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Cardiovascular Reactivity in Posttraumatic Stress Disorder and Depression

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ABSTRACT

Exaggerated cardiovascular reactivity (CVR) to stress has been implicated in the increased risk for cardiovascular disease (CVD) in individuals with posttraumatic stress disorder (PTSD), yet mixed results have been reported. The CVR research may have been confounded by underrepresentation of women, few studies using sophisticated cardiovascular measurement, and a lack of analyses of PTSD symptom clusters. The purpose of the present study was to examine if young civilian women ($M \pm SD$ = 29.89±7.33) with PTSD (n=17) demonstrate greater CVR than women with depression (n=12) or no mental illness controls (n=18), and to explore the relationships between CVR and PTSD symptom clusters. Participants were 56% Caucasian, 21% African American, 19% Hispanic, and 4% other. Systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), and impedance cardiography derived cardiac output (CO) and total peripheral resistance (TPR) were utilized to examine CVR during speech preparation/delivery and math tasks. Between-group effects were observed during speech preparation - specifically, lower DBP reactivity for the PTSD group compared to the depression group ($p < .05$). Between-group effects were also evident during speech delivery, with a trend toward lower DBP reactivity for the PTSD group than the depression group ($p < .08$), higher CO reactivity for the PTSD group than controls ($p < .01$), and lower TPR reactivity for the PTSD group than the depression ($p < .01$) and control groups ($p < .01$). PTSD severity scores for DSM-IV-TR and DSM-5 were used as independent predictors of CVR in multiple regressions variables. The DSM-IV analysis did not provide significant associations. The DSM-5 yielded significant associations of avoidance and arousal clusters with SBP reactivity during math, a significant association

avoidance with DBP reactivity during math, and significant associations of avoidance and arousal with HR reactivity during math. Further exploration of PTSD symptom clusters may provide a clearer picture of the relationship between PTSD/CVR. Higher reactivity and lower reactivity may both be associated with risk for CVD, albeit through separate mechanisms.

CHAPTER I

Statement of the Problem

Data from the National Comorbidity Survey Replication have reported lifetime posttraumatic stress disorder (PTSD) prevalence rates of 6.8% (Kessler et al., 2005). The risk of PTSD by the age of 75 has been reported at 8.7% based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria (APA, 2013). Several studies and reviews have provided evidence for negative health symptoms, increased illness, and higher all cause mortality in people with PTSD (Barrett et al., 2002; , Boscarino, 2008a; Kimerling, Clum, & Wolfe, 2000; Löwe et al., 2011; Ouimette et al., 2004; Qureshi, Pyne, Magruder, Schultz, & Kunick, 2009; Seng, Clark, McCarthy, & Ronis, 2006; Wagner, Wolfe, Rotnitsky, Proctor, & Erickson, 2000). Therefore, individuals with chronic PTSD may suffer disability and impairment from a decrease in mental health and the decline of their physical health over time (Levine, Levine, & Levine, 2014). In particular, research has demonstrated a relationship between PTSD and the development of cardiovascular disease (CVD). Recent reviews of the literature provide support for an association between PTSD and CVD risk factors such as elevated blood pressure (BP) and circulating catecholamines (i.e. norepinephrine and epinephrine; Coughlin, 2011; Dedert, Calhoun, Watkins, Sherwood, & Beckham, 2010; Kibler, 2009; McFarlane, 2010;). Support was also found for dysfunction of the hypothalamic-pituitary-adrenal axis, increased sympathetic nervous system (SNS) activation, hypertension, hyperlipidemia, and coronary heart disease (Dedert, Becker et al., 2010; McFarlane, 2010; Sareen et al., 2007; Yehuda, 2002). Additionally, Dedert, Calhoun et al. (2010) reported evidence in the literature for an association between PTSD

and endothelial dysfunction and alterations in the parasympathetic nervous system (PNS) in patients with PTSD.

The literature cited above is part of the growing evidence for the association between PTSD and CVD. Yet the mechanisms that underlie psychological risks for CVD have historically been less clear than the main effects (e.g. Carroll, 2011; Dedert, Calhoun et al., 2010; Qureshi et al., 2009). One potential mechanism that has received considerable attention, yet resulted in mixed findings in PTSD studies, is the construct of stress reactivity (Buckley & Kaloupek, 2001; Hopper, Spinazzola, Simpson, & Van der Kolk, 2006; Hughes, Dennis, & Beckham, 2007). Differences across stress reactivity lab studies have been attributed to the type of task used (e.g. cold pressor, speech task, math task; Schneiderman & McCabe, 1989), measurement techniques and equipment (Breithaupt, Erb, Neumann, Wolf, & Belz 1990; Manuck, 1994), situation and setting (at rest vs. experimental, laboratory vs. natural setting ; Beckham, Flood, Dennis, & Calhoun, 2009; Buckley & Kaloupek, 2001; Buckley, Holohan, Greif, Bedard, & Suvak, 2004), and parameters of cardiovascular function [e.g. systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), Cardiac Output (CO), and total peripheral resistance (TPR); Kelsey, 1993]. Various biological mechanisms have been shown to be involved in cardiac reactivity such as the sympathetic and parasympathic divisions of the autonomic nervous system, neuroendocrine responses, and adrenocortical hormones (e.g. Krantz & Manuck, 1984; Lovallo & Gerin, 2003; Schommer, Hellhammer, & Kirschbaum, 2003).

Investigation of the impact of PTSD on CVD has been confounded by the overlap between PTSD and depression symptoms and the degree of comorbidity among these two

disorders (Campbell et al., 2007; Gerrity, Corson, & Dobscha, 2007; Green et al., 2006, Kessler et al., 2005). Sleep difficulty, diminished pleasure and loss of interest, trouble concentrating, and irritability, are part of the symptom profile for both disorders (APA 2000; APA 2013; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Both PTSD and depression are associated with increased CVD risk (Carney, Freedland, & Veith, 2005; Dedert, Calhoun et al., 2010; Kibler, 2009; Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007; Van der Kooy et al., 2007), therefore it is necessary to evaluate the impact of PTSD while controlling for depression. Comparing PTSD and depression groups in the present study may permit investigation into whether there are different mechanisms linking PTSD and depression to CVD. Although there may be a high degree of overlap between the cardiovascular pathophysiology of PTSD and depression, there is preliminary evidence suggesting increased risk for CVD in PTSD populations, over and above the risk conferred by depression (Boscarino, 2008b; Kibler, Joshi & Ma, 2008).

Historically, research examining the relationship between CVD and PTSD was conducted with male veterans (e.g. Beckman et al., 2002; Boscarino, 2008b; Buckley et al., 2004; Prins, Kaloupek, & Keane, 1995). A limited amount of studies have focused on PTSD in civilian populations and women in particular (Beckham et al., 2009; Clum, Calhoun, & Kimerling, 2000; Dobie et al., 2004; Kibler et al., 2012; Kubzansky, Koenen, Jones, & Eaton, 2009). Results from the National Comorbidity Survey (Kessler et al., 2005) found that women exposed to traumatic experiences are over two and a half times as likely as men to have lifetime incidence of PTSD (9.7% vs. 3.6%). Results also showed that women reported more exposure to high-impact trauma and traumas with higher risk of PTSD development (e.g. rape, sexual molestation, physical attack,

childhood physical abuse or being threatened with a weapon). Additionally, exposure to trauma in women was twice as likely to develop into PTSD (20.4% vs. 8.2%; Kessler et al., 2005). Research examining gender differences, and the relationship between PTSD and CVD, have shown mixed results. Some studies have suggested that women with PTSD evidence the same degree of CVD risks relative to men with PTSD (Dobie et al., 2004; Hughes, Feldman, & Beckham, 2006; Kibler et al., 2012; Mamun et al., 2007). Other studies have found differences in BP and HR reactivity, with greater BP reactivity in men and greater HR reactivity in women (Veit, Brody, & Rau, 1997).

Another area that has begun to receive attention is the exploration of PTSD subtypes based on symptom clusters. Lanius et al. (2010) have proposed two PTSD subtypes; 1) a dissociative subtype, characterized by higher symptom loading in the avoidance and numbing cluster of PTSD symptoms, and 2) a reexperiencing/hyperaroused subtype, characterized by higher symptom loading for reexperiencing and arousal symptoms. Findings in this area point towards distinct central nervous system (CNS) correlates for each subtype based on overmodulation or undermodulations of various brain regions (Lanius et al., 2010). Although a few studies have examined correlations between health variables and symptom clusters, the research in this area is scarce and warrants further exploration (Kimerling et al., 2000).

The purpose of the current review is to examine the literature on CVD risk and CVR , the methods of measurement, the impact of PTSD after controlling for depression, the mechanisms that might underlie the relationship between PTSD and CVD, and the correlation of PTSD subtypes and cardiovascular disease and reactivity.

CHAPTER II

Review of the Literature

PTSD and CVD

The association between PTSD and CVD has been demonstrated in the literature with various populations exposed to traumatic events such as war veterans (Boscarino, 2008b), police officers (Violanti et al., 2006), survivors of childhood trauma (Goodwin & Stein, 2004), women (Kubzansky et al., 2009) and the general population (Spitzer et al., 2009). PTSD has been linked to increased CVD mortality (OR= 2.6 – 3.2; Boscarino 2008a), heart failure (OR = 3.4; Sptizer et al., 2009), angina (OR = 2.4; Sptizer et al., 2009), negative health behaviors (i.e. smoking, substance use, obesity, sleep problems; Kibler, 2009; Kibler et al., 2012; Vieweg et al., 2007; Weaver & Etzel, 2003; Woods, Hall, Campbell & Angott, 2008), and greater illness burden (Schnurr & Green, 2004). Boscarino (2008b) found evidence for an increase of early age CVD related mortality in individuals with PTSD. Being positive for PTSD at baseline in this study resulted in double the risk of early CVD onset and a 5-point increase in PTSD measures resulted in almost a 20% increase in CVD-related death. Another prospective study examining health outcomes in a cohort of adults with stable CVD, reported that individuals with PTSD had greater symptom burden (odds ratio, 1.9), more functional limitations (odds ratio, 2.2) and lower quality of life (odds ratio, 2.5) compared with non-PTSD groups (Cohen et al., 2009). These studies highlight the relationship between PTSD and negative cardiovascular outcomes.

A growing body of research has focused on the relationship between elevations in CVD behavioral risk factors and PTSD (de Assis et al., 2008; Dennis, Clancy &

Beckman, 2007; Kibler et al., 2013; LeardMann et al., 2011; McFarlane, 2010, Motivala 2011; Vrana et al., 2009). Various studies have found support for the role of PTSD in the development of obesity (Dedert, Becker et al., 2010). In particular studies of women with PTSD suggest the existence of a higher prevalence of obesity than women without PTSD. Rates of overweight and obesity in women with PTSD have been reported to be approximately 2 to 4 times higher than women without PTSD (Kibler et al., 2012; Lemieux & Coe, 1995; Mamun et al., 2007; Perkonigg, Owashi, Stein, Kirschbaum, & Wittchen 2009). Additionally, the report of a significant association between overweight and obesity in PTSD female samples has not always held for male participants. In contrast, support in the literature has been found for higher serum lipid levels in PTSD male samples, suggesting lifestyle factors such as unhealthy eating habits and inactivity (Filokovic et al., 1997; Kagan, Leskin, Haas, Wilkins & Foy, 1999). Although research examining alterations in serum lipid levels such as cholesterol, triglycerides, low density lipoproteins and reductions in high density lipoproteins in female samples are scarce, preliminary evidence reveals significantly higher triglyceride levels and significantly lower high-density lipoproteins in women with PTSD compared to a no mental illness group (Kibler et al., 2012). Preliminary evidence for higher rates of inactivity in individuals with PTSD reported significant reductions in physical activity after PTSD onset (26% vs 14%; Assis et al., 2008).

Magee, Iverson, Huang, and Caputi (2008) suggested that sleep disturbances may be one of the links between obesity and PTSD. Sleep disturbances including difficulty falling or staying asleep, nightmares, increased stage 1 sleep and REM density, and reduced slow wave sleep have been reported for individuals with PTSD (Deviva, Zayfert,

Pigeion & Mellman, 2005; Kobayashi, Boarts & Delhanty, 2007; Mellman, Pigeon, Nowell & Nolan, 2007; Zayfert & DeViva, 2004). The relationship between PTSD and increased smoking may also provide an increased risk for CVD. Individuals with PTSD have reported twice as much smoking, heavier smoking and more severe nicotine dependence than non-PTSD samples (Beckham et al., 1997; Dobie et al., 2004; Shalev, Bleich & Ursano, 1990; Weaver & Etzel, 2003).

In summary the literature has provided substantial support for the relationship between individuals with PTSD and the development of CVD. However, the mechanisms responsible for this relationship remain unclear. Additionally, the research in this area has identified gender differences, but historically women with PTSD have been understudied. Continued investigation into this relationship, particularly with female populations, is warranted.

Depression, PTSD and CVD

Reviews of the literature and meta-analysis' have indicated that major depressive disorder is a risk factor and a unique contributor to the development of cardiovascular disease (Carney, Freedland & Veith, 2005; Kibler & Ma, 2004; Rafanelli, Milaneschi, Roncuzzi, & Pancaldi, 2010; Rugulies, 2002; Van der Kooy et al., 2007). Studies have suggested that even milder forms of depression, such as dysthymia and depressive mood, present as significant risk factors for cardiac disease (Rafanelli et al., 2010; Rugulies, 2002). Major depressive disorder (MDD) ranks as the most prevalent lifetime disorder (approximately 17%; Kessler et al., 2005). Estimated rates of concurrent PTSD and depression have been reported in the literature to be between 33% and 40% (Campbell et al., 2007; Gerrity et al., 2007; Green et al, 2006; Löwe et al., 2011). Due to this high rate

of comorbidity and the relationship between MDD and CVD, research has focused on examining the relationship for PTSD and negative health outcomes, while controlling for MDD.

