Posttraumatic Stress Disorder and Impaired Autonomic Modulation in Male Twins

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Background: Posttraumatic stress disorder (PTSD) has been linked to increased morbidity. An inflexibility of the autonomic nervous system might be the underlying mechanism. We aimed to assess whether PTSD and combat trauma exposure are associated with lower heart rate variability (HRV), a measure of autonomic function and a predictor of death.

Methods: We measured HRV by power spectral analysis on 24-hour ambulatory electrocardiogram in 459 middle-aged veteran male twins. Combat trauma was assessed with the combat exposure scale, and current and remitted PTSD was assessed with the Structured Clinical Interview for Psychiatry Disorders. Mixed-effects regression models were used to test associations of PTSD and HRV between and within twin pairs.

Results: Of all twins, 211 had combat exposure, 31 had current PTSD, and 43 had remitted PTSD. Current PTSD was inversely associated with very-low-frequency and low-frequency HRV both in individual twins and within 20 pairs discordant for current PTSD. Twins with current PTSD had a 49% lower low-frequency HRV than their brothers without PTSD ($p < .001$). Remitted PTSD was not associated with HRV. Results were robust to adjustment for depression and other risk factors. Combat exposure was inversely associated with most HRV frequencies, but this association mostly diminished after adjustment for current PTSD.

Conclusion: In middle-aged veteran men, combat exposure and current PTSD are associated with measures of autonomic inflexibility previously shown to have prognostic significance. The negative health impact of combat exposure on autonomic function is mediated largely through PTSD and might reverse with remission of PTSD.

Key Words: Autonomic nervous system, heart disease, heart rate variability, mental stress, military combat trauma, posttraumatic stress disorder

Military combat is associated with increased morbidity and mortality in veterans after return from service, although the mechanisms are not clear (1). Posttraumatic stress disorder (PTSD), a disabling psychiatric condition characterized by a persistent maladaptive reaction resulting from exposure to severe psychological stress, is common in combat veterans. The lifetime prevalence in Vietnam veterans is 15% to 19% (2–6) and possibly higher among military personnel of the Iraq and Afghanistan conflicts (7,8). In the US general population, it is approximately 8% (9–12).

Recent studies have suggested a link between PTSD and the risk of ischemic heart disease incidence and mortality (13). A commonly endorsed explanation for this association is possible "wear and tear" of the cardiovascular system due to repeated sympathetic nervous system stimulation and parasympathetic nervous system (PNS) withdrawal caused by trauma-reminiscent stimuli in everyday life (14,15). Over time, these repeated insults might lead to increased risk for a variety of chronic somatic conditions, including cardiovascular disease (16,17).

Heart rate variability (HRV), a measure of beat-to-beat heart rate fluctuations over time (18), is a useful indicator of autonomic function and a strong independent predictor of mortality (19). Thus far, PTSD and some other anxiety disorders have been associated with lower respiratory sinus arrhythmia and baroreflex sensitivity, suggesting impaired autonomic modulation (20–24). However, PTSD has also been related to increased 24-hour low-frequency HRV (25). With these previous conflicting data, larger studies with careful consideration of potential confounders are needed (26). Genetic predisposition, which is substantial for both PTSD and HRV (27,28) as well as the early environmental and developmental factors, could also confound this association (29).

Building upon these prior studies, we sought to examine the associations among combat trauma, PTSD, and long-term measures of HRV assessed by means of 24-hour electrocardiographic recordings in a large, well-characterized study of middle-aged veteran twins. We were able to adjust for a comprehensive set of potential confounding factors, such as other psychiatric diagnoses and behavioral/cardiovascular risk factors. Taking advantage of the twin design, we were also able to account for genetic and early environmental influences. We hypothesized that combat exposure and PTSD are both associated with lower HRV, and that the association of combat exposure with HRV occurs primarily through PTSD. Furthermore, we hypothesized that these associations are independent of possible genetic and early environmental confounders as well as cardiovascular risk factors and depression.

Methods and Materials

Subjects

The ETS (Emory Twin Studies) includes samples recruited in two companion studies: the THS (Twins Heart Study) and the SAVEIT (Stress and Vascular Evaluation in Twins) as described

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previously (30,31). Their purpose was to elucidate the role of depression and PTSD on subclinical cardiovascular disease. Because of the similarity in protocols, these two samples were combined. Both projects recruited middle-aged male monozygotic (MZ) and dizygotic (DZ) twin pairs from the VET (Vietnam Era Twin) Registry (32) who were born between 1946 and 1956 and were discordant for major depression or PTSD or unaffected (control subjects). Pairs of twins were examined at the same time at the Emory University General Clinical Research Center, and all data collection, including ambulatory electrocardiogram (ECG) monitoring, occurred during a 24-hour admission under controlled conditions. The two twins maintained an identical schedule while in the study at Emory. Activity was limited to leisurely ambulation within the Emory facilities, and all assessment, including the ambulatory ECG monitoring, began and ended at the same time. Zygosity information by means of DNA typing was available for all twin pairs. Both studies were approved by the Emory Institutional Review Board, and all twins signed an informed consent.

