Objective Evidence of Myocardial Ischemia in Patients with Posttraumatic Stress Disorder

Jesse H. Turner, Thomas C. Neylan, Nelson B. Schiller, Yongmei Li, and Beth E. Cohen

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 Veterans Affairs Medical Centers were enrolled from 2008 to 2010. Posttraumatic stress disorder was identified using the Clinician Administered PTSD Scale, and standardized exercise treadmill tests were performed to detect myocardial ischemia.

Results: Of the 663 participants with complete data, ischemia was present in 17% of patients with PTSD versus 10% of patients without PTSD ($p = .006$). 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 odds ratio (OR) 2.42, 95% confidence interval (CI) 1.39 to 4.22, $p = .002$. Findings remained significant when those with prior CVD were excluded (fully adjusted OR 2.24, 95% CI 1.20–4.18, $p = .01$) and when continuous PTSD symptom score was used as the predictor (fully adjusted OR per 10-point change in Clinician Administered PTSD Scale score 1.12, 95% CI 1.03–1.22, $p = .01$).

Conclusions: Posttraumatic stress disorder was associated with ischemic changes on exercise treadmill tests 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.

Key Words: Cardiovascular disease, cardiovascular stress testing, inflammation, lifestyle behaviors, myocardial ischemia, posttraumatic stress disorder

Despite advances in prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death worldwide and accounts for one of every six health care 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). Posttraumatic stress disorder (PTSD) is a common, often chronic anxiety disorder with a prevalence of 8% to 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 nonveteran 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 the increased likelihood of self-reporting of physical illness in patients with PTSD or misclassification may bias findings (10–12). Boscarino and Chang (13) did find that PTSD was associated with evidence of myocardial infarction on electrocardiograms among a large sample of nonhospitalized male veterans, providing some objective support for the association of PTSD and CVD. Johnson *et al.* (14) found that police officers, a population at risk for PTSD, had greater carotid intima-media thickness than general population control subjects. However, PTSD symptoms and diagnoses were not examined in this study. Finally, a recent study by Vaccarino *et al.* (15) 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. 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

From the Department of Medicine (JHT, NBS, BEC), University of California, San Francisco; Department of Psychiatry (TCN), University of California, San Francisco, and Department of Veterans Affairs Medical Center; and Medical Service (NBS, YL, BEC), Department of Veterans Affairs Medical Center, San Francisco, California.

Address correspondence to Beth E. Cohen, M.D., M.A.S., Department of Veterans Affairs Medical Center, General Internal Medicine Section (111A1), 4150 Clement Street, San Francisco, CA 94121; E-mail: Beth.Cohen@ucsf.edu.

Received Nov 8, 2012; revised Jun 28, 2013; accepted Jul 2, 2013.

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 history of myocardial infarction in the previous 6 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 DSM-IV (24). The CAPS is the most widely used structured interview for diagnosing PTSD (25,26) and has excellent test-retest reliability (r = .92–.99) and internal consistency (alpha = .80–.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 re-experiencing 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. Exercise treadmill testing 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 (.1 mV) for at least three beats in two or more contiguous leads. Tests were terminated if participants developed chest pain, hemodynamic instability, or 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 (N.B.S.), with all readers being blinded to PTSD status. Tests were categorized as having evidence of ischemia, no evidence of ischemia, or being noninterpretable (i.e., baseline left bundle branch block). The portion of tests classified as noninterpretable 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 was used to evaluate depressive symptoms. A standard cut point of ≥10 was used to define depression and has demonstrated excellent validity when compared with 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, a validated screening questionnaire (34).

Body mass index was calculated from height and weight measured with standard protocols. Obesity was defined as body mass index ≥30 according to the Centers for Disease Control and Prevention 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 low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured by enzymatic assays using a Synchron LX 20 (Beckman Coulter Inc, Fullerton, California). High-sensitivity C-reactive protein (CRP) was measured using a BNII nephelometer (Seimens Health Care Diagnostics, Tarrytown, New York) with interassay coefficients of variation of 3.1% to 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 to 4, with higher values indicating a 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