Published in final edited form as:

Psychosom Med. 2017 June ; 79(5): 496–505. doi:10.1097/PSY.0000000000000438.

Trauma and Autonomic Dysregulation: Episodic – Versus Systemic – Negative Affect Underlying Cardiovascular Risk in Posttraumatic Stress Disorder

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Abstract

Objective—Posttraumatic stress disorder (PTSD) has been linked to elevated heart rate (HR) and reduced heart-rate variability (HRV) in cross-sectional research. Recent evidence suggests that this link may be driven by individual differences in autonomic arousal associated with momentary negative affect (NA). Using ecological momentary assessment (EMA) of NA and minute-to-minute HR/HRV monitoring, we examined whether NA-related HR/HRV mediated the association of PTSD symptom severity with 24-hour HRV and endothelial functioning.

Methods—One hundred ninety-seven young adults (18–39 years old), 93 with PTSD, underwent one day of Holter monitoring while concurrently reporting NA levels *via* EMA. Two non-invasive measures of endothelial functioning—flow-mediated dilation (FMD) and hyperemic flow—were also collected. Multilevel modeling was used to assess the associations of momentary NA with HR and low- (LF) and high-frequency (HF) HRV during the 5-minute intervals following each EMA reading. Latent variable modeling was then used to determine whether individual differences in these associations mediated the association of PTSD symptom severity with 24-hour HRV, FMD, and hyperemic flow

Results—PTSD symptom severity was positively associated with NA-related autonomic arousal ($\beta = .21, p < .001$), which significantly mediated the association of PTSD symptom severity with 24-hour HRV and hyperemic flow, accounting for 62% and 34% of their associations, respectively,

while overshadowing the influence of smoking, lifetime alcohol dependence, sleep duration, mean NA, and episodes of acute NA.

Conclusions—Results suggest that NA-related autonomic arousal is both a primary factor driving cardiovascular risk in PTSD and a potential point of intervention.

Keywords

posttraumatic stress disorder; heart rate variability; autonomic functioning; negative affect; cardiovascular risk; endothelial functioning

Introduction

Acute stress has long been linked to cardiovascular risk (1). For individuals with posttraumatic stress disorder (PTSD)—a chronic condition associated with hyperarousal and frequent physiological symptoms related to anxiety and negative affect—this risk is thought to be mediated largely by autonomic nervous system (ANS) imbalance (2). Indeed, PTSD diagnosis and symptom severity have been associated with reduced heart-rate variability (HRV) (3), a non-invasive set of indices of autonomic control of cardiac rhythm (4). In turn, attenuated HRV has been identified as a precursor to cardiovascular disease (5).

Nearly all prior research linking PTSD with ANS dysregulation has relied on cross-sectional analyses of aggregated data, leading to the conclusion that PTSD is linked with an overall reduction in HRV. However, emerging evidence suggests that this association may be more situational than static. For instance, in a recent study (6), we found that, amongst individuals meeting DSM-IV criteria for PTSD, minute-to-minute readings of low- (LF) and high-frequency (HF) HRV varied with momentary symptomatology. In a subsequent study (7) with a broader sample of participants with and without PTSD, we found that minute-to-minute LF and HF HRV also varied with momentary distress, particularly amongst individuals with the most severe PTSD. In fact, distress-related HRV appeared to be what sets aside individuals with severe PTSD from individuals with little or no posttraumatic stress symptoms. During moments of low distress, HR and HRV of individuals with severe PTSD were indistinguishable from those with no PTSD. Given evidence that PTSD may be characterized primarily by a hypoactive parasympathetic nervous system (PNS) (8, 9), these findings suggest that individuals with severe PTSD may fail to down-regulate their distress arousal. They also suggest that previously noted associations between PTSD and attenuated HRV may be the result of situational decreases in HRV during episodes of acute distress.

Aside from being an indicator of underlying dysfunction, attenuated HRV is also a precursor to cardiovascular disease, accelerating atherosclerosis (10) *via* endothelial dysfunction (11). The endothelium is a single layer of cells lining the interior surface of blood and lymphatic vessels. These cells regulate vascular tone by stimulating vasodilation or vasoconstriction in response to signals in the blood. Endothelial cells also possess adrenergic and acetylcholinergic receptors. As a result, they are responsive to direct influences by both the sympathetic nervous system (SNS) and PNS (12). Over time, an impaired endothelium can affect the extent to which the ANS regulates vascular tone *via* the release of nitric oxide, a vasodilator that offsets the vasoconstrictive effects of the SNS. The exact mechanisms by

which autonomic dysregulation leads to endothelial dysfunction is not entirely clear at present. However, evidence from animal models indicates that unregulated SNS activity may impair endothelial function by stimulating inflammatory processes within the endothelium (13, 14), including apoptosis, adhesion of macrophages to wall surfaces, and formation of smooth muscle fibers over the resulting lesions (15), all of which accelerate atherosclerosis and potentiate thrombosis (16).

Objectives and Hypotheses

Given the role that autonomic dysfunction appears to play in endothelial impairment as well as our previous findings that PTSD-related reductions in HRV are primarily evident during moments of acute distress, the primary goal of the present study was to examine if NA-related autonomic arousal may be a mechanism linking PTSD with attenuated HRV and ultimately poor endothelial functioning. Put differently, does NA-related autonomic arousal mediate the association of PTSD symptom severity with 24-hour HRV and endothelial functioning? Considering our previous findings that behavioral risk factors (i.e., smoking, alcohol dependence, sleep disturbance) mediate the association between PTSD and cardiovascular risk (17–20), a secondary goal was to compare the hypothesized mediating effects of NA-related autonomic arousal with those of the behavioral risk factors. We also investigated the potential mediating role that 24-hour NA—including mean NA observed during EMA monitoring and frequency of acute NA episodes—might play in linking PTSD symptom severity with 24-hour HRV and endothelial functioning. Thus, in the present analyses, we examined three sets of mechanisms potentially linking PTSD with autonomic dysregulation and vascular function, measured noninvasively by brachial artery flow-mediated dilation (FMD). These hypothesized mechanisms are summarized in Figure 1.

Methods

Participants and Procedure

The present paper builds on prior publications from on a broader study examining health risks associated with PTSD in young adults (6, 17–21). For the present analysis, potential participants were 211 young adults (18–39 years old), 93 of whom (44%) met DSM-IV criteria for PTSD. Participants were recruited from hospital clinics and waiting rooms as well as *via* online ads as part of a larger study focused on trauma and health risk factors among young adults (19). Exclusion criteria included: a) organic mental disorder; b) schizophrenia; c) bipolar I mixed state or bipolar II; d) lifetime PTSD without current PTSD; e) current substance abuse/dependence; f) current major depressive disorder without PTSD; g) pregnancy; h) AIDS or HIV; and i) uncontrolled medical condition (e.g., liver failure). The study was approved by both the Durham Veterans Affairs and Duke University Medical Center Institutional Review Boards. All patients gave written informed consent prior to participation. Data were collected between August 2008 and September 2013.