Measurement of HRV

Twins wore an ambulatory ECG (Holter) monitor (GE Marquette SEER digital system; GE Medical Systems, Waukesha, Wisconsin) for 24 hours and had matched recording times, schedules, and activity levels. Activity was restricted to quiet walking around the campus, and participants were instructed to refrain from smoking and drinking alcohol or coffee during the recording. The HRV data were analyzed following published methodology as previously described (30,33). The heart rate spectrum was computed with a fast Fourier transform with a Parzen window. Because long-term autonomic function was the goal of this study, the fast Fourier transform was performed on the 24-hour R-R interval file. The power spectrum was integrated over four discrete frequency bands: ultra-low frequency (ULF) $<$.0033 Hz; very low frequency (VLF) .0033 to $<$.04 Hz; low frequency (LF) .04 to $<$.15 Hz; and high frequency (HF) .15 to $<$.40 Hz (34). These frequency bands integrate heart rate fluctuations in response to many physiological stimuli. These include, among others, circadian patterns and physical activity (ULF), influences of the renin-angiotensin-aldosterone system (VLF), baroreceptor activity (LF), and respiration (HF) (18,35,36). Other than HF HRV, which is almost exclusively influenced by the PNS, both sympathetic nervous system and PNS together affect the other frequency bands. Total power, incorporating the full spectrum $<$.40 Hz, was also measured. Twins whose recordings showed $>$20% interpolation or $<$18 recorded hours were excluded from the analysis.

Assessment of PTSD, Depression, and Combat Trauma

We administered the Structured Clinical Interview for DSM-IV (37) to classify twins on the basis of a lifetime history and current PTSD. Remitted PTSD was defined as having a lifetime but not current diagnosis of PTSD. The Structured Clinical Interview for DSM-IV also provided a diagnosis of other psychiatric disorders, including major depression, a lifetime history of alcohol and of drug abuse or dependence, as well as generalized anxiety disorder and panic disorder. The Clinician-Administered PTSD Scale (CAPS) was also administered to the SAVEIT subgroup to assess PTSD symptom severity; therefore, it was available in approximately 36% of the sample (38). Combat exposure was assessed with the Combat Exposure Scale (CES), a validated seven-question survey instrument (score range 0–28) (39).

Other Measurements

A medical history and a physical exam were obtained by a research nurse or physician assistant. Abdominal and hip circumferences were measured to derive the waist/hip ratio (WHR). Hypertension was defined by a measured systolic blood pressure $>$140 mm Hg or current treatment with antihypertensive medications. Diabetes mellitus was defined as having a fasting glucose level $>$126 mg/dL or current treatment with antidiabetic medications. Venous blood samples were drawn for the measurement of glucose and lipid profile after an overnight fast. Glucose was measured on the Beckman CX7 chemistry autoanalyzer. Direct high-density lipoprotein and low density lipoprotein cholesterol were measured with homogeneous assays (Equal Diagnostics, Exton, Pennsylvania). Physical activity was assessed with a modified version of the Baecke Questionnaire of Habitual Physical Activity that documented physical activity at work and during sports and nonsports activities (40). The global physical activity score was used in the analysis. Cigarette smoking was classified into current, never, or past smoker. Wine, beer, liquor, coffee, tea, and soda consumption were measured in drinks/day. A history of coronary heart disease was defined as a previous diagnosis of myocardial infarction or previous coronary revascularization procedures. Detailed information on current use of medications was also collected.

Statistical Analysis

Generalized estimating equations (GEE) were used to account for clustering within twin pairs in all analyses. Baseline characteristic differences were compared among twins with no PTSD, current PTSD, and remitted PTSD, with both linear (for continuous variables) and log (for binary variables) analysis of variance testing. The maximum pair-wise *Z* scores comparing no PTSD, current PTSD, and remitted PTSD were reported for each characteristic. The association between combat exposure and PTSD status (current, remitted, or neither) with HRV was first examined by analyzing twins as separate individuals. Each frequency spectra of HRV was log-transformed so that it could be analyzed as a normally distributed outcome variable. Combat exposure and the CAPS PTSD symptom severity scores were analyzed primarily as continuous variables; to assess a dose-response relationship, additional analyses were performed with CAPS and CES as three-level ordinal variables, where the first category was zero (which included approximately half of the sample or first 2 quartiles), and the remaining two categories corresponded approximately to the third and fourth quartile. Current PTSD was analyzed as a mediator of the association between combat exposure and HRV by evaluating the change in β coefficient that occurred after adding it to the multivariable model. The Sobel's *Z* test was performed to test the statistical significance of PTSD as a mediator between combat exposure and HRV (41).

Multivariate Modeling

The GEE models were used with log-transformed HRV as the dependent variable. Potential confounding factors to be included in multivariate analysis were carefully chosen a priori as those factors that might potentially be related to both HRV and PTSD. These included age, hypertension, diabetes mellitus, low-density lipoprotein cholesterol, current and past smoking, and physical activity. Additional covariates were evaluated for possible confounding, including lifetime history of major depression, use of antidepressants, aspirin, statins, beta-blockers, angiotensin converting enzyme inhibitors, anxiolytic drugs, body mass index,