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Objective Evidence of Myocardial Ischemia in Patients with Posttraumatic Stress Disorder

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Abstract

Background—Patients with posttraumatic stress disorder (PTSD) are at increased risk for cardiovascular disease (CVD), but few studies have included objective measures of CVD, and how PTSD causes CVD remains unknown. We sought to determine the association between PTSD and objectively-assessed CVD and examine potential underlying mechanisms.

Methods—Outpatients from two VA Medical Centers were enrolled from 2008 to 2010. PTSD was identified using the Clinician Administered PTSD Scale (CAPS), and standardized exercise treadmill tests (ETT) were performed to detect myocardial ischemia.

Results—Of the 663 participants with complete data, ischemia was present in 17% percent of patients with PTSD versus 10% of patients without PTSD ($P=0.006$). The association between PTSD and ischemia remained significant after adjusting for potential confounders (age, sex, prior CVD) and mediators (traditional cardiac risk factors, C-reactive protein, obesity, alcohol use, sleep quality, social support and depression), adjusted OR 2.42, 95% CI 1.39-4.22, $P=0.002$. Findings remained significant when those with prior CVD were excluded (fully adjusted OR 2.24, 95% CI 1.20 - 4.18, $P=0.01$) and when continuous PTSD symptom score was used as the predictor (fully adjusted OR per 10-point change in CAPS score 1.12, 95% CI 1.03-1.22, $P=0.01$).

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Conclusions—PTSD was associated with ischemic changes on ETT independent of traditional cardiac risk factors, C-reactive protein, and several health behaviors and psychosocial risk factors, suggesting additional mechanisms linking PTSD and ischemia should be explored. The association of PTSD and ischemia among patients without known CVD highlights an opportunity for early interventions to prevent progression of cardiovascular disease.

Keywords

Posttraumatic Stress Disorder; Cardiovascular Disease; Myocardial Ischemia; Cardiovascular Stress Testing; Inflammation; Lifestyle Behaviors

Introduction

Despite advances in prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death worldwide and accounts for one of every six healthcare dollars spent in the United States (1). Only half of the variance in CVD is accounted for by traditional cardiac risk factors, with psychosocial factors explaining much of the remaining risk (2). PTSD is a common, often chronic anxiety disorder with a prevalence of 8-12% in the general population and up to 30% in veteran populations, and multiple studies have found patients with PTSD are at increased risk of developing and dying from CVD (3-9). Notably, two large prospective studies of male veterans found those with a PTSD diagnosis or more severe PTSD symptoms had an elevated risk of CVD (3; 8), and these findings have been confirmed in non-veteran populations (7).

However, there is a need for additional research on PTSD and CVD to address concerns from prior studies, including the limited use of objective measures of CVD and the lack of data on the mechanisms responsible for this association. As much study in this field has depended upon unsubstantiated self-report or administrative data to establish CVD outcomes, there is concern that increased likelihood of self-reporting of physical illness in patients with PTSD or misclassification may bias findings (10-12). Boscarino and colleagues did find that PTSD was associated with evidence of myocardial infarction on electrocardiograms among a large sample of non-hospitalized male veterans, providing some objective support for the association of PTSD and CVD (13). Johnson and colleagues found that police officers, a population at risk for PTSD, had greater carotid intima-media thickness than general population controls (14). However, PTSD symptoms and diagnosis were not examined in this study. Finally, a recent study by Vaccarino and colleagues of 281 Vietnam era veteran twin pairs found those with PTSD at baseline had decreased myocardial perfusion on cardiac positron emission tomography scans at a clinical visit a median of 13 years later (15). Patients with PTSD at baseline were also significantly more likely to report incident clinical CVD events. Further use of objective methods to identify CVD will validate this important prior work and provide greater information about the physiologic effects of PTSD. In addition, objective cardiovascular testing can allow us to detect patients at risk before they present with a clinical CVD event and can inform efforts to prevent progression to clinical disease.

