Associations among Pain, PTSD, mTBI, and Heart Rate Variability in Veterans of Operation Enduring and Iraqi Freedom: A Pilot Study

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ABSTRACT

Objective. The objective of the study was to determine if there is dysregulated autonomic nervous system activity as manifested by depressed heart rate variability (HRV) among veterans of Operations Enduring and Iraqi Freedom (OEF/OIF).

Participants and Setting. The study used a convenience sample of OEF/OIF veterans (n = 28) seen at a Level II Polytrauma Network Site at the Michael E. DeBakey VA Medical Center. Participants were similar to other OEF/OIF veterans who received care at this site.

Design. Cross sectional study.

Measures. Time domain analysis (standard deviation of beat-to-beat intervals [SDNN]) of HRV, diagnoses of mild traumatic brain injury and post-traumatic stress disorder (PTSD), and pain ratings from medical records.

Results. As a group, the sample evidenced markedly depressed HRV (as reflected by SDNN) as compared with available age and gender corrected normative data. Pain (71%), PTSD (57%), and mild traumatic brain injury (mTBI) (64%) were prevalent. Thirty-six percent had all three measures (P3). Pain and P3 were significantly and negatively associated with SDNN ($r = -0.460, P = 0.014$; $r = -0.373, P = 0.05$, respectively).

Conclusions. These preliminary findings support the high prevalence of depressed HRV and P3 among veterans seen in a level II Polytrauma Center. The findings also suggest a possible synergistic effect of pain, PTSD, and mTBI on depressed HRV. The nature and implications of these relationships require additional research to elucidate.

Key Words. Pain; PTSD; mTBI; Heart Rate Variability; Polytrauma

Background

In an overview of the assessment and treatment of pain associated with combat-related polytrauma, Clark et al. [1] pointed out the complexity of care and rehabilitation of returning veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). The extent of multiple and massive wounds has been unprecedented, and many veterans have been kept alive
by virtue of medical advances not previously known or available. Pain is an especially common problem. Gironda et al. [2] reported that 46.5% of 1,800 OEF/OIF veterans reported experiencing pain, with 59% exceeding the VA clinical threshold of 4 on a 0 to 10 points numeric rating scale (NRS) [3,4]. In another sample of veterans with polytrauma, defined as “... two or more injuries to physical regions or organ systems, one of which may be life threatening” [2], approximately 96% experienced pain problems during rehabilitation [1], and approximately 65% of combat injuries were caused by various forms of blast phenomena resulting in multiple visible and hidden damages.

A substantial portion of veterans exposed to combat develop post-traumatic stress disorder (PTSD) [5], and chronic pain is commonly co-morbid with PTSD, especially among OEF/OIF veterans. Conversely, pain following trauma is a risk factor for the development of PTSD [6,7]. Research shows that 20–34% of patients with chronic pain also have PTSD, 45–87% of patients with PTSD have chronic pain diagnoses, and that 49% of patients with PTSD meet criteria for fibromyalgia [8]. Helmer et al. [9] reported that almost two-thirds of OIF/OEF veterans have discussed a musculoskeletal concern with their healthcare provider and almost half were diagnosed with PTSD. Similarly, Shipherd et al. [10] found that among PTSD patients seen at the Boston Healthcare System, 66% had chronic pain diagnoses at pretreatment. They also found reductions in pain during PTSD treatment and in the 4 months following PTSD treatment [10].

Key risk factors for the occurrence of pain in individuals with PTSD include: 1) a history of physical injury, 2) hyper-arousal (muscle tension), and 3) depression. Possible biological mechanisms that underlie the commonly observed links between pain and PTSD include: sympathetic hyperarousal (decreased regulation of noradrenaline, NE); altered HPA functioning; alterations in the endogenous opioid system; and sleep disruption [11]. One theory regarding the co-morbidity between pain and PTSD discusses a “shared vulnerability” of underlying processes [12].

