A Multisite Study of Initial Respiration Rate and Heart Rate as Predictors of Posttraumatic Stress Disorder

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Objective: Fear-conditioning models posit that increased arousal at the time of trauma predicts subsequent posttraumatic stress disorder (PTSD). This multisite study evaluated the extent to which acute heart rate and respiration rate predict subsequent chronic PTSD.

Method: Traumatically injured patients admitted to 4 hospitals across Australia between April 2004 and February 2006 were initially assessed during hospital admission (N = 1105) and were reassessed 3 months later for PTSD by using the Clinician-Administered PTSD Scale-IV and for major depressive disorder (MDD) by using the Mini-International Neuropsychiatric Interview (English version 5.0.0) (N = 955). Heart rate, respiration rate, and blood pressure were assessed on the initial day of traumatic injury.

Results: Ninety patients (10%) met criteria for PTSD and 159 patients (17%) met criteria for MDD at the 3-month assessment. Patients with PTSD compared to those without PTSD had higher heart rate (90.16 ± 18.66 vs. 84.84 ± 17.41, t = 2.74, p < .01) and respiration rate (20.24 ± 5.16 vs. 18.58 ± 4.29, t = 3.43, p < .001) immediately after injury. There were no heart rate or respiration rate differences between patients who did and did not develop MDD. Patients were more likely to develop PTSD at 3 months if they had a heart rate of at least 96 beats per minute (15% vs. 8%, OR = 2.12, 95% CI = 1.34 to 3.33) or respiration rate of at least 22 breaths per minute (18% vs. 8%, OR = 2.42, 95% CI = 1.48 to 3.94).

Conclusions: Elevated heart rate and respiration rate are predictors of subsequent PTSD. These data underscore the need for future research into secondary prevention strategies that reduce acute arousal immediately after trauma and may limit PTSD development in some individuals.

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The last decade has seen unprecedented attention to potential early markers of trauma survivors who will subsequently develop posttraumatic stress disorder (PTSD). This task has proven difficult, partly because the majority of trauma survivors who initially display acute stress reactions adapt in the following 3 months.[1] Psychological predictors have limited success in identifying people who will develop PTSD,[2] and these approaches are labor-intensive and costly. An alternative approach has been to identify biological markers in the acute phase that can be readily assessed in trauma survivors. The theoretical basis for this approach has been fear-conditioning models that posit that the fear elicited during a traumatic event results in conditioning in which subsequent reminders of the trauma elicit anxiety in response to trauma reminders (conditioned stimuli).[3] This model proposes that extreme sympathetic arousal at the time of a traumatic event may result in the release of stress neurochemicals (including norepinephrine and epinephrine), mediating an overconsolidation of trauma memories.[4] This proposal is consistent with animal studies that indicate that epinephrine administration after an aversive experience enhances fear conditioning.[5] Fear-conditioning models are also supported by considerable evidence that people with chronic PTSD are hyperresponsive to trauma reminders.[6,7] The increased activation in the sympathetic nervous system and the adrenal medulla occurring after trauma exposure may contribute to fear conditioning, and

this increase may be reflected in faster resting heart rate and respiration.

On the basis of fear-conditioning models, numerous longitudinal studies have assessed the relationship between resting heart rate shortly after traumatic injury and subsequent PTSD development. These studies have presumed that increased sympathetic nervous system, or impaired parasympathetic nervous system activity, in the immediate aftermath of trauma exposure will be reflected in elevated heart rate. A number of these studies have found that adults who subsequently develop PTSD display higher resting heart rate initially than those who do not develop PTSD.[8–13] Three studies of childhood PTSD have reported a similar pattern.[14–16] Although recent early intervention treatment studies have employed elevated heart rate as a marker for high risk for PTSD,[17,18] the evidence that heart rate is a reliable marker for PTSD development is limited. Elevated heart rate has not been observed in several samples[19,20] or has been only partially replicated in others.[21,22] Although one of these studies was methodologically flawed,[19] there are marked discrepancies between studies concerning the relationship between initial heart rate and subsequent PTSD. A major limitation of the research to date is that it relies on modest sample sizes and tends to be limited to 1 or 2 recruitment sites. This pattern may contribute to the discrepant findings across sites. Accordingly, a primary goal of the present study was to conduct a large-scale longitudinal study across 4 different sites to assess the relationship between initial heart rate and subsequent PTSD.

Another possible index of strength of initial fear-conditioning may be respiration rate immediately after trauma. The control of respiratory function is complex and is linked to heart rate by respiratory sinus arrhythmia,[23] which is in turn modulated by cholinergic and adrenergic mechanisms.[24] The central respiratory rhythm, although influenced by peripheral feedback, depends upon interneuronal communication between the nucleus ambiguus and the nucleus of the solitary tract.[25] Increased respiration is a classic manifestation of fear conditioning in humans and animals.[26] There is evidence of increased respiration in veterans on exposure to sounds of combat, even though trauma victims with and without PTSD do not differ on measures of respiratory sinus arrhythmia.[27] The possibility that elevated respiration rate is a manifestation of fear conditioning is consistent with evidence that respiration in humans is increased by elevated catecholamine levels.[28,29] To date, no studies have investigated the relationship between acute respiration rate and subsequent development of PTSD.

