

Posttraumatic Stress Disorder Is Associated With Worse Endothelial Function Among Veterans

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Background—Current research in behavioral cardiology reveals a significant association between posttraumatic stress disorder (PTSD) and increased risk for cardiovascular disease and mortality; however, the underlying mechanisms remain poorly understood. We hypothesized that patients with PTSD would exhibit endothelial dysfunction, a potential mechanism involved in the development and progression of cardiovascular disease.

Methods and Results—A total of 214 outpatients treated at the San Francisco Veterans Affairs Medical Center underwent tests of endothelial function and evaluation for PTSD. Flow-mediated vasodilation of the brachial artery was performed to assess endothelial function, and current PTSD status was defined by the PTSD Checklist, based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), with a score ≥ 40 . Multivariable linear regression models were used to estimate the association between PTSD status and endothelial function. Patients with PTSD ($n=67$) were more likely to be male (99% versus 91%, $P=0.04$) and to have depression (58% versus 8%, $P<0.0001$) and were less likely to be on an angiotensin-converting enzyme inhibitor (17% versus 36%, $P=0.007$) or β -blocker treatment (25% versus 41%, $P=0.03$). Univariate analysis demonstrated that patients with PTSD had significantly lower flow-mediated vasodilation ($5.8\pm 3.4\%$ versus $7.5\pm 3.7\%$; $P=0.003$); furthermore, lower flow-mediated vasodilation was associated with increasing age ($P=0.008$), decreasing estimated glomerular filtration rate ($P=0.003$), hypertension ($P=0.002$), aspirin ($P=0.03$), and β -blocker treatments ($P=0.01$). In multivariable analysis, PTSD remained independently associated with lower flow-mediated vasodilation ($P=0.0005$).

Conclusions—After adjusting for demographic, comorbidity, and treatment characteristics, PTSD remained associated with worse endothelial function in an outpatient population. Whether poor endothelial function contributes to the higher risk of cardiovascular disease in patients with PTSD deserves further study. (*J Am Heart Assoc.* 2016;5:e003010 doi: 10.1161/JAHA.115.003010)

Key Words: endothelial dysfunction • endothelial function • mental disorder • posttraumatic stress disorder

Allostasis is the process by which living organisms maintain biological homeostasis during a diverse array

of challenges, including those of an environmental or physiological nature.^{1,2} It is thought that cumulative effects of stress (repetitive or continuous), referred to as *allostatic load*, affect several physiological systems including the hypothalamic–pituitary–adrenal axis; the autonomic nervous system; and the cardiovascular, metabolic, and immune systems.^{1,2} Because ≈ 7.7 million US persons suffer from posttraumatic stress disorder (PTSD) in a given year³ and the expected lifetime prevalence of PTSD is 8% in the general population,⁴ better understanding of the impact of PTSD on cardiovascular health has become critical.

In a large internationally representative epidemiologic research study,⁵ the effects of psychosocial factors on myocardial infarction were even larger than well-established medical risk factors such as diabetes, hypertension, and obesity. Multiple prospective cohort studies have estimated the association of PTSD with incident cardiovascular events and/or cardiovascular death with hazard ratios ranging from 1.46 to 3.28 compared with those of patients without PTSD (reviewed by Edmondson and Cohen⁶). Despite the dispropo-

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portionate association of PTSD and cardiovascular disease (CVD), the underlying mechanisms remain poorly understood. A possible explanation is that patients with PTSD have higher rates of traditional CVD risk factors, including hypertension, dyslipidemia, diabetes, obesity, and tobacco use,⁷ but neither these risk factors nor depression fully account for the increased rate of CVD in the PTSD population.⁶

Nitric oxide is known to be a key mediator of endothelial function,⁸ and a recent study reports that biomarkers of nitric oxide synthetic capacity are significantly impaired in veterans with PTSD compared with those without PTSD.⁹ Acute stress has been shown to increase circulating markers of endothelial dysfunction and to impair vasoreactivity, as assessed by endothelium-dependent flow-mediated vasodilation (FMD).^{10–12} We hypothesized that chronic stress, as experienced by veterans with PTSD, leads to less vasoreactivity (ie, worse endothelial function) than that of an age-matched control veteran population without PTSD.