Though prior studies have not determined the mechanisms responsible for increased CVD risk in patients with PTSD, several risk factors deserve further exploration. Populations with PTSD have been noted to have a higher prevalence of traditional CVD risk factors, such as tobacco use and hypertension (16; 17). Nevertheless, prior studies that have included adjustment for traditional CVD risk factors found they explained only a minor portion of the association of PTSD and CVD (8). Therefore, we must evaluate other risk factors. Inflammation plays a key role in the pathogenesis of CVD, and patients with PTSD have elevations in circulating levels of multiple inflammatory biomarkers as well as greater induction of inflammation in response to acute stressors (10). Additional behavioral factors, such as sleep quality, and psychosocial factors, such as social support, are also linked to increased CVD risk (18-21). Yet, none of these potential mediators have been specifically examined in studies of PTSD and CVD.

Given these gaps in our understanding of how PTSD impacts cardiovascular health, we evaluated the association of PTSD and CVD using exercise treadmill testing (ETT), a widely accepted objective, standardized method of detecting myocardial ischemia (22; 23). We hypothesized that PTSD would be associated with a higher prevalence of myocardial ischemia and that this association would be attributable to a greater burden of biological, behavioral, and psychosocial risk factors, such as diabetes, dyslipidemia, inflammation, obesity, tobacco and alcohol use, poor sleep quality, and low social support.

Methods and Materials

Participants

The Mind Your Heart Study is a prospective cohort study designed to examine the association between PTSD and cardiovascular outcomes. Participants were recruited between February 2008 and June 2010 from outpatient clinics affiliated with two Department of Veterans Affairs (VA) Medical Centers (the San Francisco VA Medical Center and the VA Palo Alto Health Care System, California). Since the study planned to follow patients prospectively, those who intended to leave the area and those without contact information were excluded. Potential participants were also excluded if they had a myocardial infarction in the previous six months, due to concern for increased risk of an adverse event with exercise testing, or if they could not perform an exercise treadmill test due to severe physical limitations. All participants provided written informed consent and the research protocol was approved by the institutional review board of the University of California San Francisco and the research committee of the San Francisco VA Medical Center Research and Development office.

PTSD

We evaluated PTSD with the Clinician Administered PTSD Scale (CAPS) using criteria from the Diagnostic and Statistical Manual of Mental Disorders IV (24). The CAPS is the most widely used structured interview for diagnosing PTSD (25; 26) and has excellent test-retest reliability ($r=0.92-0.99$) and internal consistency ($\alpha=0.80-0.90$) (26). The CAPS generates both a diagnosis and a PTSD severity score on a continuous scale from zero to 136. These diagnostic interviews were conducted by masters-level clinicians and supervised

by a licensed clinical psychologist with expertise in the CAPS and PTSD diagnosis. Interviews were reviewed in weekly case conferences with the supervising study psychologist. In addition to full PTSD, partial PTSD is associated with significant impairment in health and functioning (27; 28). There are multiple definitions of partial PTSD, and we chose a conservative definition of meeting diagnostic criteria for reexperiencing and either avoidance or hyperarousal in addition to the other CAPS criteria (29). We also required this group to exhibit symptoms meeting a total CAPS score > 40, as defined by the authors of the CAPS as signifying moderate or threshold PTSD (26). Twenty participants in this study met these criteria and were combined with participants with full PTSD in our analyses. In sensitivity analyses, excluding these participants or combining them with the group without PTSD did not substantially change our findings.

Ischemia

Participants underwent ETT using a standard or modified Bruce Protocol with treadmill speed and incline increased every 3 minutes. ETT is a widely accepted objective measure of CVD, and ischemia on ETT is correlated with future CVD events and mortality (30). Based on a meta-analysis of 24,000 patients in 132 studies, the average sensitivity of ETT is 68% and specificity is 77% with coronary angiography as the gold standard (31). Ischemia was defined as ST segment deviation of ≥ 1 mm (0.1mV) for at least 3 beats in 2 or more contiguous leads. Tests were terminated if participants developed chest pain, hemodynamic instability, electrocardiogram changes concerning for myocardial injury, or if participants were unable to continue for other reasons, including fatigue, shortness of breath, or musculoskeletal pain. All tests were read by cardiology fellows supervised by a cardiologist (NBS), with all readers being blinded to PTSD status. Tests were categorized as having evidence of ischemia, no evidence of ischemia, or being non-interpretable (i.e., baseline left bundle branch block). The portion of tests classified as non-interpretable did not differ by PTSD status. Patients were mailed copies of ETT results, and results were placed in the patient's electronic medical record. Primary care providers also received notification of any positive ETTs.

