Peritraumatic Heart Rate and Posttraumatic Stress Disorder in Patients With Severe Burns

Neda F. Gould, PhD; Jodi B. McKibben, PhD; Ryan Hall, MD; Nida H. Corry, PhD; Nicole A. Amoyal, BA; Shawn T. Mason, PhD; Una D. McCann, MD; and James A. Fauerbach, PhD

Objective: Previous studies have suggested a link between heart rate (HR) following trauma and the development of posttraumatic stress disorder (PTSD). This study expands on previous work by evaluating HR in burn patients followed longitudinally for symptoms of acute stress disorder (ASD) and PTSD.

Method: Data were collected from consecutive patients admitted to the Johns Hopkins Burn Center, Baltimore, Maryland, between 1997 and 2002. Patients completed the Stanford Acute Stress Reaction Questionnaire (n = 157) to assess symptoms of ASD. The Davidson Trauma Scale was completed at 1 (n = 145), 6 (n = 106), 12 (n = 94), and 24 (n = 66) months postdischarge to assess symptoms of PTSD. Heart rate in the ambulance, emergency room, and burn unit were obtained by retrospective medical chart review.

Results: Pearson correlations revealed a significant relationship between HR in the ambulance ($r = 0.32$, $P = .016$) and burn unit ($r = 0.30$, $P = .001$) and ASD scores at baseline. Heart rate in the ambulance was related to PTSD avoidance cluster scores at 1, 6, 12, and 24 months. In women, HR in the ambulance was correlated with PTSD scores at 6 ($r = 0.65$, $P = .005$) and 12 ($r = 0.78$, $P = .005$) months. When covariates (gender, β-blockers, Brief Symptom Inventory Global Severity Index score) were included in multivariate linear regression analyses, ambulance HR was associated with ASD and PTSD scores at baseline and 1 month, and the interaction of ambulance HR and gender was associated with PTSD scores at 6 and 12 months. Multivariate logistic regression results were similar at baseline and 12 months, which included an HR association yet no interaction at 6 months and a marginal interaction at 1 month.

Conclusions: While peritraumatic HR is most robustly associated with PTSD symptom severity, HR on admission to burn unit also predicts the development of ASD. Gender and avoidance symptoms appear particularly salient in this relationship, and these factors may aid in the identification of subgroups for which HR serves as a biomarker for PTSD. Future work may identify endophenotypic measures of increased risk for PTSD, targeting subgroups for early intervention.

J Clin Psychiatry 2011;72(4):539–547

Submitted: *May 31, 2009; accepted September 28, 2009.*
Online ahead of print: *October 19, 2010 (doi:10.4088/JCP.09m05405blu).*
Corresponding author: *Neda F. Gould, PhD, Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, 4940 Eastern Ave, Asthma and Allergy Center, 5B.71B, Baltimore, MD 21224 (ngould1@jhmi.edu).*

Acute stress disorder (ASD) and posttraumatic stress disorder (PTSD) are frequently observed after exposure to traumatic events and they can be extremely debilitating disorders. Posttraumatic stress disorder occurs in approximately 20% of trauma victims, often resulting in significant impairment in physical, occupational, and social functioning,[1] and 80% of individuals with ASD may go on to develop PTSD.[2] Given the devastating impact of PTSD, efforts to understand the psychological and physiologic variables associated with fear conditioning provide an opportunity for advances in treatment. Currently, attempts to identify individuals at risk for the development of ASD and PTSD after a trauma have produced inconsistent findings. Although self-report and clinician-assessed information are useful, identification of biologic markers or endophenotypes[3] associated with these disorders may yield more accurate diagnosis and highlight the dynamic interplay between traumatic events, time parameters, psychological interpretation, and physiologic reactivity.

Acute physiologic responses following trauma may provide useful markers for predicting subsequent PTSD. Increased arousal is a necessary criterion in the diagnosis of PTSD, and physiologic reactivity is a common form of re-experiencing associated with the disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[4] In fact, hyperarousal symptoms often remain even after the remission of other symptoms.[5] It has been postulated that sympathetic arousal immediately after a traumatic event may lead to overconsolidation of trauma memories[6] and that hyperactivity of the sympathetic nervous system may prevent normal memory processing.[7] Memory processing is believed to be mediated by overstimulated endogenous stress hormones and neuromodulators after the traumatic event.[6] This series of events may ultimately lead to the development of PTSD.[7] Indeed, preclinical research has revealed that epinephrine may enhance the consolidation of learning of a traumatic memory and fear conditioning in both human[6] and animal models.[8,9] As such, understanding the pathophysiology of hyperarousal may lead to a clearer understanding of the development of PTSD.

Elevated heart rate (HR) is among the most salient by-products of increased sympathetic arousal. However, to date, there has been some inconsistency in extant investigations of the relationship between HR and the development of PTSD. In their initial study, Shalev et al[10] reported that elevated HR after trauma was predictive of the subsequent development of PTSD. This finding was replicated in adults[11,12] and children,[13] and, most recently, in an elegantly

designed, large, multisite study by Bryant and colleagues.[14] In contrast, in a study by Blanchard et al,[15] elevated HR was not predictive of PTSD. In fact, in this latter study, patients with elevated HR were *less* likely to develop PTSD.

Possible reasons for discrepancies across studies include differences in methodology, such as symptom assessment (self vs clinician report), composition of samples, and timing of PTSD assessment,[16] as well as the temporal assessment of HR, injury severity, and PTSD symptom criteria.[17] In this regard, even minor differences in patient samples may result in differences across studies.[17] Nevertheless, recent meta-analytic reviews have revealed a significant association between PTSD and elevated HR[18] and have identified HR as one of the most reliable psychophysiological correlates of PTSD.[19]

Thus, the purpose of the present study was to more clearly elucidate factors involved in the relationship between physiologic arousal and the development and maintenance of PTSD. The present study expands on previous work in this realm by examining the relationship between HR and blood pressure (BP) and both in-hospital ASD and PTSD through 2-year follow-up in a group of trauma survivors who underwent a similar type of trauma, therefore minimizing the variability within the study sample. To our knowledge, this study is the first to examine this relationship that (1) examines a sample of adult patients with severe burn injury, (2) assesses the potential relationship between HR and BP and specific symptom clusters of ASD and PTSD (a largely unexamined topic), (3) accounts for the role of relevant demographic (eg, gender) and clinical (eg, use of β-blockers) variables, and (4) obtains HR and BP measurements at various time points following the trauma (ie, in the ambulance, emergency room, and burn unit).

