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,

WHR, drug abuse history, alcohol abuse history, high-density lipoprotein cholesterol, and history of coronary heart disease. Of these variables, a history of major depression, use of antidepressants, body mass index, and a history of drug abuse were found to cause >5% change on the effect size of PTSD on HRV and were added to the model. The same covariates were used in the models of combat exposure (CES) and PTSD symptom severity (CAPS). Models that examined remitted PTSD additionally adjusted for current PTSD. Analyses were repeated in a subgroup of twins free from coronary heart disease. Other anxiety disorders, including generalized anxiety disorder and panic disorder, were added to the models separately as a sensitivity analysis, because of their known association with reduced HRV (20).

Within-Pair Analysis

We performed within-pair analyses that examined differences in HRV between twins that were discordant for PTSD. This analysis inherently controls for demographic, shared familial, and early environmental influences; in addition, daily activities, season, and other environmental factors during the ambulatory ECG recording are controlled in this analysis, because co-twins were examined at the same time and under nearly identical conditions. We fitted GEE models adapted for twin research (42), which allow for examination of HRV effects within and between twin pairs as a function PTSD and other possible confounders. In these models the within-pair parameter is the individual twin variation from the twin pair average. This coefficient is identical to the coefficient from a model that fits the absolute difference between the co-twins (42). A similar analysis was done for combat exposure (CES) as well as for PTSD severity (CAPS) as continuous measures. In such cases, discordance was measured on a continuous scale, because the difference in score between brothers and all pairs with differences > zero were considered discordant.

Genetic Influences

In addition to sharing early environment, MZ twins share 100% of their genes, whereas DZ twins share on average 50% of their genetic material; therefore, if a significant within-pair association is found in DZ but not in MZ twins, this suggests genetic confounding (i.e., similar genetic influences underlie PTSD and HRV) (41). If, by contrast, within-pair associations are similar in MZ and DZ twin pairs, then genes may not be considered as a confounder in the association. To statistically measure the difference in effect between MZ and DZ, we tested for the interaction of the within-pair effect with zygosity.

Results

Baseline Characteristics

Of the 562 twins in the dataset, usable HRV data were available on 459 (80%). The mean age ± SD was 55.5 ± 3.1 years, 46% served in Southeast Asia, 95% were Caucasian, and 3% were black. Forty-six percent of twins had reported some combat trauma exposure (CES >0); of these, the median CES score was 10 (interquartile range, 5–17), and all of them served in Southeast Asia. Seventy-four (16%) had PTSD in their lifetime; of these, 31 had current PTSD, whereas 43 had remitted PTSD. Thirty-five of 43 twins with remitted PTSD and 30 of 31 twins with current PTSD were exposed to military combat. The 103 twins with missing HRV data were more likely to be smokers (37% vs. 23%) but otherwise had characteristics similar to those without missing HRV data.

Twins with current and remitted PTSD were compared with those without PTSD (Table 1). Those with current or remitted PTSD were older, less likely to be employed, and more likely to smoke, to have served in Vietnam, to be taking antidepressants, and to have a history of drug and alcohol abuse, heart disease, and major depression. No remarkable difference was found among groups with regard to current alcohol or caffeinated beverage consumption, physical activity, cholesterol levels, body mass index, and WHR.

PTSD and HRV

Current PTSD was associated with significantly lower HRV for all spectra except ULF in bivariate analysis (Table 2). In analyses adjusted for demographic factors, cardiovascular risk factors, physical activity, body mass index, history of substance abuse, major depression and, use of antidepressants, current PTSD continued to show significant associations with VLF and LF HRV, with the largest adjusted effect size being a 39% lower LF HRV ($p < .001$). Similar associations were found within 20 twin pairs discordant for current PTSD (Table 2), and no significant interaction between PTSD and zygosity was found. In contrast, remitted PTSD was not associated with a lower HRV. Twins with remitted PTSD actually tended to have higher HRV than twins without PTSD; this was noted both in analyses of twins as individuals and the 29 within twin pairs discordant for remitted PTSD. Figure 1 illustrates the associations of VLF, LF, and HF HRV with current and remitted PTSD within discordant twin pairs. Results were similar when analyses were limited to individuals without previous history of coronary heart disease ($n = 409$). Generalized anxiety disorder ($n = 9$) and panic disorder ($n = 5$) occurred infrequently and did not significantly alter results when added to the models.