This large, longitudinal study of survivors of traumatic injury was conducted across 4 hospital sites and assessed heart rate and respiration rate recorded at the time of the trauma. Participants were reassessed 3 months later to determine the relationship between these measures of acute sympathetic activation and PTSD development. We predicted that patients with elevated acute heart rate and respiration rate would be more likely to develop PTSD than those with lower heart rate and respiration rate.

METHOD

Participants

Patients admitted to 4 level-1 trauma centers across 3 states in Australia were recruited and randomly selected into the study between April 2004 and February 2006. The study was approved by the research and ethics committee at each hospital. Inclusion criteria included individuals who were aged between 16 and 70 years, could understand and speak English proficiently, and had a hospital admission of greater than 24 hours following traumatic injury. Individuals were excluded from the study if they had moderate or severe head injury (mild traumatic brain injury [MTBI], defined as a loss of consciousness of approximately 30 minutes or less, a Glasgow Coma Scale score of 13–15 after 30 minutes, or posttraumatic amnesia not greater that 24 hours[30]); were currently psychotic or suicidal; and were not Australian visitors, cognitively impaired, or under police guard. Individuals who met entry criteria were randomly selected using an automated, random assignment procedure, stratified by length of stay; this procedure guarded against preferential recruitment of patients who were admitted for longer time periods. After patients' written informed consent was obtained, trained clinicians conducted clinical interviews assessing past psychiatric history, current PTSD, and depression. They obtained permission to follow up patients 3 months after hospital admission, with a telephone interview for a second clinical interview assessing PTSD and depression, combined with self-report measures of anxiety and depression.

Measurement of Heart Rate, Blood Pressure, and Respiration Rate

Multiple heart rate recordings were taken at the first contact with the patient, which was either at the scene of the injury by paramedics or at initial admission to the emergency department, by using radial, brachial, or carotid pulse palpation measured during a 60-second period. The first 4 records of heart rate were drawn from the patient's file by the researchers and the mean heart rate recorded. This use of routinely collected heart rate data is similar to the method employed by a majority of studies that have examined the relationship between heart rate and PTSD. Systolic and diastolic blood pressure was also recorded at the same time intervals with automatic blood pressure monitors. Multiple assessments of respiration rate were taken at the same time as heart rate by paramedics using observation measurement during a period of 60 seconds. Researchers collected the first 4 measures of

respiration rate from the file and recorded the mean respiration rate score. We used initial assessment of heart rate and respiration rate to obtain levels immediately after trauma exposure (which should be a marker of the unconditioned response) and to ensure that we obtained these responses prior to the administration of opioid analgesia, which may have confounded heart rate or respiration rate response.

Measurement of PTSD, Depression, and Anxiety

Trained clinicians assessed PTSD symptoms during the hospital admission and at 3 months post injury using the Clinician-Administered PTSD Scale-IV (CAPS-IV).[31] The CAPS-IV possesses good sensitivity (.84) and specificity (.95) relative to PTSD diagnosis according to the Structured Clinical Interview for DSM-IV Axis I Disorders, and it also possesses sound test-retest reliability (.90). Prior psychiatric disorder was assessed during hospitalization using the Mini-International Neuropsychiatric Interview (English version 5.0.0; MINI).[32] Patients also completed the Hospital Anxiety and Depression Scale (HADS).[33] At the 3-month assessment, patients were assessed for PTSD by using the CAPS-IV and for major depressive disorder by using the MINI, and they completed the HADS.

Other Measures

Information regarding demographic, hospital admission, and injury-related factors was obtained from medical records and trauma registries from each of the hospitals. Injury information included the Injury Severity Score (ISS),[34] which is a measure of overall injury severity; cause of traumatic injury; hospitalization length; and presence of MTBI.

Statistical Analysis

Demographic, injury characteristics, heart rate, and respiration rate measures for participants and those lost to 3-month follow-up were compared using t tests for continuous measures or χ^2 for categorical measures with a Bonferroni adjustment ($\alpha = .005$) to allow for the multiple comparisons.

Heart rate and respiration rate data were examined in 2 ways. First, we used t tests to compare heart rate and respiration rate in patients who did and did not develop PTSD at 3 months using t tests. Second, we followed previous heart rate studies[13] by determining an appropriate cutoff for heart rate to identify participants who would develop PTSD by (1) studying previously reported heart rate cutoff scores,[8,12,13] (2) conducting a receiver operating characteristic (ROC) curve analysis, and (3) visually examining the PTSD diagnostic data to determine an initial heart rate cutoff that optimized prediction of PTSD caseness at 3 months. This approach resulted in adopting a cutoff of 96 beats per minute. A similar approach was adopted for respiration rate, except no literature exists on the relationship between initial respiration rate and PTSD, so we arrived at a cutoff of 22 breaths per minute on the basis of ROC analysis and examination of the longitudinal data. We calculated sensitivity, specificity, positive predictive power, and negative predictive power for elevated heart rate and respiration rate as predictors of PTSD diagnosis. Positive predictive power is the probability that a patient with elevated heart rate or respiration rate will develop PTSD, and negative predictive power is the probability that a patient without elevated heart rate or respiration rate will not develop PTSD.