Covariates

Participants completed standard questionnaires to determine age, sex, race, income, highest level of education, and medical history, including tobacco and illicit drug use (32). Prior CVD was defined by report of myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty. The 9-item Patient Health Questionnaire (PHQ-9) was used to evaluate depressive symptoms. A standard cut-point of ≥ 10 was used to define depression and has demonstrated excellent validity when compared to a mental health interview, with a sensitivity of 88% and a specificity of 88% (33). Alcohol use was assessed with the Alcohol Use Disorders Identification Test-Consumption questions (AUDIT-C), a validated screening questionnaire (34).

Body mass index (BMI) was calculated from height and weight measured with standard protocols. Obesity was defined as BMI ≥ 30 according to the Centers for Disease Control criterion. Blood pressure was measured with a standardized protocol after 5 minutes of rest. Participants completed a morning fasting venous blood draw, and total cholesterol, direct-

LDL cholesterol, HDL-cholesterol, and triglycerides were measured by enzymatic assays using a Synchron LX 20 (Beckman Coulter Inc, Fullerton, CA). High sensitivity C-reactive protein (CRP) was measured using a BNII nephelometer (Seimens Health Care Diagnostics, Tarrytown, NY) with inter-assay coefficients of variation of 3.1-4.9%. We also used standard protocols to determine the maximum exercise capacity achieved during the treadmill test in metabolic equivalent tasks (1 metabolic equivalent task = 3.5 mL/kg/min) (23).

We assessed social support with the Berkman-Syme Social Network Index, which assesses frequency and number of contacts with family and close friends, marital status, and affiliation with community groups and yields a score from 0-4, with higher values indicating greater social support network (21). Subjective sleep quality was measured using an item from the Pittsburgh Sleep Quality Index, a self-rated questionnaire that assesses sleep quality and disturbances (35). Participants were asked: "During the past month, how would you rate your overall sleep quality?" and indicated: "very good", "fairly good", "good", "fairly bad", or "very bad". For descriptive purposes, participants who rated their sleep as "fairly bad" or "very bad" were coded as having poor sleep quality (36).

Statistical Analysis

We compared differences in characteristics between patients with and without PTSD using *t* tests or Mann-Whitney U tests for continuous variables and chi-square tests for dichotomous variables. We adjusted for patient characteristics from Table 1 that differed by PTSD status with a *P*-value 0.10 to capture additional potential confounders and mediators. We used staged logistic regression models, first adjusting for potential confounders (age, sex, prior CVD), traditional cardiac risk factors (history of diabetes, HDL-cholesterol, triglycerides, C-reactive protein), additional health behaviors and psychosocial factors (obesity, alcohol use score, sleep quality, social network score), and depression. Models were repeated using past month continuous PTSD symptom score from the CAPS (per 10 points) as the independent variable. To evaluate the association of PTSD and subclinical CVD, we excluded participants with prior reported CVD and repeated the models described above. To evaluate the effect of reclassifying patients with partial PTSD, we conducted two sets of additional sensitivity analyses: (1) excluding those with partial PTSD and a CAPS score >40 and (2) combining this group with participants without PTSD. Finally, to ensure that associations of PTSD and ischemia were not due to variability in exertion during the treadmill test, we conducted sensitivity analyses adding maximum exercise capacity achieved during the test to the models described above. All statistical tests were two-sided with $\alpha=0.05$. We used Stata version 11 (StataCorp; College Station, Texas) to perform all analyses.