Furthermore, the combination of mild traumatic brain injury (mTBI), PTSD, and chronic pain has been found to be very common among the polytrauma population (e.g., [1,13,14]). Schwab et al. [15] report that 16% of individuals in their sample received deployment injuries that resulted in a loss of consciousness consistent with mTBI. In addition, these injuries are associated with diagnoses of PTSD, with estimates of 32% of injured active-duty OIF personnel meeting criteria for PTSD vs 14% of uninjured personnel [16]. While studies of civilians with mTBI generally show that there is complete recovery within 3–6 months [17], the mechanisms of blast injuries and the psychological sequelae among combat veterans [14–17], complicate recommendations for treatment and the process of recovery in this population [17,18]. For example, autonomic parameters are commonly elevated immediately following moderate to severe TBI and these changes can sometimes persist, severely complicating recovery. In one prospective study, 92% of patients being treated for moderate to severe TBI exhibited elevated autonomic parameters within the first week post-injury [18]. Dysautonomia, a condition characterized by simultaneous and paroxysmal sympathetic and muscle over activity, occurs in approximately 8–33% of intensive care unit patients receiving treatment for TBI and complicates the clinical management of these patients [19].

**Autonomic Nervous System Dysregulation**

Autonomic nervous system (ANS) dysregulation, characterized by a high baseline state of hyper-arousal and decreased parasympathetic activity, is a potential pathogenic mechanism in the development and maintenance of PTSD [20]. Heart rate variability (HRV) is one component of the ANS and has often been used as an indicator of ANS dysregulation [21,22]. The sympathetic branch of the ANS is primarily geared toward mobilizing the body for action by increasing heart rate (HR) and blood pressure, stimulating sweat glands and inhibiting the gastrointestinal tract. The parasympathetic branch of the ANS has an independent and opposite influence on basal HR than the sympathetic branch, and parasympathetic dysregulation has been specifically implicated in many disease processes, including cardiovascular disease [23]. Power spectral analysis of HRV has been shown to provide the best means of measuring the interaction between sympathetic and parasympathetic tone [22].

Research indicates that HRV reflects the degree to which cardiac activity can be modulated in the face of changing situational demands. High HRV (a marker of ANS activation) is considered adaptive as it has been consistently associated with greater capacities to regulate stress, emotional arousal, and attention, resistance to stress, and
positive emotions [24,25]. Low HRV, on the other hand, is considered maladaptive as it has been associated with cardiac complications and other pathologic conditions, such as hypertension and mortality in extreme cases [22] and with several psychological disorders including anxiety disorders [21] and depression [26,27]. Studies have suggested that the ANS activity in individuals with PTSD reflects chronically increased sympathetic and decreased parasympathetic activity [28–30], and that these individuals suffer from baseline autonomic hyperarousal and low resting HRV compared with controls [31]. Those with PTSD also show more arousal and less vagal control over their HR when presented with mental challenges such as arithmetic tasks [32], which also suggest a fundamental dysregulation of arousal modulation.

Furthermore, it has been established that exposure to extreme traumatic events can lead to complex physiological abnormalities [33], resulting in symptoms such as elevated HR, increased HR responses to physical stressors, and increased blood pressure [4,32]. These symptoms often persist long after the precipitating stressor has been removed [34]. These observed changes at the physiological level have led to the proposition that autonomic function, including the reactions of the sympathetic nervous system, may be altered in PTSD patients. In fact, Orr and Roth [35] found that physiological reactivity can discriminate between 80 and 100% of persons with and without PTSD.