The extent to which elevated heart rate and respiration rate predict subsequent PTSD in relation to other factors that may account for posttraumatic adjustment was examined through hierarchical logistic regression. The order of factors entered in regression analyses was based on demographic and injury-related factors that may influence the effect of heart rate or respiration rate on subsequent PTSD. Specifically, at the first step, we entered hospital site; at the second step, we entered ISS, Glasgow Coma Scale score, and days in hospital as measures of injury severity; at the third step, we entered patient's gender; at the fourth step, we entered patient's age; at the fifth step, we entered type of injury; at the sixth step, we entered patient's psychiatric history; at the seventh step, we entered baseline CAPS-IV score; at the eighth step, we entered initial respiration rate; and at the ninth step, we entered initial heart rate. We repeated these factors in a logistic regression analysis to predict MDD at follow-up, except that we entered baseline HADS-depression score at step 7 rather than baseline CAPS-IV.

RESULTS

Among the participants, 1593 were approached, 1167 (73%) agreed to participate, 1105 (69%) had heart rate data collected, and 1071 (67%) had respiration rate data collected during admission. Participants comprised 813 men and 292 women with a mean age of 37.60 years (SD = 13.91). Four hundred fifty-nine participants experienced an MTBI, and the mean ISS was 10.98 (SD = 8.11). Participants spent a mean of 12.28 (SD = 12.84) days in hospital. Types of injury included transport accidents (N = 718, 65%), falls (N = 155, 14%), assaults (N = 77, 7%), work-related accidents (N = 77, 7%), and other injuries (N = 78, 7%). The mean initial resting heart rate for the sample was 85.41 (SD = 17.67) beats per minute. The mean initial respiration rate for the sample was 18.71 (SD = 4.41) breaths per minute.

Individuals who refused to participate in the current study did not differ from participants in terms of gender ($\chi^2 = 1.76$, df = 1, p = .13), days in hospital (t = .75, df = 1574, p = .52), or ISS (t = 1.43, df = 1574, p = .20).

Table 1. Association of Psychopathology Outcome With Continuous Inpatient Heart Rate and Respiration Rate Predictors

	PTSD Status at Follow-Up				MDD Status at Follow-Up			
	No PTSD	PTSD	Test[a]		No MDD	MDD	Test[a]	
Predictor	(N = 865)	(N = 90)	t	p	(N = 795)	(N = 159)	t	p
Heart rate, mean ± SD, beats per min	84.84 ± 17.41	90.16 ± 18.66	2.74	.006	85.13 ± 17.88	86.19 ± 15.99	0.70	.48
Respiration rate, mean ± SD, breaths per min	18.58 ± 4.29	20.24 ± 5.16	3.43	< .001	18.69 ± 4.97	18.94 ± 3.92	0.64	.52
Systolic blood pressure, mean ± SD, beats per min	72.64 ± 18.01	72.89 ± 14.99	0.11	.91	72.49 ± 16.54	73.63 ± 22.86	0.64	.52
Diastolic blood pressure, mean ± SD, beats per min	127.87 ± 20.07	126.99 ± 22.80	0.39	.70	128.01 ± 120.55	126.39 ± 19.37	0.92	.36

[a]df = 918.
Abbreviations: MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

Figure 1. Frequency Distribution of Initial Heart Rate by Posttraumatic Stress Disorder (PTSD) at Follow-Up

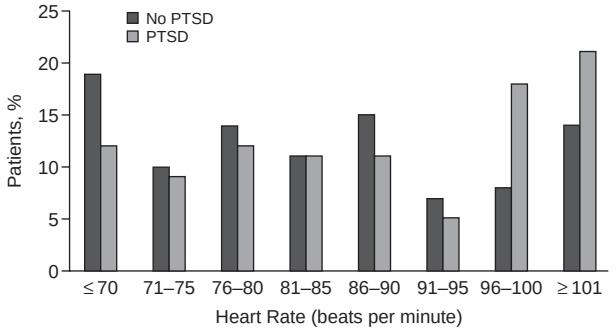
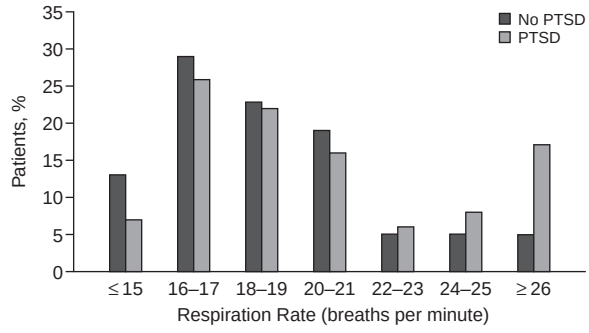


Figure 2. Frequency Distribution of Initial Respiration Rate in Hospital by Posttraumatic Stress Disorder (PTSD) at Follow-Up



At the 3-month follow-up assessment, 150 patients could not be contacted or declined to participate; 955 were interviewed by telephone, representing 86% of the initial sample. Patients at the follow-up assessment did not differ from those who did not participate in terms of age, length of hospital stay, ISS, initial heart rate, or initial respiration rate.