Methods

Study Participants

Between June 2011 and August 2015, 214 patients were recruited from the San Francisco Veterans Affairs Medical Center (VAMC) for evaluation of their vascular function and for the presence of PTSD (cross-sectional design), including 136 veterans who were referred to the surgery clinic and 78 veterans who were receiving care in the medical clinic. The investigator-initiated protocol was approved by the University of California, San Francisco (UCSF), Committee on Human Research, and all patients gave informed consent.

PTSD and Comorbid Psychiatric Diagnosis

The research team administered the PTSD Checklist (PCL), a self-report measure composed of 17 five-point Likert scales that provide a total score for PTSD (range 17–85 points), according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).¹³ Only patients with completed PCL testing were included. A score of ≥ 40 was used to define the presence of PTSD, as suggested by the VAMC National Center for PTSD.¹⁴ In a sample of male veterans in PTSD treatment, the correlation of the PCL with the Clinician-Administered PTSD Scale is reported to be 0.79.¹⁵ To assess comorbid psychiatric diagnosis, the Patient Health Questionnaire was also used to evaluate depressive symptoms (score of ≥ 10). This self-report instrument measures the frequency of depressive symptoms corresponding to the 9-symptom criteria in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).¹⁶

Vascular Reactivity of Brachial Arteries

Endothelial function was measured using brachial artery endothelium-dependent FMD in the Vascular Integrated Physiology and Experimental Therapeutics (VIPERx) Laboratory at UCSF, according to current guidelines and standards previously described by our group.^{17–22} Under fasting conditions, including abstention from nicotine and caffeine, participants acclimated in the laboratory for 10 minutes in a supine position in a temperature-controlled, low-lit room. A 5-cm tourniquet blood pressure cuff was placed on the upper arm distal to the insertion of the deltoid. Although there is no consensus on the location of the cuff (upper arm versus lower arm), our laboratory has adopted the upper arm technique, which is supported by current guidelines.²³ The patient's blood pressure was recorded in the contralateral arm. The brachial artery was surveyed by B-mode ultrasound (Philips HD11; Philips) using a broadband linear array transducer with a range of 3 to 12 MHz (Philips L12-3; Philips) to identify a segment suitable for imaging. Criteria for a suitable segment include a straight arterial segment with adequate visualization of a “double line sign” on the near- and far-wall intima–media lines and an accompanying registration structure such as a crossing vein. The baseline diameter of the vessel was recorded using EKG-gated image-capture software (Brachial Imager; Medical Imaging Applications LLC), and baseline Doppler spectral waveform was recorded using an insonation angle of 60°. Mean diameter and velocity at baseline were calculated from measurements collected for 60 seconds.

The blood pressure cuff was then inflated to 250 or 50 mm Hg above the participant's systolic blood pressure, whichever first induced cessation of brachial artery blood flow by sonography, for a period of 5 minutes. Blood flow cessation was confirmed by sonographic monitoring of the brachial artery during cuff inflation. Following cuff deflation, hyperemia-stimulated brachial artery luminal diameter and Doppler spectral waveforms were again recorded for a total duration of 3 minutes after cuff release. Vasorelaxation determined by this method has been shown to be mediated predominantly by nitric oxide with little influence from other endothelium-derived relaxing factors.

Postacquisition image analysis and calculation of hemodynamic parameters was performed using continuous edge-detection software (Brachial Analyzer; Medical Imaging Applications LLC). The lumen diameter was measured from the near-wall lumen–intima interface to the far-wall lumen–intima interface. The velocity–time integral was calculated by the peak velocity method of integrating the spectral waveform over the first 4 cardiac cycles after cuff release. Blood flow was calculated as the product of blood vessel cross-sectional area and velocity–time integral modeling the artery as a circle. Mean shear stress was calculated by the

Hagen-Poiseuille equation, in which T_w is shear stress in dynes/cm² and mean volumetric flow is Q . The viscosity of blood (μ) is assumed to be 0.0035 poise, and lumen radius (r) is in centimeters:

$$T_w = \frac{4\mu Q}{\pi r^3} \quad (1)$$

Corresponding hyperemia parameters were calculated over a predetermined time window of 55 to 65 seconds after cuff release. FMD% was calculated as [(60-second Hyperemia diameter–mean baseline diameter/mean baseline diameter) × 100].