Studies have found that individuals with PTSD report worse health outcomes, increased negative health symptoms (i.e. muscular, gastrointestinal, respiratory, sexual, pain), reduced physical health functioning (Zayfert, Dums, Ferguson, & Hegel, 2002); more disability and lower health quality of life (Campbell et al., 2007; Clum et al., 2000; Cohen et al., 2009), increased risk factors for CVD and CVD mortality (Boscarino, 2008a; Kibler, 2009; Kibler et al., 2012), than individuals with depression. Higher levels of PTSD symptoms have been related to increased risk of CVD in older men (Kubzanzsky et al., 2007) and women (Kubzansky et al., 2009) even after controlling for depression.

In research assessing CVD risk variables such as alterations in lipid levels, differences between patients with PTSD alone and patients with PTSD plus depression were compared. Increased serum cholesterol, low-density lipoproteins, triglycerides and reduced high-density lipoproteins were found in Vietnam veterans with PTSD, but no differences were found between veterans with PTSD and depression or without depression (Kagan et al., 1999). An investigation using data from the National Comorbidity Survey found evidence for higher rates of hypertension among individual with depression compared to individuals with no mental illness. Results from this study also indicated significantly higher rates of hypertension for individuals with PTSD only and individuals with PTSD and a history of depression, over and above the rates for individuals with depression alone (Kibler, 2009).

A depression treatment outcome study comparing individuals with depression and PTSD, and a depression only group, revealed delayed treatment response and more impairment after treatment, for the depression plus PTSD group, despite having similar rates of change in depression (Green et al., 2006). O'Donnell, Creamer and Pattison (2004) examined the relationships between PTSD, depression and comorbid PTSD/depression at 3 months and 12 months post trauma in a group of 363 injury survivors. In this study, 92% of the participants with depression at 3 months, no longer met criteria at 12 months. Yet for the PTSD group and PTSD/depression group 63% and 60%, respectively, still met diagnosis for one of the three diagnoses at 12 months (PTSD, depression or comorbid PTSD/depression). These researchers suggest that single depression at 3 months may be a different construct, while PTSD and PTSD/depression at 3 months are more similar and may represent the same construct. This research highlights the impact of PTSD over and above depression and suggests that further research should control for depression.

Link between Cardiovascular Stress Reactivity and CVD

The association between psychological stress and markers for cardiovascular disease such as myocardial ischemia, hypertension, endothelial dysfunction, lipid variables [i.e. elevated cholesterol, triglycerides and low-density lipoproteins (LDL) and lower high density lipoproteins (HDL)], autonomic dysregulation in both sympathetic and parasympathetic branches, baroreceptor sensitivity, and dysfunction in the HPA axis, have received attention in the literature for some time (Dedert, Calhoun et al., 2010, Kendall-Tackett, 2009, Krantz & Manuck, 1984; Pickering, Phil & Gerin, 1990; Proietti et al., 2011; Schommer et al., 2003; Sheps et al., 2002; Sherwood & Turner, 1995).

Proietti et al. (2011) reported that myocardial ischemia may be induced by a variety of responses to psychological stress. This review supported findings that a combination of endothelial dysfunction, hemodynamic effects and coronary vasoreactivity could play a role in myocardial ischemia. Studies supporting this connection have reported mental stress induced ischemia to be predictive of death in patients with coronary heart disease (Sheps et al., 2002). Additionally, in patients with silent myocardial ischemia (SI), HR reactivity during a speech role-play task was associated with SI (Brown, Katzel, Neumann, Maier & Waldstein, 2007). In spite of the evidence for a relationship between psychological stress to CVD endpoints, research has not been able to identify direct effects for this relationship. Yet evidence for CVR as an intervening variable in this relationship has received substantial support (Bongard, Al'Absi & Lovallo, 2012). Of particular interest is the examination of cardiovascular reactivity (CVR) markers such as BP and HR, and the variety of factors that influence them. Investigators have put forth a reactivity hypothesis wherein risk for hypertension and cardiovascular disease can be identified by the degree of exaggerated CVR to laboratory psychological stressors (Krantz & Manuck, 1984; Manuck, 1994). This hypothesis may also provide a mechanism for identifying individuals or subgroups that may be at risk for the development of CVD (Lovallo & Gerin, 2003). More recently, investigations have suggested that instances of blunted CVR may also represent a risk for CVD through different pathophysiological mechanisms than hyperreactivity (Lovallo, 2011; Phillips & Hughes, 2011).

The impact of psychological stressors on CVR has been examined in order to understand the mechanisms which may underlie the development of cardiovascular

disease (Bongard et al., 2012; Kamark & Lovallo, 2003; Krantz & Manuck, 1984; Manuck, 1994; Phillips & Hughes, 2011; Sherwood & Turner, 1995; Treiber et al., 2003). Much of the work in the area of CVR has focused on exaggerated HR and BP responses to behavioral stimuli as mediators in the development of primary or essential hypertension (EH) and CHD (Carroll, Ring, Hunt, Ford & MacIntire, 2003; Manuck, Kamarck, Kasprowicz, & Waldstein, 1993; Orr, Lasko, Shalev, & Pitman, 1995; Saab, Llabre, Hurowitz, & Frame, 1992). The use of HR and BP for studying the hemodynamic changes related to stress may provide a limited picture and may have led to conflicting results in earlier research in this area (Larsen, Schneiderman, & Pasin, 1986; Manuck, 1994; Pickering et al., 1990; Sherwood & Turner, 1995). A brief review of factors underlying HR and BP is necessary for a more thorough consideration of CVR and disease risk outcomes.

Mechanical and Neural Influences on Cardiovascular Functioning

Heart rate is influenced by hormonal and neural influences and is under the control of both the sympathetic and parasympathetic divisions of the autonomic nervous system (Krantz & Falconer, 1997). The increased or decreased innervation of sympathetic nerve fibers causes corresponding increases or decreases in HR and force of ventricular contractions (or contractility). Additionally, heart rate can increase as a function of hormonal release of epinephrine and norepinephrine into the blood stream by the adrenal medulla (Larsen et al., 1986). Heart rate alterations are also a result of parasympathetic activation via the vagus nerve. Increases in vagus nerve activity on the heart functions to reduce HR, while the inverse, causes increased HR (Krantz & Falconer, 1997). The mean resting HR for healthy adult individuals is about 70 beats per minute

(bpm). Increases in HR in excess of 150 bpm can be found as a result of exercise or emotional stress. During sleep HR can decrease by 10 to 20 bpm (Krantz & Falconer, 1997). Cardiac output is the amount of blood pumped out of the left ventricle per minute and is measured as the product of blood volume ejected during a heart beat (SV) and HR. In turn, SV is determined by; 1) the amount of blood in the ventricle before contraction, 2) output resistance during a cardiac cycle resulting from arterial circulatory pressure, and 3) contractility of the ventricle (Krantz & Falconer, 1997). The peripheral vasculature consists of arteries and arterioles which distribute blood from the heart to various body tissues. Blood ejected from the heart flows into arteries which expand passively and then contract moving the blood to the next vascular segment, and so on. As the distance increases between the heart and the arteries, their diameter also decreases. They become less elastic and rely on the constriction of smooth muscles within the vessels to propel the blood. A change in small arteries and arterioles occurs as a function of sympathetic stimulation on alpha-adrenergic and beta-adrenergic receptors in the smooth muscle cells in the arteries.

Systemic arterial BP is determined by the pumping action of the heart (CO) and the impedance or resistance in the systemic circulation (TPR; Larsen et al., 1986; Manuck et al., 1993, Manuck, 1994). The pumping action of the heart consists of diastole (filling of the ventricles with blood during relaxation and during atrial contractions) and systole (ventricular contraction which pushes blood out of the ventricles and into circulation). Systemic circulation is influenced by sympathetic release of epinephrine and norepinephrine by the adrenal medulla into the blood stream, whereby, alpha-adrenergic receptors in the arteries mediate vasoconstriction and

beta-adrenergic receptors mediate the strength of cardiac contractions and HR (Larsen et al., 1986; Krantz & Falconer, 1997). Thus, mean arterial BP (average arterial pressure during a cardiac cycle), is equal to the product of CO and TPR. Therefore, BP changes can result from factors that impact either CO or TPR.

Mechanisms Mediating between CVR and Disease

The literature continues to address the complexity of the physiological and psychological mechanisms through which CVR may pose health risks and lead to the development of disease states. Elevated automatic activation has been reported in the literature both at rest and during stress for individuals with PTSD. Basal HR elevations of 5.4 to 6.63 bpm have been reported in PTSD groups compared to control samples (Buckley et al., 2004; Forneris, Butterfield, & Bosworth, 2004), as well as a positive relationship between PTSD chronicity and elevated basal HR (Buckley & Kaloupek, 2001). Reviews and studies with PTSD veteran and civilian populations have reported elevations in basal HR and BP in both laboratory settings and during ambulatory monitoring (e.g. Buckley & Kaloupek, 2001; Buckley et al., 2004, Muraoka, Carlson & Chemtob, 1998; Orr, Meyerhoff, Edward, & Pitman, 1998).

Sustained elevations in BP may lead to the development of essential hypertension and endothelial damage, which in turn may lead to coronary artery disease, ventricular hypertrophy, angina pectoris, congestive heart failure, myocardial infarction, atherosclerosis, renal complications and sudden death (Huether & McCance, 2007; Krantz & Manuck, 1984; Treiber et al., 2003). Carroll, Ring, Hunt, Fore and MacIntyre (2003) examined BP reactivity to psychological stress in a large epidemiological study and found that SBP reactivity was predictive of SPB at 5-year follow-up. Upward drift of

DBP was also correlated significantly with DBP reactions to mental stress, and initial resting BP remained a strong predictor of higher resting BP at 5-year follow-up. Data from the 12-year follow-up of this study showed that SBP reactivity was still predictive of resting SBP and upward drift in SBP. Additionally at 12-year follow-up SBP reactivity was significantly associated with increased hypotensive risk (Carroll, Phillips, Der, Hunt, & Benzeval, 2011). Tuomisto, Majahalme, Kähönen, Fredrikson, & Turjanmaa (2005) found similar result for the prediction of future casual and ambulatory SBP from reactivity to active coping tasks.

A review of the literature supports the theory of CVR in the development of preclinical and clinical disease states (Treiber et al., 2003). In particular, endothelial dysfunction has been examined as a factor in the early development of atherosclerosis. Studies examining CVR to mental stress with young populations have found that increased CVR may be linked to impaired parasympathetic and sympathetic regulation leading to carotid artery intima-media thickness (IMT; Chumaeva et al., 2009; Chumaeva et al., 2010; Lambiase, Dorn & Roemmich, 2012; Roemmich et al. 2009; Salomon, 2005). Carotid artery intima-thickness has been observed as an index of subclinical atherosclerosis and has therefore been used to examine the role of CVR in the development of CVD (Heponiemi et al., 2007; Lambiase et al. 2012; Roemmich et al., 2009). Eller, Malmberg & Bruhn (2006) found support for a relationship between CVR to psychological stress and IMT by examining HRV during stress tests and sleep. This study examined the relationship between HRV and IMT in 2002 and progression of IMT over a 4-year period (1998-2000) in a sample of men and women. Heart rate variability (HRV) is expressed as the ratio of low frequency (LF = 0.04-0.18Hz; resulting from

changes in sympathetic and vagal tone) and high frequency (HF = .018 – 0.4 Hz; primarily resulting from changes in vagal tone; Malik, 1996). An association has been found between increased HR and reduced HRV (Malik, 1996). Heart rate variability during stress tasks and sleep were analyzed recorded and reanalyzed 4 years later (Eller et al., 2006). Results revealed a negative association between HRV during the stress tasks and IMT and IMT progression for men only. Women had a non-significant association in the same direction. Additionally, men with greater IMT measures showed higher HRV during sleep. Higher HRV during sleep could reflect more sympathetic tone, low vagal tone or both concurrently. Heponiemi et al. (2007) examined the association between HR, respiratory sinus arrhythmia (RSA; an index of parasympathetic control) and PEP (an index of cardiac sympathetic regulation) and IMT during a mental arithmetic task and speech delivery task in a prospective epidemiological study. Results from this study found evidence that, after controlling for CVD risk factors (e.g. BP, obesity, lipid levels), higher reactivity in HR, RSA and PEP and better HR recovery were associated with lower IMT. These results indicate that CVR's effect on IMT may be mediated by HR recovery.

Studies examining IMT in younger samples also found evidence for CVR stress reactivity (e.g. arithmetic, speech, mirror tracing) as a predictor. Chumaeva et al., (2010) found that participants (age 24-29) with higher flow-mediated dilatation (FMD; an index of endothelial dysfunction) and better RSA recovery after acute mental stress had lower IMT. Participants with low FMD and slower PEP recovery had higher IMT. These results indicate that better recovery after acute mental stress may be associated with less preclinical atherosclerosis. Low RSA reactivity during laboratory tasks has been found

to be predictive of resting RSA 3 years later in children and adolescents, indicating that vagal control is predictive of future vagal control (Salomon, 2005). A positive association between greater SBP reactivity and greater IMT, in healthy children (ages 8-12), points to increased risk of developing CVD in adulthood (Roemmich et al. 2009). Increased carotid artery intima-media thickness (CIMT) in adolescents (ages 13-16) was also found to be associated with increased traditional, as well as excess, SBP during psychological stress (Lambiase et al., 2012). In these studies SBP reactivity, but not HR reactivity was predictive of higher IMT (Roemmich et al., 2009; Lambiase et al., 2012). These results indicate that SBP reactivity may be particularly useful in early detection of CV pathogenesis.