Combat Exposure and HRV

Combat exposure was reported in 84% of twins with current or remitted PTSD and 39% of twins without PTSD. In individual twins, the combat exposure score, as a continuous measurement, was significantly associated with all frequencies of HRV (Table 3). After multivariate adjustment, all frequencies except VLF and HF remained significantly associated with the combat exposure scale score. The largest effect size was seen for LF, where a 9-point (interquartile range) increase in CES score was associated with a nearly 10% adjusted decrease in LF HRV ($p = .04$). Similar results were found within 132 pairs discordant for combat exposure, defined as a within-pair differences > zero, where twins with a higher combat exposure than their brothers showed a 13% adjusted lower LF HRV/each 9-point CES difference ($p < .01$). However, the associations with HRV were substantially reduced (Table 3), when current PTSD was additionally controlled for. The largest reduction in effect size was found for LF power, where adjustment for current PTSD reduced the association by over 50% (from −8.9% to −4.2%), followed by VLF, were the association was reduced by 34%. The Sobel's test confirmed that current PTSD was a statistically significant mediator of CES for both VLF (Z score = 2.16, $p = .03$) and LF (Z score = 3.0, $p = .003$) HRV, whereas mediation was not significant for the other frequency ranges. Among veterans not exposed to combat ($n = 247$), service in Southeast Asia ($n = 14$) was not significantly associated with HRV.

Subgroup Analysis with Continuous Measures

In the subgroup of subjects ($n = 165$) for whom CAPS data were available, current and lifetime CAPS (as a continuous

Table 1. Characteristics of Individuals According to PTSD History

Characteristics	No PTSD ($n = 385$)	Current PTSD ($n = 31$)	Remitted PTSD ($n = 43$)	Max Z Score	p
Age (mean yrs ± SD)	55.2 ± 3.1	57.0 ± 1.7	57.1 ± 2.5	2.81	.005
Education (mean yrs ± SD)	14.3 ± 2.2	13.9 ± 2.4	13.7 ± 2.1	1.61	.11
Employed (%)	77.3	45.2	65.1	4.76	<.001
Smoking History					
Current (%)	21.3	25.8	34.9	2.58	.01
Past smoker (%)	43.4	48.4	41.9		
Never smoked (%)	35.3	25.8	23.2		
Alcohol, mean drinks/day ± SD	4.6 ± 8.4	6.1 ± 12.3	6.6 ± 9.4	1.27	.20
Caffeinated Drinks/Day, mean ± SD	4.7 ± 4.7	6.3 ± 3.6	5.3 ± 3.1	1.99	.046
Lifetime History of Alcohol Dependence (%)	43.3	80.6	55.8	3.12	.002
History of Drug Dependence (%)	19.5	54.8	37.2	2.63	.009
History of Heart Disease (%)	9.4	22.6	16.3	1.77	.08
History of Hypertension (%)	28.7	22.6	39.5	−1.24	.21
History of Diabetes (%)	11.4	12.9	14.0	.88	.38
Baecke Physical Activity Score, mean ± SD	7.3 ± 1.7	6.7 ± 2.5	7.3 ± 2.0	1.63	.10
LDL Cholesterol (mg/dL), mean ± SD	122 ± 35	122 ± 38	119 ± 38	.98	.33
HDL Cholesterol (mg/dL), mean ± SD	39 ± 10	39.5 ± 12.5	40 ± 11	.72	.47
Antidepressant Use (%)	12.2	51.6	25.6	3.16	.002
Beta Blocker Use (%)	13.0	12.9	18.6	.8	.42
BMI (kg/m^2), mean ± SD	29.7 ± 4.8	29.4 ± 4.8	30.2 ± 4.7	.52	.61
WHR, mean ± SD	.95 ± .06	.97 ± .06	.95 ± .08	1.88	.06
Lifetime History of Major Depression (%)	20.7	64.5	58.1	3.77	<.001
History of Military Activity in Southeast Asia	38.7	96.8	74.4	3.45	<.001
Combat Exposure Scale Score, mean ± SD	3.3 ± 5.7	16.9 ± 6.6	11.8 ± 7.4	11.04	<.001
HRV, mean (ln ms^2) ± SD[a]					
ln (TP)	9.32 ± .53	9.23 ± .57	9.37 ± .52	1.98	.048
ln (ULF power)	9.11 ± .57	8.98 ± .60	9.07 ± .56	1.28	.19
ln (VLF power)	7.54 ± .65	7.17 ± .70	7.46 ± .57	3.09	.002
ln (LF power)	6.59 ± .81	6.05 ± .77	6.59 ± .76	4.25	<.001
ln (HF power)	5.33 ± .91	4.96 ± .83	5.20 ± .80	2.81	.005