METHOD

Sample

Data were collected from consecutive patients admitted to the Johns Hopkins Burn Center, Baltimore, Maryland, between 1997 and 2002. Eligible participants met at least 1 criterion for major burn injury as determined by the American Burn Association, and they were at least 18 years of age. The American Burn Association criteria for major burn injury included deep second and third degree burns with the following variations: greater than 10% total body surface area (TBSA) in patients over 50 years old; greater than 20% TBSA in other age groups; burns with serious threat of functional or cosmetic threat that involve face, hands, feet, genitalia, perineum, or major joints; third degree burns greater than 5% TBSA in any age group; deep electrical burns, including lightning injury; inhalation injury with burn injury; or circumferential burns of the extremity or chest. Participants were excluded if they presented with cognitive limitations precluding adequate consent, comprehension, or benefit, or if their level of fluency in English would prevent them from understanding the consent or protocol. Additionally, patients were excluded from further participation if they were incarcerated after discharge.

Table 1. Sample Demographics and Descriptive Statistics (total N = 167)

Variable	n (%)
Sex, male	120 (71.9)
Ethnicity	
White	101 (60.5)
African American	56 (33.5)
Hispanic	4 (2.4)
Other	1 (0.6)
Participants employed	124 (74.3)
Etiology of burn	
Flame	92 (55.1)
Scald	30 (18.0)
Grease	15 (9.0)
Hot object	11 (6.6)
Chemical	4 (2.4)
Electricity	5 (3.0)
Tar	4 (2.4)
Other	6 (3.6)
	Mean (SD)
Age, y	40.2 (14.4)
Length of hospital stay, d	16.8 (14.1)
Heart rate measurement, location[a]	
Ambulance	105.0 (16.2)
Emergency room	94.7 (17.3)
Burn unit	87.3 (18.0)
SASRQ total score	39.5 (29.0)
DTS total score, time postdischarge	
1 mo	33.2 (31.4)
6 mo	31.9 (31.6)
12 mo	28.3 (29.3)
24 mo	28.7 (30.2)

[a]Heart rate values reported in beats per minute.
Abbreviations: DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.

Our sample included 167 adult burn patients (mean age = 40.2 years, SD = 14.4) who were predominantly male (71.9%), white (60.5%), had an average TBSA of 15.5% (SD = 14.8), and the majority of whom worked at the time of injury (74.3%). The primary etiology of burn injuries in our sample was due to flame/fire (55.1%), followed by scald (18.0%), grease (9.0%), and thermal contact (6.6%) burns (sample demographic characteristics and descriptive statistics for variables are presented in Table 1). Participation in this study was voluntary, and the protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board.

Measures

Psychiatric measures. The Davidson Trauma Scale (DTS)[20] is a 17-item self-report measure based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*).[21] Frequency and severity items for symptoms are rated on a 0–4 scale, with higher scores indicative of greater severity or frequency. Analyses of the DTS have demonstrated test-retest reliability with a coefficient of 0.86 ($P < .01$) and high internal consistency ($\alpha = .99$) for the frequency and severity items.[20] Furthermore, the DTS has been shown to reliably predict PTSD diagnosis as measured by the Structured Clinical Interview for the *DSM-IV* when a diagnostic cutoff score of 40 is used.[20]

The Stanford Acute Stress Reaction Questionnaire (SASRQ)[22] is a 30-item self-report measure used for the

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 2. Clinical Characteristics of Participants Dichotomized by SASRQ and DTS Cutoff Scores[a]

Characteristic	SASRQ < Diagnostic Cutoff (n = 119)	SASRQ ≥ Diagnostic Cutoff (n = 38)	DTS < 40, 1 mo (n = 91)	DTS ≥ 40, 1 mo (n = 54)	DTS < 40, 6 mo (n = 70)	DTS ≥ 40, 6 mo (n = 36)	DTS < 40, 12 mo (n = 65)	DTS ≥ 40, 12 mo (n = 29)	DTS < 40, 24 mo (n = 45)	DTS ≥ 40, 24 mo (n = 21)
Age, y	38.0 (14.6)	38.1 (10.5)	37.6 (13.5)	39.3 (12.5)	40.4 (15.5)	36.5 (10.8)	39.5 (15.0)	36.1 (11.7)	38.7 (15.0)	36.2 (10.7)
Heart rate[b]										
Ambulance	101.8 (14.8)	110.7 (17.1)	103.8 (13.8)	108.9 (17.1)	101.5 (14.8)	113.4 (16.3)	103.2 (16.8)	107.8 (16.5)	100.4 (18.1)	111.2 (11.9)
Emergency room	93.2 (16.2)	98.6 (19.9)	95.3 (17.2)	96.8 (15.5)	94.6 (18.2)	96.0 (18.3)	92.7 (20.4)	93.5 (18.6)	93.2 (18.5)	92.6 (14.3)
Burn unit	85.0 (16.5)	93.3 (21.3)	86.5 (16.0)	90.0 (19.7)	86.1 (17.1)	90.3 (20.4)	84.2 (17.4)	87.8 (20.7)	86.1 (17.3)	88.8 (19.7)
SASRQ total score	27.3 (19.3)	77.5 (19.9)	…	…	…	…	…	…	…	…
DTS total score	…	…	12.4 (11.2)	68.2 (21.6)	12.3 (11.8)	70.2 (20.9)	11.0 (10.7)	67.1 (18.4)	11.3 (12.2)	65.8 (22.6)

[a]All values reported as means and standard deviations.
[b]Heart rate values reported in beats per minute, in locations where heart rate was measured.
Abbreviations: DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.

assessment of ASD. Frequency of symptoms, including re-experiencing, dissociation, avoidance, hyperarousal, and impairment in functioning were rated on a Likert-type scale ranging from 0 to 5. A previously published algorithm was used on the basis of the *DSM-IV* criteria[23] that indicate a diagnostic cutoff score of 3 for each of the items and require the endorsement of 3 of the 5 dissociative symptoms (that correspond to the 5 *DSM-IV* dissociative symptoms), and 1 symptom each from the reexperiencing, avoidance, hyperarousal, and impairment domains. Table 2 shows clinical characteristics of participants dichotomized by SASRQ and DTS cutoff scores. α Coefficients for the SASRQ demonstrate high internal consistency for anxiety and dissociative symptoms (α = .91 and α = .90, respectively[22]).