PTSD status was assessed using the Clinician Administered PTSD Scale (CAPS) (22). The interview was administered by a licensed clinical psychologist or by a trainee under the direct supervision of a licensed clinical psychologist. Interrater reliability among interviewers was high (Fleiss' kappa = .94) across five training tapes. Baseline Davidson

Trauma Scale (DTS) (23) scores were used to quantify PTSD symptom severity. Smoking status was operationalized based on participants' responses to the Fagerström Test for Nicotine Dependence (24) as follows: non-smokers were assigned a value of 0; past—but not present—smokers, 1; current smokers who consume 10 or fewer cigarettes/day, 2; and current smokers who consume 11 or more cigarettes/day, 3. Lifetime alcohol dependence was assessed using the Structured Clinical Interview for the DSM-IV (25). Demographic information, including age, sex, racial minority status, use of prescription medications, and anthropometric measures, from which waist-hip ratio was calculated, were collected at baseline.

Ten individuals ($n = 4$ with PTSD) using anti-hypertensives (i.e., beta blockers, calcium-channel blockers, ACE inhibitors) were excluded from the present analyses due to the potential effects of these medications on HR, HRV, and endothelial functioning (26, 27). Similarly, four individuals ($n = 3$ with PTSD) using tricyclic antidepressants or norepinephrine reuptake inhibitors were excluded (28, 29), leaving 197 participants. We also omitted endothelial functioning data for 13 women ($n = 1$ with PTSD) using birth control, 4 participants ($n = 3$ with PTSD) using cholesterol medication (i.e., statins, fibrates), and 1 participant with PTSD who had diabetes, given their potential effects on vascular functioning (30–32).

Ecological Momentary Assessment (EMA) and Sleep Diary

One week after baseline, participants returned to the laboratory to complete biometric measurements, including FMD and hyperemic flow. Immediately afterwards, they were fitted with a 24-hour digital ECG Holter monitor (Lifecard CF, Del Mar Reynolds, Irvine, CA) and given a PalmPilot to complete EMA ratings of mood in response to random alarms, which were timed to alert at semi-random intervals approximately every two to three hours. Monitoring sessions began at approximately 2:00 PM and lasted 20 to 24 hours. Seven items in the diary captured participants' current level of NA ("Indicate to what extent you have felt this way [irritated/annoyed/angry/distressed/upset/hostile/stressed] over the last five minutes before the alarm") using a scale ranging from 0 ("very slightly/not at all") to 4 ("extremely"). Parallel analysis (33) indicated that these items corresponded to a single latent factor, and internal reliability among the items was high ($\alpha = .93$, not adjusting for non-independence of repeated measurements). NA was calculated as the mean of the seven item, and acute NA episodes were deemed those readings in which NA level was greater than 3 ("quite a bit"). Participants also recorded their current activity level during each reading: lying down, sitting, standing up and engaging in light activity (e.g., walking slowly), or standing up and engaging in heavy activity (e.g., running). Diary entries were timestamped at the beginning of each entry.

During two days overlapping the Holter and EMA monitoring period, participants were asked to record when they went to bed, the approximate time that they fell asleep, and the time that they woke up. Sleep duration was calculated as the difference between the latter two recordings, the mean of which was tabulated across both nights of the observation period. Because short and long sleep duration are significant risk factors for poor cardiovascular outcomes (34) and are both relatively common in PTSD (35), quadratic sleep

duration effects were analyzed in addition to linear effects. The quadratic term was calculated by squaring the centered sleep-duration values.

Electrocardiogram (ECG) Monitoring

The exact procedures for collecting and processing 24-hour and minute-to-minute HRV data are reported here (19) and here (7). Briefly, 24-hour HRV was quantified using four indices: standard deviation of all normal R-R intervals (SDNN), triangular (TR) index, two-hour post-awakening low-frequency (LF) power in the range of 0.04 Hz to 0.15 Hz and high-frequency (HF) power in the range of 0.15 to 0.40 Hz. The LF component is controlled by both branches of the autonomic nervous system and reflects baroreceptor regulation of blood pressure, whereas the HF component is generally associated with parasympathetic responses and is closely linked to respiratory influences (36, 37). The latter two values were log-transformed prior to analyses. Minute-to-minute changes in the amplitude of the LF and HF components of HRV were extracted continuously by demodulating the frequency bands of 0.04–0.15 Hz and 0.15–0.45 Hz, respectively, and the amplitude time series of LF and HF components were averaged over every 1-minute segment, as was HR.

Flow-Mediated Dilatation (FMD) and Hyperemic Flow

All participants completed FMD assessments at least 4 hours following a light, low-fat breakfast. Vascular imaging was performed by a single sonographer using an Acuson Aspen ultrasound platform equipped with an Acuson L10 (7–10 MHz) linear array transducer, following guidelines described elsewhere (38). After participants rested for 10 minutes in the supine posture, longitudinal B-mode images of the brachial artery 4 to 6 cm proximal to the antecubital fossa were acquired. Images were then captured during the first 120 seconds of reactive hyperemia achieved by inflation of a pneumatic occlusion cuff located around the forearm to supra-systolic pressure (~200 mm Hg) for 5 minutes. Gated end-diastolic images of the artery were stored and arterial diameters were measured as the distance between the proximal and distal arterial wall intima-media interfaces using PC-based software (Brachial Analyzer - Version 5.0, Medical Imaging Applications LLC, Iowa City, Iowa). Peak FMD response was assessed from 10–120 seconds post-deflation of the cuff, with peak arterial diameter quantified using polynomial curve fitting. FMD was expressed as percent increase in arterial diameter. Because the percent change index may result in bias towards greater vasodilation in smaller arteries, baseline arterial diameter was used as a covariate in all analyses of FMD. Pulsed Doppler flow signals in the brachial artery were recorded at baseline and for up to 15 seconds after cuff release. The velocity-time integral for baseline and reactive hyperemia was based upon the mean of triplicate pulsed-Doppler flow tracings recorded at each phase. Hyperemic velocity was derived by dividing the velocity-time integral by the inter-beat interval, and hyperemic flow was calculated from hyperemic velocity and brachial artery cross-sectional area. All ultrasound image analyses were performed blinded to participants' identities. In an unpublished evaluation of 20 healthy men and women who underwent our FMD assessment protocol on consecutive days, repeat FMD values showed a correlation of $r = .81$, $p < .001$, a mean difference of $0.6 \pm 2.7\%$, and a coefficient of variation of 26.73%.

Data Setup and Analyses

EMA and minute-to-minute HR/HRV data were merged into a single dataset, matching upon diary timestamps and those for each HR/HRV reading. Mean HR/HRV values were calculated from the 5-minute intervals following the initiation of each diary reading. These 5-minute means were then modeled as a function of momentary NA. Given the nested structure of the minute-to-minute HR/HRV and EMA data (i.e., multiple observations within each person), with varying numbers of observations across participants, we used multilevel modeling (MLM) (39) to compute the within-person association of NA with HR and HRV. We specified three models corresponding to LF HRV, HF HRV, and HR. These were random-slopes-and-intercepts models, whereby the intercepts, or mean outcome levels, and slopes (i.e., associations between NA and the outcome variables) were allowed to vary across individuals in the sample. Age, sex, waist-hip ratio, and momentary activity level—factors unassociated with PTSD symptom severity, but potentially affecting HR and HRV—were covaried. Individual NA-HR/HRV slopes were extracted and merged with baseline data.