Role of HPA-Axis and Allostatic Load

In addition to the damage caused by mechanical (hemodynamic) processes, various biochemical processes, in the form of adrenal-cortical hormones and catecholamines, can also cause damage to vascular structures and promote cardiac disease (Huether & McCance, 2007; Krantz & Manuck, 1984). Chronic activation of the HPA axis can begin a cascade of physiological responses increasing allostatic load and promoting cardiovascular disease (Kendall-Tackett, 2009). The normal stress response is characterized by arousal of the sympathetic nervous system, which causes adrenergic stimulation and the release of norepinephrine. In turn the adrenal medulla releases catecholamines (epinephrine and norepinephrine) into the blood stream. Concurrently the corticotrophin releasing hormone (CRH) released by the hypothalamus promotes release of prolactin, growth hormone, adrenocorticotropic hormone (ACTH), and antidiuretic hormone (ADH) by the pituitary gland. Thereafter ACTH stimulates the

adrenal cortex which releases cortisol, which acts as a feedback loop returning the system to homeostasis (Huether & McCance, 2007; Yehuda, 2009). Evidence for the role of sympathetic and parasympathetic nervous system dysregulation has gained attention in the PTSD literature.

The allostatic load model proposes that in the short term these adrenocortical and autonomic nervous system reactions serve as protective mechanisms for the human organism (McEwen, 2000). During acute stress, cortisol and catecholamines mediate the adaptation of several body systems necessary for dealing with psychological or physical threats to the integrity of the individual. This activation occurs in response to both real and imagined threats. Allostatic load (maintaining stability or homeostasis through change), is the cost of engaging these systems to deal with challenges and then restoring them to homeostasis (McEwen, 2000). This model proposes 4 conditions that lead to allostatic load; 1) repeated exposure to various novel stressors, 2) a lack of adaptation by the organism, 3) extended exposure to stress response variables due to delayed shut down of stress response, and 4) inadequate response. These four conditions individually and together, may play a role in the connection between stress reactivity and negative health outcomes, in particular CVD endpoints (e.g. endothelial dysfunction, hypertension, myocardial ischemia). An example of this can be seen when the HPA axis stimulates the release of catecholamines which serve to increase HR and BP in the face of a stressor. Yet over time, if the organism continues to perceive additional stressors or does not "turn off" once the stressors have passed these elevations in BP and HR can lead to pathological changes in the cardiovascular system which could lead to atherosclerosis, resulting in strokes and myocardial infarctions (McEwen, 2007). In contrast, inadequate

response to stress may lead to immune dysfunction and behavioral dysregulation (e.g. addictive behaviors, over consumption of food; Lovallo, 2011). Research examining CVR provides evidence for the model of allostatic load.

Measurement of CVR

Measurement of cardiac reactivity using BP alone may yield identical responses for various individuals, yet examination of various measures of cardiac function may show a different picture. Manuck (1994) demonstrated that while mean BP might reveal no significant differences between individuals after engaging in two stress tasks (i.e. Stroop Color-Word Interference Test and a mental arithmetic task), other cardiovascular measures could reveal two distinct patterns of reactivity, cardiac and vascular reactivity. Marked HR acceleration, rise in CO, or shortening of PEP identified cardiac reactivity. While vascular reactivity response patterns demonstrated an increase in TPR, significantly higher DBP and a non-significant yet elevated rise in SBP. Kline, Saab and Llabre (2005) examined myocardial, vascular or mixed (mild or moderate increases in CO and TPR) reactivity in adolescents and found improved recovery for myocardial responders in measures of CO and TPR, while vascular responders did not achieve recovery of CO and TPR at the end of a 30 minute recovery period. These finding are consistent with past work which reported an association between delayed recovery and vascular reactivity (Kelsey, 1993). Vascular reactivity during mental stress has been shown to be associated with endothelial dysfunction (Sherwood, Johnson, Blumenthal and Hinderliter, 1999), stress-induced myocardial ischemia (Goldberg et al., 1996) and left ventricular mass in children (Cook et al., 2001). In addition, Kline et al. (2005) suggested that the delayed recovery in vascular responders may play a role in the

development of CVD. This variation in cardiac response patterns among different individuals highlights the need to observe various components of cardiac and vascular function in order to develop a better understanding of the relationship between stress and the development of CVD.

Task Implications

An important factor in the study of CVR is the understanding that different laboratory task characteristics may elicit different patterns of response and may account for variations in research results (Hurwitz, Nelesen, Saab, & Nagel, 1993; Karmark & Lovallo, 2003). Schneiderman and McCabe (1989) reported that although both active coping tasks (i.e. mental arithmetic; Stroop color-word test; public speaking) and passive coping tasks (i.e. cold pressor; star tracing) produced increases in BP, they did so via two different reactivity patterns. The reactivity pattern in active coping presents as an increase in SBP, skeletal muscle vasodilation, tachycardia, increased CO, increased β_1-adrenergic activity and decreased vagal tone. Reactivity in passive coping tasks, however, presents as increased DBP, skeletal muscle vasoconstriction, bradycardia, increased peripheral resistance, increased α-adrenergic activity and increased vagal tone. Among different active coping tasks differences in reactivity patterns have also been noted. During the two phases of the speech delivery task variations have been noted wherein elevations in blood pressure for the speech preparation phase appeared to be a result of increases in CO (myocardial reactivity), while elevations during the speech presentation appear to result from greater myocardial and vascular reactivity (Hurwitz et al., 1993). Studies using the math stress task have shown a pattern of myocardial reactivity (Pickering et al., 1990; Schneiderman & McCabe, 1989). Task choice alone is

not sufficient to determine pressor response, other factors that need to be considered such as duration of a stimulus, task instruction, novelty, competition, incentive, predictability, controllability, emotional arousal, and social support (Kamark & Lovallo, 2003; Schwartz et al., 2003; Schniederman & McCabe, 1989). Therefore, these factors should be taken into consideration when choosing laboratory task in the study of cardiovascular reactivity.

Kamark and Lovallo (2003) provided a review of the conceptualization and measurement of CVR during psychological tasks. In terms of the reliability of CVR measurement, they reported that test-retest reliability appears to be high when a single task is repeated within a single session and the scores are aggregated or if multiple tasks are measured and data is aggregated across two sessions. These findings lend support for the conceptualization of reactivity as a stable trait. Yet there is currently insufficient data examining reactivity as a stable trait over long periods of time. It is suggested within this review that tasks should be used that capture the greatest amount of variability in reactivity response, such that it is possible to identify high reactors as well as low reactors. Differences in the content validity of CVR tasks should be considered when designing experiments. If tasks are selected that measure different dimensions of reactivity, then aggregated results may no longer provide reliability. The cold pressor test which has been used in various studies on reactivity provides an example of the variability that can exist within one task. In the studies reviewed, hand or foot immersion tends to show increased BP due to peripheral vascular response, and neural responses to pain and temperature. While forehead cold pressor was associated with vasoconstriction and bradycardia. Differences in administration instructions, such as emphasizing

difficulty and effort, may result in larger CV changes (Kamark & Lovallo, 2003). Based on this review, the use of speech preparation, speech delivery and math tasks would provide information for assessing cardiac and vascular reactivity.

Investigating the Relationship between Blunted CVR and CVD

The literature on the relationship of CVR and CVD has shed light on the complexity of this area of research. Although much work has been done in this area, this relationship remains unclear (Phillips & Hughes, 2011). In the last few years the examination of the CVR relationship to CVD has begun to focus on a new paradigm, the role of blunted CVR in the development of CVD (De Rooij & Roseboom, 2010; Lovallo, 2011; Phillips, 2011a). Phillips, Der and Carroll (2009) examined self-reported health data collected from a large community sample in the "West of Scotland Twenty-07" study. Individuals with higher cardiovascular (SBP, DBP, HR) reactivity during the paced auditory serial addition test, were more likely to report excellent or good health at current assessment and at 5 year follow-up. Results from another large cohort study (n=1,423) concurred with these findings (De Rooj & Roseboom, 2010). Improved health may be mediated through the immunological responses during acute exposure to moderate behavioral challenges (Phillips et al., 2009).

Data from the "West of Scotland Twenty-07" study revealed significant negative associations between low reactivity and higher depressive symptoms both currently and at 5 year follow-up (Phillips, 2011b). A relationship between blunted CVR and obesity has also been found in this large community sample (Phillips, 2011b). These authors suggest that high CVR may play a direct role in the development of CVD, while low reactivity may have an indirect effect through behavioral risk factors (i.e. smoking,

obesity). York et al., (2007) reported similar findings, in which a negative association was found for depressive symptoms and CVR in coronary artery disease (CAD) patients during a public speaking task. It is postulated that individuals with high levels of depression may display decreased adrenergic receptor sensitivity and density (York et al., 2007). These results appear to conflict with previous research which has reported a positive relationship between increased CVR and depression.

Lovallo (2011) suggests that we should view any significant deviation in response, whether hyperreactivity or hyporeactivity, as an indication of interruptions in the body's ability to achieve homeostasis and the cost of allostatic load (McEwen, 2007). Therefore we can infer that the relationship between CVR and CVD could be a result of over, under or inefficient activation of the body's defense mechanisms. Additional research assessing both ends of the reactivity spectrum should shed light on the factors impacting the pathophysiology of prolonged stress.

Support for role of cognitive and emotional processes in psychological stress, and it's behavioral, motivational and biological sequela, has been found in the study of neurobiological and physiological adaptations to stress. Lovallo (2005) has proposed a three-level model of neurophysiological activities that may underlie appraisal of and response to stressful events. The first level includes the function of the cerebral hemispheres above the hypothalamus (e.g. hippocampus, frontal cortex, amygdala, bed nuclei of the stria terminals, nucleus accumbens). These structures play a role in the classification and interpretation of events and the formulation of emotional responses. According to this model, sensory inputs into structures at this level are processed by the hippocampus and amygdala. Therefore, these inputs are filtered by memories of previous

events and conditioned emotional responses to the stimuli which result in motivational responses. Outputs from these structures to the second level structures may initiate the fight-or-flight response. In the second level the hypothalamus and brainstem formulate behavioral and physiological responses
(e.g. increased CO, changes in vascular resistance, sympathetic activation, and parasympathetic inhibition). Outputs from the second level act upon peripheral organs and tissues (e.g. heart and vasculature) in the third level, impacting cardiovascular functioning (e.g. CO, peripheral resistance). This mind-body connection may serve to explain the relationship between PTSD and negative cardiovascular outcomes.

Cardiovascular Reactivity and PTSD

Early research on PTSD and CVD focused on stress reactivity as a psychophysiological assessment of the disorder (Orr & Kaloupek, 1997). The emphasis of earlier work with war veterans focused on tasks geared towards measurement of re-experiencing symptoms and hyperarousal as evidenced by the startle response (e.g. Orr & Kaloupek, 1997; Pole, 2007; Shalev & Rogel-Fuchs, 1993). Script driven imagery, combat pictures and/or sounds and loud tones were used to provoke internal and external cues related to traumatic events. Eyeblink or facial electromyogram (EMG), skin conductance (SC) and HR reactivity were measured to assess the magnitude of responses and rates of habituation in PTSD populations (Shalev & Rogel-Fuchs, 1993). Findings suggested a reduction in habituation and increased sensitization in individuals with PTSD as evidenced by larger average EMG and HR responses and slower declines in SC responses in both male veterans and women with histories of childhood sexual

abuse (Orr et al., 1995; Orr, Meyerhoff, Edwards, & Pitman 1998, Pole, 2007; Shalev, Orr, Peri & Schreiber, 1992; Shalev et al., 2000; Shalev & Rogel-Fuchs, 1993).

The PTSD literature has focused on the link between CVD and the effects on the autonomic nervous system in the context of stress reactivity (e.g. Kibler, 2009; Dedert et al. 2010). Earlier work focused on veterans with PTSD and found increased autonomic activation during exposure to war/combat related cues (McFall, Murburg, Roszell, & Veith, 1989; McFall, Murburg, Ko, & Veith, 1990). The relationship between symptoms of hyperarousal and reexperiencing in PTSD and CVR has been a central focus of PTSD and CVD research (Bedi & Arora, 2007). In particular, the exaggerated startle response seen in individuals with PTSD has been hypothesized to cause increases in autonomic nervous system arousal (Pole, 2007). Research using loud sounds or combat sounds produced increases in HR for PTSD participants but not for controls (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Pole, 2007).

Research has also focused on the role of parasympathetic system dysregulation in the development of CVD in PTSD populations (Hughes et al., 2006, Hughes et al., 2007, Pole, 2007). Findings of lower HR variability among PTSD groups may provide some evidence of autonomic dysregulation due to increased sympathetic hyperactivation and reduced parasympathetic activity (Cohen, Kotler, Matar, & Kaplan, 1997; Cohen et al., 1998). Blechert, Michael, Grossman, Lajtman, & Wilhelm (2007) reported increased HR and low respiratory sinus arrhythmia (a measure of vagal control) during a threat of shock stressor in individuals with PTSD, indicating increased sympathetic activity and reduced parasympathetic control.