The Brief Symptom Inventory (BSI)[24] is a 53-item version of the Symptom Checklist 90-Revised[25] that measures severity of psychological distress over the previous 7 days. Respondents rate how much they were distressed by each symptom using a 5-point Likert scale (0 = not at all, 4 = always). The BSI has good internal consistency and retest reliability.[24] The Global Severity Index (GSI) is the BSI's most sensitive index of psychological distress,[26] and it has been shown to discern among clinical and normative populations.[27] The GSI was dichotomized at T-score ≥ 63 (high distress) versus T-score < 63 (low distress). This GSI cutoff has been shown to be a valid and reliable marker for the presence of a significant psychiatric condition (ie, clinically significant psychological distress) warranting evaluation and possible intervention[24] and has been used in other large-scale, multisite studies in injured populations.[28] Rather than a gold-standard structured clinical interview, a self-report psychological assessment tool was used—primarily to minimize the burden on participants given the long-term nature of the study.

Cardiovascular Measures

Heart rate and BP were measured manually by stethoscope and sphygmomanometer administered by the emergency medical technicians in the ambulance during transportation to the hospital. A Simmons monitor (Siemens, Danvers, Massachusetts) was used to assess HR and BP in the emergency room and inpatient intensive care unit (ICU). Both Simmons and Spacelab monitoring equipment (Spacelab Medical Inc, Issaquah, Washington) were used to measure HR and BP during the patients' stay in the surgical intermediate care center, a step-down inpatient unit from the ICU.

Procedures

This study was part of a national study targeting the assessment and treatment of patients with major burn injuries. As part of a larger, multisite study, participants' demographic and clinical variables including age, gender, TBSA, ethnicity, etiology, location of burn, and employment were obtained by chart review. Patients were approached for consent within 72 hours of accessibility during their stay in the inpatient unit if they met eligibility criteria. All participants were 18 years or older and met American Burn Association criteria for severe burns, as described above.

Participants completed the SASRQ and BSI at discharge (n = 157), and the DTS, BSI, and other psychological questionnaires at 1 month (n = 145), 6 months (n = 106), 12 months (n = 94), and 24 months (n = 66) after discharge from the hospital. A retrospective medical chart review was conducted to acquire participants' HR, systolic BP, and diastolic BP in the ambulance and on admission to the emergency room and burn unit. Total body surface area burned was also gathered from chart review.

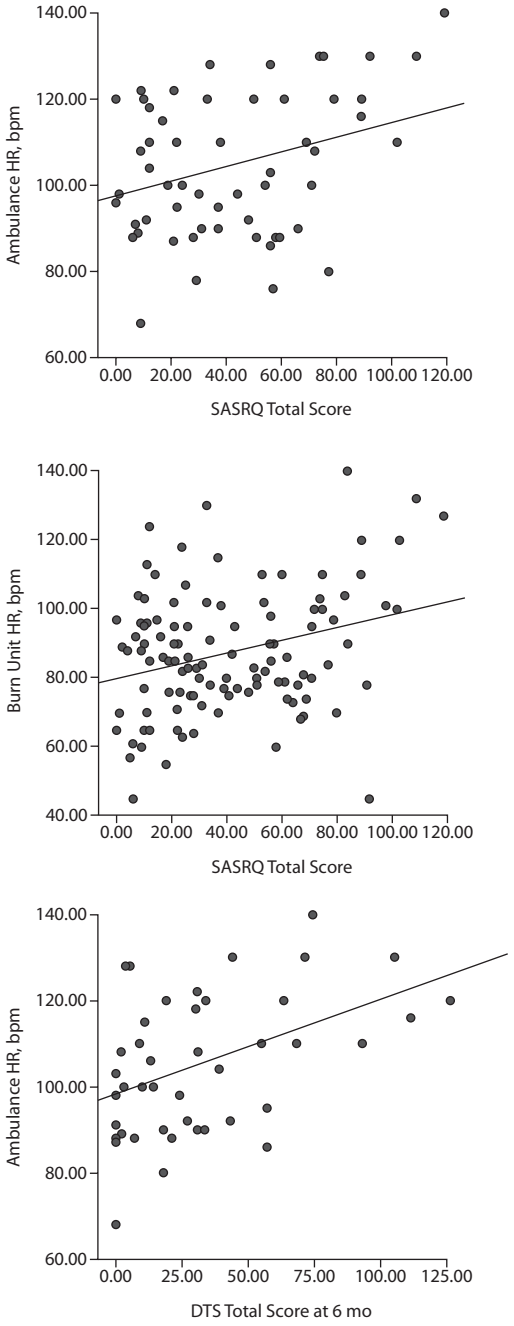
Statistical Analyses

Normality of data distribution for all outcome measures was established by evaluating skew and kurtosis, which ranged from 0.60 to 1.1, well within the normal range.

Pearson correlations were calculated to assess the relationship between HR and BP at each of the time points (ie, ambulance, admittance to emergency room, transfer to burn unit) with total SASRQ and DTS scores at 1, 6, 12, and 24 months. In addition, SASRQ and DTS subscale scores were analyzed. Subscales for the SASRQ included reexperiencing, avoidance, arousal, and dissociative symptom clusters; while the DTS included re-experiencing, avoidance, and hyperarousal symptom cluster scores. Finally, post hoc analyses assessed HR correlations for male and female patients separately.

To test the hypothesis that HR is predictive of posttraumatic stress symptom severity, linear regression analyses

Figure 1. Significant Correlations Between Heart Rate (HR) and Continuous Outcome Variables



Abbreviations: bpm = beats per minute, DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.

were used to evaluate the role of HR readings in the ambulance in accounting for SASRQ and DTS continuous scores at 1, 6, 12, and 24 months. Logistic regression analyses were used to examine SASRQ and DTS dichotomous variables (ie, diagnostic status) across assessment periods. Due to attrition, a ubiquitous problem among longitudinal studies, only a limited subset of covariates were included in the analyses, and they were selected on the basis of theoretical significance. Thus, the following variables were used as predictors in the regression analyses: gender, β-blockers (present or absent), BSI GSI score (high and low distress, as defined above), and the HR × gender interaction. Goodness of fit for each of the models was evaluated using the Hosmer-Lemeshow statistic.

Table 3. Significant Correlations Between Ambulance Heart Rate and DTS Subscale Scores at Various Time Points[a]

DTS Subscale	Pearson *R*	*P* Value	n
Avoidance, at 1 mo	0.274	.039	57
Avoidance, at 6 mo	0.461	.001	45
Avoidance, at 12 mo	0.330	.033	42
Avoidance, at 24 mo	0.344	.021	45
Reexperiencing, at 6 mo	0.397	.037	28
Arousal, at 6 mo	0.414	.005	44

[a]All variables are continuous.
Abbreviation: DTS = Davidson Trauma Scale.