Quality control was assessed at all points in data acquisition. Image quality was evaluated by a second person and graded on a 6-point scale that included registration structure (landmark), horizontally directed artery, correct longitudinal alignment, clearly visualized near- and far-wall intima–media thickness, and at least 5 mm of clearly visualized artery. The interobserver variability in our laboratory is 0.05±0.16%, and the intraobserver variability is 0±0.15%.

Other Patient Characteristics

Demographic and anthropometric data were collected at the time of FMD testing to better characterize research participants and included age, race, sex, hip and waist circumference, and body mass index. Blood pressure was measured using standard sphygmomanometry. We collected from the participants a history of CVD, such as coronary artery disease, cerebrovascular disease, and previous lower extremity vascular disease, as well as risk factors including hypertension, diabetes mellitus types 1 and 2, hyperlipidemia, and history of current or past tobacco use. History of smoking was defined as current or former smoker. Concurrent medications and pertinent cardiovascular examination findings were also recorded.

Lipid, Metabolic, and Inflammatory Measurements

Blood samples were collected in a fasting state for measurement of albumin, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, high-sensitivity C-reactive protein, and hemoglobin A1c by the VAMC clinical laboratory per standard methodology (Beckman Coulter analyzer). The coefficient of variation for high-sensitivity C-reactive protein using this procedure was 5.1%. Estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease formula based on age, sex, race, and serum creatinine level.²⁴

Statistical Analysis

Characteristics of patients with and without PTSD were compared, and statistically significant associations were identified with *t* tests for continuous variables and with chi-square tests for categorical variables. We used maximum likelihood regression models to estimate mean (95% CI) values of FMD by levels of patient characteristics, singly (univariate) and together (multivariable), and to test the significance of these associations using likelihood ratio tests. Multivariable adjustment was made for demographic characteristics and traditional cardiovascular risk factors with $P<0.05$ in univariate models; however, depression status was omitted from the multivariable model of FMD because it is very strongly associated with PTSD status, and our goal was to study association of FMD with PTSD.

In addition to analyzing associations with PTSD status, if PCL scores ≥ 40 defined the presence of PTSD, we used linear regression models to estimate associations of patient characteristics and mean brachial artery FMD with PCL quartiles and to test for statistically significant associations using 1- and 3-*df* likelihood ratio statistics, respectively. An illustrative plot of predicted FMD by PCL quartile, against a background of observed FMD values by logarithm base-10 PCL scores, was created using SAS transreg (SAS Institute). Statistical analyses were performed using Stata/SE 12 (StataCorp) and SAS version 9.4.

Results

Among the 214 participants in this study, the range of PCL scores was 17 to 85, and 64 (31%) were found to have PTSD, as defined by a score ≥ 40 (Table 1). Patients with PTSD were more likely to be male (99% versus 91%, $P=0.04$) and to have depression (56% versus 8%, $P<0.0001$) but were less likely to be on an angiotensin-converting enzyme inhibitor (17% versus 36%, $P=0.007$) or β -blocker treatment (25% versus 41%, $P=0.03$). There was no difference in the proportion of patients who were active smokers between the 2 groups (PTSD 27% versus non-PTSD 25%, $P=0.81$). Quartiles of PCL scores showed that the majority of the sample was at lower risk levels (17–20, 21–30, 31–46, 47–85). When patient characteristics were examined by PCL quartile (Table S1), the trends were similar to those observed by PTSD status.

Among 209 participants with nonmissing outcomes, the overall brachial artery FMD was 6.9±3.7%. Patients with PTSD had worse endothelial function, as measured by significantly lower brachial artery FMD (5.8±3.4% versus 7.5±3.7%; $P=0.003$) (Table 2).