Latent variable modeling was used to test the hypotheses that PTSD symptom severity would be associated with 24-hour HRV as well as FMD and hyperemic flow, with subsequent analyses conducted to test the mediation hypotheses. Specifically, latent variables were specified using SDNN, TR index, log LF power and log HF power to model 24-hour HRV and NA-HR, -LF HRV, and -HF HRV slopes to model NA-related autonomic arousal in order to minimize the measurement error in both constructs. Adequacy of the HRV latent variable model was examined and adjusted to maximize model fit using standard fit criteria: standardized root mean square residual (SRMR) < .05, root mean square error of approximation (RMSEA) < .08, and comparative fit index (CFI) > .90. The chi-squared test of model fit was also consulted, with non-significance indicative of good model fit. Fit statistics were unavailable for the NA-related autonomic arousal latent variable due to model saturation, which occurs with specification of latent variables using just three indices. Factor scores were generated for each measurement model and used in subsequent analyses.

We examined the relationship between PTSD symptom severity and 24-hour HRV, first without mediators and then in independent models with smoking status, lifetime alcohol dependence, sleep duration and its quadratic term, mean EMA NA, number of acute NA episodes per 24 hours, and NA-related autonomic arousal entered as mediators. Consistent with MacKinnon's approach to testing mediation (40), we examined the effect of PTSD symptom severity on each mediator (Path A); then we examined the effect of each mediator on 24-hour HRV (Path B) independent of the effect of PTSD symptom severity. The indirect, or mediation, effect of PTSD symptom severity on 24-hour HRV was calculated as the product of Paths A and B. We similarly examined the relationship between PTSD symptom severity and endothelial functioning (i.e., FMD and hyperemic flow), the primary difference being that HRV was included as a potential mediator in that round of analyses.

To test significance of mediation effects, bootstrapped confidence intervals (CI) around indirect effects were generated using resampling. Resampling offers an advantage over conventional tests, such as Sobel's *z*, because it takes into account the positive skew inherent to indirect effects (41). As such, bootstrapping methods are more powerful than conventional

tests, with mediation deemed significant when the resulting CI does not span 0. After examining the independent effects of each of the above mediators, significant mediators were included in a single comprehensive model to determine which mediation effect was strongest.

In each model, age, sex, and waist-hip ratio were included as covariates. We applied multiple imputation to address missing data using 10 imputation datasets and Monte Carlo Markov chain method. Where bootstrapping was used, cases were resampled from all 197 participants with matching imputation datasets analyzed. Thus, missingness did not influence bootstrapped results. All analyses were conducted using SAS 9.4.

Given our inclusion of both participants with and without current PTSD in the present analyses, both subsamples of which were characterized by wide variability in PTSD symptom severity (non-PTSD: DTS total $M = 17.17$, $SD = 24.35$; PTSD: DTS total $M = 70.42$, $SD = 32.66$), an important question concerns whether the hypothesized mediation processes are evident amongst both individuals meeting criteria for PTSD as well as those not meeting criteria for a PTSD diagnosis. In order to examine this question, we conducted multiple-group path analyses where mediation was found. For instance, given significant mediation of the association between PTSD symptom severity and the factor score for HR/HRV means by the factor scores for HR/HRV slopes, the path model would include the path from PTSD symptom severity to mean HR/HRV as well as the paths from PTSD symptom severity, HR/HRV mean, age, sex, and waist-hip ratio to HR/HRV slopes. To examine whether these path models varied significantly by PTSD status, we first examined the corresponding configural models, in which the means, variances, and path coefficients were allowed to vary across both groups. We then examined constrained models, in which the path coefficients, but not the means and variances, were forced to be equivalent across both groups. Fit of the configural and constrained models were evaluated in the same way as the latent variable measurement models above, using RMSEA, CFI, SRMR, and model chi-square. Chi-square difference testing was then used to determine whether the constrained models fit the data significantly worse than the configural models. SAS does not have the capability to conduct multiple-group analyses *via* multiple imputations. Thus, multiple-group path analyses were based on complete data only.

Results

Participant characteristics and intercorrelations are displayed Table 1. Although HRV monitoring lasted between 20 and 24 hours, combined EMA and HRV monitoring was truncated by the first and last diary entries ($M = 17.81$ hours, $SD = 5.74$). Participants recorded $M = 6.95$ diary entries ($SD = 2.63$) during that time. Response rate to random alarms was 86%, and participants took $M = 54.42$ seconds ($SD = 19.04$) to complete each diary entry. Consistent with previous findings (7), PTSD symptom severity was positively associated with EMA NA level and mean HR and was negatively associated with mean LF and HF HRV (see Table 1).

As described above, data on baseline brachial artery diameter, FMD, and hyperemic flow were deleted and thus missing for 19 participants. Morning LF and HF HRV were also

missing for 11 participants ($n = 2$ with PTSD) who awakened subsequent to the end of Holter monitoring. Missingness of morning HRV data was not associated with sex, waist-hip ratio, PTSD symptom severity, smoking status, lifetime alcohol dependence, SNDD, TR index, hyperemic flow, or FMD (all p s $> .28$). However, participants with missing morning HRV data were younger than those without missing data (25.09 vs. 29.09 years, respectively; $t(195) = 2.34$, $p = .020$) and reported longer sleep duration (11.44 vs. 8.07 hours, respectively; $t(189) = 5.28$, $p < .001$). Sleep diary data were missing for six participants. Missingness of those data was not associated with any of the above variables (all p s $> .08$).

Multilevel Modeling of Heart Rate and Heart-Rate Variability

Results from the MLM analyses are depicted in Table 2. Across the entire sample, momentary NA was not significantly associated with HR and HRV. However, random effects representing the intraindividual associations of momentary NA with HR and HF HRV were both significant, indicating that the variances corresponding to interindividual differences in those associations were greater than 0. Variance associated with interindividual differences in the NA-LF HRV slopes was marginally significant. Inspection of individual slopes revealed that the associations of NA with HR (mean $\beta = .01$; range: $-.70$ to 1.25), LF HF (mean $\beta = -.03$; range: $-.79$ to $.51$), and HF HRV (median $\beta = -.07$; range: -2.11 to $.73$) were significant for 41% ($n = 80$), 20% ($n = 39$), and 22% ($n = 43$) of the sample, respectively.

24-Hour Heart-Rate Variability

The initial measurement model for the 24-hour HRV latent variable yielded a poor fit: SRMR = .092, RMSEA = .436, CFI = .849, and $X^2(2) = 76.56$, $p < .001$. However, after specifying a correlation ($r = .35$, $p < .001$) between the residuals for SDNN and TR index, the model improved significantly, $X^2(1) = 73.55$, $p < .001$, rendering an adequate fit: SRMR = .010, RMSEA = .010, CFI = .996, and $X^2(1) = 3.01$, $p = .092$. The loadings for the 24-hour HRV latent variable were .63 for SDNN, .64 for TR index, .98 for log LF HRV, and .84 for log HF HRV (all p s $< .001$). The loadings for the NA-related autonomic arousal latent variable were .78 for the HR slope, $-.88$ for the LF HRV slope, and $-.81$ for the HF HRV slope (all p s $< .001$).