All tests were 2-tailed and considered significant at $P < .05$. Analyses were conducted using SPSS version 16.0 (SPSS Inc, Chicago, Illinois) and Stata Statistical Software, Release 9.2 (StataCorp LP, College Station, Texas).

RESULTS

Pearson correlations revealed a significant relationship between HR in the ambulance and SASRQ ($r = 0.32$, $P = .016$, n = 58) and total DTS scores at 6 months ($r = 0.44$, $P = .003$, n = 44). In addition, burn unit HR was significantly correlated with total SASRQ score ($r = 0.30$, $P = .001$, n = 112) (Figure 1). Importantly, when the aforementioned relationships were assessed by gender, a significant HR × gender interaction was revealed whereby HR in the ambulance corresponded to higher total DTS scores at 6 ($r = 0.65$, $P = .005$, n = 17) and 12 ($r = 0.78$, $P = .005$, n = 11) months in women only. These findings were not significant for male participants. Blood pressure was not related to SASRQ or DTS scores.

When SASRQ and DTS overall scores were divided into their respective subscales, HR in the ambulance was significantly related to the following continuous subscale scores: DTS avoidance at 1, 6, 12, and 24 months and DTS reexperiencing and arousal at 6 months. Thus, initial HR measurements in the ambulance appear to be most consistently related to PTSD/DTS avoidance symptom clusters up to 2 years postinjury (Table 3). When dichotomized into those meeting and not meeting criteria for ASD, the SASRQ reexperiencing cluster was significantly correlated with HR in the ambulance, and the arousal cluster was correlated with HR on the burn unit.

Linear Regression Analyses

An important objective of this study is to determine whether HR (obtained in the ambulance) would predict ASD scores at baseline (as assessed with the SASRQ) and PTSD scores (as assessed with the DTS) at 1, 6, 12, and 24 months. First, simple/crude linear regression analyses were completed, and the results indicated significant associations between HR and ASD/PTSD scores at baseline and 6 months (Tables 4A and 4B). In the multiple linear regression analyses used to address the question above, HR and the

aforementioned covariates (ie, gender, β-blockers, and BSI) were used. Once missing data across the predictor variables were accounted for, 56 cases remained for the analysis at baseline, 52 for the 1-month follow-up period, 44 at 6 months, and 41 at 12 months, and 27 at 24 months. The initial model contained all covariates. Using a backward elimination linear regression procedure, covariates were removed on the basis of the Wald tests. In the case of significant interactions, all lower-order covariates in the interaction were retained in the model, regardless of significance. When all eligible nonsignificant covariates were removed, the following variables were retained in models assessing the relationship of ambulance HR with ASD and PTSD: Heart rate and BSI score at baseline (adjusted $R^2 = 0.55$, $\hat{\sigma} = 20.63$); HR and BSI score at 1 month (adjusted $R^2 = 0.18$, $\hat{\sigma} = 27.86$); HR, gender, BSI score, and HR × gender at 6 months (adjusted $R^2 = 0.36$, $\hat{\sigma} = 26.00$); HR, gender, and HR × gender at 12 months (adjusted $R^2 = 0.14$, $\hat{\sigma} = 24.40$); and gender and β-blockers at 24 months (adjusted $R^2 = 0.31$, $\hat{\sigma} = 24.87$).

At baseline and 1 month postdischarge, a 1-unit increase in HR was associated with a 0.67 increase in the total SASRQ score and an increase of 0.52 in the total DTS score (see Tables 4A and 4B). In order to put this finding into perspective, it may be useful to consider an SD increase in HR as well (SD = 16.22 at baseline and 15.15 at 1 month). A 1-SD increase in HR was associated at baseline and 1 month with an increase of 10.94 in the total SASRQ score and an increase of 7.94 in the total DTS score. At 6 and 12 months, there were differential effects across sex/gender. For men and women, a unit increase in HR was associated at 6 months with a 0.51 and a 1.93 increase in the total DTS

Table 4A. Results of Linear Regression Analyses Relating Heart Rate to SASRQ (algorithm-based cutoff) and DTS (cutoff ≥ 40)[a]

	Baseline (n = 56)		1 Month Postdischarge (n = 52)		6 Months Postdischarge (n = 44)	
Predictors at Baseline	Crude B[b] (95% CI)	Adjusted B[c] (95% CI)	Crude B (95% CI)	Adjusted B (95% CI)	Crude B (95% CI)	Adjusted B (95% CI)
Heart rate						
1-unit increase	0.55* (0.06 to 1.05)	0.67*** (0.33 to 1.02)	0.43 (–0.13 to 1.00)	0.52* (0.004 to 1.04)	0.89** (0.33 to 1.45)	0.51 (–0.07 to 1.09)
1-SD increase	9.00	10.94	6.54	7.94	14.43	8.24
Gender, male vs female	14.90 (–1.85 to 31.66)	…	13.73 (–3.48 to 30.94)	…	20.28* (0.65 to 39.92)	–130.95* (–250.41 to –11.49)
Heart rate × gender[d]						
1-unit increase	…	…	…	…	…	1.93* (0.97 to 2.88)
1-SD increase	…	…	…	…	…	31.36
BSI score, ≥ 63 vs < 63	41.81*** (29.08 to 54.54)	43.80*** (32.43 to 55.17)	24.32** (7.71 to 40.92)	26.12** (9.90 to 42.34)	11.66 (–8.65 to 31.96)	17.60* (1.11 to 34.09)
β-blockers, yes vs no	29.85* (7.43 to 52.28)	…	21.22 (–2.02 to 44.45)	…	23.60 (–1.38 to 48.58)	…

[a]SASRQ used at baseline; DTS used at 1, 6, 12, and 24 months postdischarge. [b]Univariate association between predictors and SASRQ. [c]Multivariate association between predictors and SASRQ/DTS after adjusting for all remaining predictors in the model. [d]Values displayed are for women.
*$P < .05$; **$P < .01$; ***$P < .001$.
Abbreviations: BSI = Brief Symptom Inventory, DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.
Symbol: … = not included in model.