Baroreceptors are mechanoreceptors that respond to arterial pressure and are under the control of the parasympathetic nervous system. A decrease in HR and BP generally occurs when there is an increase in the stimulation of baroreceptor. The vagus nerve mediates this HR slowing (bradycardia; Larsen et al., 1986). Respiratory sinus arrhythmia (RSA; a cardiac measure of vagal tone) and baroreceptor sensitivity (BRS; a measure of parasympathetic cardiac functioning) have both been shown to have a negative association with increased HR at rest and during stress tasks. Results from studies show that individuals with PTSD demonstrate elevated HR and lower RSA, both at rest and during a threat of shock task, (Blechert et al., 2007, Hopper et al., 2006) Baroreceptor sensitivity was found to be negatively associated with basal HR, further implicating reduced parasympathetic control in individuals with PTSD (Hughes et al., 2006, Hughes et al., 2007). Lower BRS, a BP regulation index, has been associated with poorer sleep in women with PTSD (Ulmer, Calhoun, Edinger, Wagner, & Beckham, 2009), although the direction of the relationship is uncertain. It is unclear whether poorer sleep decreases BP regulation via BRS or reduced parasympathetic regulation increases the risk of developing sleep disturbances.

CVD and Women with PTSD

Results from a meta-analysis on the psychophysiology of PTSD highlight the paucity of and need for research on the consequences of PTSD in civilian female populations (Pole, 2007). In this meta-analysis of 58 studies, the majority of the subjects were survivors of military trauma while less than 11% examined survivors of motor vehicle accidents or sexual assault. Additionally, 73% percent of the subjects with PTSD

in these studies were men. In contrast, lifetime rates of PTSD in women have been found to be double the rates for men (Kessler et al., 2005).

A literature review by Olff, Langeland, Net, and Gersons (2007) suggests that one contributor to higher PTSD rates in women may be higher perceptions of loss of control or threat by women than men. Women may also use more emotion-focused and avoidance-based coping strategies. This review found some evidence for gender differences in trauma responses, wherein women appear to have more dissociative trauma reactions while men show more arousal-related trauma reactions. The literature points towards a more sensitized HPA system in women. Additionally, the influence of sex hormones and oxytocin-mediated responses may play a role in the increased vulnerability and delayed recovery for women with PTSD.

Some of the literature examining CVD and PTSD has highlighted increased negative health effects for women with PTSD (Hughes et al., 2006; Mamum et al., 2007; Perkonigg et al., 2009; Seng et al., 2006; Wagner et al., 2000). Wagner et al. (2000) compared PTSD symptoms in a large sample (n = 2301) of male and female veterans upon return from the Gulf War and their self-reported health 18-24 months later. They found significantly greater self-reports of health problems for female veterans. Women with PTSD may be at greater risk for CVD through increased rates of obesity (Mamum et al., 2007). Perkonigg et al. (2009) reported an odds ratio of 4.3 for obesity in young women with PTSD compared to women without PTSD. Evidence in the literature has revealed lower BRS and greater HR reactivity in women (Hughes et al., 2006; Veit et al., 1997). Women with PTSD have shown a dose-response association between severity and chronicity of PTSD and physical comorbidity (Seng et al., 2006). Kubzansky et al. (2009)

reported a threefold increase in the development of CVD in women with 5 or more symptoms of PTSD. Given the higher rates of PTSD among women and the growing evidence that women with PTSD may be at greater risk for increased negative health effects, more research on CVR with women is needed in order to address the disparity in the literature.

PTSD Symptom Clusters and Health Outcomes

The current diagnosis of PTSD in DMS-IV-TR (APA, 2000) includes a broad range of symptoms which appear to be on one end of a spectrum or the other (i.e. restricted range of affect to irritability and outburst of anger, inability to recall aspects of the trauma to intrusive recollection, avoidance/numbing and hyperarousal). Therefore two individuals with a diagnosis of PTSD may exhibit very different symptom profiles. There exists the potential that an individual with PTSD may not exhibit significant increases in psychophysiological arousal (Pickering et al., 1990), yet much of the research on PTSD and CVD has not accounted for this variability. There is some preliminary evidence in the literature of the physiological and health implications for subtypes of PTSD.

A regression analysis examining the predictive power of the PTSD symptom clusters of re-experiencing, avoidance/numbing and hyperarousal revealed a significant difference for health perception, with only hyperarousal symptoms showing a significant association with poorer health perception. Hyperarousal was the only symptom significantly associated with increased levels of physical symptoms (Kimerling et al., 2000). Hyperarousal symptoms have been implicated as a factor in lower quality of life (QOL) among individuals with PTSD (Doctor, Zoellner, & Feeny, 2011). Somewhat

different results were reported by Woods et al. (2008), wherein only the avoidance cluster predicted physical health problems (i.e. gynecologic, stress, sleep and neuromuscular symptoms). Zoellner, Goodwin, & Foa (2000) found only the reexperiencing cluster to be related to self-reported physical symptoms. These studies present a need for further investigation into the relationship of PTSD symptom cluster loading and health outcomes.

Research on the associations between PTSD symptom clusters and CVD risk and outcomes is also sparse. Symptom clusters may be predictive of CVD risk behaviors such as sleep disturbances. After controlling for depression, drug use, age, gender and age at trauma, Babson et al. (2011) found a relationship between hyperarousal and reexperiencing symptoms and disturbances in sleep maintenance and nightmares. An association was noted between reexperiencing symptoms and sleep onset, whereas, avoidance symptoms were not related to sleep disturbances in this study. In addition to the differences mentioned above, differences in symptom cluster distribution have been found in research comparing individuals with current PTSD, lifetime PTSD, and no PTSD. In a sample of female military veterans, Wolfe et al. (2000) found that those with current PTSD had greater reexperiencing, avoidance/numbing and hyperarousal scores than women with lifetime PTSD or no PTSD. In turn, the lifetime PTSD group reported more hyperarousal than the no PTSD group. The current PTSD group had significantly higher skin conductance response (SCR) and SBP than the other groups. However HR reactivity was not significant. Measures of SCR and SBP were positively associated with hyperarousal symptoms and measures of HR, SCR and SBP positively associated with reexperiencing symptoms. Only SCR was significantly correlated with

avoidance/numbing symptoms. Research examining these associations between symptom clusters and CVR variables may lead to a better understanding of variations in symptom profiles in the PTSD population allowing for more targeted interventions.

Lanius et al. (2010) presented evidence in the literature for two PTSD subtypes, a dissociative subtype and a reexperiencing/hyperaroused subtype, which display different patterns of neural activation. This theory is consistent with findings previously reported suggesting a gender difference in response types, wherein women are more disposed to a dissociative response pattern and men are more disposed towards an arousal response pattern (Olff et al., 2007). The dissociative subtype presents with overmodulation of emotions resulting from a neural activation pattern of midline prefrontal inhibition of limbic regions. The reexperiencing/hyperaroused subtype presents with undermodulation of emotion which may be a result of decreased prefrontal inhibition of limbic regions. Differences in these PTSD subtypes may have implication for treatment as well as for research paradigms. Additionally, these differences in neural response patterns may have a mediating role in the development of CVD. Whereas, increased reactivity may have an effect on CVD through hemodynamic processes and endothelial dysfunction, decreased reactivity may lead to CVD through behavioral risks (e.g. obesity, smoking). Further research is needed to explore the extent to which differences in scores on the PTSD symptom clusters are associated with cardiovascular responses, which may in turn help to explain heightened risk for CVD in this population.

Changes in the Diagnostic Criteria for PTSD in DSM-5

Changes proposed by the posttraumatic stress disorder workgroup have been incorporated into the latest version of the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; APA, 2013; Friedman, Resick, Bryant, & Brewin, 2011). The most distinct change is that Posttraumatic Stress Disorder has been moved from the Anxiety Disorders section to the newly created Trauma- and Stressor-Related Disorders section (APA, 2013; Schnurr, 2013). The criteria for DSM-IV-TR and DSM-5 have been presented side by side in Appendix A. Friedman et al. (2011) summarized the criteria changes as follows: Criterion A1 has been clarified to include: (1) direct exposure to traumatic event; (2) personally witnessing a traumatic event occurring to someone else, (3) learning of a traumatic event occurring to a close relative/friend or aversive details of unnatural death, serious injury or assault, or (4) work-related exposure (e.g. police, first responders) to horrific/gruesome traumatic events. Criterion A2, requiring that a person respond with feelings of intense fear, helplessness or horror, has been eliminated. The 17 symptoms, from DSM-IV-TR criteria B, C and D, have been retained with slight modifications for clarification, and three additional symptoms have been added. Based on the review of studies using confirmatory factor analysis to determine the factor structure of PTSD, the symptoms have been re-organized into four symptom clusters (intrusion, avoidance, cognitions and mood, arousal and reactivity; Friedman et al., 2011; Miller et al., 2013). This new structure was developed by splitting the DSM-IV-TR avoidance and numbing cluster into two distinct symptom clusters, avoidance and cognitions/mood. Two of the new symptoms (erroneous self-blame or other-blame and persistent negative emotional

states) were added to the cognitions/mood cluster. The final new symptom (reckless and maladaptive behaviors) was added to the arousal/reactivity cluster. The chronicity specifiers for acute or chronic PTSD have been removed and the specifier for delayed onset has been changed to delayed expression because many individuals have some symptoms after trauma exposure, but may not experience full PTSD symptoms until a reminder or new trauma exposure occurs (Friedman, 2013).

A specifier has been added to the diagnosis in order to identify a dissociative subtype of the disorder (depersonalization and derealization symptoms). Friedman (2013) reported that the addition of these subtypes was supported by work reflecting four lines of research among individuals with dissociative symptoms and PTSD: (1) studies using functional magnetic resonance imaging (fMRI) indicating that individuals presenting with a dissociative subtype demonstrate elevated prefrontal cortical activation and reductions in amygdala activity; (2) investigations showing an association between individuals with dissociative symptoms and higher incidences of functional impairment, increased severity and chronicity and higher suicidality; (3) work demonstrating that depersonalization and derealization symptoms distinguish individuals with the dissociative subtype; and (4) differences in treatment results for those individuals demonstrating this symptom profile (Friedman, 2013). This subtype was added to facilitate further research consistent with the trauma profile of individuals exposed to prolonged, repeated trauma, referred to as complex PTSD (Herman, 1992).

Summary

Although a growing body of literature supports the relationship between PTSD and CVD, this review indicates the need for further investigation of the mechanisms

underlying this relationship. The role of exaggerated CVR as the mechanism behind this relationship has received support in the literature, but additional research controlling for confounding factors such as comorbid depression, laboratory task, and measurement are needed. In addition, the examination of various parameters of cardiovascular function and reactivity patterns (i.e. cardiac vs. vascular reactivity) may also contribute to the understanding of the impact of PTSD on the development of CVD. This review has also highlighted the need for research investigating the differences in CVD and reactivity based on PTSD subtypes. Additionally, an analyses of the association between the cardiovascular variables and PTSD symptom clusters (DSM-IV-TR three-factor symptom structure and DSM-5 four-factor symptom structure), may provide a better understanding of the variability in CVR. If evidence for differences in CVR patterns is found, then assessment and treatment of PTSD could be better targeted towards these subtypes.

Purpose of the Study

The objectives of this study are: 1) to examine differences in parameters of CVR (SBP, DBP, HR, CO, TPR), between women with PTSD (with or without depression), depression only, and a no mental illness group (control; 2) to examine the relationships of CVR with the severity scores on DSM-IV-TR's three-factor symptom clusters for the PTSD group; and 3) to examine if severity scores on DSM-5's four-factor symptoms clusters for PTSD provide a clearer understanding of these relationships.

Hypotheses

1. Women in the PTSD group will demonstrate significantly greater impedance cardiography derived CVR values (SBP, DBP, HR, CO, TPR) than women in the depression or control groups.

2. Within the PTSD group, the severity scores for the three DSM-IV-TR symptom clusters will account for a statistically significant proportion of the variance in the CVR variables.
3. This exploratory analysis will test whether using the four DSM-5 symptom clusters produces similar results as hypothesis 2.

CHAPTER III

Method

The current study will analyze a subset of data collected from a larger study that examines relationships of PTSD and depression with cardiovascular health risks. The following is a description of the applicable methods and procedures employed.

Participants

Participants were 49 women screened via telephone and recruited into three groups; 1) PTSD group (with or without depression) consisting of women with a PTSD diagnosis or women who did not meet full diagnosis but had significant PTSD symptoms (≥ 4 symptoms with ≥ 1 re-experiencing), 2) depression only group, and 3) a no mental illness group (control). Data from two participants were excluded after outlier analyses. The final sample consisted of 47 women, ages 19 to 49 ($M \pm SD$ age = 29.89 ± 7.33; see Appendix B). Participants self reported ethnicity (55.4% were Caucasian, 10.6% African American, 17.1% Hispanic White, 2.1% Hispanic Black, 10.6% Caribbean Black, 2.1% Asian, 2.1% Bi-racial), income levels (10.6% reported less than $5,000, 6.4% from $5,001 to $10,000, 6.4% from $10,001 to $15,000, 10.6% from $15,001 to $20,000, 6.4% from $20,001 to $30,000, 10.6% from $30,001 to $40,000, 17.1% from $40,001 to $50,000, 14.9% from $50,001 to $75,000, 8.5% from $75,001 to $100,000, and 8.5% over $100,001), education (31.9% reported high school or equivalent, 19.1% associates degree (junior college), 29.8% bachelor's degree, 14.9% master's degree, and 4.3% professional degree (MD, JD, DDS, etc)., and relationship status (63.8% single/never married, 12.8% divorced/separated, and 23.4% married/domestic partner; see Appendix A). Participants for all groups were recruited via therapist referral, through posting and distributing fliers at a community mental health clinic and health fairs, and through

posting an ad on scientific and public websites. All candidates were screened for inclusion and exclusion criteria which included; 1) no history of major chronic illness, 2) pre-menopausal, 3) not currently taking any medication which might significantly influence the physiological measures (e.g. cholesterol lowering agents, beta-blockers, muscle relaxants), and 4) ability to read and speak English fluently.

