ELECTROCARDIOGRAM ABNORMALITIES AMONG MEN WITH STRESS-RELATED PSYCHIATRIC DISORDERS: IMPLICATIONS FOR CORONARY HEART DISEASE AND CLINICAL RESEARCH[1,2,3]

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ABSTRACT

Research suggests psychological distress could result in arterial endothelial injury and coronary heart disease (CHD). Studies also show Posttraumatic Stress Disorder (PTSD) victims have higher circulating catecholamines and other sympathoadrenal–neuroendocrine bioactive agents implicated in arterial damage. Here we analyzed resting 12-lead electrocardiographic (ECG) results among a national sample of 4,462 nonhospitalized male veterans (mean age = 38) about 20 years after military service by current posttraumatic stress (n = 54), general anxiety (n = 186), and depression (n = 157) disorders. ECGs were interpreted by board-certified cardiologists and summarized using the Minnesota Code Manual of Electrocardiographic Findings. *Psychiatric disorders were diagnosed based on the* Diagnostic Interview Schedule, *Version III. Controlling for age, place of service, illicit drug use, medication use, race, body mass index, alcohol use, cigarette smoking, and education, PTSD (odds ratio [OR] = 2.23, 95% confidence interval [CI] = 1.17–4.26, $p < 0.05$), anxiety (OR = 1.51, 95% CI = 1.03–2.22, $p < 0.05$), and depression (OR = 1.71, 95% CI = 1.13–2.58, $p < 0.01$) were associated with having a positive ECG finding. Specific results indicate PTSD was associated with atrioventricular (AV) conduction defects (OR = 2.81, 95% CI = 1.03–7.66, $p < 0.05$) and infarctions (OR = 4.44, 95% CI = 1.20–16.43, $p < 0.05$), while depression was associated with arrhythmias (OR = 1.98, 95% CI = 1.22–3.23, $p < 0.01$). The PTSD associations for AV conduction defects and infarctions held, even after controlling for current anxiety and depression. These findings suggest psychological distress may result in CHD, because we controlled for obvious biases and confounders, the men studied had current PTSD due to combat exposures 20 years ago, combat exposure was associated with anxiety and depression among these men, and the men were disease free at military induction. These findings suggest the need for clinical surveillance among combat veterans, better psychobiologic models of CHD pathogenesis, and additional research.*

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INTRODUCTION

Psychological factors often have been implicated in atherosclerosis and coronary heart disease (CHD) (1–5). For example, studies with male macaque monkeys suggest that distress caused by introducing frequent social instability among these animals results in exacerbated coronary atherosclerosis (6). It has been suggested that exposure to environmental stressors induce behavioral neuroendocrine changes that contribute to the atherogenic process (2,3,6,7). In humans, it is thought that CHD develops in response to recurrent sympathoadrenal arousal, which promotes arterial injury via hemodynamic (e.g. turbulence and sheer stress) and metabolic (e.g. platelet aggregation and lipolysis) changes associated with the release of catecholamines (6). Over time, it is thought that plaque rupture and thrombus formation and vasospasm and arrhythmogenesis eventually lead to coronary atherosclerosis due to chronic challenges to the arterial endothelium (6). In addition, administration of beta-adrenergic blocking agents appear to prevent such arterial injury (3,6). Furthermore, at least based on animal studies, repeated sympathoadrenal activity due to repeated stress exposures appears to injure arterial endothelium and initiate atherogenesis, even in the absence of hypercholesterolemia (6).

Although other factors are implicated, evidence suggests that a major pathogenetic mechanism involved with CHD development appears to include activation of the sympathetic–adrenomedullary (SA) and hypothalamic–pituitary–adrenocortical (HPA) axes of the mammalian stress system (8–13). As suggested below, in the case of severe psychological distress, such as those afflicted with posttraumatic stress disorder (PTSD), hyperactivation of the SA and HPA axes appears to result in chronically increased catecholamine and chronically decreased cortisol secretions (8,14). To date, a number of studies with male Vietnam veterans with PTSD have confirmed these alterations (15–20). Since these men were "disease free" at military induction, we thought that study of the development of PTSD and subsequent CHD among these veterans could provide insights on the role of psychological distress in human heart disease. Furthermore, since anxiety and depression also have been implicated in CHD (21–25), and Vietnam-positive veterans tend to have these two disorders concurrent with PTSD (26,27), we also thought it possible to evaluate the impact of these other psychiatric conditions on CHD development as well.