Table 4B. Results of Linear Regression Analyses Relating Heart Rate to SASRQ (algorithm-based cutoff) and DTS (cutoff ≥ 40)[a]

	12 Months Postdischarge (n = 41)		24 Months Postdischarge (n = 27)	
Predictors at Baseline	Crude B[b] (95% CI)	Adjusted B[c] (95% CI)	Crude B (95% CI)	Adjusted B (95% CI)
Heart rate				
1-unit increase	0.42 (–0.08 to 0.91)	0.13 (–0.40 to 0.66)	0.54 (–0.14 to 1.21)	…
1-SD increase	6.93	2.18	9.36	…
Gender, male vs female	9.75 (–9.03 to 28.52)	–130.45* (–253.97 to –6.92)	20.83 (–3.41 to 45.07)	23.16* (2.14 to 44.17)
Heart rate × gender[d]				
1-unit increase	…	1.45* (0.42–2.48)	…	…
1-SD increase	…	24.13	…	…
BSI score, ≥ 63 vs < 63	14.39 (–2.26 to 31.04)	…	24.33* (0.65 to 48.01)	…
β-blockers, yes vs no	16.73 (–5.02 to 38.48)	…	39.55* (9.58 to 69.53)	41.82** (13.93 to 69.71)

[a]SASRQ used at baseline; DTS used at 1, 6, 12, and 24 months postdischarge. [b]Univariate association between predictors and SASRQ. [c]Multivariate association between predictors and SASRQ/DTS after adjusting for all remaining predictors in the model. [d]Values displayed are for women.
*$P < .05$; **$P < .01$; ***$P < .001$.
Abbreviations: BSI = Brief Symptom Inventory, DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.
Symbol: … = not included in model.

Table 5A. Results of Logistic Regression Analyses Relating Heart Rate to SASRQ (algorithm-based cutoff) and DTS (cutoff ≥ 40)[a]

	Baseline (n = 56)		1 Month Postdischarge (n = 52)		6 Months Postdischarge (n = 44)	
Predictors at Baseline	Crude OR[b] (95% CI)	Adjusted OR[c] (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Heart rate						
1-unit increase	1.03 (1.00 to 1.07)	1.05* (1.01 to 1.10)	1.01 (0.98 to 1.05)	…	1.06* (1.01 to 1.12)	1.06* (1.01 to 1.12)
1-SD increase	1.72	2.18	1.22	…	2.51	2.51
Gender, male vs female	1.64 (0.53 to 5.08)	…	1.91 (0.61 to 6.09)	…	2.45 (0.65 to 9.58)	…
Heart rate × gender[d]						
1-unit increase	…	…	…	…	…	…
1-SD increase	…	…	…	…	…	…
BSI score, ≥ 63 vs < 63	5.57** (1.76 to 19.33)	8.01** (2.23 to 35.44)	5.36** (1.63 to 19.31)	5.36** (1.63 to 19.31)	1.56 (0.41 to 5.89)	…
β-blockers, yes vs no	3.67 (0.80 to 19.83)	…	3.22 (0.70 to 17.49)	…	5.83* (1.18 to 33.92)	…

[a]SASRQ used at baseline; DTS used at 1, 6, 12, and 24 months postdischarge. [b]Univariate association between predictors and SASRQ/DTS. [c]Multivariate association between predictors and SASRQ/DTS after adjusting for all remaining predictors in the model. [d]Values displayed are for women.
*P < .05; **P < .01; ***P < .001.
Abbreviations: BSI = Brief Symptom Inventory, DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.
Symbol: … = not included in model.

Table 5B. Results of Logistic Regression Analyses Relating Heart Rate to SASRQ (algorithm-based cutoff) and DTS (cutoff ≥ 40)[a]

	12 Months Postdischarge (n = 41)		24 Months Postdischarge (n = 27)	
Predictors at Baseline	Crude OR[b] (95% CI)	Adjusted OR[c] (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Heart rate				
1-unit increase	1.01 (0.97 to 1.06)	0.99 (0.94 to 1.04)	1.03 (0.98 to 1.10)	…
1-SD increase	1.28	0.82	1.67	…
Gender, male vs female	1.33 (0.29 to 5.65)	6.94e-10** (9.53e-20 to 0.01)	2.50 (0.37 to 17.29)	…
Heart rate × gender[d]				
1-unit increase	…	1.20** (1.04 to 1.72)	…	…
1-SD increase	…	21.40	…	…
BSI score, ≥ 63 vs < 63	4.00* (1.03 to 17.10)	5.18* (1.15 to 27.25)	6.40 (0.96 to 57.70)	…
β-blockers, yes vs no	1.80 (0.31 to 9.69)	…	4.75 (0.46 to 51.20)	…

[a]SASRQ used at baseline; DTS used at 1, 6, 12, and 24 months postdischarge. [b]Univariate association between predictors and SASRQ/DTS. [c]Multivariate association between predictors and SASRQ/DTS after adjusting for all remaining predictors in the model. [d]Values displayed are for women.
*P < .05; **P < .01; ***P < .001.
Abbreviations: BSI = Brief Symptom Inventory, DTS = Davidson Trauma Scale, SASRQ = Stanford Acute Stress Reaction Questionnaire.
Symbol: … = not included in model.

score, respectively. A 1-SD increase in HR was associated at 6 months (SD = 16.26) with an increase of only 8.24 for men but 31.36 for women in total DTS scores. Further, for men and women, a unit increase in HR was associated at 12 months with a 0.13 and 1.45 increase in the total DTS score, respectively. For a 1-SD increase in HR (SD = 16.63), the increases in the total DTS scores at 12 months were 2.18 and 24.13, respectively.

Logistic Regression Analyses

The aforementioned analyses were replicated with the dichotomous PTSD and ASD diagnostic status dependent variables described above. Once again, simple/crude logistic regression analyses were completed, and the results indicated significant associations between HR and the PTSD cutoff score at 6 months (see Tables 5A and 5B). In the multiple logistic regression analyses, HR and the aforementioned predictor variables (ie, gender, β-blockers, and BSI score) were used once again and the number of cases available for each of the time periods was the same as indicated above. The initial model contained all covariates. Using a backward elimination procedure, covariates were removed on the basis of the likelihood ratio tests. In the case of significant interactions, all lower-order covariates in the interaction were retained in the model, regardless of significance. When all eligible nonsignificant covariates were removed, the following variables were retained in models assessing the relationship of ambulance HR with ASD and PTSD: HR and BSI score at baseline (Nagelkerke $R^2 = 0.31$); BSI score at 1 month (Nagelkerke $R^2 = 0.19$); HR at 6 months (Nagelkerke $R^2 = 0.19$); and HR, gender, BSI score, and HR × gender at 12 months (Nagelkerke $R^2 = 0.36$). No variables were retained at the 24-month time period. The Hosmer-Lemeshow goodness of fit χ^2 statistics were shown to be nonsignificant for the aforementioned logistic regression analyses with the exception of the 1-month time period. However, if an alternative model that includes BSI score and a trend for HR × gender ($P = .07$), along with HR and gender, is considered, then the Hosmer-Lemeshow is nonsignificant (Nagelkerke $R^2 = 0.30$).