At the follow-up assessment, 90 patients (10%) met criteria for PTSD and 159 (17%) met criteria for MDD. In terms of comorbidity, 62 patients (69%) with PTSD also had MDD. Table 1 shows that patients who developed PTSD had higher heart rate and respiration rate than patients who did not develop PTSD. Patients who developed MDD did not display higher heart rate or respiration rate than those who did not develop MDD. There were comparable rates of patients with and without MTBI who developed PTSD (MTBI, 12%; no MTBI, 8%) and MDD (MTBI, 17%; no MTBI, 16%). In terms of patients with PTSD, those who also had MDD did not differ from patients who had PTSD without MDD in terms of mean ± SD heart rate (PTSD/MDD = 89.87 ± 18.46, PTSD = 90.79 ± 19.44; t = 0.21, df = 88, p = .83) or mean ± SD respiration rate (PTSD/MDD = 20.11 ± 4.53, PTSD = 20.54 ± 6.43; t = 0.36, df = 88, p = .72). In terms of patients with no MTBI, those who had PTSD versus those without PTSD had greater mean ± SD heart rate (PTSD = 90.83 ± 20.07, no PTSD = 82.95 ± 16.22; t = 2.92, df = 538, p = .004) and mean ± SD respiration rate (PTSD = 20.66 ± 4.80, no PTSD = 18.20 ± 4.04; t = 3.68, df = 538, p = .001). In terms of patients with MTBI, those who had PTSD versus those without PTSD had comparable mean ± SD heart rate (PTSD = 89.59 ± 17.00, no PTSD = 87.42 ± 18.63; t = 0.77, df = 412, p = .44) and mean ± SD respiration rate (PTSD = 19.10 ± 4.57, no PTSD = 19.90 ± 5.47; t = 1.12, df = 412, p = .26). Figures 1 and 2 present the distribution of heart rate and respiration rate on initial day of hospitalization for patients who did and did not develop PTSD. Patients did not differ on systolic or diastolic blood pressure in terms of follow-up PTSD or MDD diagnosis.

Table 2 presents the mean baseline and 3-month data for patients according to their elevated heart rate and respiration rate classification. Patients with elevated heart rate were younger, more likely to have an MTBI, and scored higher on ISS, Glasgow Coma Scale, hospitalization length, initial PTSD severity, and 3-month PTSD severity than those with lower acute heart rate. Patients with elevated respiration rate scored higher on ISS, hospitalization length, initial PTSD severity, initial HADS-anxiety, 3-month PTSD severity, and 3-month HADS-anxiety than those with lower acute respiration rate. Patients with

Table 2. Patient Characteristics According to Initial and 3-Month Heart Rate and Respiration Rate

Characteristic	Heart Rate < 96[a]	Heart Rate ≥ 96[a]	Test Result	p	Respiration Rate < 22[b]	Respiration Rate ≥ 22[b]	Test Result	p
Initial assessment								
N	840	265			898	173		
Male gender, % (N)	74 (622)	72 (191)	$\chi^2 = 0.78$	.42	73 (658)	79 (136)	$\chi^2 = 5.50$	.05
Brain injury, % (N)	41 (344)	54 (143)	$\chi^2 = 13.24$	.001	42 (379)	53 (91)	$\chi^2 = 6.23$	.05
Motor vehicle accident, % (N)	64 (538)	68 (180)	$\chi^2 = 1.73$	.19	64 (577)	69 (119)	$\chi^2 = 0.79$	.38
Age, mean ± SD, y	38.41 ± 13.91	35.14 ± 13.65	t = 3.35[c]	.001	37.43 ± 14.12	38.56 ± 12.99	t = 1.00[d]	.31
Injury Severity Score, mean ± SD	10.35 ± 7.73	12.87 ± 8.57	t = 4.74[c]	.001	10.21 ± 7.25	14.78 ± 10.66	t = 6.83[d]	.001
Glasgow Coma Scale score, mean ± SD	14.82 ± 0.51	14.66 ± 0.80	t = 2.92[c]	.005	3.98 ± 0.17	3.88 ± 0.36	t = 2.02[d]	.05
Days in hospital, mean ± SD	11.18 ± 10.60	16.15 ± 18.06	t = 5.63[c]	.001	11.86 ± 12.02	15.03 ± 15.56	t = 3.08[d]	.002
CAPS, mean ± SD	19.14 ± 16.44	26.22 ± 21.58	t = 5.57[c]	.001	20.46 ± 17.78	25.67 ± 20.82	t = 3.65[d]	.001
HADS-anxiety, mean ± SD	4.98 ± 3.98	5.92 ± 4.57	t = 3.04[c]	.05	5.18 ± 4.23	6.05 ± 4.69	t = 2.64[d]	.008
HADS-depression, mean ± SD	4.78 ± 3.88	5.34 ± 4.42	t = 2.02[c]	.05	4.14 ± 3.99	5.48 ± 4.42	t = 1.80[d]	.08
3-Month assessment								
N	725	230			770	150		
PTSD, % (N)	8 (55)	15 (35)	$\chi^2 = 10.84$	.001	8 (63)	18 (27)	$\chi^2 = 13.14$	.001
CAPS, mean ± SD	19.19 ± 19.84	24.81 ± 24.42	t = 3.36[e]	.001	20.12 ± 21.01	24.79 ± 24.08	t = 2.44[f]	.05
MDD, % (N)	16 (117)	18 (42)	$\chi^2 = 0.17$	.68	16 (126)	21 (32)	$\chi^2 = 0.17$	.68
HADS-anxiety, mean ± SD	5.52 ± 4.24	6.49 ± 5.03	t = 2.87[e]	.05	5.58 ± 4.35	6.94 ± 4.98	t = 3.26[f]	.001
HADS-depression, mean ± SD	4.66 ± 3.94	5.36 ± 4.35	t = 2.32[e]	.05	4.74 ± 3.97	5.52 ± 4.28	t = 2.08[f]	.05