According to the initial 24-hour HRV model, PTSD symptom severity was negatively associated with 24-hour HRV (see Table 3). PTSD symptom severity was also positively associated with smoking, lifetime alcohol dependence, mean EMA NA, number of acute NA episodes per 24 hours, and NA-related autonomic arousal. Moreover, the association between PTSD symptom severity and 24-hour HRV appeared to be partially mediated by smoking status, lifetime alcohol dependence, and NA-related autonomic arousal.

Bootstrapped mediation analyses indicated that smoking status (bootstrapped 95% CI of standardized effect: $-0.12 - -0.01$) and NA-related autonomic arousal (bootstrapped 95% CI of standardized effect: $-0.20 - -0.05$) each independently mediated the association of PTSD symptom severity with HRV, accounting for 27% and 62% of their covariance, respectively. The indirect effect of PTSD symptom severity on HRV *via* lifetime alcohol dependence

(bootstrapped 95% CI of standardized effect: $-0.09 - 0.01$) was not significant. In a final model of 24-hour HRV in which smoking status and NA-related autonomic arousal were entered simultaneously, neither PTSD symptom severity ($\beta = -.07, p = .22$) nor smoking status ($\beta = -.02, p = .78$) was significantly associated with 24-hour HRV; however, NA-related autonomic arousal was ($\beta = -.58, p < .001$). In follow-up bootstrapped analyses, the indirect effect of PTSD symptom severity on 24-hour HRV *via* NA-related autonomic arousal was significant (bootstrapped 95% CI of standardized effect: $-.32 - -.16$), explaining 77% of the covariance between PTSD symptom severity and HRV, whereas the indirect effect *via* smoking status was not (bootstrapped 95% CI of standardized effect: $-.03 - .02$).

Endothelial Functioning

PTSD symptom severity was not significantly associated with FMD ($\beta = -.03, p = .69$) after controlling for age ($\beta = .07, p = .37$), female sex ($\beta = -.12, p = .21$), waist-hip ratio ($\beta = .06, p = .40$), and baseline brachial artery diameter ($\beta = -.51, p < .001$). However, PTSD symptom severity was negatively associated with hyperemic flow (see Table 4). Of the potential mediators, only NA-related autonomic arousal was significantly associated with hyperemic flow. However, smoking status had a marginally significant association with hyperemic flow, and both smoking status and 24-hour HRV modestly reduced the effect of PTSD symptom severity on hyperemic flow. Follow-up mediation analyses indicated that the indirect effects of PTSD symptom severity on hyperemic flow *via* smoking status (bootstrapped 95% CI of standardized effect: $-.13 - .00$) and 24-hour HRV (bootstrapped 95% CI of standardized effect: $-.07 - .01$) were not significant. By contrast, the indirect effect for NA-related autonomic arousal (bootstrapped 95% CI of standardized effect: $-.10 - -.01$) was significant, accounting for 34% of the effect of PTSD symptom severity on hyperemic flow.

Model Invariance by PTSD Status

Model invariance by PTSD status was examined for three mediation models: the association between PTSD symptom severity and HR/HRV factor scores by smoking status, the association between PTSD symptom severity and HR/HRV factor scores by HR/HRV slope factor scores, and the association between PTSD symptom severity and hyperemic flow by HR/HRV slope factor scores. According to the configural model for the first mediation process, the model provided a poor fit to the data: RMSEA = .14, CFI = .90, SRMR = .07, $\chi^2(6) = 17.14, p = .009$. Constraining the paths to be equivalent across both groups did not significantly diminish model fit: $\chi^2(6) = 6.06, p = .11$. In fact, the fit indices suggested a slightly better fit for this model: RMSEA = .10, CFI = .90, SRMR = .07, and $\chi^2(12) = 12.82, p = .026$.

According to the configural mediation model in which HR/HRV slope factor scores mediate the association between PTSD symptom severity and factor scores for HR/HRV means, the mediation pathways modeled independently for individuals with and without PTSD provided a good fit to the data: RMSEA = .05, CFI = .99, SRMR = .05, and $\chi^2(6) = 8.23, p = .22$. Constraining the paths to be equivalent across each group did not significantly

diminish fit: $X^2(6) = 4.59, p = .13$. In fact, the fit indices suggested a slightly better fit for this model: RMSEA = .03, CFI > .99, SRMR = .05, and $X^2(12) = 12.82, p = .38$.

The configural mediation model of hyperemic flow also indicated a good fit to the data: RMSEA = .04, CFI = .98, SRMR = .04, and $X^2(6) = 6.90, p = .33$. Similar to the HRV factor score model, constraining the paths of the hyperemic flow mediation model to be equivalent across each group did not diminish fit: RMSEA = .04, CFI = .97, SRMR = .05, $X^2(12) = 13.36, p = .34$, and $X^2(6) = 6.46, p = .10$. In sum, we found no evidence that any of the above mediation processes were specific to one group over another.

Discussion

Increasingly, PTSD has been linked with attenuated HRV (3, 42), an indicator of autonomic dysregulation (5, 43) and cardiovascular risk (44). In light of recent evidence that PTSD is associated with heightened distress-related autonomic arousal (i.e., increased HR, attenuated HRV) (7), we examined whether NA-related autonomic arousal accounted for the association of PTSD symptom severity with HRV and ultimately endothelial functioning within a mixed sample of young adults with and without PTSD. We also examined the mediating roles of behavioral health risks (i.e., smoking, lifetime alcohol dependence, and sleep impairment) and baseline NA. In our analysis of momentary NA and autonomic arousal, we did not find an overall association between the two across the entire sample. However, we did find significant interindividual differences in these associations. That is, for some individuals in the sample, there was a positive association between NA and arousal, and for others there was not. Not only was NA-related autonomic arousal associated with PTSD symptom severity, it was the largest mediator of PTSD symptom severity and 24-hour HRV, accounting for 62% of their covariance, and it was the only significant mediator of PTSD symptom severity and hyperemic flow, accounting for 34% of their covariance. Moreover, these mediation processes were evident among both participants with PTSD and those without PTSD, suggesting that there is a continuum of risk posed by PTSD symptomatology and NA-related autonomic arousal. These findings complement research from the past decade indicating that increased autonomic reactivity to laboratory-induced stress is predictive of future cardiovascular risk (45, 46), even after controlling for 24-hour HRV levels (47, 48). However, the present data go beyond that, doing so with ecologically valid data while demonstrating that greater overall negative affect and higher frequency of negative affect may have little bearing on markers of cardiovascular risk; neither do smoking, drinking, and sleep duration once NA-related autonomic arousal is taken into account.

These findings have a number of potential implications for the treatment of PTSD and, more broadly, conditions characterized by acute physiological responses to negative affect (e.g., panic disorder, intermittent explosive disorder). Specifically, these findings suggest that interventions that help patients gain control over their physiological arousal during moments of acute NA could potentially reap far greater health benefits than those primarily focused on decreasing NA in general. There are already several interventions that aim to teach patients to better regulate their physiological arousal during moments of acute NA and stress, such as HRV biofeedback (49–51) and mindfulness-based interventions (52).