A 1-unit increase/1-SD increase in HR (SD = 16.23) was associated with it being 1.05 times/2.18 times more likely for participants to have an SASRQ score above the cutoff for ASD at baseline (Tables 5A and 5B). Heart rate was not correlated with PTSD at 1 month. However, in the previously mentioned model that included a trend for HR × gender at 1 month, a 1-unit increase in HR was associated with it being 1.00 times as likely for men and 1.08 times more likely for women to have a DTS score above the cutoff for PTSD.

A 1-SD increase in HR (SD = 15.15) resulted in it being 0.94 times less likely for men and 3.29 times more likely for women to be above the DTS cutoff for PTSD at 1 month. A 1-unit increase/SD increase in HR (SD = 16.26) was associated at 6 months with it being 1.06 times/2.51 times more likely for patients to be above the DTS cutoff for PTSD. Finally, at 12 months, there were differential effects across sex/gender. For men and women, a 1-unit increase in HR was associated with it being 0.99 times less likely and 1.20 times more likely to be above the DTS cutoff for PTSD. A 1-SD increase (SD = 16.63) in HR resulted in it being 0.82 times less likely for men and 21.40 times more likely for women to be above the DTS cutoff for PTSD.

DISCUSSION

The present study is the first to assess the predictive value of HR and BP for the subsequent development of ASD and PTSD in patients with severe burns. Our results revealed that increased HR immediately following major burn injury was associated with higher rates of ASD and PTSD 6 months after hospital discharge. Further, elevated HR levels during hospital admission were associated with the development of ASD. An interactive effect for gender indicated that elevated HR at the time of hospital admission was associated with more PTSD symptoms at 6 and 12 months after discharge for females only. This finding suggests that gender influences the relationship between elevated HR following trauma and subsequent PTSD severity. This gender finding is of particular importance given that the type of trauma was consistent across sexes and less gender-specific than previously studied traumas.

Gender differences in the association between peritraumatic physiologic markers and the later development of PTSD may be better understood if placed in the context of the complex relationship between gender and PTSD. Previous research in the field of PTSD has not consistently reported gender differences because they were not of central interest in those studies[29]; however, several previous studies shed light on the influence of gender on PTSD development. Despite the fact that men experience more trauma during their lifetime, PTSD is more prevalent among women. Several explanations have been posited to account for this discrepancy, including women's increased exposure to traumas that often involve developmental disruptions (ie, sexual abuse and violation of physical integrity) and may increase vulnerability to develop PTSD and other psychopathology. Compared to men, women tend to engage in more ruminative styles of coping, which are associated with more prolonged or severe depressive episodes[30] and also predict PTSD.[31] Biologic explanations include endogenous opioid peptides, which vary across the menstrual cycle for women and coincide with observed changes in PTSD symptoms. Women have been found to be more physiologically reactive than men to trauma,[32] and previous research has revealed that specific symptom clusters, such as hyperarousal and numbing, are particularly salient in women.[33] It is well-established that women have higher resting HR,[34] longer corrected QT intervals,[35–37] and a shorter sinus node recovery time[38] than men, possibly due to differences in exercise tolerance, autonomic modulation, sinus node properties, and gender hormones.[39] Nevertheless, while women have been shown to have higher HRs[34] and a higher incidence of PTSD,[40,41] our findings revealed a significant relationship between ambulance HR and PTSD scores at 6 and 12 months even while controlling for gender. Although the clinical significance of these gender differences in cardiac variables is unclear, we can speculate that women may tend to have greater sympathetic arousal and release of stress hormones during a trauma, due to baseline physiologic differences.

Consistent with several previous studies,[10,11,14] BP immediately following trauma and during hospital stay was not significantly related to total ASD or PTSD symptoms at any subsequent assessments in the current study (ie, 1, 6, 12, or 24 months). The lack of predictive utility of BP in light of significant HR findings suggests that PTSD may be influenced by excessive adrenergic activation via enhanced memory consolidation rather than noradrenergic activation.[10] The lack of a relationship between BP and subsequent ASD or PTSD in the current study could also be attributed to a potentially larger representation of patients whose stress response patterns involve more cardiac- than vascular-based reactivity.[42]

A unique finding of the current study was that peritraumatic HR was most consistently related to PTSD avoidance symptoms up to 2 years after hospital discharge. As noted in a recent synthesizing review, avoidance cluster symptoms are emerging as the strongest indicators for PTSD risk.[43] Given this finding, it is potentially of great importance that future investigations examine the means by which early HR is related to increased severity of future avoidance symptoms. Fear-conditioning models suggest that, after a traumatic event, cues reminiscent of the trauma result in the resurgence of anxiety symptoms,[44] and that these symptoms are maintained through negative reinforcement associated with avoidance of these cues.[45] Indeed, increased HR, along with other psychophysiological responses, may reflect changes in amygdala activation, and conditioned fear and continued avoidance may contribute to a failure to extinguish emotional responses to trauma-related cues.[46] Thus, our findings may represent impaired extinction pathways and processes. Of great interest is the identification of subgroups of individuals with PTSD on the basis of varying physiologic and psychological response patterns (eg, specific symptom clusters), which may help elucidate the contributions of various markers to the development of PTSD. In accordance with our current findings, different biologic markers may be related to different subgroups of patients (eg, those with greater endorsement of avoidance symptoms). Thus, clinical literature on human responses following traumatic injury should continue to conduct mechanistic studies to identify the basic processes and pathways to clarify how, when, and for what clinical subphenotypes HR serves as a biomarker for PTSD.