[a]Measured in beats per minute.
[b]Measured in breaths per minute.
[c]df = 1103.
[d]df = 1069.
[e]df = 953.
[f]df = 918.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, HADS = Hospital Anxiety Depression Scale, MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

elevated heart rate were more likely to meet criteria for PTSD than those without elevated heart rate (15% vs. 8%, Fisher exact test, p = .002, OR = 2.12, 95% CI = 1.34 to 3.33). Patients with elevated respiration rate were more likely to meet criteria for PTSD at 3 months than those without elevated respiration rate (18% vs. 8%, Fisher exact test, p = .001, OR = 2.42, 95% CI = 1.48 to 3.94). Patients with elevated heart rate were not more likely to meet criteria for MDD at 3 months than those without elevated heart rate (18% vs. 16%, Fisher exact test, p = .48, OR = 1.16, 95% CI = 0.78 to 1.71). Patients with elevated respiration rate were not more likely to meet criteria for MDD than those without elevated respiration rate (21% vs. 16%, Fisher exact test, p = .15, OR = 1.39, 95% CI = 0.90 to 2.15). Table 3 presents the sensitivity, specificity, positive predictive power, and negative predictive power for elevated heart rate and respiration rate.

Table 3. Sensitivity, Specificity, Positive Predictive Power, and Negative Predictive Power of Elevated Heart Rate and Respiration Rate

	Elevated Heart Rate (≥ 96 beats per minute)		Elevated Respiration Rate (≥ 22 breaths per minute)	
Variable	PTSD	MDD	PTSD	MDD
Sensitivity	.15	.18	.18	.21
Specificity	.92	.84	.92	.84
Positive predictive power	.39	.27	.30	.21
Negative predictive power	.77	.76	.85	.84

Abbreviations: MDD = major depressive disorder, PTSD = posttraumatic stress disorder.

The hierarchical logistic regression indicated that after adjusting for hospital site, injury severity, Glasgow Coma Scale score, length of hospitalization, age, gender, type of traumatic injury, prior psychiatric history, and baseline PTSD severity, respiration rate (adjusted OR = 1.07, 95% CI = 1.02 to 1.12) significantly predicted PTSD diagnosis at 3 months. PTSD was also predicted by female gender (adjusted OR = 2.10, 95% CI = 1.20 to 2.67), prior psychiatric history (adjusted OR = 2.72, 95% CI = 1.46 to 5.06), and baseline CAPS-IV score (adjusted OR = 1.06, 95% CI = 1.04 to 1.07). Major depressive disorder was predicted by ISS (adjusted OR = 0.95, 95% CI = 0.92 to 0.99), prior psychiatric history (adjusted OR = 2.38, 95% CI = 1.51 to 3.73), and baseline HADS-depression score (adjusted OR = 1.17, 95% CI = 1.11 to 1.23). Neither respiration rate nor heart rate was a significant predictor of MDD.

DISCUSSION

This study provides the first large-scale multisite evidence that elevated heart rate and respiration rate in the

immediate aftermath of traumatic injury are associated with subsequent PTSD. Further, the relationship between acute respiration rate and subsequent PTSD was significant beyond the effect of hospital site, injury severity, type of injury, gender, age, prior psychiatric history, and baseline PTSD severity. Taken together, these findings support fear-conditioning models of PTSD because both increased heart rate and respiration rate may reflect the strength of the unconditioned response in the immediate aftermath of trauma exposure. The observed increase in arousal in the acute phase may lead to stronger conditioning in the critical phase after the trauma that subsequently contributes to ongoing PTSD symptoms. This finding accords with evidence that subjective reports of arousal are strongly associated with subsequent PTSD.[35] The finding that heart rate was not associated with subsequent MDD accords with previous reports.[12,13] This convergent evidence highlights that development of posttraumatic depression is mediated by different factors than PTSD, and the role of fear conditioning in the acute phase appears to be specific to PTSD development.

The finding of elevated heart rate being associated with subsequent PTSD accords with previous evidence in adults[8–12] and children,[14–16] although it contrasts with several others.[19–21] Importantly, the current study overcomes previous methodological limitations by studying a very large sample from 4 hospitals in diverse regions, demonstrating that the relationship between initial heart rate and subsequent PTSD is a robust phenomenon. This study also addressed a previous limitation by controlling for the influence of prior psychiatric disorder on the role of heart rate on PTSD development. It has been argued that elevated heart rate may reflect elevated adrenergic activation associated with preexisting psychiatric disorders that are compounded by recent trauma.[12] Although this study found that heart rate contributed to subsequent PTSD beyond the influence of prior psychiatric disorder, we cannot exclude the possibility that patients with elevated heart rate had higher heart rate levels prior to their traumatic injury. It is possible that individuals who are hyperresponsive prior to trauma are more likely to acquire fear conditioning if exposed to a traumatic event. There is mixed evidence for this possibility. A recent study of twins either exposed or not exposed to combat found that larger heart rate responses to loud tones was unique to veterans with PTSD and not their nonexposed twins, suggesting that this reactivity is acquired as a result of PTSD.[36] In contrast, elevated acoustic startle in firefighters prior to commencing fire fighting duties predicts acute stress reactions after being exposed to traumatic events.[37] To date, there are no studies that have examined the relationship between resting heart rate prior to trauma exposure and subsequent PTSD.