However, applying these principles *in situ* can prove challenging (53). Thus, a promising avenue for intervention lies in harnessing the power of mobile-health technology to aid in the early detection of adverse states of arousal in order to prompt patients to apply their coping skills to prevent sharp increases in NA-related autonomic arousal. Beyond enhancing patients' capacity to manage acute psychological distress, such interventions also have the potential to modulate deleterious patterns of autonomic dysfunction and perhaps improve endothelial functioning.

The present findings also raise two important questions. The first concerns whether NA-related autonomic arousal is primarily the result of increased SNS activity in response to NA or whether it is due to diminished PNS regulation of NA. Broadly speaking, this question is unanswerable in the current dataset. Absent knowledge of the onset and duration of each episode of negative affect, we cannot directly assess how autonomic processes underlie the progression of negative affect. However, future projects could potentially collect this information *via* mood induction procedures. Prior researchers have done just this with mixed samples (45–48). Absent these data in a sample with PTSD, we must extrapolate from prior work, which suggests that individuals with PTSD and other anxiety disorders primarily suffer from PNS dysfunction. For instance, whereas administration of catecholamine (SNS) antagonists prior to a panic attack does little to reduce HR (54), lactate—a known suppressor of vagal (PNS) activity—accumulates during panic attacks (55) and is sometimes administered in laboratory studies to induce PTSD symptoms (8). Thus, suppressed PNS activity and consequently reduced HRV are implied in individuals with anxiety or trauma-related disorders such as PTSD.

A second question concerns why we failed to find evidence of any association of PTSD symptom severity or HRV with FMD even though both were associated with hyperemic flow. FMD is considered a measure of general vascular endothelial function, whereas hyperemic flow is more reflective of peripheral microvascular function, with impaired hyperemic flow associated with microvascular disease (56). Although the microvasculature may receive ANS inputs, endothelial cells in major conduit arteries such as the brachial artery do not receive direct innervation from the ANS (57). Thus, peripheral vascular function, as indexed by hyperemic flow, is more likely to be affected by autonomic dysfunction.

Study Limitations

Of course, there are several notable limitations to the present study. First, subjective NA was measured in response to random prompts over the 24-hour period. Consequently, antecedents of acute NA were unknown, as was the trajectory of NA levels (i.e., whether they were increasing, holding steady, or decreasing). By using HR and HRV measurements taken directly after the initiation of each diary entry, we made an assumption that any variance in the trajectory of NA levels across the readings was, apart from individual differences in NA management, randomly distributed across readings and participants. Given that we were expressly modeling individual differences in NA-related arousal, we stand by our interpretation of the present findings. Another limitation was our use of lifetime alcohol dependence as a measurement of impact of alcohol use on HRV and endothelial

functioning, as was our use of self-reported sleep duration over a fairly brief period of time (i.e., two days). It is possible that more precise measurements of these variables might have yielded stronger effects.

Summary and Conclusions

The present study provides the first evidence to date that NA-related autonomic arousal may mediate the association of PTSD symptom severity with 24-hour HRV and endothelial functioning. While preliminary, these findings suggest that heightened autonomic arousal accompanying NA may be an important factor underlying autonomic dysfunction in PTSD. Thus, interventions that help patients to gain control over physiological arousal during moments of acute NA (e.g., biofeedback, mindfulness) may be an especially effective way of reducing risk for cardiovascular disease. That said, additional research aimed at replicating and expanding upon these findings (e.g., by incorporating mood induction procedures into the study design) is still needed.

Acknowledgments

Source of Funding: Preparation of this work was supported by the National Institute of Mental Health (2R01MH062482), the Durham, NC Veterans Affairs Medical Center; and the Department of Veterans Affairs office of Research and Development Clinical Science. Dr. Kimbrel was supported by a Career Development Award (IK2 CX000525) from the Clinical Science Research and Development Service of the Department of Veterans Affairs Office of Research and Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Department of Veterans Affairs, or the United States Government.

Abbreviations

PTSD	posttraumatic stress disorder
HR	heart rate
HRV	heart-rate variability
NA	negative affect
EMA	ecological momentary assessment
FMD	flow-mediated mediation
LF	low frequency
HF	high frequency
ANS	autonomic nervous system
PNS	parasympathetic nervous system
SNS	sympathetic nervous system
DTS	Davidson Trauma Scale
SDNN	standard deviation of R-R intervals

TR index	triangular index
MLM	multilevel modeling
SRMR	standardized root mean square residual
RMSEA	root mean square error of approximation
CFI	comparative fit index
CI	confidence interval

References

1. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: A review and methodologic critique. *Psychological Bulletin*. 1984; 96:435–464. [PubMed: 6393178]
2. Blechert J, Michael T, Grossman P, Lajtman M, Wilhelm FH. Autonomic and respiratory characteristics of posttraumatic stress disorder and panic disorder. *Psychosomatic Medicine*. 2007; 69:935–943. [PubMed: 17991823]
3. Chalmers JA, Quintana DS, Maree J, Abbott A, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Frontiers in Psychiatry*. 2014; 5:1–11. [PubMed: 24478729]
4. Task Force of the European Society of Cardiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *European Heart Journal*. 1996; 17:354–381. [PubMed: 8737210]
5. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*. 2010; 141:122–131. [PubMed: 19910061]
6. Green KT, Dennis PA, Neal LD, Hobkirk AL, Hicks TA, Watkins LL, Hayano J, Sherwood A, Calhoun PS, Beckham JC. Exploring the relationship between posttraumatic stress disorder symptoms and momentary heart rate variability. *Journal of Psychosomatic Research*. 2016:31–34.
7. Dennis PA, Dedert EA, van Voorhees EE, Watkins LL, Hayano J, Calhoun PS, Sherwood A, Dennis MF, Beckham JC. Examining the crux of autonomic dysfunction in PTSD: Whether chronic or situational distress underlies elevated heart rate and attenuated heart-rate variability. *Psychosom Med*. in press.
8. Jensen CF, Keller TW, Peskind ER, McFall ME, Veith RC, Martin D, Wilkinson CW, Raskind MA. Behavioral and neuroendocrine responses to sodium lactate infusion in subjects with posttraumatic stress disorder. *American Journal of Psychiatry*. 1997; 154:266–268. [PubMed: 9016280]
9. Johnson PL, Sajdyk TJ, Fitz SD, Hale MW, Lowry CA, Hay-Schmidt A, Shekhar A. Angiotensin II's role in sodium lactate-induced panic-like responses in rats with repeated urocortin 1 injections into the basolateral amygdala: Amygdalar angiotensin receptors and panic. *Progress in Neuro-psychopharmacology and Biological Psychiatry*. 2013; 44:248–256. [PubMed: 23523745]
10. Sloan RP, Shapiro PA, Bagiella E, Myers MM, Gormon JM. Cardiac autonomic control buffers blood pressure variability responses to challenge: A psychophysiologic model of coronary artery disease. *Psychosomatic Medicine*. 1999; 61:58–68. [PubMed: 10024068]
11. Celermajer DS, Sorenson KE, Gooch VM, Spiegelhalter DJ, Miler OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet*. 1992; 340:1111–1115. [PubMed: 1359209]
12. Harris KF, Matthews KA. Interactions between autonomic nervous system activity and endothelial function: A model for the development of cardiovascular disease. *Psychosomatic Medicine*. 2004; 66:153–164. [PubMed: 15039499]
13. Loesch A, Maynard K, Burnstock G. Calcitonin gene-related peptide-and neuropeptide Y-like immunoreactivity in endothelial cells after long-term stimulation of perivascular nerves. *Neuroscience*. 1992; 48:723–726. [PubMed: 1603338]