Interestingly, it has been reported that individuals who are predisposed to coronary heart disease often have exaggerated cardiovascular and catecholamine responses to stressful experimen-

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tal conditions (6,28,29). In addition, patients with coronary heart disease have been found to undergo larger pressor reactions to behavioral stressors than do patients without this condition or nonpatient controls (3,6). Furthermore, one study reported that cardiovascular reactivity to psychological distress was predictive of the severity of coronary artery disease among patients referred for coronary angiography (30). In addition, it has been speculated that beta-adrenergic hyperreactivity to psychological distress, principally due to increased epinephrine production, can result in specific inotropic effects that lead to increased contractility and stroke volume, increased systolic blood pressure, increased vasodilator effects, and decreased peripheral vascular resistance—all factors believed to contribute to arterial injury (30).

The association between exposure to severe environmental stressors and the onset of stress-related psychiatric disorders has been documented (26,27,31–36): Exposure to these conditions often is associated with mental distress years after this occurred (37). In some cases, the psychological sequelae of this exposure are severe enough to result in posttraumatic stress disorder (7,15,26,27,36). Furthermore, studies show that the biological alterations found with PTSD appear to differ from those described in more "normative" stress responses (38), and the HPA axis findings in PTSD appear distinct from those reported for other psychiatric conditions (38). For example, findings suggest that, rather than having a consistent pattern of increased adrenocortical activity and resultant dysregulation, individuals with PTSD show evidence of a highly sensitized HPA axis characterized by a decrease in basal cortisol, an increase in lymphocyte glucocorticoid receptors, a greater suppression of cortisol to dexamethasone, and a more sensitized pituitary gland, compared to individuals without PTSD (38–40). In addition, studies of psychophysiologic, electrophysiologic, and neurochemical alterations associated with PTSD repeatedly have revealed similar abnormalities of the sympathetic nervous system and other neuromodulatory systems (15,40). As we note below, in aggregate, the data suggest that those suffering from the long-term effects of PTSD often have altered biological systems that appear to put them at risk for not only CHD, but a spectrum of diseases (7).

Based on evidence linking CHD to stress (21), we hypothesized that veterans with current PTSD, anxiety, and depression should show evidence of CHD for several reasons. First, research indicates that Vietnam veterans with current PTSD had this chiefly due to combat exposures decades ago in Vietnam (15,26,27,33,36). Second, as we suggested, research indicates that PTSD-positive Vietnam veterans have altered SA–HPA stress axes, including higher circulating catecholamines (15–20). Third, in most cases the initial onset of PTSD symptoms for veterans was shortly after return from Vietnam service (15,26,27,36). Fourth, given the above factors, Vietnam veterans with current PTSD would be chronic sufferers of this condition and, consequently, exposed to the long-term effects of sympathoadrenal arousal. Fifth, since anxiety and depression also are associated with CHD (21–25), and these conditions often are clinical sequelae of PTSD (7,26,27,37), these two disorders should be associated with CHD among veterans as well.

MATERIALS AND METHODS

Sample

The subjects for this study were selected from all U.S. Army veterans who served during the Vietnam War (27,33,41–43). Altogether, 48,513 records were randomly selected from 4.9 million U.S. Army records from this period to serve as the primary study sample. From this primary random sample, two groups—"theater" veterans who served in Vietnam (N = 9,078) and "era" veterans (N = 8,789) who did not—were randomly selected among all veterans known not to be deceased and traced. From these two random subsamples, 87% of the theater veterans (7,924/9,078) and 84% of the era veterans (7,364/8,789) were located and interviewed by telephone. Among those interviewed by telephone, two more random subsamples were selected for personal interviews and medical examinations. Altogether, 66% of the theater veterans (2,490/3,745) and 53% of the era veterans (1,972/3,703) participated in the medical examination phase, for an overall exam participation rate of 60% (4,462/7,448). A "nonresponse" analysis indicated that the participation rates did not appear to bias study results, because the reasons for not participating, the demographic characteristics, and the health histories associated with participation were similar in both groups (41). The average time from combat exposure in Vietnam to the study follow-up was 17 years for theater veterans. The average age of first onset of PTSD symptoms was 21 years of age for both veteran groups combined. All psychological testing and the physical exams were administered at one medical facility between June 1985 and September 1986. As described elsewhere, all veterans who participated in the personal interview and medical examination phases of this study provided their consent before taking part in these, after the risks and benefits of study participation were explained (41).