We used a regression model to examine linearity of FMD as a function of logarithm base-10 PCL scores, stratified by PCL

Table 1. Characteristics of Patients With and Without PTSD*

	No PTSD (147)	PTSD (n=67)	P Value
Demographics			
Age, y	69±9	68±6	0.39
Male sex	91%	99%	0.04
White	74%	81%	0.31
Comorbidities and risk factors			
History of smoking	83%	78%	0.36
Hypertension	73%	84%	0.11
Hyperlipidemia	71%	79%	0.22
Diabetes mellitus	27%	27%	0.93
Coronary artery disease	26%	30%	0.49
Depression (PHQ-9 score ≥10)	8%	58%	<0.0001
Systolic blood pressure, mm Hg	138±18	143±21	0.08
Diastolic blood pressure, mm Hg	79±10	81±11	0.26
Medications			
Aspirin	59%	71%	0.15
ACEI	36%	17%	0.007
β-Blocker	41%	25%	0.03
Statin	75%	74%	0.90
Laboratory studies			
Total cholesterol, mg/dL	169±40	164±44	0.44
LDL, mg/dL	92±34	89±35	0.59
HDL, mg/dL	49±14	49±13	0.91
Triglycerides, mg/dL	137±87	127±72	0.40
CRP, mg/L	4.3±5.1	3.7±3.6	0.40
eGFR, mL/min	77±22	81±19	0.19
HgA1c (%)	5.9±1.0	6.0±1.0	0.78

ACEI indicates angiotensin-converting enzyme inhibitor; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HgA1c, hemoglobin A1c; LDL, low-density lipoprotein; PHQ-9, Patient Health Questionnaire; PTSD, posttraumatic stress disorder.

*Continuous characteristics are summarized by mean±SD and categorical characteristics as percentage of PTSD level having the characteristic.

quartile (Figure). This model estimated that FMD declines nonlinearly with logarithm base-10 PCL scores, with mean differences between quartiles of −1.8%, −1.0%, and −0.45%, respectively (3-*df* likelihood ratio test $P=0.060$) (Figure and Table S2).

Univariate analysis demonstrated that lower FMD also was significantly associated with a diagnosis of PTSD ($P=0.003$), increasing age ($P=0.008$), decreasing estimated glomerular filtration rate ($P=0.003$), hypertension ($P=0.002$), aspirin use ($P=0.03$), and β-blocker treatment ($P=0.01$). In multivariate analysis (Table 3), PTSD remained independently associated with FMD ($P=0.0005$). In an adjusted model, this corresponded to an FMD of 4.9% (95% CI 3.7–6.0%) in

Table 2. Brachial Artery Flow-Mediated Vasodilation in Patients Without and With PTSD

Measure*	No PTSD (147)	PTSD (n=67)	P Value†
Baseline diameter, cm	0.38±0.07	0.41±0.05	0.01
Reactive hyperemia diameter, cm	0.41±0.07	0.43±0.05	—
Change from baseline with RH	0.03±0.01	0.02±0.01	—
% Change from baseline (brachial FMD)	7.5±3.7	5.8±3.4	0.003
Baseline velocity, m/s	0.16±0.07	0.15±0.06	0.54
Reactive hyperemia velocity, m/s	0.78±0.28	0.82±0.25	—
Change from baseline with RH, m/s	0.62±0.28	0.66±0.26	0.25
Baseline flow, mL/min	113±64	121±54	0.36
Reactive hyperemia flow, mL/min	651±315	726±248	—
Change from baseline with RH, mL/min	537±287	604±241	0.10
Baseline shear stress, dynes/cm ²	12±7	11±5	0.14
Reactive hyperemia shear stress, dynes/cm ²	54±21	54±19	—
Change from baseline with RH, dynes/cm ²	41±20	43±19	0.57

FMD indicates flow-mediated vasodilation; PTSD, posttraumatic stress disorder; RH, reactive hyperemia.

*Continuous characteristics are summarized by mean±SD.