14. Coutinho G, Durieu-Trautmann O, Strosberg A, Couraud P. Catecholamines stimulate the IFN-gamma-induced class II MHC expression on bovine brain capillary endothelial cells. *Journal of Immunology*. 1991; 147:2525–2529.
15. Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochemical Pharmacology*. 2009; 78:539–552. [PubMed: 19413999]
16. Tousoulis D, Antoniades C, Koumallos N, Stefanadis C. Pro-inflammatory cytokines in acute coronary syndromes: From bench to bedside. *Cytokine and Growth Factor Reviews*. 2006; 17:225–233. [PubMed: 16750416]
17. Oddone A, Dennis PA, Calhoun PS, Watkins L, Sherwood A, Dedert EA, Green KT, Stein JN, Dennis MF, Beckham JC. Orthostatic hypotension in younger individuals with and without posttraumatic stress disorder. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2015; 7:229–233.
18. Dennis PA, Ulmer CS, Calhoun PS, Sherwood A, Watkins LL, Dennis MF, Beckham JC. Behavioral health mediators of the link between posttraumatic stress disorder and dyslipidemia. *Journal of Psychosomatic Research*. 2014; 77:45–50. [PubMed: 24913341]
19. Dennis PA, Watkins L, Calhoun PS, Oddone A, Sherwood A, Dennis MF, Rissling MB, Beckham JC. Posttraumatic stress disorder, heart-rate variability, and the mediating role of behavioral health risks. *Psychosomatic Medicine*. 2014; 76:629–637. [PubMed: 25264973]
20. Dennis PA, Weinberg JB, Calhoun PS, Watkins LL, Sherwood A, Dennis MF, Beckham JC. An investigation of vago-regulatory and health-behavior accounts for increased inflammation in posttraumatic stress disorder. *Journal of Psychosomatic Research*. 2016; 83:33–39. [PubMed: 27020074]
21. Dennis PA, Dedert EA, van Voorhees EE, Watkins LL, Hayano J, Calhoun PS, Sherwood A, Dennis MF, Beckham JC. Examining the crux of autonomic dysfunction in PTSD: Whether chronic or situational distress underlies elevated heart rate and attenuated heart-rate variability. *Psychosomatic Medicine*. 2016; 78:805–809. [PubMed: 27057817]
22. Blake DD, Weathers FS, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. *Journal of Trauma Stress*. 1995; 8:75–90.
23. Davidson JRT, Book SW, Colket JT, Tupler LA, Roth S, David D, Hertzberg MA, Mellman T, Beckham JC, Smith RD, Davidson RM, Katz R, Feldman ME. Assessment of a new self-rating scale for posttraumatic stress disorder: The Davidson Trauma Scale. *Psychological Medicine*. 1997; 27:153–160. [PubMed: 9122295]
24. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*. 1991; 86:1119–1127. [PubMed: 1932883]
25. Rogers, RG. Structured Clinical Interview for DSM-IV Disorders (SCID) and other Axis 1 interviews. In: Rogers, R., editor. *Handbook of Diagnostic and Structured Interviewing*. New York: Guilford Press; 2001. p. 103-148.
26. Tomiyama H, Kimura Y, Sakuma Y, Shiojima K, Yamamoto A, Saito I, Ishikawa Y, Yoshida H, Morita S, Doba N. Effects of an ACE inhibitor and a calcium channel blocker on cardiovascular autonomic nervous system and carotid distensibility in patients with mild to moderate hypertension. *American Journal of Hypertension*. 1998; 11:682–689. [PubMed: 9657627]
27. Barenbrock M, Spieker C, Hoeks A, Zidek W, Rahn K. Effect of lisinopril and metoprolol on arterial distensibility. *Hypertension*. 1994; 23:1161–1163. [PubMed: 8282350]
28. Kemp AH, Quintana DS, Gray MA, Felmingham KL, Brown K, Gatt JM. Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry*. 2010; 67:1067–1074. [PubMed: 20138254]
29. Schroeder C, Tank J, Boschmann M, Diedrich A, Sharma AM, Biaggioni I, Luft FC, Jordan J. Selective norepinephrine reuptake inhibition as a human model of orthostatic intolerance. *Circulation*. 2002; 105:347–353. [PubMed: 11804991]
30. Baillargeon J-P, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism*. 2005; 90:3863–3870. [PubMed: 15814774]

31. Suzuki M, Takamisawa I, Yoshimasa Y, Harano Y. Association between insulin resistance and endothelial dysfunction in type 2 diabetes and the effects of pioglitazone. *Diabetes Research and Clinical Practice*. 2007; 76:12–17. [PubMed: 17007957]
32. Wang T-D, Chen W-J, Lin J-W, Cheng C-C, Chen M-F, Lee Y-T. Efficacy of fenofibrate and simvastatin on endothelial function and inflammatory markers in patients with combined hyperlipidemia: Relations with baseline lipid profiles. *Atherosclerosis*. 2003; 170:315–323. [PubMed: 14612213]
33. O'Connor BP. SPSS and SAS programs for determining the number of components using parallel analysis and Velicer's MAP test. *Behavior Research Methods, Instruments, and Computers*. 2000; 32:396–402.
34. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *European Heart Journal*. 2011; 32:1484–1492. [PubMed: 21300732]
35. Park S, Cho MJ, Chang SM, Bae JN, Jeon HJ, Cho Sj, Kim Bs, Chung Iw, Ahn JH, Lee HW. Relationships of sleep duration with sociodemographic and health-related factors, psychiatric disorders and sleep disturbances in a community sample of Korean adults. *Journal of Sleep Research*. 2010; 19:567–577. [PubMed: 20477953]
36. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clinical Autonomic Research*. 2011; 21:133–141. [PubMed: 21279414]
37. Reyes del Paso GA, Langewitz W, Mulder LJ, Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology*. 2013; 50:477–487. [PubMed: 23445494]
38. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gernard-Herman M, Herrington D, Vallance P, Vita J, Vogel R. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force.[erratum appears in *Journal of the American College of Cardiology*, 39, 1082]. *Journal of the American College of Cardiology*. 2002; 39:257–265. [PubMed: 11788217]
39. Searle, SR., Casella, G., McCulloch, CE. *Variance components*. New York: Wiley; 1992.
40. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*. 2002; 7:83–104. [PubMed: 11928892]
41. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods*. 2008; 40:879–891. [PubMed: 18697684]
42. Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. *Biological Psychiatry*. 2013; 73:1103–1110. [PubMed: 23434412]
43. Bikkina M, Alpert MA, Mukerji R, Mulekar M, Cheng B-Y, Mukerji V. Diminished short-term heart rate variability predicts inducible ventricular tachycardia. *Chest Journal*. 1998; 113:312–316.
44. Huikuri HV, Jokinen V, Syväne M, Nieminen MS, Airaksinen KJ, Ikäheimo MJ, Koistinen JM, Kauma H, Kesäniemi AY, Majahalme S. Heart rate variability and progression of coronary atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1999; 19:1979–1985.
45. Heponiemi T, Elovainio M, Pulkki L, Puttonen S, Raitakari O, Keltikangas-Järvinen L. Cardiac autonomic reactivity and recovery in predicting carotid atherosclerosis: The cardiovascular risk in young Finns study. *Health Psychology*. 2007; 26:13–21. [PubMed: 17209693]
46. Matthews KA, Salomon K, Brady SS, Allen MT. Cardiovascular reactivity to stress predicts future blood pressure in adolescence. *Psychosomatic Medicine*. 2003; 65:410–415. [PubMed: 12764214]
47. Gianaros PJ, Salomon K, Zhou F, Owens JF, Edmundowicz D, Kuller LH, Matthews KA. A greater reduction in high-frequency heart rate variability to a psychological stressor is associated with subclinical coronary and aortic calcification in postmenopausal women. *Psychosomatic Medicine*. 2005; 67:553. [PubMed: 16046367]