BMI, body mass index; HDL, high-density lipoprotein; HRV, heart rate variability; IQR, interquartile range (25th percentile–75th percentile); LDL, low-density lipoprotein; ln, natural logarithm; PTSD, posttraumatic stress disorder; WHR, waist/hip ratio.

[a]Total power (TP) <.40 Hz; 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.

measure) were significantly associated with VLF, LF, and HF in unadjusted models. After multivariable adjustment, the association between current CAPS and LF persisted in individual twins ($p = .049$) and within 49 CAPS discordant twin pairs ($p < .01$).

Table 2. Percentage Difference in HRV Comparing Twins With Current PTSD with Those without Current PTSD

	Individual Twins ($n = 459$, 31 with PTSD)				PTSD Discordant Pairs (20 pairs)	
	Unadjusted		Adjusted[b]		Adjusted[b]	
HRV[a]	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p
TP	−18.2%	.05	−13.7%	.12	−20.5%	.03
ULF	−13.1%	.20	−9.5%	.33	−16.5%	.15
VLF	−30.3%	<.01	−21.0%	.03	−24.2%	.02
LF	−44.0%	<.001	−39.3%	<.001	−48.9%	<.001
HF	−28.8%	.01	−18.4%	.13	−26.7%	.06

No significant interaction of PTSD with zygosity.

% Δ HRV, percentage change in HRV due to PTSD; other abbreviations as in Table 1.

[a]TP <.40 Hz; ULF <.0033 Hz; VLF .0033 to <.04 Hz; LF .04 to <.15 Hz; and HF .15 to <.40 Hz.

[b]Adjusted for age, Baecke physical activity score, current/past smoking, hypertension, diabetes, LDL cholesterol, antidepressant use, lifetime history of major depression, BMI, and history of drug abuse.

Figure 2 illustrates the dose-response associations between increasing levels of CES and CAPS as ordinal variables and decreasing VLF, LF, and HF HRV in individual twins.

Discussion

In a large, predominantly healthy sample of middle-aged veteran men, we found a robust association between current PTSD and impaired autonomic modulation measured by means of 24-hour HRV. Combat exposure was also associated with lower HRV; however, this association was mainly accounted for by current PTSD, suggesting that autonomic inflexibility in individuals exposed to combat trauma is in large part mediated by PTSD. By studying twins, who share 50%–100% genes and early familial influences, we were able to show that this association was independent of genetic, familial, and sociodemographic factors. Results were also overall robust to adjustment for cardiovascular risk factors, depression, and history of substance abuse. Furthermore, we were able to demonstrate a dose-response relationship between PTSD symptom severity and HRV. In contrast, we found a mostly null association between remitted PTSD and autonomic function, suggesting possible reversibility of autonomic dysregulation after PTSD symptom resolution.