Research also indicated an association between pain and ANS dysregulation. For instance, a recent study showed that fibromyalgia syndrome has a strong autonomic component which can be improved by HRV biofeedback [36]. There is also some evidence that the motor disturbance in reflex sympathetic dystrophy (complex regional pain syndrome-1) is related to autonomic dysregulation [37]. It is also not uncommon for veterans with TBI to show dystonia related to musculoskeletal pain [38]. Finally, HRV has been shown to be related to important TBI-related factors. For example, in the acute stage of recovery following severe TBI, HRV has been correlated with greater injury severity and poorer outcome [39–43]. Furthermore, improvements in HRV parameters have been associated with corresponding improvements in neurologic function [44]. Limited evidence also suggests that neuroautonomic cardiovascular dysfunction, as measured by HRV, exists in concussed athletes relative to healthy athletes during exercise [45]. Overall, there appears to be considerable evidence of altered HRV following TBI.

**Study Rationale**

Based on the research reviewed, there appears to be support for the hypothesis that each of the three conditions in question, pain, PTSD, and mTBI would potentially contribute to HRV abnormalities, and that in combination, the effect on HRV might be stronger. The current pilot study was designed to investigate the relationships between the three conditions of pain, PTSD symptoms, and mTBI, and HRV among a sample of OEF/OIF veterans who presented to the Michael E. DeBakey VA Medical Center Level II Polytrauma Network Site. It was hypothesized that the conditions of pain, PTSD, and mTBI would be quite prevalent among this group of veterans, and that this group of veterans would show depressed HRV as compared with available age and gender corrected normative data. It was also hypothesized that veterans who had all three of the conditions of pain, PTSD and mTBI (here after referred to as “P3”) would show a stronger association with depressed HRV than veterans with only one or two of the conditions.

**Method**

The study was approved by the local IRB and all participants gave written informed consent before commencement of the study. The Polytrauma Center at the Michael E DeBakey VA Medical Center (MEDVAMC), in Houston, TX is a Level II polytrauma site. Returning OEF/OIF veterans are administered a four-item screening measure as part of their routine clinical care at the MEDVAMC and its associated outpatient clinics in the surrounding communities. The items evaluate the veteran’s 1) exposure to physically traumatic events, 2) the presence of alteration in mental status associated with these events, 3) the presence of immediate, and 4) residual post-concussive symptoms. Veterans who respond “yes” to each of the four items are referred to the polytrauma center for a comprehensive evaluation. The evaluation conducted by polytrauma medical providers includes a thorough, semi-structured interview to determine the veteran’s history of potential traumatic brain injuries, including information regarding the mechanism and severity of each potential TBI. The veteran is also asked to complete validated self-report instruments of
post-concussive [46,47] and PTSD symptoms [48]. This information is used to determine the likelihood that the veteran experienced mTBI and whether current symptoms are related to this injury (e.g., post-concussive syndrome).

Participants
A convenience sample of 28 OEF/OIF veterans was recruited from a Level II Polytrauma Network Site at the MEDVAMC in Houston, TX. The participants were recruited through flier advertisements distributed to veterans receiving the comprehensive evaluation at the polytrauma center. The recruitment fliers announced the study as one investigating the relationship between pain, PTSD symptoms, mTBI, and HRV in a polytrauma sample. Interested participants provided their names and contact information to the staff conducting the comprehensive evaluation. These veterans were then contacted by study staff, provided additional information, and scheduled for the study session.

Inclusion and Exclusion Criteria
The primary study inclusion criterion was having completed a comprehensive evaluation at the polytrauma center. There were no exclusion criteria. We did not find any veteran who volunteered to have significant cognitive or psychotic behavior that would prevent him or her from participating in the activities required by the study.

Measures
HRV
HRV activity was assessed using a measure called SDNN, which stands for the standard deviation of all normal beat-to-beat interval measures between consecutive sinus beats. SDNN is considered the most straightforward measure of HRV and is the most commonly used metric of HRV analysis [36,49,51]. Time domain measures such as SDNN are simpler than frequency domain measures but do not provide the same information as spectral analysis (which does provide measurement of the frequency domain).