Medical History, Exams, and Electrocardiograms

The examination schedule for the study required 4 days onsite. A standardized medical questionnaire was administered by physician's assistants (PAs). All medical examiners, technicians, and interviewers received comprehensive data collection training and were monitored by a clinic manager and the Centers for Disease Control's staff (41,43). In addition, data forms were reviewed by clerks for accuracy and problems were resolved before the veteran returned home (41,43). Electrocardiograms (ECGs) were obtained during the morning of the physical exam and were administered before the psychiatric examinations (41,43). Participants were told not to drink any caffeine-containing beverages or to smoke for 12 hours before the ECG, but told to continue taking any medications prescribed by their physicians. Trained technicians took standard 12-lead ECGs, using a Marquette Microcomputer Augmented Cardiograph (MAC) II automated ECG machine (Marquette Electronics). Initial ECGs were analyzed by a Marquette computer analysis program and then reconfirmed by board-certified cardiologists, who reviewed all ECG tracings and their computer analyses (41,43). Only physician-confirmed ECG readings are used in this study.

Since there were hundreds of different ECG interpretations collected for this study, we summarized these findings using the *Minnesota Code Manual of Electrocardiographic Findings* (44). The Minnesota code is now the most widely-used ECG coding scheme in the world, and recently has been used in the World Health Organization's "MONICA Project," a myocardial infarction (MI) study conducted in 21 countries and four continents (45). The ECG coding classifications used in our study included indications of ventricular conduction defects, atrioventricular (AV) conduction defects, arrhythmias, ST wave junction/segment abnormalities, infarctions, and ST/T wave abnormalities. We also examined corrected QT intervals (QTc) and developed a category to indicate the presence of any nonspecific positive ECG findings (44). The latter was defined as a case in which ECG findings were *not* classified as normal, otherwise normal, or borderline. (The

detailed ECG categories we used are available from the first author.) As noted, all ECG findings in this study were confirmed by board-certified cardiologists. It also should be realized that a positive finding for any of the first seven ECG classifications mentioned above often generally meant that some degree of pathophysiology was present. For example, based on the Minnesota code we used, veterans were coded as having infarctions only if they had ECG evidence of anterior, lateral, inferior, posterior extention, anteroseptal, anterolateral, or possibly acute infarctions. Likewise, veterans were coded for AV conduction defects if they had ECG evidence of such atrioventricular disturbances as first-degree heart block, second-degree heart block, third-degree heart block (complete), abnormal PR intervals, etc. (44).

Psychiatric Evaluations

Psychiatric evaluations in our study included the *Diagnostic Interview Schedule* (DIS) (46). The DIS is a standardized questionnaire designed to assess the prevalence of psychiatric conditions based on the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition) (DSM-III) (46,47). Studies of the reliability and validity of the main DIS classifications have been published and considered acceptable (48,49). The DIS was administered by psychology technicians under the supervision of licensed clinical psychologists. Both "lifetime" and "current" disorders were assessed in this project. For this article, current PTSD was defined as having ever met the full diagnostic criteria for PTSD in the past month, based on the DIS and DSM-III criteria (36). Only the current PTSD, anxiety, and depression are analyzed in this study. As noted above, in part, we focused on current disorders because the onset of these disorders for most veterans was shortly after military service (15,26,27,36). Hence, those with a current disorder would likely be long-term sufferers of this condition.