Our findings add to a growing literature linking exposure to combat trauma and PTSD with adverse health outcomes. Combat

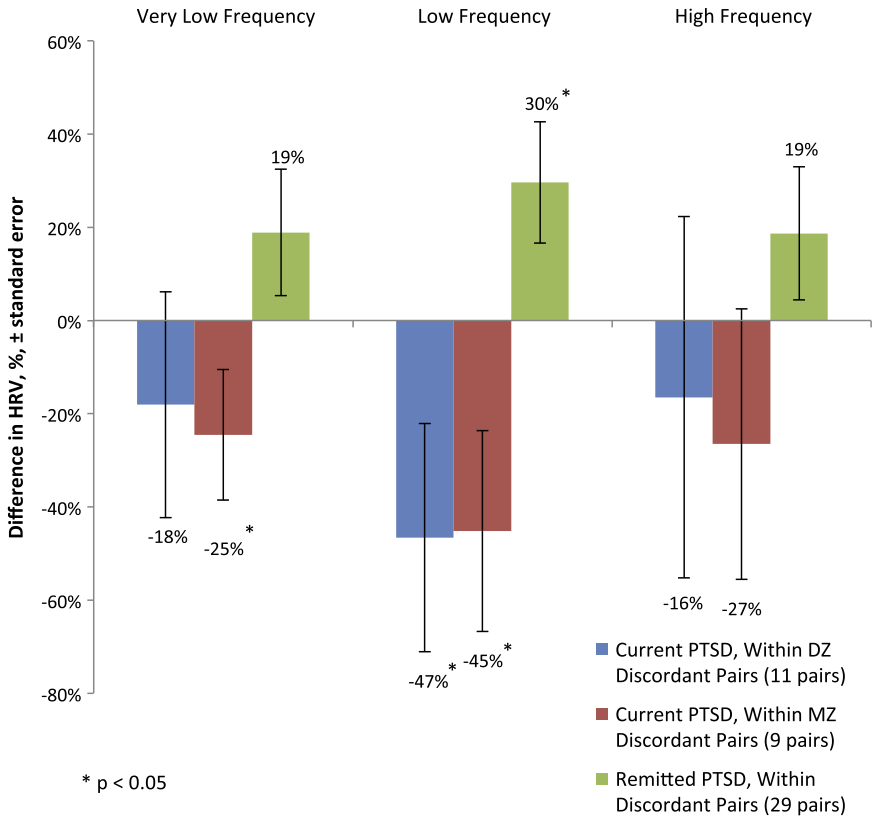

Figure 1. Adjusted percentage difference in very-low-frequency, low-frequency, and high-frequency heart rate variability (HRV) comparing twins with and without current or remitted posttraumatic stress disorder (PTSD). Adjusted for age, Baecke physical activity score, current/past smoking, lifetime history of hypertension, diabetes, low density lipoprotein cholesterol, antidepressant use, lifetime history of major depression, body mass index, and history of drug abuse. When examining remitted PTSD, models additionally adjusted for current PTSD. DZ, dizygotic; MZ, monozygotic.

veterans suffer from higher levels of unexplained complaints (43) and more often experience physical health problems than non-combat veterans (1). Because poor autonomic flexibility has been linked to both psychiatric conditions (26,44) and adverse health related outcomes (19,34), our finding of reduced autonomic flexibility in those with increasing levels of combat exposure and PTSD provides mechanistic insight to explain these previous findings. Importantly, our data show that the effects of exposure to combat trauma on autonomic function largely occur through PTSD, because we observed that the association was reduced after adjustment for current PTSD. Our study corroborates previous findings showing that combat exposure had only an indirect effect on health status, through PTSD (45).

Table 3. Difference in HRV for a 9-Point (Interquartile Range) Increase in CES Score

	Individual Twins (n = 459)						CES-Discordant Pairs (132 pairs)[b]	
	Unadjusted		Adjusted[c]		Adjusted[c] + Current PTSD		Adjusted[c]	
HRV[a]	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p	% Δ HRV	p
TP	−8.6%	< .01	−7.3%	< .01	−6.5%	.02	−9.2%	< .01
ULF	−6.9%	.02	−6.9%	.02	−6.6%	.03	−7.9%	.06
VLF	−8.9%	.01	−6.2%	.06	−4.1%	.21	−7.7%	.07
LF	−13.7%	< .01	−8.9%	.04	−4.2%	.37	−12.9%	< .01
HF	−11.3%	.01	−6.1%	.18	−4.3%	.35	−9.8%	.08

% Δ HRV = percentage change in HRV due to 9-point increase in CES score; CES, combat exposure scale; other abbreviations as in Table 1.