Participants who were screened as prospective candidates for inclusion into one of the three study groups (PTSD, depression or control) were invited to participate in session I. Further evaluation for inclusion in the study was carried out using the Traumatic Life Events Questionnaire (TLEQ), the Clinician-Administered PTSD Scale (CAPS) and the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID). The TLEQ was used to identify events which qualified for criterion "A" trauma incidents for the PTSD group, and to evaluate the comparisons groups in terms of exposure to extremely stressful events. Participants who reported an extreme stress event were administered the CAPS to determine if they evidenced PTSD symptoms. Additionally, the SCID was administered to assess the presence of any other AXIS I DSM-IV-TR Disorder. Participants who met criteria for PTSD and subthreshold PTSD on the CAPS, without the presence of any other Axis I disorder (except depressive disorders) on the SCID, were invited to participate in the remainder of the study. Participants in the control group who reported exposure to an extremely stressful event on the TLEQ were only eligible to continue in the study if they reported a complete absence of PTSD symptoms during the CAPS interview. Participants in the depression group who reported an extreme stress event on the TLEQ were only eligible to continue participation if they met criteria for a unipolar depressive disorder on the SCID and reported three or less

PTSD symptoms on the CAPS. Participants who met criteria for any other Axis I disorders were excluded from participating in the rest of the study. Participants received an honorarium of $40.00 for the first session and $50.00 for the second session.

Measures

Assessment of Demographic Information and Psychological Distress

Self-Report Questionnaire: Self-report questionnaires were administered to collect demographic information including age, race, ethnicity, family income, marital status and educational level.

Traumatic Life Events Questionnaire (TLEQ). The TLEQ is a brief questionnaire designed to assess exposure to a broad range of traumatic events (e.g. natural disasters, childhood and adolescent sexual contact, physical abuse by intimate partners, severe physical assault). The overall temporal stability (ranged from 5 to 45 days) averaged 8% and the average overall (with a 1-week delay) convergent validity and test-retest reliability were 85% and 88%, respectively (Kubany et al., 2000). Pierce, Burke, Stoller, Neufeld & Brooner, (2009) compared responses to the TLEQ vs. the SCID and found a greater disparity of reported events for women than men. Most of the difference was due to women reporting more events in response to the TLEQ (women *M* = 24.96, *SEM* = 1.07 vs. men *M* = 17.96, *SEM* = 1.09; IRR =1.39, 95% CI = 1.13-1.71).

Clinician-Administered Interview for DSM-IV-TR (CAPS). The CAPS (Blake, 1994) is a structured diagnostic interview for assessment of the 17 core symptoms defined by the DSM-IV-TR for PTSD diagnosis. High scores for reliability and validity have been reported in the literature (Weathers, Keane, & Davidson 2001). Blake (1994) reported a Kappa coefficient of .94 for all symptoms, and Kappa coefficients ranging

from .85 to .87 for the three primary symptom clusters. Strong conversion validity of .84 with the PK Scale (Keane, Malloy, & Fairbanks, 1984) of the Minnosota Multiphasic Personality Inventory-2 (MMPI-2; Butcher, Dahlstrom, Graham, Tellegegen, & Kaemmer, 1989), and .70 with the Mississippi Scale (Keane, Caddell, & Taylor, 1988), has also been reported in the literature. Control group participants were only eligible if they did not meet criteria for any Axis I DSM-IV-TR disorder and did not endorse any PTSD symptoms on the CAPS. The depression group participants were included if they meet criteria for major depressive disorder but did not meet criteria for any other Axis I DSM-IV-TR disorder and reported ≤3 PTSD symptoms on the CAPS.

Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID), research version. The SCID-I is considered the gold standard in semi-structured instruments for the assessment of clinical disorders. The SCID is designed to be administered by a trained clinician and is divided into separate modules which correspond to DSM-IV-TR diagnostic categories. Lobbestael, Leurgans and Arntz (2011) have reported inter-rater Kappa values from 0.61 to 0.83 (M = 0.71). The SCID-I was used to ensure that participants met inclusion and exclusion criteria.

Physiological Assessment

Cardiovascular Reactivity using ECG and Impedance Cardiography. Automated blood pressure measurements during stress tasks were collected and recorded using an automated BP cuff connected to a personal computer. ECG electrodes were placed in a standard 3-lead configuration in order to measure HR and to identify the onset of electromechanical systole. Impedance cardiography is a reliable, non-invasive method of assessing CO, TPR, systolic time intervals and thoracic impedance (Saab et al., 1992).

A standard full band tetrapolar configuration was used to records CVR measures. Four impedance cardiograph tape electrodes were placed at the neck (Z_1, Z_2) and the thorax (Z_3, Z_4) in order to assess CO, TPR and thoracic impedance. Z_1 was placed superior to the suprasternal notch of the thorax, Z_2 was placed exactly 3 cm above it, Z_3 was placed at the xiphoid process, and Z_4 was placed exactly 5 cm below it. Signals from the ECG and impedance cardiography electrodes were sent to a personal computer for data scoring and reduction.

***Stress Tasks*.** Two tasks were employed to induce psychological stress (a speech preparation and speech delivery task, and a mental arithmetic task). For the speech task, the participants were given instructions to formulate and deliver a speech in response to a hypothetical situation where a store security guard accuses them of stealing a belt that they are wearing (which they had purchased at the store three weeks prior) and gets the store manager. The participants were asked to pretend that they requested to speak to the store manager and told him/her their side of the story. The speaking task consisted of a 3-minute preparation phase, followed immediately by a 3-minute speech delivery stage. The arithmetic task consists of performing serial subtractions by steps of 13, out loud for 3 minutes. The participants were told that their performances on both tasks was being videotaped and rated by experts. The speech preparation task and arithmetic tasks have been used to produce cardiac reactivity responses, and the speech delivery task has been used to record both cardiac and vascular reactivity.

Procedures

Participants who were screened as possible candidates for the PTSD group, depression or control group were invited to participate in the study. In order to control

for changes in symptom presentation, the first session (interview) was scheduled in tandem with the second session (laboratory assessment). Participants who failed to attend session two after completing session one were re-interviewed prior to the rescheduled laboratory session. In order to control for menstrual cycle effects on CVR, the participants were asked to call in on the first day of their cycle. Session one was schedule within the first week of the menstrual cycle, and session two was scheduled after menstruation stopped, during the follicular stage (based on the participants estimated cycle length approximately days 4-10) of the menstrual cycle.

At session one, consent was obtained and participants were asked to complete the TLE, and the CAPS and SCID were administered by research assistants (advanced clinical psychology doctoral students). The CAPS and SCID were scored and eligible participants were invited to participate in session two.

At session two, consents were obtained and the participants were asked to complete demographic information (e.g. age, race, ethnicity, family income, marital status and education) and health behavior information (e.g. smoking, physical activity, alcohol use). The participants were provided with an overview of the laboratory protocol. Height, weight, waist circumference and hip circumference measurements were taken. After a five minute rest period, three seated resting BP readings were taken (minutes 05:00, 07:00 and 09:00) using a mercury sphygmomanometer, to assess casual BP. The automated BP cuff and sensors for the ECG and impedance cardiography were attached to the participant and connected to the impedance cardiography equipment (as described above). Cardiograph and ECG sampling was initiated and signals were sampled at 1 kHz per second and stored in a personal computer The participant's gender,

birth date, height, and weight, and the measurement of the distance between the Z_2 and Z_3 electrodes (while standing) were entered into the COP-WIN/HRV software program on a personal computer. The participants were instructed to sit quietly (without talking or moving, keeping eyes open). Timing for the initial rest period was initiated and BP measurements were taken at 11:00 minutes, 12:30 minutes and 14:00 minutes after the beginning of the rest period. The instructions for the speech delivery task (described above) were given and BP was sampled at 00:15 minutes and 01:45 minutes during the speech preparation stage. Instructions to begin delivering the speech out loud were given at 03:00 minutes and BP sampling was taken at 03:15 minutes and 4:45 minutes. At 06:00 minutes the participant was told that the speech delivery task was over and to sit quietly for another rest period. Blood pressure measurements were taken at 00:15, 01:45, 3:15, 04:45, 06:15, 7:45, 9:15, 11:00, 12:30 and 14:00 minutes after the beginning of the rest period. At 15:00 minutes instructions for the arithmetic tasks were given (described above). Blood pressure sampling was done at 00:15minutes and 1:45 minutes from the beginning of the math task. The participant was informed that the task was complete at 03:00 minutes and to sit quietly for another rest period. Blood pressure sampling was taken in the same manner as the post-speech rest period described above. The task order was counterbalanced for each subsequent participant within each group in order to control for task order effects. At 15:00 minutes the participant was advised that the study was over, they were debriefed, questions were answered and the compensation procedure was explained.

Statistical Analyses

Data Reduction

A computer scoring program (COP-WIN) was used to derive average waveform ensembles for the ECG and impedance cardiography signals over 1-minute intervals covering the 15 minutes of the baseline, and speech and math task periods. Cardiac output was calculated as (HR × SV) / 1000. TPR was calculated as MAP/CO × 80. The baseline scores for each task were calculated using the average of the last three values (automated SBP and DBP, HR, CO and TPR calculated by the COP-WIN software) during the rest period preceding each task. There were two measurements taken during task performances which were averaged to represent the cardiovascular reactivity values for each task. Change scores were calculated for all measures (average reactivity value minus average baseline value) as an index of task-induced changes in SBP, DBP, HR, CO, and TPR.

Data Analyses

Demographic characteristics (age, ethnicity, education level, family income, and marital status) and baseline reactivity measures (SBP, DBP, HR, CO and TPR) for the PTSD, depression and control groups were analyzed for significant differences and all data were inspected for normality. A total of 49 women completed both sessions. Data from two participants (one PTSD and one depression) were excluded after outlier analyses were performed. Baseline cardiovascular scores for participants are presented in Appendix B

Test of hypothesis #1: [*Women in the PTSD group will demonstrate significantly greater CVR (SBP, DBP, HR, CO, TPR) than women in the depression or control*

groups.] Three separate (speech preparation, speech delivery and math tasks) multivariate analyses of variance (MANOVA's) were performed comparing task change scores (a residual score calculated by subtracting the baseline level from the task level) for the reactivity values (SBP, DBP, HR, CO, and TPR) among the PTSD, depression and control groups. Post Hoc comparisons were performed using Games-Howell procedure for significant main effects.

Test of hypothesis #2: [*Within the PTSD group, the severity scores for the three DSM-IV-TR symptom clusters will account for a statistically significant proportion of the variance in the CVR variables.]* Exploratory multivariate multiple regression analyses (speech preparation, speech task, math task) were executed, treating the PTSD severity scores for the three DSM-IV-TR symptom clusters (reexperiencing, avoidance/numbing, and arousal) as independent predictor variables, and the reactivity values (SBP, DBP, HR, CO, and TPR) as dependent measures. These analyses examined the unique relationship of each symptom cluster with the cardiovascular reactivity values controlling for other symptoms clusters, and any significant prediction by control variables (i.e. age, education, income). The semi-partial correlation coefficients were analyzed to determine the contribution of variance in CVR variables accounted for by each symptom cluster.

Test of hypothesis #3: [*Explore whether using the four DSM-5 symptom clusters produces similar results as hypothesis 2.*] Exploratory multivariate multiple regression analyses (speech preparation, speech task, math task) were executed, treating the PTSD severity scores for the four DSM-5 symptom clusters (intrusion, avoidance, cognition and mood, arousal and reactivity) as independent predictor variables, and the reactivity values (SBP, DBP, HR, CO, and TPR) as dependent measures. These analyses examined the

unique relationship of each symptom cluster with the cardiovascular reactivity values controlling for other symptoms clusters, and any significant prediction by control variables (i.e. age, education and income). The semi-partial correlation coefficients were analyzed to determine the contribution of variance in CVR variables accounted for by each symptom cluster.

CHAPTER IV

Results

Descriptive Data

Demographic and baseline cardiovascular reactivity values are reported in Appendix B. The sample consistent of civilian women (N = 47) between the ages of 19-49 ($M \pm SD$ = 29.89 ± 7.33) recruited into three groups: 1) PTSD (n = 17), 2) depression (n = 12), and 3) a no mental illness control group (n = 18). Participants were 55.4% Caucasian, 10.6% African American, 17.1% Hispanic White, 2.1% Hispanic Black, 10.6% Caribbean Black, 2.1% Asian, 2.1% Bi-racial. There was a significant difference for group main effects for education level, $F(2,44) = 3.44$, $p = < .05$. Post hoc analysis revealed that the control group had significantly higher scholastic achievement than the PTSD group, ($p < .05$). No significant differences were found between the depression group and the other groups. No other significant differences were found for the remaining demographic variables (ethnicity, income, relationship status, age) or the baseline cardiovascular values (SPB, DPB, HR, CO, TPR).