Study Control Variables

For this study, 11 covariates were used as control variables, because it was thought that these could bias or confound the ECG results. The demographic variables controlled include current age, income, race, education, and Vietnam service history. Age was based on the veteran's age at time of the interview and was used as a continuous variable, coded in years. Income was based on the total annual household income reported during the interview and was used as a 6-point ordinal scale. Race was based on the veteran's reported race and was categorized as follows: White (82.5%); Black (11.5%); Hispanic (4.3%); and "other" (1.7%). Education was based on total years of formal education at the time of interview and was used as a continuous variable. Vietnam service was a dichotomous variable and indicated whether the veteran served in the Vietnam theater or not. Controlling for income, race, education, and Vietnam service are important, because Vietnam combat veterans are reported to come from lower socioeconomic groups (50), a background factor often found related to poorer states of health (51,52).

In addition to demographic variables, we also controlled for the veteran's alcohol consumption, body mass (Quatelet) index (BMI), current illicit drug use, smoking history, current use of cardiovascular medications, and current use of central nervous system (CNS) medications. Alcohol consumption was based on the number of reported drinks in the past month and was used as a log-transformed continuous variable. Body mass index was used as a continuous variable. Current illicit drug use was based on reported drug usage in the past 12 months and coded as no illicit drugs used in the past 12 months, marijuana only used at least once a week in the past 12 months, or hard drugs (e.g. heroin, barbiturates, amphetamines, cocaine, etc.) used at least once a week in the past 12 months. Current cardiovascular medication use was based on self-report and included cardiac glycoside, antiarrhythmic, antianginal, antihypertensive, vasodilator, and diuretic drugs. Current central nervous system medication use included sedative/hypnotic, antianxiety, antipsychotic, antidepressant, and CNS stimulant drugs and was based on self-report. Smoking history was indicated by pack-years of cigarette smoking, based on the number of years cigarette smoking was reported and the average number of cigarettes usually smoked. This variable was recoded and used as an ordinal-level variable (Coded 0–4), since this indicator was highly skewed. Detailed information on our study's variables and methods have been published and are available elsewhere (7,15,36,41,43).

Statistical Methods

Descriptive and multivariate statistical analyses were performed using SPSS® for Windows™ (Version 7.5) (53) and Stata® (Release 5) (54). Bivariate means and percents are provided for the 11 main control variables by current psychiatric status, with group differences at $p < 0.05$ noted. Unadjusted odds ratios (ORs) and their p-values also are reported for each psychiatric disorder by the eight ECG results noted, based on each respective 2×2 (bivariate) table result. For multivariate analyses, only summary logistic regression ORs are presented, adjusted for the 11 control variables noted, together with 95% confidence intervals and associated p-values.

All logistic regressions were based on maximum likelihood estimation methods (55). SAS® for Windows™ (Version 6) was used to generate the DIS diagnostic categories (56), based on a modified SAS program provided by the Centers for Disease Control (Personal Communication, Centers for Disease Control, 1992). It should be noted that logistic regression is suited for multivariate analysis of binary event data, especially where the outcomes and exposures are relatively rare (55), such as in our study. Furthermore, logistic regressions will fail to calculate if the outcome under study is associated with covariate cell patterns that are too sparse (54). Altogether, 63 cases were missing data for illicit drug use, cigarette smoking, education, BMI, or alcohol consumption and were excluded from multivariate analyses. A total of 86 cases had missing income data; however, we recoded these equal to the median value for income and used these cases in our analyses.

RESULTS

Table 1 shows the profile of the control variables used in this study by veterans' current psychiatric status. This table indicates that men with current PTSD are more likely to have lower incomes, served in Vietnam, used illicit drugs, and to have used central nervous system medications ($p < 0.05$). In comparison, those with anxiety disorders are more likely to have less education, lower incomes, served in Vietnam, consumed more alcohol, used illicit drugs, used central nervous system medications, and to have more pack-years of cigarette exposure ($p < 0.05$). Furthermore, those with current depression are more likely not only to be African–American, younger, less educated, and to have less income, but also to have served in Vietnam, to have consumed more alcohol, and to have used central nervous system medications ($p < 0.05$).