Results

Of the 744 participants enrolled in the study, 10 were excluded from these analyses because they did not complete full PTSD assessments or because the supervising study psychologist had concerns about the accuracy of the PTSD diagnosis. Another 71 participants were excluded because their treadmill results were incomplete ($n=23$) or not interpretable ($n=48$) as described below, leaving 663 participants for these analyses.

Of the 663 participants, 230 (35%) had PTSD (210 with full PTSD and 20 with partial PTSD and a CAPS score >40), and the mean CAPS score was 66.2 (SD=19.1) in this group. The mean age of participants was 58 years, 6% were women, and 59% identified their race as white. Compared to participants without PTSD, those with PTSD were significantly more likely to be female and to have higher levels of CRP (Table 1). Patients with PTSD also had a significantly greater prevalence of depression, poor sleep quality, obesity, and smaller social networks.

Ischemia was present in 10% (43 of 433) of patients without PTSD and 17% (40 of 230) of patients with PTSD ($P=0.006$). The association between PTSD and ischemia remained significant after controlling for demographics (age and sex), prior CVD, traditional cardiac risk factors (history of diabetes, HDL-cholesterol, and triglycerides) and CRP, and additional behavioral and psychosocial factors (obesity, alcohol use score, sleep quality, and social network score) (adjusted OR 2.42, 95% CI 1.39-4.22, $P=0.002$) (Table 2). In models using past month PTSD symptom score rather than PTSD diagnosis as a predictor, those with worse PTSD symptoms were also significantly more likely to have ischemia on ETT (Table 3).

In analyses excluding patients with prior CVD, the relationship between PTSD diagnosis and ischemia was not substantially changed. In fully adjusted models (all covariates from Models in Table 2 included), patients with PTSD had over twice the odds of having ischemia, with an adjusted OR of 2.24 (95% CI 1.20-4.18, $P=0.01$). In sensitivity analyses, adjusting models for peak exercise capacity achieved during the treadmill tests did not change our conclusions. The odds ratios for ischemia in the fully adjusted models were 2.38 (95% CI 1.36-4.17, $P=0.002$) for PTSD diagnosis, 1.11 (95% CI 1.02- 1.22, $P=0.02$) for PTSD symptom score, and 2.21 (95% CI 1.18-4.14, $P=0.01$) for PTSD diagnosis excluding patients with known CVD. Altering our classification of patients with partial PTSD and a current CAPS score >40 did not change our conclusions. In fully adjusted models excluding these patients, the OR for ischemia was 2.59 (95% CI 1.47-4.57, $P=0.001$) for PTSD diagnosis and 1.12 (95% CI 1.03-1.22, $P=0.01$) for PTSD symptom score (see Supplemental Tables 4 and 5 for full results). If these patients were instead combined with those without PTSD, the OR for ischemia was 2.59 (95% CI 1.48-4.51, $P=0.001$) for PTSD diagnosis in fully adjusted models and 1.12 (95% CI 1.03-1.22, $P=0.01$) for PTSD symptom score.

Discussion

In our sample of 663 patients, we found those with PTSD had a significantly greater likelihood of having myocardial ischemia on ETT independent of sociodemographics, prior CVD, traditional cardiac risk factors, CRP, health behaviors, sleep quality, social support network, and depression. Our work expands upon the important prior research in this area by using objective exercise treadmill testing to assess CVD and the established reference standard psychiatric interview to diagnose PTSD. In addition, our use of ETT enabled us to detect myocardial ischemia in asymptomatic individuals who had not reported a CVD event. Our finding of a similar association of PTSD and ischemia in this population highlights an opportunity for interventions to prevent further progression to myocardial infarction and other potentially fatal CVD events.

