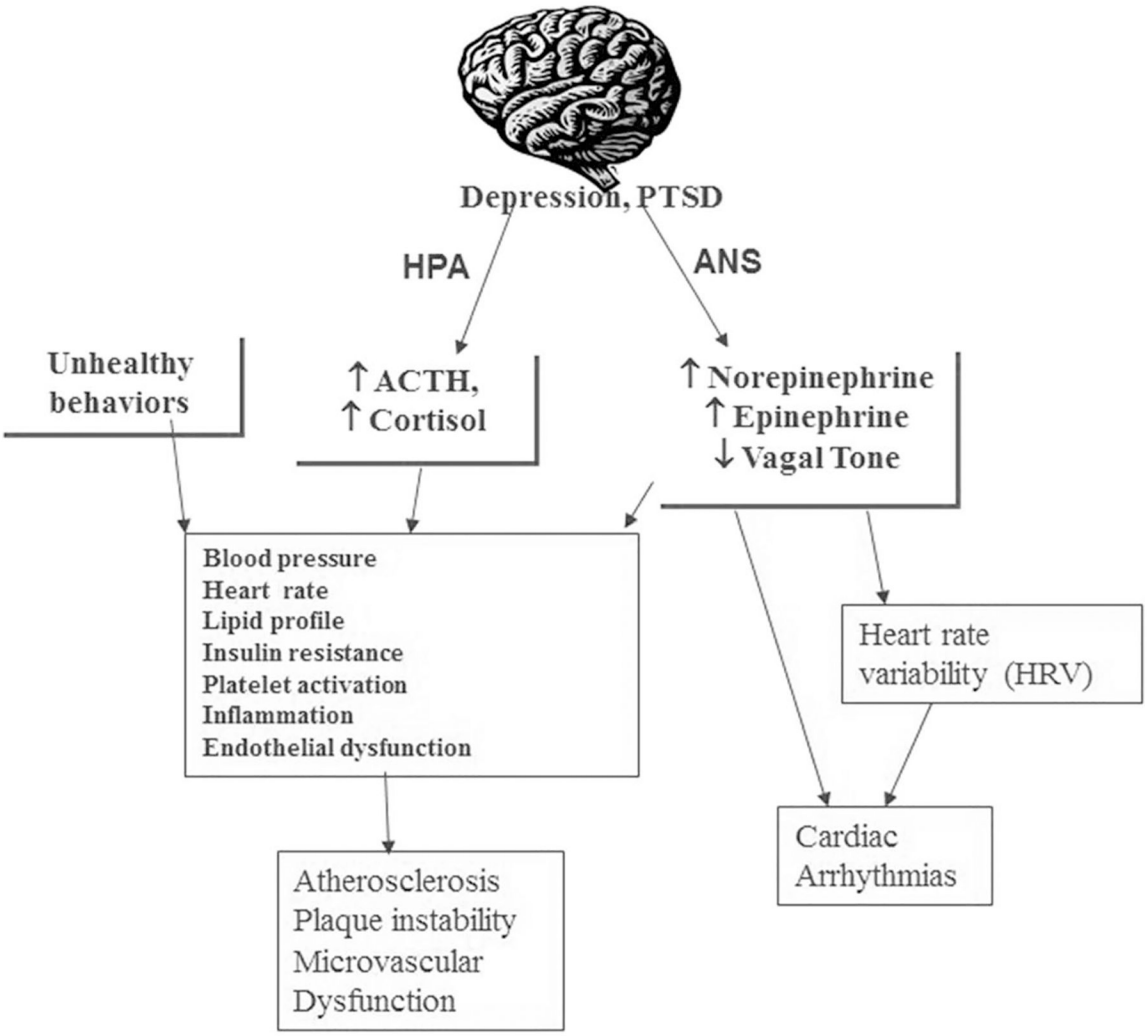

FIGURE 2.

Model of how stress acts through the brain to affect CVD in patients with PTSD and depression. Stress acts through the brain to activate the HPA axis and ANS. This leads to enhanced cortisol release and sympathetic (norepinephrine) that affect electrical properties of the heart, activation of blood pressure and heart, and changes in inflammation, which lead changes in peripheral vascular reactivity, all of which increase the risk for CD. Adapted from Vaccarino V, *Drugs of Today*, 2000.