†Student *t* test. To avoid inflating the type 1 error rate (false-positive claims), statistical tests examined 1 measure each of variation at start and at end of vasodilation challenge.

patients with PTSD compared with 7.3% (95% CI 6.7–8.0%) in those without PTSD.

FMD was also significantly associated with the presence of depressive symptoms, which are frequently comorbid with

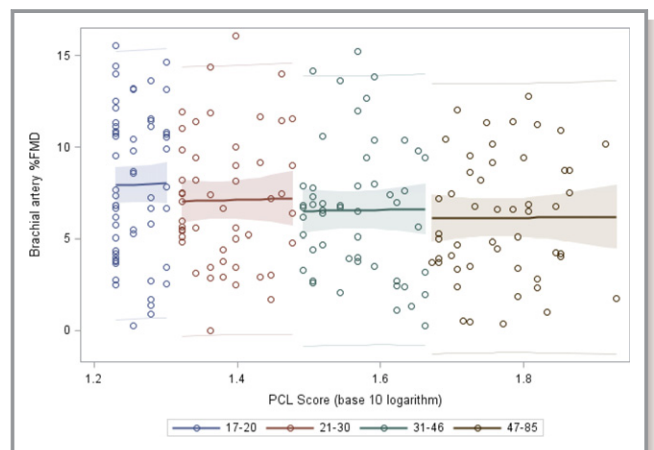


Figure. Mean (with 95% CI and prediction limits) brachial artery FMD per sample quartile of PCL score suggests that greater worsening of endothelial function occurs at earlier stages of PTSD. FMD indicates flow-mediated vasodilation; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder.

Table 3. Univariate and Multivariate Associations With Endothelial Function Measured by Brachial Artery Flow-Mediated Vasodilation

Patient Characteristic	Univariate Analysis		Multivariable Analysis	
	Mean (95% CI) Coefficient*	P Value	Mean (95% CI) Coefficient*	P Value
PTSD	−1.7 (−2.7 to −0.6)	0.002	−2.5 (−3.8 to −1.1)	0.0005
Sex (male)	0.03 (−1.98 to 2.04)	0.97	2.0 (−1.4 to 5.5)	0.25
Age	−0.09 (−0.15 to −0.02)	0.008	−0.09 (−0.17 to −0.002)	0.06
Race (white)	0.02 (−1.16 to 1.21)	0.97	0.57 (−0.92 to 2.03)	0.46
eGFR	0.04 (0.01–0.06)	0.003	0.03 (0.001–0.06)	0.04
Hypertension	−1.8 (−3.0 to −0.68)	0.002	−0.5 (−2.2 to 1.3)	0.59
ASA	−1.3 (−2.5 to −0.15)	0.03	−0.6 (−2.2 to 0.65)	0.35
β-Blockers	−1.3 (−2.3 to −0.3)	0.01	−1.1 (−2.3 to 0.16)	0.09
ACEI	−0.7 (−1.8 to 0.45)	0.24	−0.7 (−1.9 to 0.6)	0.31

ACEI indicates angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilation; PTSD, posttraumatic stress disorder. *A regression model coefficient estimates the mean (95% CI) change in FMD per unit change in a patient characteristic; for example, the univariate analysis estimated a mean change of −1.7 as PTSD status changed from 0 to 1 (Table 3), which is consistent with the FMD means of 7.5 and 5.8 for PTSD absence and presence, respectively, reported in Table 2.

PTSD (coefficient −1.3; 95% CI −2.5 to −0.12; $P=0.03$). After additional adjustment for depression in the full model presented in Table 3, the relationship between FMD and PTSD remained significant (coefficient −1.8; 95% CI −3.4 to −0.2; $P=0.03$).

Discussion

In a cohort of outpatients treated at the San Francisco VAMC, PTSD was associated with worse endothelial function, as measured by FMD. This association remained significant after adjusting for other potential cofounders. To our knowledge, these data represent the largest cohort in which endothelial function with FMD was measured in patients with PTSD. These data provide evidence of a clear association between PTSD and vascular function among veterans and illustrate the need to empirically determine the optimal multidisciplinary strategies to treat patients with comorbid PTSD and CVD risk.