48. Steptoe A, Marmot M. Impaired cardiovascular recovery following stress predicts 3-year increases in blood pressure. *Journal of Hypertension*. 2005; 23:529–536. [PubMed: 15716693]
49. Prinsloo GE, Rauch H, Lambert MI, Muench F, Noakes TD, Derman WE. The effect of short duration heart rate variability (HRV) biofeedback on cognitive performance during laboratory induced cognitive stress. *Applied Cognitive Psychology*. 2011; 25:792–801.
50. Siepmann M, Aykac V, Unterdörfer J, Petrowski K, Mueck-Weymann M. A pilot study on the effects of heart rate variability biofeedback in patients with depression and in healthy subjects. *Applied Psychophysiology and Biofeedback*. 2008; 33:195–201. [PubMed: 18807175]
51. Karavidas MK, Lehrer PM, Vaschillo E, Vaschillo B, Marin H, Buyske S, Malinovsky I, Radvanski D, Hassett A. Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Applied Psychophysiology and Biofeedback*. 2007; 32:19–30. [PubMed: 17333315]
52. Satyapriya M, Nagendra HR, Nagarathna R, Padmalatha V. Effect of integrated yoga on stress and heart rate variability in pregnant women. *International Journal of Gynecology and Obstetrics*. 2009; 104:218–222. [PubMed: 19110245]
53. Peira N, Fredrikson M, Pourtois G. Controlling the emotional heart: Heart rate biofeedback improves cardiac control during emotional reactions. *International Journal of Psychophysiology*. 2014; 91:225–231. [PubMed: 24373886]
54. Goetz M, Shah A, Goldberg J, Cheema F, Shallenberger L, Murrah NV, Bremner JD, Vaccarino V. Posttraumatic stress disorder, combat exposure, and carotid intima-media thickness in male twins. *American Journal of Epidemiology*. 2014; 180:989–996. [PubMed: 25301813]
55. Dager SR, Strauss WL, Marro KI, Richards TL, Metzger GD, Artru AA. Proton magnetic resonance spectroscopy investigation of hyperventilation in subjects with panic disorder and comparison subjects. *American Journal of Psychiatry*. 1995; 152:666–672. [PubMed: 7726305]
56. Huang AL, Silver AE, Shvenke E, Schopfer DW, Jahangir E, Titas MA, Shpilman A, Menzoian JO, Watkins MT, Raffetto JD. Predictive value of reactive hyperemia for cardiovascular events in patients with peripheral arterial disease undergoing vascular surgery. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2007; 27:2113–2119.
57. Guimarães S, Moura D. Vascular adrenoceptors: An update. *Pharmacological Reviews*. 2001; 53:319–356. [PubMed: 11356987]

Figure 1.
Pathways by which PTSD symptoms influence HRV and vascular function.

Table 1

Participant Characteristics and Intercorrelations

Variables	Mean (SD)	Freq (%)	Intercorrelations (<i>r</i> -values)																		
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age (1)	28.87 (5.57)	-																			
Females (2)		100 (51%)	.02	-																	
Minority status (3)		102 (53%)	.06	.28**	-																
Waist-hip ratio (4)	0.88 (0.08)		.19**	-.36**	-.12	-															
Smoking status (5)	0.98 (1.16)		.19**	-.13 [†]	.03	.25**	-														
Lifetime alcohol dependence (6)		60 (30%)	.28**	-.27**	-.02	.28**	.41**	-													
Sleep duration, hrs (7)	8.25 (2.10)		-.02	-.03	-.04	-.01	.07	.05	-												
Sleep duration ² (8)	72.42 (40.08)		-.01	-.04	-.03	-.03	.07	.06	.98	-											
DTS total (9)	40.42 (38.68)		.25**	-.07	.18*	.10	.41**	.06	.11	.12	-										
Mean EMA NA (10)	1.39 (0.51)		.08	-.10	.13 [†]	.07	.33**	.23**	.02	.03	.59**	-									
Acute NA per 24 hrs (11)	0.11 (0.61)		-.02	-.10	.11	.01	.20**	.01	.03	.02	.15*	.55**	-								
Mean EMA heart rate, bpm (12)	80.22 (11.59)		.17*	.26**	.24**	.20**	.35**	.27**	-.09	-.09	.34**	.14 [†]	-.04	-							
Mean EMA LF HRV, ms (13)	39.60 (15.06)		-.35**	-.33**	-.36**	-.13 [†]	-.35**	-.24**	.03	.04	-.34**	-.18*	-.06	-.75**	-						
Mean EMA HF HRV, ms (14)	27.08 (14.16)		-.44**	-.09	-.11	-.23**	-.32**	-.27**	.12	.13 [†]	-.29**	-.11	-.02	-.66**	.80**	-					
SDNN (15)	144.11 (46.86)		-.33**	-.32**	-.34**	-.20**	-.26**	-.19**	.10	.09	-.25**	-.04	.04	-.66**	.74**	.66**	-				
TR index (16)	39.34 (13.20)		-.29**	-.23**	-.27**	-.20**	-.32**	-.24**	.07	.06	-.29**	-.13 [†]	-.02	-.75**	.75**	.67**	.75**	-			
Log LF HRV (17)	6.95 (0.88)		-.30**	-.33**	-.27**	-.04	-.20**	-.18*	-.06	-.07	-.25**	-.08	-.00	-.62**	.80**	.65**	.61**	-.63**	-		
Log HF HRV (18)	5.97 (1.21)		-.40**	-.15*	-.11	-.06	-.18*	-.20**	-.02	-.04	-.22**	-.05	.01	-.51**	.65**	.76**	.56**	.52**	.82**	-	
FMD ^a , % change (19)	6.60 (4.06)		.07	-.08	-.20**	.08	-.07	-.04	.02	.01	-.01	-.05	-.12	-.08	.11	.02	.09	.11	.10	.04	-
Hyperemic flow, % change	839.05 (339.20)		.02	.22**	-.02	-.11	-.20**	-.09	-.07	-.08	-.14 [†]	-.06	-.02	-.12	.11	.12 [†]	.08	.10	.05	-.00	.26**

Note. Correlations between sex, minority status, and lifetime alcohol dependence are tetrachoric. DTS total = Davidson Trauma Scale total score; EMA = ecological momentary assessment; NA = negative affect; LF HRV = low-frequency heart-rate variability; HF HRV = high-frequency heart-rate variability; SDNN = standard deviation of normal R-R intervals; TR index = triangular index; FMD = flow-mediated dilation.