As the first study to evaluate PTSD and CVD using ETT, our findings provide important validation of the association of PTSD and increased CVD risk. Determining the mechanisms responsible for the association of PTSD and CVD was recently identified as a key direction for new research, and our study was able to examine a variety of potential biological, behavioral, and psychosocial mediators (37). Consistent with prior studies that included data on traditional CVD risk factors, we found these explained only a minor portion of the association, and therefore explored several additional potential mechanisms (8; 15). Findings regarding activity of the hypothalamic-pituitary-adrenocortical (HPA) axis in PTSD are complex, but studies demonstrate abnormal reactivity of the axis and changes in glucocorticoid receptor function in patients with PTSD that could lead to increased sympathetic nervous system activity and inflammation (10; 38; 39). Studies of inflammatory biomarkers in PTSD are also mixed, but a recent review found most indicate patients with chronic PTSD have higher levels of inflammation (10). In this study, we did not find that elevated inflammation, as indexed by CRP alone, accounted for the higher prevalence of myocardial ischemia in PTSD (40). Though CRP is a strong, independent predictor of CVD events, future studies could explore a broader array of biomarkers of inflammation and HPA activity to more thoroughly evaluate these mechanisms (40; 41). In addition, single baseline measures, such as the ones from our study, may fail to capture important variations in HPA and inflammatory activity in response to psychological stressors.

Health behaviors are also involved in the pathogenesis of CVD, and therefore, we adjusted for behavioral factors that differed by PTSD status, including alcohol use and obesity. In addition, we examined sleep quality, as sleep is commonly disturbed in PTSD and is increasingly recognized as a risk factor for cardiac disease (42-44). Finally, we evaluated psychosocial contributors to CVD risk, including social support network and depression, a condition that was highly comorbid with PTSD in our study population. The effect of these potential mediators was modest and PTSD remained an independent predictor of myocardial ischemia. Though providers should still promote healthy lifestyle behaviors and encourage treatment of comorbid depression, our results suggest we need to seek additional targets for interventions to reduce cardiovascular morbidity and mortality in patients with PTSD.

Our finding that greater PTSD symptom severity was associated with higher probability of ischemia adds to prior studies suggesting a dose response relationship, but how greater exposure to PTSD increases CVD risk remains unknown (7; 45). For example, it is not clear whether PTSD simply increases the total burden of atherosclerotic plaque, or whether it may also affect other factors involved in ischemia, such as plaque stability or coronary artery vasodilation. Longitudinal studies that include repeated assessment of PTSD symptom severity and objective measures of ischemia may help clarify the biological processes involved and shed light on their reversibility.

Our findings should be interpreted in light of the several limitations. First, our subjects were VA patients and predominantly male, and therefore our results may not generalize to other populations. Second, though ETT provides an objective measure of CVD, it is not perfectly sensitive or specific. However, ETT is a broadly accepted screening tool for myocardial ischemia and provides prognostic data not gleaned from other tests. Third, the cross-sectional design precludes determinations of causality and more detailed, prospective studies

of PTSD and CVD are needed. Though life-threatening CVD events could cause PTSD, we believe reverse causality is unlikely to explain our findings as the majority of participants did not report prior cardiac events and our conclusions were not changed by exclusion of participants with pre-existing CVD. Fourth, our assessments of substance use were via self-report that were not confirmed by laboratory measures. Likely reflecting characteristics of the San Francisco Bay Area, tobacco use was lower and educational attainment was higher than in prior studies of veterans. This may reduce the generalizability of our findings to other VA populations. Finally, there were potential factors that could directly or indirectly affect risk for PTSD and/or CVD that we did not measure in our current study, including sleep apnea, combat related injury, Intelligence Quotient, and Agent Orange exposure, and these would be welcome additions to future work.