[a]TP <.40 Hz; ULF <.0033 Hz; VLF .0033 to <.04 Hz; LF .04 to <.15 Hz; and HF .15 to <.40 Hz.

[b]Discordance was defined as a ≥1 point difference in CES score within twin pairs. Percentage difference is per 9-point difference in CES within twin pairs.

[c]Adjusted for age, Baecke physical activity score, current/past smoking, hypertension, diabetes, LDL cholesterol, antidepressant use, lifetime history of major depression, BMI, and history of drug abuse.

Previous studies of HRV and PTSD have primarily focused on short-term HRV measures and have yielded conflicting results. Although some studies have found an association between PTSD and respiratory sinus arrhythmia (22,46), which is similar to HF HRV (47), others have not (26,48). These studies were limited by small sample sizes (n < 100), and did not adjust or only partially adjusted for potential confounding factors. In our data the association between current PTSD and HF HRV was weakened in multivariable analysis, suggesting that it is confounded by other risk factors. One of the reasons behind the difference between our findings of HF HRV and that of respiratory sinus arrhythmia in some of the previous studies is our use of 24-hour measures, which are subject to additional variability, because of changes in position (18). In contrast to HF, the association with LF and VLF HRV was robust to adjusting for potential confounding factors and was confirmed in within-pair analyses.

On the basis of previous studies, LF power is a reflection of baroreflex sensitivity (BRS) (49); therefore, our results could imply