This study provides the first evidence that rapid breathing immediately after trauma exposure is predictive of subsequent PTSD. Patients with a respiration rate of at least 22 breaths per minute immediately after a traumatic injury were 2.42 times more likely to develop PTSD than other patients. Rapid breathing is one of the characteristics of fear conditioning in rats.[38] The finding that respiration rate was predictive is very novel but accords with evidence that panic attacks during a traumatic event are strongly associated with acute stress disorder,[39] and it accords with models that posit that panic reactions and strength of the arousal response during the traumatic phase may directly contribute to PTSD because of the strength of fear conditioning.[40] Interestingly, in the current study respiration rate was a stronger predictor of PTSD than heart rate. It is possible that respiration rate reflects the degree of fear conditioning more directly than heart rate, partly because it may reflect the panic reactions associated with more severe distress responses to the traumatic experience. Increased respiration involves a broad and complex network of neural regions, including pons, midbrain, hypothalamus, limbic areas, hippocampus, anterior cingulate, anterior insula, and prefrontal cortex.[41–43] It has been suggested that respiratory increases may reflect a phylogenetically primal response to threat because survival requires respiratory stability and, accordingly, it may represent a major marker of perceived threat to the well-being of the trauma survivor.[44] Respiration is implicated in complex ways with major physiologic functions, including the cardiovascular system, and it is possible that dysregulation of the respiratory system could modulate cardiac responses immediately after trauma exposure.[45]

We note that the findings of elevated heart rate and respiration rate may be associated with elevated sympathetic activation or diminished parasympathetic activation. Whereas there is some evidence that PTSD is not characterized by lower respiratory sinus arrhythmia,[23] there is increasing evidence that PTSD patients do have lower respiratory sinus arrhythmia[46,47] and that impaired parasympathetic activation contributes to elevated heart rate in PTSD.[48,49] In this context, it is worth noting that there was no relationship between acute blood pressure and subsequent PTSD, which is consistent with previous studies.[8,12] This finding supports the possibility that vagal tone, rather than sympathetic activation, may be critical in the association of heart rate and respiration rate and subsequent PTSD development.

Consistent with previous reports, the sensitivity and specificity of the heart rate and respiration rate cutoffs were poor. Further, the positive predictive power for PTSD was 39% for elevated heart rate and 30% for elevated respiration rate. Across all studies conducted to date on the relationship between heart rate and subsequent PTSD, there is no evidence that elevated heart rate provides a viable means of accurately screening the majority of people who develop PTSD. One possible reason for the limited success of heart rate in predicting subsequent

PTSD is that it may reflect the strength of the unconditioned response rather than the strength of fear conditioning. This interpretation is supported by evidence that heart rate is higher in people exposed to terrorist attacks than in those exposed to motor vehicle accidents, regardless of PTSD development.[22]

Whereas there were significant differences in both heart rate and respiration rate between PTSD and no-PTSD patients who did not sustain an MTBI, there were no differences between these patients who did sustain an MTBI. One explanation for this discrepancy may be that people who sustain an MTBI, and consequently briefly lose consciousness at the time of trauma, may be less likely to experience fear conditioning at this time. Laboratory research has shown that participants who are unaware of the contingency between a conditioned stimulus and the aversive outcome fail to successfully engage in fear conditioning.[50,51] It is possible that sustaining an MTBI limited the extent to fear conditioning at the time of trauma, and this results in heart rate and respiration rate not discriminating between PTSD and no-PTSD patients who sustain an MTBI. This pattern did not result in less PTSD among MTBI survivors (MTBI, 12%; no MTBI, 8%), which suggests that heart rate and respiration rate did not play a role in MTBI-related PTSD in the way they did in PTSD without an MTBI.

The current findings point to the potential for secondary prevention measures that limit adrenergic activation in the acute phase.[52] Preliminary indications suggest that acutely administered propranolol, a β-blocker that reduces adrenergic activation, may limit fear conditioning after trauma and possibly reduce the level of PTSD.[18,53] Commentators have also noted the potential benefits of early administration of opiate pain compounds.[54] There is evidence from animal studies that morphine administration limits fear conditioning and impairs extinction learning in rats.[55] Consistent with this proposition, there is initial evidence that acute administration of opiate pain compounds in pediatric burn patients results in lower levels of subsequent PTSD.[56] Despite the potential for these interventions, it must be noted that most people developed PTSD without elevated heart rate or respiration rate, and so the applicability of such interventions may be limited.