^aCorrelations with FMD have baseline brachial artery diameter (mm) partialled out.

[†] $p < .10$, $p < .05$, $p < .01$

Table 2

Multilevel Models of Minute-to-Minute Heart Rate, Low-Frequency HRV, and High-Frequency HRV

Parameter	Heart Rate (bpm)	LF HRV (ms)	HF HRV (ms)
Fixed Effects			
Within-Person			
Intercept	26.74 ** (9.05)	109.60 ** (11.31)	92.43 ** (9.10)
Sitting ^a	5.29 ** (0.80)	-1.75 † (1.00)	-4.71 ** (0.80)
Light activity (standing up) ^a	11.89 ** (0.88)	-2.65 * (1.10)	-8.79 ** (0.88)
Heavy activity (standing up) ^a	18.47 ** (1.70)	-11.72 ** (2.12)	-14.11 ** (1.70)
Negative Affect	0.53 (0.79)	-1.49 (1.05)	-0.19 (0.82)
Between-Person			
Age	0.21 (0.14)	-0.92 ** (0.17)	-0.93 ** (0.14)
Female sex	-7.97 ** (1.64)	12.14 ** (2.04)	3.92 * (1.64)
Waist-hip ratio	54.37 ** (10.32)	-50.25 ** (12.89)	-42.21 ** (10.38)
Random Effects			
Interindividual differences, Intercept	0	21.46 (24.72)	6.99 (14.09)
Interindividual differences, NA slope	22.34 ** (2.64)	22.94 † (12.28)	18.76 ** (7.00)
Intraindividual variability, Intercept	96.96 ** (3.99)	149.14 ** (6.38)	96.21 ** (4.12)

Note. Estimates and standard errors (in parentheses). LF HRV = low-frequency heart-rate variability; HF HRV = high-frequency heart-rate variability. $N = 197$.

^aProstrate position used as reference value.

† $p < .10$,

* $p < .05$,

** $p < .01$

Table 3
Regression Models Examining the Direct and Indirect Effects of PTSD Symptom Severity on 24-Hour HRV

Models	Path A	β (SE) for Predictors of 24-Hour HRV				24-Hour
	β (SE)	Age	Female	WH Ratio	PTSD Sx	HRV R^2
Direct effects model	-	-.23** (.07)	-.38** (.07)	-.11 (.07)	-.21** (.07)	.26
Mediation Models						
Behavioral risk factors						
Smoking status	.41** (.06)	-.22** (.07)	-.39** (.07)	-.09 (.07)	-.16* (.07)	.28
Lifetime alcohol dependence	.41** (.07)	-.22** (.07)	-.39** (.07)	-.10 (.07)	-.18** (.07)	.27
Sleep duration	.10 (.07)	-.23** (.07)	-.38** (.07)	-.11 (.07)	-.22** (.07)	.26
Sleep duration ²	.11 (.07)				-.00 (.08)	
Negative affect						
Mean EMA NA	.59** (.06)	-.23** (.07)	-.38** (.07)	-.11 (.07)	-.24** (.08)	.26
Acute EMA NA/24hrs	.15* (.07)	-.23** (.07)	-.38** (.07)	-.11 (.07)	-.21** (.07)	.26
NA-related autonomic arousal	.21** (.07)	-.27** (.05)	-.39** (.05)	-.16** (.05)	-.07 (.05)	.58

Note. Estimated effects are standardized. Path A estimates correspond to the effect of the independent variable (PTSD symptom severity) on the mediators, listed in the far-left column. Path B estimates reflect the effect of the mediators on the dependent variable (24-hour HRV) independent of the effect of the independent variable (PTSD symptom severity). WH Ratio = waist-hip ratio; PTSD Sx = posttraumatic stress disorder symptom severity; HRV = heart-rate variability; Sleep duration² = sleep duration value, squared; EMA = ecological momentary assessment; NA = negative affect. $N = 197$.

* $p < .05$,

** $p < .01$

Table 4
Regression Models Examining the Direct and Indirect Effects of PTSD Symptom Severity on Hyperemic Flow

Models	Path A		β (SE) for Predictors of Hyperemic Flow				Hyperemic Flow	
	β (SE)		Age	Female	WH Ratio	PTSD Sx	Path B	R^2
Direct effects model	-		.03 (.08)	.21** (.08)	-.06 (.08)	-.15* (.07)	-	.08
Mediation Models								
Behavioral risk factors								
Smoking status	.41** (.06)		.04 (.08)	.20** (.08)	-.04 (.08)	-.09 (.08)	-.14 [†] (.08)	.10
Lifetime alcohol dependence	.41** (.07)		.03 (.08)	.21** (.08)	-.06 (.08)	-.14 [†] (.08)	-.00 (.08)	.08
Sleep duration	.10 (.07)		.03 (.08)	.20** (.08)	-.07 (.08)	-.14 [†] (.07)	-.02 (.08)	.09
Sleep duration ²	.11 (.07)						-.03 (.08)	
Negative affect								
Mean EMA NA	.59** (.06)		.04 (.08)	.21** (.08)	-.07 (.08)	-.19* (.09)	.07 (.09)	.09
Acute EMA NA/24hrs	.15* (.07)		.04 (.08)	.21** (.08)	-.06 (.08)	-.15* (.07)	.03 (.07)	.08
24-hour HRV	-.23** (.07)		.06 (.08)	.25** (.08)	-.05 (.08)	-.12 (.07)	.11 (.09)	.09
NA-related autonomic arousal	.21** (.07)		.02 (.07)	.21** (.08)	-.08 (.08)	-.09 (.07)	-.23** (.07)	.13

Note. Estimated effects are standardized. Path A estimates correspond to the effect of the independent variable (PTSD symptom severity) on the mediators, listed in the far-left column. Path B estimates reflect the effect of the mediators on the dependent variable (hyperemic flow) independent of the effect of the independent variable (PTSD symptom severity). WH Ratio = waist-hip ratio; PTSD Sx = posttraumatic stress disorder symptom severity; HRV = heart-rate variability; Sleep duration² = sleep duration value, squared; EMA = ecological momentary assessment; NA = negative affect. $N = 197$.

[†] $p < .10$,

* $p < .05$,

** $p < .01$