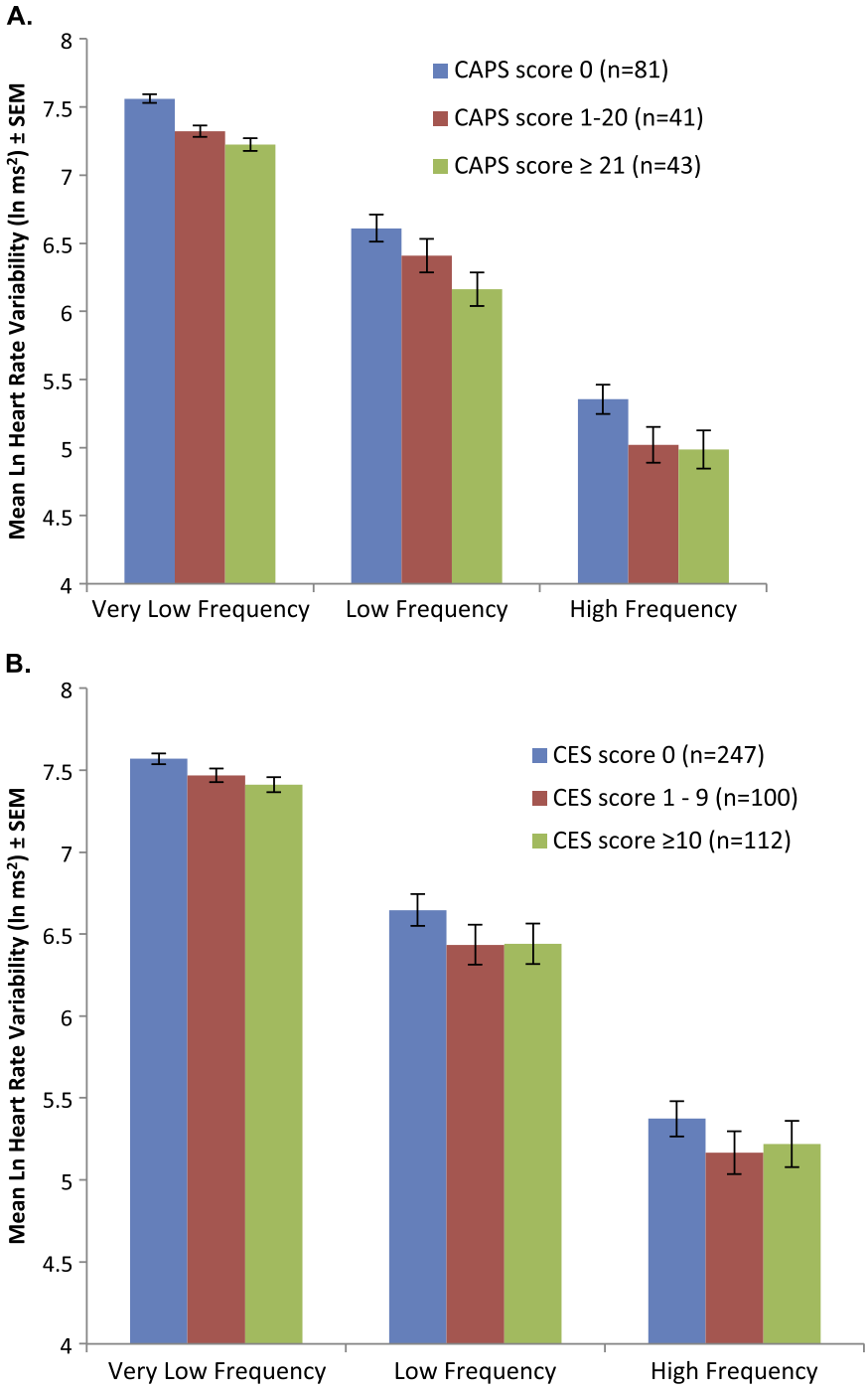

Figure 2. Mean natural log very-low-frequency, low-frequency, and high-frequency heart rate variability, according to the Clinically Administered PTSD Scale (CAPS) and Combat Exposure Scale (CES) ordinal categories. ln, natural logarithm; PTSD, posttraumatic stress disorder.

reduced BRS in individuals with current PTSD. These findings are consistent with a reported association between mental stress and reduced BRS (49). Additionally, reduced BRS might explain the lack of a significant heart rate response to acute stress found in people with PTSD (22). Both reduced BRS and reduced 24-hour ambulatory LF HRV power are associated with mortality and have important prognostic significance after myocardial infarction (50,51). According to Porges' polyvagal theory, reduced LF HRV might also suggest vagal insufficiency that arises from defects in the dorsal motor nucleus (15). This is consistent with other studies showing impaired vagal modulation, as assessed by low short-term respiratory sinus arrhythmia in subjects with PTSD and other anxiety disorders (20). Although some studies have reported higher short-term normalized LF (which differs from 24-hour LF power) in PTSD, our finding of lower 24-hour LF HRV is consistent with Porges' polyvagal theory (20).

Very-low-frequency power, a long-term frequency measure of HRV, was also significantly lower in twins with PTSD in our study.

Very-low frequency is a strong prognostic indicator in patients with myocardial infarction (52) and is thought to measure slow autonomic adjustments to changes in vasomotor tone (53). This association might imply decreased thermoregulation and increased renin-angiotensin system activity in persons with PTSD (47). In contrast, we found no consistent association between PTSD and ULF power, which is an important difference with previous research showing associations between depression and ULF HRV and suggests a different physiologic response between PTSD and depression (44).

This study is subject to some limitations. Our sample consisted of middle-aged men, primarily Caucasian; and therefore the findings might not be generalizable to other demographic groups. The design was cross-sectional, and thus temporal order in the reported associations is difficult to discern. The number of subjects with current PTSD was relatively small, thus limiting the precision of our estimates particularly after stratification for other factors such as zygosity. Despite this, many within-pair associations were significant, thus demonstrating that—overall—our findings were quite robust.

Conclusions

In this study of male veteran twins, both combat exposure and PTSD were associated with measures of autonomic inflexibility that have clinical relevance for cardiovascular risk. Furthermore, the impact of combat exposure on HRV seemed to be mostly mediated by PTSD. Our results suggest that lack of autonomic modulation is a plausible mechanism by which combat trauma, through the development of PTSD, might influence cardiovascular health. Given the growing number of veterans with PTSD from recent wars, our findings underscore the importance of appropriate care in these at-risk individuals, because it might yield both psychiatric and cardiovascular benefits.

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