We recognize that this study is limited by reliance on paramedic assessments of heart rate and respiration rate rather than controlled experimental paradigms. This approach was adopted strategically because we intended to replicate the public health approach adopted by previous studies that have attempted to identify the potential of early biological markers that can be assessed in acute health care settings.[13] We acknowledge that this approach results in data that lack optimal quality control. Although we obtained heart rate and respiration rate measures as soon as possible after injury, we could not ensure that all measures were obtained prior to administration of opioid analgesics, which may have influenced heart rate and respiration rate response. Future studies should assess the interaction of opiates administered acutely with heart rate and respiration rate to determine the combined influences on PTSD development. We also did not index heart rate and respiration rate at follow-up, and so it was not possible to determine the role of persistent elevated heart rate and respiration rate in PTSD development. Previous studies indicate that resting heart rate is not elevated in PTSD 1 and 4 months after trauma,[12] and that chronic PTSD is not generally characterized by elevated basal heart rate.[57] We also note that we conducted the follow-up interviews by telephone; however, there is convergent evidence that structured clinical interviews conducted by telephone compare favorably to personal interviews.[58] Finally, we did not control for pain levels because these were not recorded at the time heart rate and respiration rate data were collected; it is possible that heart rate and respiration rate may have been elevated after injury because of severe pain, which may contribute to subsequent PTSD.

This study provides the first large-scale evidence that elevated heart rate and respiration rate are linked to subsequent PTSD. The particularly novel finding is that increased respiration rate immediately after trauma exposure poses a risk factor for subsequent PTSD. Although there is insufficient evidence to warrant these indices being considered for early screening tools, the findings point to important avenues for future research regarding the initial mechanisms involved in the genesis of PTSD.

Drug name: propranolol (Innopran, Inderal, and others).

REFERENCES

1. Shalev AY. Acute stress reactions in adults. Biol Psychiatry 2002;51:532–543
2. Bryant RA. Early predictors of posttraumatic stress disorder. Biol Psychiatry 2003;53:789–795
3. Charney DS, Deutch AY, Krystal JH, et al. Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 1993 Apr;50(4):295–305
4. Pitman RK. Post-traumatic stress disorder, hormones, and memory. Biol Psychiatry 1989;26:221–223
5. McGaugh J, Liang K, Benet C, et al. Adrenergic influence on memory storage: interaction of peripheral and central systems. Lynch G, McGaugh J, Weinberger N, eds. Neurobiology of Learning and Memory. New York: Guilford; 1984:313–332
6. Pitman RK, Orr SP, Forgue DF, et al. Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. Arch Gen Psychiatry 1987;44:970–975
7. Blanchard EB, Kolb LC, Gerardi RJ, et al. Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. Behav Ther 1986;17:592–606
8. 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;109:341–344
9. Bryant RA, Harvey AG, Guthrie RM, et al. Acute psychophysiological arousal and posttraumatic stress disorder: a two-year prospective study. J Trauma Stress 2003;16:439–443
10. Bryant RA, Harvey AG. Delayed-onset posttraumatic stress disorder: a prospective evaluation. Aust N Z J Psychiatry 2002;36:205–209
11. Bryant RA, Marosszeky JE, Crooks J, et al. Elevated resting heart rate as a predictor of posttraumatic stress disorder after severe traumatic