In summary, we found that PTSD was associated with CVD in a large cohort of VA patients, extending prior work through the use of objective exercise treadmill testing for myocardial ischemia, a gold-standard psychiatric interview, and adjustment for a variety of possible explanatory variables. Traditional cardiac risk factors, levels of C-reactive protein, health behaviors, and psychosocial factors did not explain this association. While research continues on causal mechanisms, providers still have opportunities to intervene and prevent potentially disabling or fatal CVD events in patients with PTSD. Evidence based pharmacologic and behavioral treatments exist for PTSD, though many patients may not seek these due to stigma (46; 47). Discussing how PTSD can have a harmful impact on physical health may provide additional encouragement for patients to seek treatment. Our finding that PTSD symptom severity was linked to CVD risk also suggests that improving symptoms could lower cardiac risk, though it would be important to examine this in PTSD treatment trials. Finally, integrative care models that combine primary and mental health should continue to be explored as ways to improve treatment engagement and efficacy in patients with comorbid mental and physical health disorders (48).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Participant characteristics by posttraumatic stress disorder status

Characteristic	No PTSD N=433	PTSD N=230	P-value
Demographics			
Age	58.0 (11.6)	58.2 (10.3)	0.79
Female sex, n (%)	14 (3.2)	24 (10.4)	<0.001
White race, n (%)	247 (57.9)	141 (62.4)	0.26
Annual income < \$20,000, n (%)	144 (33.5)	65 (28.4)	0.19
College graduate, n (%)	131 (30.3)	68 (29.6)	0.86
Traditional Cardiac Risk Factors			
Prior cardiovascular disease, n (%)	46 (10.6)	40 (17.4)	0.01
Systolic blood pressure, mmHg	126 (16)	125 (16)	0.30
Diastolic blood pressure, mmHg	76 (11)	74 (10)	0.34
Diabetes mellitus, n (%)	59 (14.0)	44 (19.8)	0.06
Total cholesterol, mg/dL	184.3 (47)	178.4 (44)	0.14
Direct LDL-cholesterol, mg/dL	108.3 (35)	106.6 (38)	0.35
HDL-cholesterol, mg/dL	44.9 (14)	43.3 (14)	0.10
Triglycerides, mg/dL	129.4 (125)	143.7 (90)	<0.001
C-reactive protein, mg/L	2.4 (4.0)	2.7 (3.4)	0.02
Current tobacco use, n (%)	103 (24.0)	55 (24.4)	0.90
Additional Behavioral and Psychosocial Factors			
Obesity, n (%)	135 (31.2)	98 (42.6)	0.003
Illicit drug use, n (%)	43 (10)	29 (12.9)	0.27
Alcohol use score	3.4 (3.0)	3.1 (3.1)	0.08
Good sleep quality, n (%)	310 (72.3)	94 (41.8)	<0.001
Social network score	3.6 (2.6)	3.2 (2.5)	0.03
Depression, n (%)	64 (14.9)	133 (58.3)	<0.001

Data are presented as mean (SD) unless otherwise specified

Table 2
Association of posttraumatic stress disorder and ischemia on exercise treadmill testing

	OR (95% CI)	P-value
Unadjusted	1.93 (1.21 - 3.08)	0.006
Adjusted for age, sex, prior cardiovascular disease	2.07 (1.27 - 3.36)	0.003
+ traditional cardiac risk factors (h/o diabetes, HDL-cholesterol, triglycerides, C-reactive protein)	2.03 (1.24 - 3.32)	0.005
+ behavioral/psychosocial factors (obesity, alcohol use score, sleep quality, social network score)	2.02 (1.20 - 3.40)	0.008
+ depression	2.42 (1.39 - 4.22)	0.002

Table 3
Association of posttraumatic stress disorder symptom severity and ischemia on exercise treadmill testing*

	OR (95% CI)	P-value
Unadjusted	1.08 (1.01 – 1.16)	0.03
Adjusted for age, sex, prior cardiovascular disease	1.09 (1.01 – 1.17)	0.02
+ traditional cardiac risk factors (h/o diabetes, HDL-cholesterol, triglycerides, C-reactive protein)	1.09 (1.01 – 1.17)	0.03
+ behavioral/psychosocial factors (obesity, alcohol use score, sleep quality, social network score)	1.08 (1.00 – 1.17)	0.04
+ depression	1.12 (1.03 – 1.22)	0.01

* PTSD symptom severity measured as current month Clinician Administered PTSD Scale score per 10 points