PTSD, Depression and Control Group Differences in Cardiovascular Reactivity

Speech Preparation Multivariate Analyses of Variance (MANOVA)

A MANOVA was performed to investigate differences between groups (PTSD, depression, control) with reactivity values (SBP, DBP, HR, CO, and TPR) as the dependent variables, during the speech preparation phase. There was a statistically significant omnibus effect for group [$F(10, 82) = 1.98$, $p < .05$; Pillai's Trace = .39, partial eta squared = ..20]. A significant between-group main effects with large effect size (Cohen, 1988, pp. 284-7) was found for DBP reactivity [$F(2,44) = 4.46$, $p < .05$, $\eta^2 = .17$; see Table 1].

Post Hoc comparisons were performed using the Games-Howell adjustment, which indicated that the mean DBP reactivity for the PTSD group (M = 2.35, SD = 5.06) was significantly less ($p < .05$) than the Depression group (M = 9.14, SD = 7.15).

Table 1

MANOVA's: Group Reactivity Scores (SBP, DPB, HR, CO, TPR) for Speech Preparation.

	PTSD Mean (SD)	Depression Mean (SD)	Control Mean (SD)	F	η^2
Speech Preparation					
SBP	7.42	9.67	9.66	0.39	0.02
	(8.85)	(6.03)	(9.11)		
DBP	2.35_{b*}	9.14_{a*}	5.09	4.46*	0.17
	(5.06)	(7.15)	(6.06)		
HR	7.05	4.24	6.36	0.55	0.02
	(7.34)	(6.33)	(7.74)		
CO	.52	.42	.24	0.72	0.03
	(.55)	(.58)	(.86)		
TPR	-55.98	51.75	91.81	2.43	0.10
	(150.46)	(104.64)	(279.81)		

Note. † = $p < .10$, * = $p < .05$, ** = $p <$,01. Standard deviations appear in parentheses below means. Means with differing subscripts within rows are significantly different at the † = $p < .10$, * = $p < .05$, ** = $p < .01$ levels based on Games-Howell post hoc paired comparisons (a = PSTD, b = Depression, c = Control).

Speech Delivery Task Multivariate Analyses of Variance (MANOVA)

A MANOVA was performed to investigate differences between groups (PTSD, depression, control) with reactivity values (SBP, DBP, HR, CO, and TPR) as the dependent variables, during the speech delivery task. There was a statistically significant omnibus effect for group [$F(10, 82) = 2.10$, $p < .05$; Pillai's Trace = .41, partial eta squared = ..20]. Significant between-group main effects with large effect sizes (Cohen, 1988, pp. 284-7) were found for DBP reactivity [$F(2,44) = 3.36$, $p = <.05$, $\eta^2 = .13$]; CO reactivity [$F(2,44) = 5.67$, $p <.01$ $\eta^2 = .20$]; and TPR reactivity [$F(2,44) = 6.86$, $p < .01$, $\eta^2 = .24$; see Table 2].

Post Hoc comparisons were performed using the Games-Howell adjustment, which indicated a trend towards significance ($p < .10$) for lower mean DBP reactivity for the PTSD group ($M = 7.59$, $SD = 7.86$) compared to the depression group ($M = 14.72$, $SD = 8.48$). The CO reactivity for the PTSD group ($M = 1.11$, $SD = .87$) was significantly higher ($p < .01$) than the control group ($M = .34$, $SD = .60$). The TPR reactivity for the PTSD group ($M = -89.77$, $SD = 145.51$) was significantly lower ($p = < .01$) than the depression group ($M = 54.17$, $SD = 89.70$), and significantly lower ($p = < .01$) than the control group ($M = 113.03$, $SD = (212.97)$. There were no significant differences between the depression group and the control group.

Table 2

MANOVA's: Group Reactivity Scores (SBP, DPB, HR, CO, TPR) for Speech Delivery task..

	PTSD Mean (SD)	**Depression Mean (SD)**	**Control Mean (SD)**	**F**	**η^2**
Speech Delivery task					
SBP	14.10 (13.53)	19.00 (8.19)	18.21 (10.01)	0.89	0.04
DBP	$7.59_{b\dagger}$ (7.86)	$14.72_{a\dagger}$ (8.48)	9.93 (5.90)	3.36*	0.13
HR	7.93 (8.40)	10.19 (6.19)	10.50 (7.72)	0.56	0.02
CO	1.11_{c**} (.87)	.83 (.47)	$.34_{a**}$ (.60)	5.67**	0.20
TPR	$-89.77_{b**,c**}$ (145.51)	54.17_{a**} (89.70)	113.03_{a**} (212.97)	6.86**	0.24

Note. † = $p < .10$, * = $p < .05$, ** = $p < .01$. Standard deviations appear in parentheses below means. Means with differing subscripts within rows are significantly different at the † = $p < .10$, * = $p < .05$, ** = $p <$,01 levels based on Games-Howell post hoc paired comparisons (a = PSTD, b = Depression, c = Control).

Math Task Multivariate Analyses of Variance (MANOVA)

A MANOVA was performed to investigate differences between groups (PTSD, depression, control) with reactivity values (SBP, DBP, HR, CO, and TPR) as the dependent variables, during the math task. There was no statistically significant omnibus

effect for group [$F(10, 82) = .98$, $p = .46$; Pillai's Trace = .21, partial eta squared = ..11; see Table 3).

Table 3

MANOVA's: Group Reactivity Scores (SBP, DPB, HR, CO, TPR) for Math Task.

	PTSD Mean (SD)	Depression Mean (SD)	Control Mean (SD)	F	η^2
Math Task					
SBP	8.44	8.51	11.53	0.72	0.03
	(10.25)	(7.16)	(7.37)		
DBP	5.55	2.96	6.64	1.37	0.06
	(6.30)	(4.96)	(6.37)		
HR	5.46	3.11	7.24	1.82	0.08
	(6.90)	(4.85)	(5.22)		
CO	.25	.39	.32	0.15	0.01
	(.64)	(.67)	(.61)		
TPR	31.04	-17.71	81.22	1.65	0.07
	(158.28)	(144.88)	(138.23)		

Note. † = $p < .10$, * = $p < .05$, ** = $p <$,01. Standard deviations appear in parentheses below means. Means with differing subscripts within rows are significantly different at the † = $p < .10$, * = $p < .05$, ** = $p < .01$ levels based on Games-Howell post hoc paired comparisons (a = PSTD, b = Depression, c = Control).

DSM-IV-TR Symptom Clusters and Cardiovascular Variables

Speech Preparation Multivariate Multiple Regression Analyses

Results for the Speech Preparation task did not yield any significant associations for SBP reactivity [$F(6, 10) = 1.19$, $p = .38$]; DBP reactivity [$F(6, 10) = .51$, $p = .79$]; HR reactivity [$F(6, 10) = 1.90$, $p = .18$]; CO reactivity [$F(6, 10) = .67$, $p = .68$]; or TPR reactivity [$F(6, 10) = .81$, $p = .59$; see Tables 4 and 5].

Table 4

DSM-IV-TR PTSD Symptom Clusters and SBP, DBP and HR for Speech Preparation

	SBP Speech Prep			DBP Speech Prep			HR Speech Prep		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	-0.13	2.16	-0.02	1.45	1.42	0.31	-1.39	1.61	-0.21
Avoidance/ Numbing	-2.89	1.58	-0.61	-0.80	1.03	-0.30	-0.73	1.17	-0.19
Hyperarousal	2.18	2.00	0.33	-0.86	1.31	-0.23	0.83	1.48	0.15
R^2(adj)	0.07			-0.23			0.25		
F	1.19			0.51			1.90		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 5

DSM-IV-TR PTSD Symptom Clusters and CO and TPR for Speech Preparation

	CO Speech Prep			TPR Speech Prep		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	-0.19	0.15	-0.37	55.99	39.53	0.41
Avoidance/ Numbing	0.01	0.11	0.03	-38.18	28.81	-0.47
Hyperarousal	-0.05	0.14	-0.12	21.00	36.48	0.19
R^2(adj)	-0.14			-0.08		
F	0.67			0.81		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Speech Delivery Task Multivariate Multiple Regression Analyses

Results for the Speech Delivery task did not yield any significant associations for SBP reactivity [$F(6, 10) = 1.17$, $p = .39$]; DBP reactivity [$F(6, 10) = .38$, $p = .88$]; HR

reactivity [$F(6, 10) = 1.14$, $p = .41$]; CO reactivity [$F(6, 10) = .89$, $p = .54$]; or TPR reactivity [$F(6, 10) = 1.80$, $p = .20$; see Tables 6 and 7].

Table 6

DSM-IV-TR PTSD Symptom Clusters and SBP, DBP and HR for Speech Delivery Task

	SBP Speech Delivery			DBP Speech Delivery			HR Speech Delivery		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	-1.78	3.32	-0.14	1.72	2.27	0.24	-2.19	2.07	-0.28
Avoidance/ Numbing	-2.89	2.42	-0.40	-1.06	1.66	-0.25	-0.03	1.51	-0.01
Hyperarousal	2.19	3.07	0.22	-0.77	2.10	-0.13	1.00	1.91	0.16
R^2(adj)	0.06			-0.31			0.05		
F	1.17			0.38			1.14		

Note: $^{\dagger} = p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 7

DSM-IV-TR PTSD Symptom Clusters and CO and TPR for Speech Delivery Task

	CO Speech Delivery			TPR Speech Delivery		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	0.03	0.23	0.04	21.01	32.30	0.16
Avoidance/ Numbing	0.18	0.16	0.38	-41.38	23.54	-0.53
Hyperarousal	0.11	0.21	0.17	-21.11	29.81	-0.20
R^2(adj)	-0.04			0.23		
F	0.89			1.80		

Note: $^{\dagger} = p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Math Task Multivariate Multiple Regression Analyses

Results for the math task yielded a significant association for SBP reactivity [$F(6,10) = 3.48$, $p < .05$; see Table 8]; after adjusting for the control variables (i.e. age, education and income) only the negative association for the reexperiencing symptom cluster approached significance. ($\beta = -.40$, $p < .10$).

The regressions did not yield any significant associations for DBP reactivity [$F(6,10) = 2.56$, $p = .09$]; HR reactivity [$F(6,10) = 1.55$, $p = .26$]; CO reactivity [$F(6,10) = 2.60$, $p = .09$]; or TPR reactivity [$F(6,10) = 1.02$, $p = .47$; see Tables 8 and 9].

Table 8

DSM-IV-TR PTSD Symptom Clusters and SBP, DBP and HR for Math Task

	SBP Math Task			DBP Math Task			HR Math Task		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	-3.72†	1.87	-0.40	-0.16	1.27	-0.03	-1.98	1.59	-0.31
Avoidance/ Numbing	-2.27	1.36	-0.41	-1.96	0.92	-0.58	-1.45	1.16	-0.39
Hyperarousal	2.56	1.72	0.34	1.22	1.17	0.26	2.24	1.47	0.44
R^2(adj)	0.48			0.37			0.17		
F	3.48*			2.56			1.55		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 9

DSM-IV-TR PTSD Symptom Clusters and CO and TPR for Math Task

	CO Math Task			TPR Math Task		
DSM-IV-TR Clusters	*B*	*SE*	β	*B*	*SE*	β
Re-experiencing	0.05	0.13	0.08	-3.04	39.96	-0.02
Avoidance/ Numbing	0.00	0.09	0.00	-18.83	29.12	-0.22
Hyperarousal	0.09	0.12	0.19	-2.46	36.87	-0.02
R^2(adj)	0.38			0.01		
F	2.60			1.02		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

DSM-5 Symptom Clusters and Cardiovascular Variables

Speech Preparation Multivariate Multiple Regression Analyses

The results for the speech preparation task (see tables 10 and 11) did not yield any significant associations for SBP reactivity [$F(7,9) = .99$, $p = .49$]; DBP reactivity [$F(7,9) = .41$, $p = .87$]; HR reactivity [$F(7,9) = 1.73$ $p = .22$]; CO reactivity [$F(7,9) = 1.13$, $p = .42$]; or TPR reactivity [$F(7,9) = .96$, $p = .51$].

Table 10

DSM-5 PTSD Symptom Clusters and SBP, DBP and HR for Speech Preparation

	SBP Speech Prep			DBP Speech Prep			HR Speech Prep		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Intrusion	0.74	2.77	0.09	1.10	1.83	0.24	-0.30	1.99	-0.05
Avoidance	-1.42	1.19	-0.44	0.00	0.79	0.00	-0.95	0.86	-0.36
Cognitive/ Mood	-1.51	1.55	-0.35	-0.79	1.03	-0.32	0.17	1.12	0.05
Arousal/ Reactivity	2.36	2.10	0.36	-0.93	1.39	-0.25	1.05	1.51	0.19
R^2(adj)	0.00			-0.35			0.24		
F	0.99			0.41			1.73		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 11

DSM-5 PTSD Symptom Clusters and CO and TPR for Speech Preparation

	CO Speech Prep			TPR Speech Prep		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β
Intrusion	-0.01	0.17	-0.02	21.25	47.43	0.15
Avoidance	-0.11	0.07	-0.57	12.67	20.47	0.23
Cognitive/ Mood	0.11	0.09	0.42	-49.12	26.56	-0.66
Arousal/ Reactivity	-0.01	0.13	-0.03	13.99	35.93	0.12
R^2(adj)	0.06			-0.02		
F	1.13			0.96		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Speech Delivery Task Multivariate Multiple Regression Analyses

The results for the Speech Delivery task (see Tables 12 and 13) did not yield any significant associations for SBP reactivity [$F(7,9) = .90$, $p = .54$]; DBP reactivity

[$F(7,9) = .30$, $p = .94$]; HR reactivity [$F(7,9) = 2.26$, $p = .13$]; CO reactivity [$F(7,9) = .69$, $p = .68$]; or TPR reactivity [$F(7,9) = 1.40$, $p = .31$].