brain injury. Psychosom Med 2004;66:760–761
12. 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;55:553–559
13. Zatzick DF, Russo J, Pitman RK, et al. Reevaluating the association between emergency department heart rate and the development of posttraumatic stress disorder: a public health approach. Biol Psychiatry 2005;57:91–95
14. Bryant RA, Salmon K, Sinclair E, et al. Heart rate as a predictor of posttraumatic stress disorder in children. Gen Hosp Psychiatry 2007;29: 66–68
15. Kassam-Adams N, Garcia-Espana JF, Fein JA, et al. Heart rate and posttraumatic stress in injured children. Arch Gen Psychiatry 2005;62: 335–340
16. De Young AC, Kenardy JA, Spence SH. Elevated heart rate as a predictor of PTSD six months following accidental pediatric injury. J Trauma Stress 2007;20:751–756
17. Gidron Y, Gal R, Freedman S, et al. Translating research findings to PTSD prevention: results of a randomized-controlled pilot study. J Trauma Stress 2001;14:773–780
18. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiatry 2002;51:189–192
19. 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;15:199–204
20. Buckley B, Nugent N, Sledjeski E, et al. Evaluation of initial posttrauma cardiovascular levels in association with acute PTSD symptoms following a serious motor vehicle accident. J Trauma Stress 2004;17:317–324
21. O'Donnell M, Creamer M, Elliott P, et al. Tonic and phasic heart rate as predictors of posttraumatic stress disorder. Psychosom Med 2007;69: 256–261
22. Shalev AY, Freedman S. PTSD following terrorist attacks: a prospective evaluation. Am J Psychiatry 2005;162:1188–1191
23. Yeragani VK. Heart rate and blood pressure variability: implications for psychiatric research. Neuropsychobiology 1995;32(4):182–191
24. Sahar T, Shalev AY, Porges SW. Vagal modulation of responses to mental challenge in posttraumatic stress disorder. Biol Psychiatry 2001;49: 637–643
25. Richter DW, Spyer KM. Cardiorespiratory control. In: Loewy AD, Spyer KM, eds. Central Regulation of Autonomic Function. New York, NY: Oxford University Press; 1990:189–207
26. Delgado MR, Olsson A, Phelps EA. Extending animal models of fear conditioning to humans. Biol Psychol 2006 Jul;73(1):39–48
27. Orr SP, Metzger LJ, Pitman RK. Psychophysiology of post-traumatic stress disorder. Psychiatr Clin North Am 2002 Jun;25(2):271–293
28. Clark AL, Galloway S, MacFarlane N, et al. Catecholamines contribute to exertional dyspnoea and to the ventilatory response to exercise in normal humans. Eur Heart J 1997;18:1829–1833
29. Wheelan RF, Yound IM. The effect of adrenaline and noradrenaline infusions on respiration in man. Br J Pharmacol Chemother 1953 Mar;8(1):98–102
30. American Congress of Rehabilitation Medicine. Definition of mild traumatic brain injury. J Head Trauma Rehab 1993;8:86–87
31. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress 1995;8:75–90
32. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
33. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–370
34. American Association for Automotive Medicine. The Abbreviated Injury Scale-Revision. Des Plaines, Ill: American Association for Automotive Medicine; 1990
35. Schell TL, Marshall GN, Jaycox LH. All symptoms are not created equal: the prominent role of hyperarousal in the natural course of posttraumatic psychological distress. J Abnorm Psychol 2004;113:189–197
36. Orr SP, Metzger LJ, Lasko NB, et al. Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure: association with posttraumatic stress disorder. Arch Gen Psychiatry 2003;60:283–288
37. Guthrie RM, Bryant RA. Acoustic startle response in firefighters before and after trauma exposure. Am J Psychiatry 2005;162:283–290
38. LeDoux JE. The Emotional Brain: The Mysterious Underpinnings of Emotional Life. New York, NY: Simon & Schuster; 1996
39. Bryant RA, Panasetis P. Panic symptoms during trauma and acute stress disorder. Behav Res Ther 2001;39:961–966
40. Jones JC, Barlow DH. The etiology of posttraumatic stress disorder. Clin Psychol Rev 1990;10:299–328
41. Parsons LM, Egan G, Liotti M, et al. Neuroimaging evidence implicating cerebellum in the experience of hypercapnia and hunger for air. Proc Natl Acad Sci U S A 2001;98:2041–2046
42. Liotti M, Brannan S, Egan G, et al. Brain responses associated with consciousness of breathlessness (air hunger). Proc Natl Acad Sci U S A 2001;98:2035–2040
43. Denton D, Shade R, Zamarippa F, et al. Neuroimaging of genesis and satiation of thirst and an interoceptor-driven theory of origins of primary consciousness. Proc Natl Acad Sci U S A 1999 Apr;96(9):5304–5309
44. Klein DF. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993;50: 306–318
45. Perna G, Caldirola D, Bellodi L. Panic disorder: from respiration to the homeostatic brain. Acta Neuropsychiatr 2004;16:57–67
46. Cohen H, Kotler M, Matar MA, et al. Analysis of heart rate variability in posttraumatic stress disorder patients. Biol Psychiatry 1998;44: 1054–1059
47. Cohen H, Kotler M, Matar MA, et al. Power spectral analysis of heart rate variability in posttraumatic stress disorder patients. Biol Psychiatry 1997;41:627–629
48. Sack M, Hopper JW, Lamprecht F. Low respiratory sinus arrhythmia and prolonged psychophysiological arousal in PTSD: heart rate dynamics and individual differences in arousal regulation. Biol Psychiatry 2004;55: 284–290
49. Hopper JW, Spinazzola J, Simpson WB, et al. Preliminary evidence of parasympathetic influence on basal heart rate in posttraumatic stress disorder. J Psychosom Res 2006 Jan;60(1):83–90
50. Shanks DR, Lovibond PF. Autonomic and eyeblink conditioning are closely related to contingency awareness: reply to Wiens and Ohman (2002) and Manns et al (2002). J Exp Psychol Anim Behav Process 2002 Jan;28(1):38–42
51. Lovibond PF, Shanks DR. The role of awareness in Pavlovian conditioning: empirical evidence and theoretical implications. J Exp Psychol Anim Behav Process 2002 Jan;28(1):3–26
52. Friedman M. Future pharmacotherapy for post-traumatic stress disorder: prevention and treatment. Psychiatr Clin North Am 2002;25:427–441
53. Vaiva G, Ducrocq F, Jezequel K, et al. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. Biol Psychiatry 2003;54:947–949
54. Zatzick DF, Roy-Byrne P. Developing high quality interventions for PTSD in the acute care medical setting. Semin Clin Neuropsychiatry 2003;8:158–167
55. McNally GP, Westbrook RF. Opioid receptors regulate the extinction of Pavlovian fear conditioning. Behav Neurosci 2003 Dec;117(6): 1292–1301
56. 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 Aug;40(8):915–921
57. Prins A, Kaloupek DG, Keane TM. Psychophysiological evidence for autonomic arousal and startle in traumatized adult populations. In: Friedman MJ, Charney DS, Deutch AY, eds. Neurobiological and Clinical Consequences of Stress. Philadelphia, Pa: Lippincott-Raven; 1995:291–314
58. Aziz M, Kenford S. Comparability of telephone and face-to-face interviews in assessing patients with posttraumatic stress disorder. J Psychiatr Pract 2004;10:307–313

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