Patients with PTSD have higher rates of traditional biological and behavioral CVD risk factors, including hypertension, dyslipidemia, diabetes, obesity, and tobacco use.⁷ Nevertheless, in our work and that of others, the association of PTSD and CVD has not been fully explained by these risk factors or by depression, suggesting that the pathway is not merely related to poor health behaviors or traditional CVD risk factors.^{6,25–27} Rather, a direct relationship between PTSD and vascular function appears to be involved. In fact, our study demonstrated an association between PTSD and endothelial dysfunction measured by brachial artery FMD after adjustment for age, hypertension, and renal function. Our work expands on prior examinations of PTSD and vascular

function.^{10–12,28} To date, only 1 study in the literature focused on PTSD and vascular function measured with FMD. This study, conducted in a cohort of 100 police officers, found that higher levels of PTSD symptoms were associated with a nearly 2-fold decrease in FMD after adjustment for demographics and health behaviors.²⁹ Consequently, our current data represent the largest study reporting the association between PTSD and endothelial dysfunction using brachial artery FMD.

Our study demonstrated a 2.4% adjusted difference in FMD between patients with and without PTSD. This difference has significant predictive potential for the risk of cardiovascular events. In fact, in recent meta-analysis, it has been estimated that a 1% decrease in FMD is predictive of a 10% absolute increase in future cardiovascular events and mortality.^{30,31} It is currently unknown whether treatment of PTSD would improve vascular function or future cardiovascular risk.

Based on current data, damage to the endothelial lining of blood vessels appears to be worsened by mental or psychological stress. This supports the notion that repeated provocation of endothelial stress reactivity, as may occur with persistent PTSD, may have an atherogenic effect on the endothelium over time. Mechanisms may include impairments of nitric oxide pathways via stress-arousal mediators,^{9,32} an increase in inflammation^{10,33} (although not present in this study), and a perturbation in major stress systems such as the hypothalamic–pituitary–adrenal axis and the autonomic nervous system.² Patients with PTSD have lower peripheral cortisol levels,^{34,35} which could contribute to a proinflammatory milieu and an inflammatory activation of endothelial cells.^{36–38} It is also possible that psychological stress leads to endothelial dysfunction through an increase in oxidative stress³⁹ or through the release of potent vasoconstrictors including endothelin⁴⁰ and angiotensin II.⁴¹

Limitations

Although this work represents the largest study to date on the association between PTSD and endothelial function, this study was observational and used a cross-sectional design. The patient population studied included predominantly male white veterans from the San Francisco VAMC. It is also important to note that depression has been associated with worse FMD.⁴² In our study, a percentage of the patients met criteria for both PTSD and depression (based on scores on the Patient Health Questionnaire). Depressive symptoms in some cases can reflect the overlap of the diagnostic criteria with PTSD (anhedonia, cognitive decrements, sleep disturbance, guilt). Furthermore, some argue that unless major depressive disorder was established prior to PTSD, the co-occurrence may represent a trauma-related phenomenon that is distinct from major depressive disorder.⁴³ In the current study, the timing of occurrence of diagnosis was not established. Furthermore, in the majority of patients, use of antidepressants or anti-anxiety drugs was not recorded. This represents another limitation of the study. Although participants were recruited through both the surgery and medical clinics, all vascular testing was conducted by the same laboratory (VIPERx), and PTSD was measured in the same fashion. Last, it should be noted that the baseline diameter was different between the groups and possibly could contribute to the difference seen in FMD. This is however less likely since the FMD equation adjusts for baseline diameter as demonstrated in the methods section.

Conclusions

In summary, our results support the hypothesis that patients with PTSD have worse endothelial function, as demonstrated by lower brachial artery FMD. Prospective studies are needed to establish whether PTSD contributes to the increased risk of cardiovascular events via endothelial dysfunction. Furthermore, future research is needed to understand whether treatment of PTSD could improve measures of endothelial function and decrease the risk of CVD or CVD events.

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Disclosures

None.

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