The unadjusted (2×2 table) results for ECG by PTSD status (Table 2A) suggest that current PTSD is associated with having a

TABLE 1
Profile of 11 Control Variables by Current Psychiatric Status

Control Variables	Total		PTSD		Anxiety		Depression	
	% or Mean	(*n*)	No	Yes	No	Yes	No	Yes
% African–American	11.8	(525)	11.7	18.5	11.7	14.0	11.5	19.7*
Mean Examination Age	37.9	(4,462)	37.9	37.9	37.9	38.1	37.9	37.6*
Mean Years of Education	13.4	(4,460)	13.4	13.6	13.4	13.0*	13.4	13.0*
% $20,000 or < Income/Year	27.9	(1,244)	27.5	59.3*	27.4	39.8*	27.0	52.9*
% Vietnam Service	55.8	(2,490)	55.3	100.0*	55.4	66.1*	55.2	71.3*
Mean Drinks per Month	38.7	(4,434)	38.7	48.3	38.0	64.8*	38.3	61.0*
Mean Body Mass Index	27.0	(4,461)	27.0	27.5	27.0	27.7	27.0	27.1
% Current Illicit Drug Use	11.9	(530)	11.7	28.3*	11.6	19.4*	11.6	21.2
% Cardiovascular Drugs	5.2	(233)	5.2	3.7	5.2	6.5	5.2	5.1
% Central Nervous System Drugs	3.5	(157)	3.3	20.4*	3.1	12.9*	2.9	21.7*
Mean Cigarette Pack Years	15.3	(4,449)	15.3	15.5	15.1	20.2*	15.2	17.0
(*n* =)	—	(4,462)	(4,408)	(54)	(4,276)	(186)	(4,305)	(157)

* Indicates statistically significant difference for control variable by current psychiatric disorder ($p < 0.05$).

current nonspecific ECG abnormality (OR = 2.22, $p < 0.05$), AV conduction defects (OR = 3.01, $p < 0.05$), and infarctions (OR = 5.34, $p < 0.05$). The unadjusted results for ECG by current anxiety disorder status (Table 2B) reveal that having this diagnosis is associated with having at least one nonspecific current ECG abnormality (OR = 1.65, $p < 0.01$), as well as a ST/T wave abnormality (OR = 1.77, $p < 0.05$). Results for current depression (Table 2C) indicate that this is associated with having a current nonspecific ECG abnormality (OR = 1.86, $p < 0.01$), as well as arrhythmias (OR = 1.89, $p < 0.01$).

Although sometimes slightly decreased or slightly increased in comparison to the unadjusted results, the ORs for the adjusted results were generally similar (Tables 2A–2C). For example, PTSD is still associated with having a current nonspecific ECG abnormality (OR = 2.23, $p < 0.05$), AV conduction defects (OR = 2.81, $p < 0.05$), and infarctions (OR = 4.44, $p < 0.05$). The adjusted results for abnormal ECGs by current anxiety disorder status reveal that having this disorder still is associated with having a current nonspecific ECG abnormality (OR = 1.51, $p < 0.05$). Adjusted results for current depression indicate that this condition still is associated with having a current nonspecific ECG abnormality (OR = 1.71, $p < 0.01$) and arrhythmias (OR = 1.98, $p < 0.01$).

The association between cigarette smoking and mental illness has been well-established (57). Clearly, this variable could be a confounder in this situation: Veterans with stress-related psychiatric disorders may smoke more often and have a higher prevalence of heart disease because of this behavioral risk factor, not because of the neuroendocrine pathway discussed (57). Because of this, we eliminated this variable from our multivariate models and compared the results. Our findings were essentially the same, however. For example, the adjusted ORs for PTSD without controlling for smoking history were 2.25 (versus 2.23) for a nonspecific ECG finding, 2.80 (versus 2.81) for an AV conduction defect, and 4.38 (versus 4.44) for infarction. Without smoking history, the adjusted OR for anxiety and a nonspecific ECG finding was 1.50 (versus 1.51). The adjusted ORs for depression without smoking history were 1.71 (versus 1.71) for a nonspecific ECG finding and 1.96 (versus 1.98) for arrhythmia.