Limitations

It is important to note that these findings must be interpreted in light of several limitations of the present study. Inherent to retrospective analyses, the number and type of variables available for examination were limited. Most notably, preinjury measures of psychological and physiologic function or indications of pretrauma arousal (eg, HR and BP) were not available. For example, data on previous traumas or PTSD diagnosis in our sample are unknown, a factor that could have impacted the current findings. Also unavailable was medical information such as premorbid aerobic health, respiratory disease, cardiovascular disease, and presence of stimulants such as illicit drugs, as well as other medications that have been shown to impact the development of PTSD (eg, morphine in trauma patients).[47,48] Variability in the measurement and collection of physiologic data was also likely. For example, the time lag from burn injury to emergency care and variation in the measurement of HR and BP between emergency care personnel were not known. Although not possible for this study, some authors have suggested obtaining multiple assessments at each time point to account for the natural variability of HR.[49] Although the DTS has been well-examined in burn samples and has an established cutoff score for clinically significant distress,[50] more exact diagnostic information was not available (eg, structured clinical interviews). Statistical analyses were also limited by the sample size and attrition, in that power was only suitable to examine a small number of covariates or predictors. Finally, the timing of symptom assessment is inherent to all trauma studies and may account for mixed findings in the literature. For example, initial nonpathological distress following an injury may augment endorsement of symptoms if measured immediately after the event.[16] Clearly, empirical investigation of this topic is challenging due to the life-threatening nature and emergency care needed for many traumatic events. Despite confounds, our findings reveal a relationship between immediate posttrauma physiologic markers and the later development of traumatic stress symptoms.

It remains premature at this time to use HR as a mechanism to identify at-risk individuals in a clinical setting.[14] The accumulating evidence in this area encourages further examination of the role of acute HR in the development of PTSD. Utilizing multiple methods for assessing sympathetic tone (eg, HR, HR responsivity, HR variability) would refine the utility of a predictive algorithm.[51] Understanding the changes in HR pretrauma and posttrauma (ie, determining if individuals with PTSD had higher HR levels long before their trauma or simply higher HR around the time of the trauma) will be critical to our understanding of the role of HR as a reliable predictor of PTSD development. Substantial work remains to be done elucidating the processes, pathways, and modulators by which risk and resilience after traumatic injuries are linked to cognitive and behavioral responses (eg, catastrophizing, approach/avoidance,[52] perceived controllability[53,54] and environmental qualities (eg, support, safety).[55] Future work that incorporates these considerations may help to refine knowledge regarding endophenotypes identifying groups of trauma-exposed individuals at increased risk of developing PTSD.[3,56] This knowledge may, in turn, provide additional targets for early psychological and pharmacologic intervention. In this regard, while studies have assessed the role of secondary preventive pharmacologic agents for PTSD,[47,48,57] this area of research remains in its infancy. Promising avenues of future work will optimally assess biologic, cognitive, and behavioral correlates and predictors of PTSD symptoms in an effort to elucidate mechanisms in the development of PTSD.[46] The pathophysiology of PTSD can only be understood in the context of such related and co-occurring factors.[17]

Author affiliations: Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland (Drs Gould, Hall, Corry, Mason, McCann and Fauerbach and Ms Amoyal); and Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, Maryland (Dr McKibben).
Potential conflicts of interest: **Dr McCann** has been a consultant to and served on the speakers/advisory board for Jazz. **Drs Gould**, **McKibben**, **Hall**, **Corry**, **Mason**, and **Fauerbach** and **Ms Amoyal** report no potential conflicts of interest to disclose relative to the subject of this article.
Funding/support: This project was funded by Burn Model Systems Grant (H133A070045) supported by the National Institute of Disability and Rehabilitation Research, Office of Special Education and Rehabilitation Services in the US Department of Education.
Disclaimer: The views expressed in this article are those of the authors and do not reflect official policy or position of the Department of Defense, the U.S. Government, or any of the institutional affiliations listed.
Previous presentation: Previously presented at the 41st annual meeting of the American Burn Association; March 24–27, 2009; San Antonio, Texas.

REFERENCES

1. Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. *Clin Psychol Rev*. 2007;27(5):572–581.
2. Harvey AG, Bryant RA. The relationship between acute stress disorder and posttraumatic stress disorder: a prospective evaluation of motor vehicle accident survivors. *J Consult Clin Psychol*. 1998;66(3):507–512.
3. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636–645.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC; American Psychiatric Association; 2000.
5. Blanchard EB, Hickling EJ, Vollmer AJ, et al. Short-term follow-up of post-traumatic stress symptoms in motor vehicle accident victims. *Behav Res Ther*. 1995;33(4):369–377.
6. Pitman RK. Post-traumatic stress disorder, hormones, and memory. *Biol Psychiatry*. 1989;26(3):221–223.
7. Yehuda R, McFarlane AC, Shalev AY. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. *Biol Psychiatry*. 1998;44(12):1305–1313.
8. Cahill L, Prins B, Weber M, et al. Beta-adrenergic activation and memory for emotional events. *Nature*. 1994;371(6499):702–704.
9. McGaugh JL. Peripheral and central adrenergic influences on brain systems involved in the modulation of memory storage. *Ann N Y Acad Sci*. 1985;444:150–161.
10. Shalev AY, Sahar T, Freedman S, et al. A prospective study of heart rate response following trauma and the subsequent development of posttraumatic stress disorder. *Arch Gen Psychiatry*. 1998;55(6):553–559.
11. Bryant RA, Harvey AG, Guthrie RM, et al. A prospective study of psychophysiological arousal, acute stress disorder, and posttraumatic stress disorder. *J Abnorm Psychol*. 2000;109(2):341–344.
12. Shalev AY, Freedman S. PTSD following terrorist attacks: a prospective evaluation. *Am J Psychiatry*. 2005;162(6):1188–1191.
13. Kassam-Adams N, Garcia-España JF, Fein JA, et al. Heart rate and posttraumatic stress in injured children. *Arch Gen Psychiatry*. 2005;62(3):335–340.
14. Bryant RA, Creamer M, O'Donnell M, et al. A multisite study of initial

© Copyright 2010 Physicians Postgraduate Press, Inc.