The assessment of HRV was gathered via recordings of electrocardiogram (EKG) and respiration using the Nexus 10 BioTrace equipment and associated software version 1.16. Electrodes were silver/silver chloride EKG electrodes (STENS Corporation, San Rafael, CA) that include adhesive and gel ready for application. Study recordings were made in the Psychophysiology Lab at the MEDVAMC.

PTSD, mTBI
In addition to the HRV measures, all participants were assessed for the presence of PTSD on the most recent mental health psychiatrist note in the medical records. All participants had been seen by a psychiatrist to determine the presence or absence of PTSD diagnosis. The mTBI diagnoses were obtained via a review of the participants’ comprehensive evaluation performed by the polytrauma center in their respective medical charts. For each participant, a “yes” or “no” response was recorded to reflect presence or absence of PTSD and/or mTBI diagnosis.

Pain Assessment
It is Veterans Health Administration (VHA) policy that a pain assessment be conducted at medical appointments. Pain assessment is considered the “fifth vital sign” by the VHA with a self-reported pain rating of four or more on an NRS scale of 0–10 [4] as requiring medical intervention. Pain intensity scores were computed by averaging self-reported pain intensity scores over the 30 days preceding each participant’s study assessment. These pain intensity assessments were obtained from the “pain assessment” notes in the participants’ medical records; the typical frequency for this study was three to five but varied substantially between patients (e.g., inpatients require more frequent assessment than outpatients and the more a veteran visited his/her medical care providers, the more pain assessments would be done). An average score of 4 or more was used to determine if a patient had pain (yes/no) for the analyses.

Procedures
Upon arrival at the Psychophysiology Lab at MEDVAMC, participating veterans completed written informed consent and were seated in a comfortable upright lounge chair in the laboratory. EKG electrodes were applied one to each wrist and a ground lead was applied to the back of neck. Participants were then instructed to maintain open eyes and avoid moving their wrists during the recording session. To maintain normal alertness levels the experimenter read excerpts from a collection of innocuous travel stories. HRV was recorded for 15 minutes for each participant. At the end of the session the recordings were coded and saved for subsequent analysis.

Data Selection and SDNN Calculation
While collecting SDNN and in order to eliminate movement artifacts at beginning and end of the
recording period, 10 minutes of data was selected from the middle section of the record. After highlighting the interval, the 10-minute section was submitted to the analysis functions for HRV that provided a printout of the SDNN values. These values are presented in Table 1.

Data Analysis

Statistical analysis was performed using SPSS version 16.0. The diagnoses of PTSD and mTBI were “dummy” coded for their presence or absence. The pain variable was coded as “1” when the medical chart review identified an average pain intensity of 4 or more (on a NRT scale) and “0” otherwise. The data analyses proceeded in three sequential steps. First, we described the characteristics of the 28 interested subjects in terms of their diagnoses of pain, PTSD symptoms, mTBI, and respective SDNN. Data was collected with all 28 patients who completed the intervention. Sixteen of these subjects had diagnoses of PTSD and were maintained for inclusion in subsequent analyses. Next, bivariate correlations were computed among SDNN, pain, PTSD symptoms, mTBI, and the composite of the three. Lastly, bivariate correlations were computed between SDNN and multiple combinations of any two of the three conditions of pain, PTSD symptoms and mTBI.

Results

All 16 of the study participants were male (Table 1). Seven participants were between the ages of 20–29, seven were ages 30–39, and two were ages 40–49. Nine study participants identified themselves as Caucasian, four as African American, and three as Hispanic. In addition, 10 study participants had a high school education or equivalent and six reported at least some college.

Table 1 provides a listing of the 28 participants indicating the presence or absence of pain, PTSD, and mTBI as well as participants’ respective SDNN. Ten of the 28 (35.7%) had P3; 10 of 28 had at least two of the conditions, and 16 of the 28 met criteria for PTSD. Ten of the original 28 did not have an mTBI diagnosis recorded in their records. Eight of the original 28 did not report moderate or greater severity of pain (NRS ≥ 4).
As a group, the participants displayed markedly depressed SDNN compared with age and gender corrected normative data [52]. SDNN normative data used for comparison was taken from the average of each 5 minute segment over 24 hours recorded in 240 health volunteers using the Holter monitor system [51]. All 16 participants who met full criteria for PTSD in our sample had SDNNs two more standard deviations below expected SDNN values.