Table 12

DSM-5 PTSD Symptom Clusters and SBP, DP and HR for Speech Delivery Task

	SBP Speech Delivery			DBP Speech Delivery			HR Speech Delivery		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Intrusion	-1.49	4.32	-0.12	2.18	2.94	0.30	0.77	2.11	0.10
Avoidance	-1.02	1.86	-0.21	-0.62	1.27	-0.22	-2.02	0.91	-0.66
Cognitive/ Mood	-1.88	2.42	-0.28	-0.47	1.65	-0.12	1.83	1.18	0.44
Arousal/ Reactivity	2.25	3.27	0.22	-0.68	2.23	-0.12	1.60	1.60	0.26
R^2(adj)	-0.04			-0.44			0.36		
F	0.90			0.30			2.26		

Note: $^{\dagger} = p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 13

DSM-5 PTSD Symptom Clusters and CO and TPR for Speech Delivery Task

	CO Speech Delivery			TPR Speech Delivery		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β
Intrusion	0.02	0.29	0.03	26.38	41.88	0.20
Avoidance	0.06	0.13	0.18	-15.47	18.07	-0.29
Cognitive/ Mood	0.12	0.16	0.28	-26.18	23.45	-0.37
Arousal/ Reactivity	0.11	0.22	0.17	-20.03	31.73	-0.19
R^2(adj)	-0.16			0.15		
F	0.69			1.40		

Note: $^{\dagger} = p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Math Task Multivariate Multiple Regression Analyses

The results for the Math task yielded a significant association for SBP reactivity [$F(7,9) = 6.19$, $p < .01$; see Tables 14], with a negative association and a unique contribution of 23% of the variance accounted for by the Avoidance symptom cluster ($sr^2 = -.48$, $\beta = -.71$, $p < .01$), and a positive association and a unique contribution of 11% of the variance accounted for by the Arousal/Reactivity symptom cluster ($sr^2 = .33$, $\beta = .41$, $p < .05$).

The results also yielded a significant association for DBP reactivity [$F(7,9) = 3.88$, $p < .05$; see Tables 14], with a negative association and a unique contribution of 27% of the variance accounted for by the Avoidance symptom cluster ($sr^2 = -.52$, $\beta = -.77$, $p < .05$). A significant association was found for HR reactivity for the Math task [$F(7,9) = 4.84$, $p < .05$; see Tables 14, with a negative association and a unique contribution of 39% of the variance accounted for by the Avoidance symptom cluster ($sr^2 = -.62$, $\beta = -.92$, $p < .01$), and a positive association and a unique contribution of 18% of the variance accounted for by the Arousal/Reactivity symptom cluster ($sr^2 = .43$, $\beta = .55$, $p < .05$).

The regressions analyses did not yield any significant associations for CO reactivity [$F(7,9) = 2.30$, $p = .12$]; or TPR reactivity [$F(7,9) = ,.86$, $p = .57$; see Table 15].

Table 14

DSM-5 PTSD Symptom Clusters and SBP, DBP and HR for Math Task

	SBP Math Task			DBP Math Task			HR Math Task		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β	*B*	*SE*	β
Intrusion	-0.81	1.77	-0.09	1.60	1.31	0.28	0.82	1.32	0.13
Avoidance	-2.63**	0.76	-0.71	-1.75*	0.56	-0.77	-2.31**	0.57	-0.92
Cognitive/ Mood	0.22	0.99	0.04	-0.29	0.73	-0.10	0.72	0.74	0.21
Arousal/ Reactivity	3.15*	1.34	0.41	1.57	0.99	0.34	2.80*	1.00	0.55
R^2(adj)	0.69			0.56			0.63		
F	6.19**			3.88*			4.84*		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

Table 15

DSM-5 PTSD Symptom Clusters and CO and TPR for Math Task

	CO Math Task			TPR Math Task		
DSM-5 Clusters	*B*	*SE*	β	*B*	*SE*	β
Intrusion	0.13	0.16	0.23	13.74	51.06	0.10
Avoidance	-0.06	0.07	-0.25	-16.76	22.03	-0.29
Cognitive/ Mood	0.05	0.09	0.17	-2.90	28.59	-0.04
Arousal/ Reactivity	0.11	0.12	0.22	0.93	38.68	0.01
R^2(adj)	0.36			-0.07		
F	2.30			0.86		

Note: † = $p < .10$, * = $p < .05$, ** = $p < .01$. All estimates adjusted for age, education and income. SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, CO=cardiac output, TPR= total peripheral resistance.

CHAPTER V

Discussion

In a large meta-analysis of PTSD studies, Pole (2007) concluded that the PTSD psychophysiology literature had a disproportionate amount of male veterans, had few studies using more sophisticated methods of physiological measurement (e.g. impedance cardiography), and did not address differences in PTSD presentation (e.g. subtypes, childhood trauma). These gaps in the literature may account for the heterogeneity in reactivity responses, making it difficult to generalize findings. The current study addresses the gap in the literature by examining a community sample of women and exploring the associations between PTSD symptom clusters and measures of CVR. The use of impedance cardiography provided a clearer picture of cardiovascular reactivity (SBP, DPB, HR, CO and TPR) during active coping stress tasks (speech preparation/delivery and math tasks) in women with PTSD, depression and a no mental illness control group. Using this study design we were able to identify significant between-group differences in CVR between the diagnostic groups. However, these group differences were not consistently in the predicted direction. Only CO was significantly greater in the PTSD group compared to the control group (speech delivery only). This larger increase in CO may be related to the negative relationship between CO and TPR values observed previously (Larsen, et al., 1986). Yet, across most of the measures the PTSD group demonstrated no difference or significantly lower CVR variables than the depression or control group. The DBP reactivity was significantly lower for the PTSD group compared to the depression group (speech preparation). Total peripheral resistance reactivity was significantly lower for the PTSD group compared to both the depression group and the control group (speech delivery only).

Previous work has revealed different reactivity patterns between active coping tasks (Hurwitz, et al., 1993), wherein the speech preparation and the math task elicit a myocardial response pattern, and the speech delivery task results in both myocardial and vascular reactivity. This may explain why the speech delivery task in the current study provided more differentiation between the groups. Although these results were not as expected, there is growing evidence in the stress reactivity literature providing explanations for these results.

A study examining CVR in patients with coronary artery disease and depression symptoms found preliminary evidence for a negative relationship between depression scores and cardiovascular variables (SBP, DBP and HR; York et al., 2007). The attenuated response to laboratory-induced mental stress in this study was contrary to previous findings showing increased CVR in depressed individuals (Kibler & Ma, 2004). For the York et al. (2007) study, it was proposed that reduced β-adrenergic receptor density, sensitivity or both may play a role in decreased hemodynamic responses to acute stress. Support for this explanation can be found in studies examining blunted cardiac responses to intravenously administered terbutaline (Brodde, et al., 2001). A relationship between increased risk for CVD and disease progression may be explained by polymorphism of the β_2-adrenoreceptors in individuals with the Ile164 genotype; participants with this genotype demonstrated blunted cardiac β_2-adrenoreceptors responses (Brodde, et al., 2001). Polymorphisms in β_2-adrenoreceptors have been implicated in the variability of vascular responses in humans (Cockcroft, et al., 2000). Variations in β_2-adrenoreceptors genotypes were associated with differences in norepinephrine sensitivity, with some individual requiring twice the level of NE to

achieve similar vasoconstriction as others. These results indicate that although the organism may mount a sympathetic nervous system response (releasing epinephrine and norepinephrine) the downstream physiological changes, such as loss or alterations in β_2-adrenoreceptors, may present as attenuated cardiovascular responses.

Black & Garbutt (2002) propose that stress via the release of stress hormones (i.e. catecholamines, corticosteroids), the mounting of inflammatory responses (e.g. increased cytokines), and the oxidation of lipids, may lead to elevated CVD risk through vascular dysfunction even in the absence of elevated cardiovascular responses. Research examining chronic stress in spousal caregivers of Alzheimer Disease (AD) patients suggests that being a vulnerable caregiver (providing constant care without adequate respite) is associated with reduced density and sensitivity in lymphocyte β_2-adrenoreceptors. These alternations in receptors may lead to reduced cardiovascular reactivity and immunity in this chronically stressed population.

Elevations in CVD within PTSD populations may be conferred through chronic alterations in inflammatory as well as neuroendocrine processes (Black & Garbutt, 2002; Kibler et al., 2014). These reviews emphasized a link between PTSD and alterations in inflammatory biomarkers (e.g. pro-inflammatory cytokines, C-reactive, fibrinogen). Support for this relationship was demonstrated in a recent meta-analysis including 36 studies (n=14,991) which identified moderate correlations between trauma exposure and interleukins (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP; Tursich, et al., 2014)). In particular the relationship between childhood trauma and autoimmune disease in adulthood has been examined using data from a large retrospective study cohort, the Adverse Childhood Experiences study (ACE; Dube et al.,

2009). An examination of individuals with >2 ACEs compared to individuals without ACEs revealed much higher risk for immunopathological hospitalization. Risk percentages varied by immunopathological group, demonstrating 70% increased risk for T-helper 1 diseases (e.g. idiopathic myocarditis), 80% increased risk for T-helper diseases (e.g. scleroderma) and 80% increased risk for T-helper rheumatic diseases (e.g. rheumatoid arthritis). The risk of first hospitalization increased for every increase in ACE Score (20% for women and 10% for men). These results suggest that chronicity of childhood trauma may play an important role in immune dysfunction and negative health outcomes.

The results of the current study are consistent with a small but growing body of stress reactivity research reporting attenuated cardiovascular and cortisol responses to laboratory stressors (Ginty, Phillips, Roseboom, Carroll, & de Rooij., 2012; Phillips, Ginty, & Hughes, 2013). In contrast to exaggerated reactivity, attenuated reactivity would appear to be desirable or at the very least benign. However, several studies have demonstrated a relationship between low cardiovascular reactivity and negative health and behaviors. An association has been reported between blunted CVR and obesity (Phillips, 2011; Singh & Shen, 2013), self-reported health (Phillips, 2011), disorder eating (Ginty, Phillips, Higgs, Heaney & Carroll, 2012; Koo-Loeb, Pedersen & Girder, 1998), impulsive behaviors (Lovallo, 2013), cognitive functioning (Ginty, Phillips, & Roseboom, et al., 2012; Lovallo, et al., 2013), dysphoric and depressed populations (Carroll, Phillips, Hunt & Der, 2007; Phillips, 2011b; Phillips, Hunt, Der & Carroll, 2011; Salomon, Clift, Karlsdottir & Rottenberg, 2009; Schwerdtfeger & Gerteis, 2013), trauma and PTSD (D'Andrea, Pole, DePierro, Freed & Wallace, 2013; Lovallo, Farag,

Sorocco, Cohoon, & Vincent, 2012), and large community cohorts (Carroll, et al, 2007; Ginty, et al., 2012; Lovallo, et al., 2012; Phillips, 2011b; de Rooij, Schene, Phillips, & Roseboom, 2010).

There is a paucity of research examining mediators and moderators of psychological disorders and blunted reactivity. The mediating role of perceived stress and coping ability in CVR to stress has been documented in the literature for some time (Tomaka, Blascovich, Kelsey & Leitten, 1993, Tomaka, Blascovich, Kibler & Ernst, 1997). Allen, Bocek and Burch (2011) found evidence for decreased DBP reactivity in women who reported high psychological stress, and decreased HR reactivity for women reporting high levels of perceived and psychological distress. More recently, support has been found for the role of perceived stress as a mediator between depression and decreased SBP, DBP, HR and cortisol reactivity (Brindle, Ginty, & Conklin, 2013; de Rooij, et al., 2010; Ginty & Conklin, 2011). These studies report that increased depression was associated with increased perceived stress and reduced CVR. The high perception of stress may signal neurobiological structures responsible for initiation of the stress response which subsequently trigger either increased or attenuated reactivity in the vascular system (Lovallo, 2005). Schauer and Elbet (2010) propose that when faced with a threat the organism evaluates its ability to cope, consequently its neurobiological response is based on the perception of danger to the self, and the power differential between the perpetrator and the organism's ability to take action. This model suggests that the fear responses of flight and fight are predominantly activated via the sympathetic nervous system, whereas fright, flag and faint responses are primarily regulated via the parasympathic nervous system. Activation of the latter peritraumatic responses may

manifest as the dissociative response pattern seen in children and women who may not have the resources to overtake the perpetrator of abuse. In our sample, the PTSD group reported more incidences of trauma than the depression group (58.8% with ≥ 5 incidents vs. 33.3%, respectively; see Appendix C). The attenuated reactivity in the PTSD group may be related to the amount of childhood trauma exposure. Frewen and Lanius (2006) propose that higher incidences of childhood trauma may play a role in the development of the dissociative type of PTSD and that this trauma-related fear processing style may generalize to non-trauma cued situations.