respiration rate and heart rate as predictors of posttraumatic stress disorder. *J Clin Psychiatry.* 2008;69(11):1694–1701.
15. Blanchard EB, Hickling EJ, Galovski T, et al. Emergency room vital signs and PTSD in a treatment seeking sample of motor vehicle accident survivors. *J Trauma Stress*. 2002;15(3):199–204.
16. Kuhn E, Blanchard EB, Fuse T, et al. Heart rate of motor vehicle accident survivors in the emergency department, peritraumatic psychological reactions, ASD, and PTSD severity: a 6-month prospective study. *J Trauma Stress*. 2006;19(5):735–740.
17. Shalev AY, Segman RH. Commentary: biological findings in PTSD—too much or too little? *Prog Brain Res*. 2008;167:187–199.
18. Buckley TC, Kaloupek DG. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. *Psychosom Med*. 2001; 63(4):585–594.
19. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol Bull*. 2007;133(5):725–746.
20. Davidson JR, Book SW, Colket JT, et al. Assessment of a new self-rating scale for post-traumatic stress disorder. *Psychol Med*. 1997;27(1):153–160.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
22. Cardeña E, Koopman C, Classen C, et al. Psychometric properties of the Stanford Acute Stress Reaction Questionnaire (SASRQ): a valid and reliable measure of acute stress. *J Trauma Stress*. 2000;13(4):719–734.
23. Koopman C, Gore-Felton C, Classen C, et al. Acute stress reactions to everyday stressful life events among sexual abuse survivors with PTSD. *J Child Sex Abuse*. 2002;10(2):83–99.
24. Derogatis LR. *BSI: Brief Symptom Inventory*. 3rd ed. Minneapolis, MN: National Computer Systems; 1993.
25. Derogatis LR. *SCL-90-R: Administration, Scoring, and Procedures Manual*. 3rd ed. Minneapolis, MN: National Computer Systems, Inc; 1994.
26. Boulet J, Boss MW. Reliability and validity of the Brief Symptom Inventory. *Psychol Assess.* 1991;3(3):433–437.
27. Piersma HL, Reaume WM, Boes JL. The Brief Symptom Inventory (BSI) as an outcome measure for adult psychiatric inpatients. *J Clin Psychol.* 1994;50(4):555–563.
28. McCarthy ML, MacKenzie EJ, Edwin D, et al; LEAP study group. Psychological distress associated with severe lower-limb injury. *J Bone Joint Surg Am*. 2003;85-A(9):1689–1697.
29. Gavranidou M, Rosner R. The weaker sex? gender and post-traumatic stress disorder. *Depress Anxiety*. 2003;17(3):130–139.
30. Nolen-Hoeksema S. Epidemiology and theories of gender differences in unipolar depression. In: Seeman MV, ed. *Gender and Psychopathology*. Washington, DC: American Psychiatric Association; 1995: 63–87.
31. Ehlers A, Mayou RA, Bryant B. Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *J Abnorm Psychol*. 1998;107(3):508–519.
32. Norris FH, Perilla JL, Ibanez GE, et al. Sex differences in symptoms of posttraumatic stress: does culture play a role? *J Trauma Stress*. 2001;14(1): 7–28.
33. Fullerton CS, Ursano RJ, Epstein RS, et al. Gender differences in posttraumatic stress disorder after motor vehicle accidents. *Am J Psychiatry*. 2001;158(9):1486–1491.
34. Liu K, Ballew C, Jacobs DR Jr, et al. Ethnic differences in blood pressure, pulse rate, and related characteristics in young adults: The CARDIA study. *Hypertension*. 1989;14(2):218–226.
35. Bazette H. An analysis of the time relations of electrocardiograms. *Heart*. 1920;7:353–370.
36. Ashman R. The normal duration of the QT interval. *Am Heart J*. 1942; 23(4):522–534.
37. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged? possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol*. 1996;27(1):76–83.
38. Kadish AH. The effect of gender on cardiac electrophysiology and arrhythmias. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside*. 2nd ed. Philadelphia, PA: WB Saunders; 1995: 1268–1275.
39. Yarnoz MJ, Curtis AB. More reasons why men and women are not the same (gender differences in electrophysiology and arrhythmias). *Am J Cardiol*. 2008;101(9):1291–1296.
40. Breslau N. Epidemiologic studies of trauma, posttraumatic stress disorder, and other psychiatric disorders. *Can J Psychiatry*. 2002;47(10):923–929.
41. Breslau N. Gender differences in trauma and posttraumatic stress disorder. *J Gend Specif Med*. 2002;5(1):34–40.
42. Manuck SB, Kamarck TW, Kasprowicz AS, et al. Stability and patterning of behaviorally evoked cardiovascular reactivity. In: Blascovic J, Katkin ES, eds. *Cardiovascular Reactivity to Psychological Stress and Disease*. Washington, DC: American Psychological Association; 1995:111–134.
43. North CS, Suris AM, Davis M, et al. Toward validation of the diagnosis of posttraumatic stress disorder. *Am J Psychiatry*. 2009;166(1):34–41.
44. Charney DS, Deutch AY, Krystal JH, et al. Psychobiologic mechanisms of posttraumatic stress disorder. *Arch Gen Psychiatry*. 1993;50(4):295–305.
45. Keane TM, Zimmering RT, Caddell JM. A behavioral formulation of post traumatic stress disorder in Vietnam veterans. *Behav Therapist*. 1985;8: 9–12.
46. Bryant RA. Early predictors of posttraumatic stress disorder. *Biol Psychiatry*. 2003;53(9):789–795.
47. Bryant RA, Creamer M, O'Donnell M, et al. A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. *Biol Psychiatry*. 2009;65(5):438–440.
48. Saxe G, Stoddard F, Courtney D, et al. Relationship between acute morphine and the course of PTSD in children with burns. *J Am Acad Child Adolesc Psychiatry*. 2001;40(8):915–921.
49. Buckley TC, Holohan D, Greif JL, et al. Twenty-four-hour ambulatory assessment of heart rate and blood pressure in chronic PTSD and non-PTSD veterans. *J Trauma Stress*. 2004;17(2):163–171.
50. Fauerbach JA, McKibben J, Bienvenu OJ, et al. Psychological distress after major burn injury. *Psychosom Med*. 2007;69(5):473–482.
51. Cohen H, Benjamin J, Geva AB, et al. Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Res*. 2000;96(1):1–13.
52. Ehlers A, Clark DM. A cognitive model of posttraumatic stress disorder. *Behav Res Ther*. 2000;38(4):319–345.
53. Ehlers A, Clark DM, Dunmore E, et al. Predicting response to exposure treatment in PTSD: the role of mental defeat and alienation. *J Trauma Stress*. 1998;11(3):457–471.
54. Kushner MG, Riggs DS, Foa EB, et al. Perceived controllability and the development of posttraumatic stress disorder (PTSD) in crime victims. *Behav Res Ther*. 1993;31(1):105–110.
55. Charuvastra A, Cloitre M. Social bonds and posttraumatic stress disorder. *Annu Rev Psychol.* 2008;59(1):301–328.
56. Broekman BF, Olff M, Boer F. The genetic background to PTSD. *Neurosci Biobehav Rev*. 2007;31(3):348–362.
57. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry*. 2002;51(2):189–192.