Table 2 shows bivariate correlations among HRV as measured by the SDNN, pain, PTSD symptoms, and mTBI. Neither pain, PTSD nor mTBI was significantly correlated with each other individually. Further examination indicates, however, that each predictor significantly contributed to the variance explained by the composite of the three measures, P3, which was itself significantly and negatively associated with SDNN ($r = -0.373$, $P < 0.05$).

Table 3 shows the bivariate correlations between the SDNN and combinations of any two of mTBI, PTSD, and pain. There were no significant associations between any of the paired combined conditions and SDNN.

### Discussion

The findings of significantly depressed HRV in the sample of OEF/OIF veterans who were referred to the MEDVAMC Level II Polytrauma Center support the hypothesis that these veterans display compromised ANS function as manifested by depressed SDNN compared with existing gender and age corrected normative data. The prevalence of each the three conditions of pain, PTSD, or mTBI were high in this sample, and over 50% of those who completed the study had P3. These findings are particularly relevant to the OEF/OIF veteran and support those of Gironda et al. [52] and Clark [53] in which they discuss an emerging syndrome in the population of returning OEF/OIF veterans who appear to have significant overlap in symptoms of pain, mTBI, and PTSD. These findings also suggest that autonomic abnormality or dysregulation may contribute to, result from, or be a useful marker of symptoms of pain, mTBI and PTSD.

Although we found a significant association between P3 and SDNN, neither PTSD nor moderate-to-severe pain was significantly associated with SDNN. Furthermore, the finding of no significant associations between paired combinations of the three conditions and SDNN (as shown in Table 3) would suggest that the relationship may be more complex and interactive than simply additive, mediativ, or synergistic. Nonetheless, the finding of overall depressed HRV in this population suggests the potential value of developing and testing of interventions that could reduce ANS dysregulation by increasing HRV [36,37,49,50].

### Limitations and Future Directions

Limitations of this pilot study include the use of normative data in lieu of a recruited comparison group, its small sample size and the use of a convenience sample. Veterans with pain, mTBI or PTSD may have been more likely to self-select to enroll in the study. However, the study participants were comparable in gender, age, ethnicity, education, pain, PTSD symptoms, and mTBI to other veterans referred for comprehensive evaluation to the Level II Polytrauma Network Site at the MEDVAMC. Additionally, the pilot study was limited by the use of chart review to obtain key

### Table 2

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>SDNN Index*</th>
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<tbody>
<tr>
<td>mTBI and PTSD</td>
<td>-0.166</td>
</tr>
<tr>
<td>mTBI and Pain</td>
<td>-0.190</td>
</tr>
<tr>
<td>PTSD Symptoms</td>
<td>-0.237</td>
</tr>
</tbody>
</table>

* There were no significant associations between paired combinations and SDNN index (all $P > 0.05$).

† Pearson’s r.

PTSD = post-traumatic stress disorder; mTBI = mild traumatic brain injury; SDNN = Standard deviation of the averaged beat-to-beat interval over a 10-minute period.
variables, and categorization of mTBI, PTSD symptoms, and pain severity as “present” or “absent.” Also, not included was an information on cardiovascular disease, asthma, and other medical conditions that have been shown to affect HRV. A future, larger scale study should include a structured assessment for these conditions as well as a veteran comparison group. As such, it should be emphasized that the reported findings and conclusions based upon these analyses should be considered preliminary and would require replication and validation by a larger scale study. Finally, the use of full spectral analyses instead of just time domain measure (SDNN) in future research could provide a richer understanding of the relationship between ANS dysregulation and veterans exposed to polytrauma.

Acknowledgment

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