Support for the importance of assessing childhood trauma can be found in the Adverse Childhood Experiences (ACE) Study. The ACE study data comes from a large (n = 9,508) retrospective and prospective investigation of the role of childhood abuse and household dysfunction on adult health status, disease and risk behaviors (Felitti, et al., 1998). Results from this study indicated a dose response relationship between the number of ACE's and mental health issues (e.g. suicide, depression), physical health problems (e.g. ischemic heart disease, cancer), and negative health behaviors (e.g. substance abuse, risky sexual behaviors, obesity). In 2009 the Behavioral Risk Factor Surveillance System (BRFSS) added a module using ACE questions and analyzed data for 26,229 adults in five states (Bynum, et al., 2011). Fifty-nine percent of the respondents endorsed at least one ACE, and 8.7% reported five or more ACE's. Women reported significantly higher incidences of childhood sexual abuse (17.2% vs. 6.7%), living with a substance-abusing family member (30.6% vs. 27.5), and living with a mentally ill household member (22.0% vs. 16.7%), than men. Evidence from The Oklahoma Family Health Patterns Project, a large cohort study (n = 426), found an

association between early life adversity and reduced heart rate and cortisol reactivity (Lovallo, 2013). Additionally high degrees of adversity were related to unstable emotional regulation and diminished cognitive capacity leading towards a tendency for antisocial and impulsive behavioral tendencies (Lovallo, 2013). In particular, childhood trauma may play an important role in the development of obesity in individuals with PTSD (Dedert, et al., 2010). This may explain higher rates of obesity (see Appendix D) in the current sample for the PTSD group (70.6%), than the depression (33.3%) or control group (11.1%). These data suggest childhood adversity may confer risk for cardiovascular disease via negative health behaviors even in light of lower CVR responses.

The present study found that the DSM-5 four-factor symptom cluster structure provided a clearer picture of the relationship between different symptom profiles and CVR than the DSM-IV-TR three-factor model. Lanius et al. (2010) suggest that research on individuals with PTSD would benefit from grouping study participants by two PTSD subtypes. The first group characterized by a predominance of reexperiencing and hyperarousal symptoms, and the other group by predominance of dissociative symptoms. The sample size in the present study did not permit separating our PTSD group into PTSD subtypes. However, our examination of the four-factor structure of DSM-5 produced significant associations for CVR during the math task, revealing an association between the avoidance cluster and blunted reactivity for SBP, DBP and HR reactivity, while the arousal/reactivity cluster demonstrated a significant association with increased SBP and HR reactivity. Frewen and Lanius (2006) propose that the dissociative subtype of PTSD is associated with an overmodulation of limbic regions, which may have

implications for dampening of sympathetic outputs and may explain the predominantly blunted reactivity in our sample. As proposed by Lovallo (2011), emotional reactivity may initiate interactions at level 1, between the prefrontal cortex and the limbic system which in turn signal alternations in level 2 prompting either increased or diminished stress reactions. The blunted reactivity found in the current study may be related to emotional reactivity leading to the use of behavioral avoidance and dissociative reactions as a way of coping with stressors. This reactivity may in turn produce a dampening of CVR. As postulated by McEwen (2007), any disruption in achieving homeostasis (over, under or inefficient) may lead to negative health effects including increased CVD risk.

Research and Clinical Implications

As noted in the literature, the understanding of PTSD and the mechanisms by which it confers additional health risks on traumatized individuals is complicated by many factors such as the type of trauma (e.g. childhood abuse, combat, rape), length of trauma exposure (e.g. single vs. multiple trauma), populations studied (e.g. gender, veterans), sophistication of the biological parameters of health (e.g. cardiovascular, immunological, neurobiological) and the diagnostic criteria used to define the disorder itself (e.g. symptom clusters, subtypes; Pole, 2007). The CVR research has been confounded by differences in study results, with the majority of studies showing greater CVR in PTSD, while a small body of evidence demonstrates the opposite response, no difference in reactivity or blunted reactivity. It is possible that these different reactivity styles were not more extensively noted in the past due to publication bias in the CVR literature. The strength of the current study is that it addresses several of these factors. The current study adds to the literature by using impedance cardiography, allowing for a

more sophisticated analysis of cardiovascular reactivity to stress, in a community-based sample of women with PTSD, depression and no mental illness control. To the best of our knowledge this is the first study to examine the contribution of PTSD symptom clusters on impedance derived CVR variables using the DSM-IV-TR and DSM-5 symptom cluster criteria. The results of our study support the recommendations from the DSM-5 task force that additional research should be conducted exploring the implications of PTSD subtypes and prolonged exposure to trauma during childhood (Friedman, 2013). Although our sample size did not allow for factor analysis of subtypes, the findings for the association of reduced CVR and the avoidance cluster highlights the importance of examining differences in PTSD symptom profiles. In our sample we noted that individuals with PTSD were twice as likely to have experienced higher incidences of trauma (i.e. > 5 incidences) than our depression group. These data point towards the importance of assessing childhood and prolonged trauma in PTSD and depression studies. The high rate of obesity in our PTSD sample compared to the depression and control group is consistent with the model which proposes that low reactivity or blunted reactivity may confer risk through behavioral mechanism such as disorder eating and obesity (e.g. Ginty, et al., 2012; Phillips, 2011b). It also compliments the neurobiological research indicating two distinct patterns of affect arousal regulations (overmodulation, undermodulation; Frewen and Lanius, 2006) and different pathways and mechanisms towards cardiovascular disease (exaggerated CVR reactivity, coping and risk behaviors; Lovallo, 2005). Although caution should be taken when interpreting our exploratory results, these findings make an important contribution to this complex area of research.

These results have important implications for the treatment of PTSD, suggesting that the complexity in the psychological, biological and comorbid presentations of PTSD should be mirrored in clinical practice and training (Gold, 2008). A systematic review of the literature found support for improvements in PTSD symptoms and corresponding changes in brain function and structure in pharmacological and psychological treatments (e.g. prolonged exposure; Thomaes, et al, 2014). However, this review reported few studies on complicated forms trauma (e.g. childhood adversity, prolonged abuse) and insufficient information on dissociation and personality disorders. Support has been found for the use of mindfulness based therapies such as Dialectical Behavioral Therapy (Linehan, 1993) for patients who are poor candidates for exposure therapy (Becker & Zayfert, 2001). Frewen and Lanius (2006) propose that the psychobiology of PTSD involves dysregulation in affect arousal neurobiological structures and recommend mindfulness based therapies such as DBT (Linehan, 1993) which may promote awareness and regulation of emotions. The use of mindfulness based stress reduction (MBSR; Kabat-Zinn, 2005) may prove helpful for childhood sexual abuse survivors who may present with a more complicated PTSD symptom profile. Recent mindfulness based studies have reported improvements in all DSM-IV-TR PTSD symptom clusters, with the symptoms of avoidance/numbing demonstrating the most reduction (Kimbrough et. al., 2012). The improvements in this study, including reductions in PTSD, depression, anxiety and increases in mindfulness, were still significant at 2.5 years follow-up (Earley, et al., 2014). Mindfulness based therapies have also been found to reduce health risk behaviors such as disordered eating (Kristeller, Wolever, & Sheets, 2014), substance abuse and craving, (Black, 2014; Witkiewitz, Bowen, Douglas, & Hsu, 2013), and

improved coping (Vujanovic, Bonn-Miller, & Marlatt, 2011). Brewer, Elwafi and Davis (2014) reviewed neuroimaging studies of mindfulness training for addictions and found support for positive neurological alterations which may lead to more adaptive behavioral choices and a reduction in unhealthy behaviors. These finding combined with the data from the current study suggest that the treatment of more complex forms of trauma should have equally complex treatment protocols which use a mind-body approach to healing.

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APPENDIX A: DSV-IV –TR and DSV-V Criteria

Criterion	DSM IV	Criterion	DSM V
			Note: The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see corresponding criteria below.
A	The person has been exposed to a traumatic event in which both of the following were present	A	Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
	(1) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.		(1) Directly experiencing the traumatic event(s).
	(2) The person's response involved intense fear, helplessness, or horror.		(2) Witnessing, in person, the event(s) as it occurred to others.
			(3) Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
			(4) Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
	Note: In children, this may be expressed instead by disorganized or agitated behavior.		**Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.
B	The traumatic event is persistently reexperienced in one (or more) of the following ways:	B	Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred.
	(1) Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. **Note:** In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.		(1) Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). **Note:** In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

APPENDIX A: DSV-IV–TR and DSV-V Criteria (continued)

	(2) Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.		(2) Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s). Note: In children, there may be frightening dreams without recognizable content.
	(3) Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated). **Note:** In young children, trauma-specific reenactment may occur.		(3) Dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings. **Note:** In children, trauma-specific reenactment may occur in play.
	(4) Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event		(4) Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
	(5) Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.		(5) Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C	Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:	C	Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
	(1) Efforts to avoid thoughts, feelings, or conversations associated with the trauma.		(1) Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
	(2) Efforts to avoid activities, places, or people that arouse recollections of the trauma		(2). Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
	(3) Inability to recall an important aspect of the trauma	D	Negative alterations in cognitions and mood associated with the traumatic event(s),beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

APPENDIX A: DSV-IV –TR and DSV-V Criteria (continued)

	(4) Markedly diminished interest or participation in significant activities		(1) Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
	(5) Feeling of detachment or estrangement from others		(2) Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g. "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
	(6) Restricted range of affect (e.g. unable to have loving feelings)		(3) Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
	(7) Sense of a foreshortened future (e.g. does not expect to have a career, marriage, children, or a normal life span)		(4) Persistent negative emotional state (e.g. fear, horror, anger, guilt, or shame).
			(5) Markedly diminished interest or participation in significant activities.
			(6) Feelings of detachment or estrangement from others.
			(7) Persistent inability to experience positive emotions (e.g. inability to experience happiness, satisfaction, or loving feelings).
D	Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:	E	Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
	(1) Difficulty falling or staying asleep		(1) Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
	(2) Irritability or outbursts of anger		(2) Reckless or self-destructive behavior.
	(3) Difficulty concentrating		(3) Hypervigilance.
	(4) Hypervigilance		(4) Exaggerated startle response.
	(5) Exaggerated startle response		(5) Problems with concentration.
			(6) Sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep).
E	Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.	F	Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

APPENDIX A: DSV-IV –TR and DSV-V Criteria (continued)

F	The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	G	The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
		H	The disturbance is not attributable to the physiological effects of a substance (e.g. medication, alcohol) or another medical condition.
	Specify if:		*Specify* whether:
	Acute: If duration of symptoms is less than 3 months		**With dissociative symptoms:** The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:
	Chronic: If duration of symptoms is 3 months or more		(1) **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g. feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
			(2) **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g. the world around the individual is experienced as unreal, dreamlike, distant, or distorted).
			Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g. blackouts, behavior during alcohol intoxication) or another medical condition (e.g. complex partial seizures).
	Specify if:		*Specify if:*
	With Delayed Onset: If onset of symptoms is at least 6 months after the stressor		**With delayed expression:** If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be may be immediate).

APPENDIX B: Participants Demographics

	n	%	Mean	SD
PTSD group	17	36.2		
Depression group	12	25.5		
Control group	18	38.3		
Ethnicity:				
Caucasian	26	55.4		
African American	5	10.6		
Hispanic White	8	17.1		
Hispanic Black	1	2.1		
Caribbean Black	5	10.6		
Asian	1	2.1		
Bi-racial	1	2.1		
I**ncome**				
$0- 5000	5	10.6		
5,001– 10,000	3	6.4		
10,001 – 15,000	3	6.4		
15,001 – 20,000	5	10.6		
20,001 – 30,000	3	6.4		
30,001 – 40,000	5	10.6		
40,001 – 50,000	8	17.1		
50,001 – 75,000	7	14.9		
75,001 – 100,000	4	8.5		
100,001 or more	4	8.5		
Education*				
High School or equivalent	15	31.9		
Associates (Junior college)	9	19.1		
Bachelor's Degree	14	29.8		
Master's Degree	7	14.9		
Professional (MD, JD, DDS, etc.)	2	4.3		
Relationship Status				
Single, never married	30	63.8		
Divorced or separated	6	12.8		
Married/Domestic Partner	11	23.4		

Note: There was a significant difference at the .05 level for Education between the PTSD and Control group. No other significant differences were found for demographic variables (ethnic, income, relationship status or age), or baseline reactivity variables (SPB, DPB, HR, CO or TPR).

APPENDIX C: Age and Baseline Cardiovascular Values by Group

	Total (n = 47)	PTSD (n = 17)	Depression (n= 12)	Control (n = 18)
	M(SD)	*M(SD)*	*M(SD)*	*M(SD)*
Age	29.89 (7.33)	31.53 (9.63)	29.92 (6.10)	28.33 (5.37)
Baseline SBP	104.01(11.24)	72.76 (9.61)	66.86 (8.66)	68.09 (10.08)
Baseline DBP	67.00 (8.56)	5.38 (1.14)	5.79 (1.31)	5.84 (1.34)
Baseline HR	69.47 (9.70)	107.94 (12.52)	104.33 (11.73)	100.09 (8.55)
Baseline CO	5.67 (1.26)	69.73 (6.77)	66.14 (8.38)	65.00 (9.88)
Baseline TPR	1186.92 (343.32)	1278.25 (296.62)	1167.25 (392.32)	1113.78 (349.66)

APPENDIX D: Childhood Trauma Severity by Group

	Total (n – 47)		PTSD (n = 17)		Depression (n= 12)		Control (n = 18)	
Childhood Trauma Severity	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
No traumatic events	24	51.1	4	23.5	4	33.3	16	88.9
1 – 5 traumatic events	9	19.1	3	17.6	4	33.3	2	11.1
> 5 traumatic events	14	29.8	10	58.8	4	33.3	--	--

APPENDIX E: Body Mass Index by Group

	Total (n – 47)		PTSD (n = 17)		Depression (n= 12)		Control (n = 18)	
BMI	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Underweight (< 18.5)	1	2.1	--	--	--	--	1	5.6
Normal (18.5 – 24.9)	23	48.9	4	23.5	7	58.3	12	66.7
Overweight (25.0 – 29.9)	5	10.6	1	5.9	1	8.3	3	16.7
Obesity (> 30)	18	38.3	12	70.6	4	33.3	2	11.1