Finally, as we noted, among Vietnam veterans PTSD often is associated with anxiety and depression disorders, both of which also have been associated with CHD in some studies. For example, in our study, 44% of veterans with current PTSD also had current anxiety and 56% with current PTSD also had current depression. In an effort to determine if PTSD was associated with our original ECG findings independent of current anxiety and depression, we controlled for these latter disorders and then reexamined our results for PTSD. These indicated that while the results for positive nonspecific ECG findings now were no longer statistically significant (OR = 1.75, $p > 0.10$), those for infarction increased somewhat (OR = 6.14, $p < 0.05$), while those for AV conduction defect remained about the same (OR = 3.19, $p < 0.05$).

DISCUSSION

Controlling for selection bias and confounding, veterans with current PTSD, depression, or current anxiety appear to have a higher occurrence of at least one or more positive ECG findings. Specific findings indicate veterans with current PTSD show ECG evidence of AV conduction defects and infarctions, while those with current depression show evidence of arrhythmias. As was suggested, the associations between infarctions and AV conduction defects and PTSD held, even after controlling for both anxiety and depression and also were not related to smoking history. It should be noted that an AV conduction defect suggests a delay or failure of conduction of electrical impulses from the atria to the ventricles. In addition, ECG evidence of infarction suggests injured regions of the heart and necrosis, indicating a past heart attack. ECG evidence of arrhythmias suggests heart rhythm disorders of the sinus node and electrical conduction through the heart and can be affected by diseases of the heart muscle, a disordered metabolism, or the effects of certain drugs, such as the ones we controlled here. In summary, we conclude that our findings suggest an association between long-term exposure to severe psychological distress and ECG findings that are physiological markers for coronary heart disease.

Interpreting these findings, we think, requires the recognition of several factors. First, although the sympathoadrenal–neuroendocrine model discussed here was premised on a biological framework, it has wider conceptual implications because the effectors involved also evoke emotional and cognitive states (58–60). For example, there is ample evidence that severe environmental stressors function as "unconditioned" aversive psychological stimuli capable of evoking severe psychophysiological distress in most individuals (58–60). Consequently, neutral stimuli that accompanied these environmental stressors often can function as "conditioned" stimuli capable of producing psychological distress when the original stressors are no longer present (58–60). Further-

TABLE 2A

Electrocardiographic Abnormalities by Current Psychiatric Status

Abnormal ECG Results*	Total Population (N = 4,462) No.	%	Total with PTSD in Past Month (n = 54) No.	%	Unadjusted O.R.	p-Value	Adjusted** O.R.	p-Value	Adjusted OR (95% CI)
Any ECG Abnormality	648	14.5	15	27.8	2.22	<0.05	2.23	<0.05	(1.17–4.26)
Ventricular Conduction Defect	142	3.2	3	5.6	1.81	NS	2.04	NS	(0.61–6.87)
AV Conduction Defect	147	3.3	5	9.3	3.01	<0.05	2.81	<0.05	(1.03–7.66)
Arrhythmias	381	8.5	8	14.8	1.88	NS	1.94	NS	(0.88–4.30)
ST Wave Junction/Segment Abnormality	49	1.1	1	1.9	1.71	NS	1.67	NS	(0.20–14.18)
Infarction	51	1.1	3	5.6	5.34	<0.05	4.44	<0.05	(1.20–16.43)
ST/T Wave Abnormality	247	5.5	5	9.3	1.76	NS	1.56	NS	(0.53–4.57)
QTc (ms)	13	0.3	0	0.0	***	***	***	***	***

* ECG classifications based on *The Minnesota Code Manual of Electrocardiographic Findings* (44).

** All results are adjusted for race, age, education, income, place of military service, alcohol consumption in the past month, body mass index, current illicit drug use, current use of cardiovascular drugs, pack-years of cigarette smoking, and current use of central nervous system drugs using logistic regression.

*** Could not calculate ORs because of missing data. OR = Odds Ratio; CI = Confidence Interval; ECG = Electrocardiogram.

TABLE 2B

Electrocardiographic Abnormalities by Current Psychiatric Status

Abnormal ECG Results*	Total Population (N = 4,462) No.	%	Total with Anxiety Disorder in Past Month (n = 186) No.	%	Unadjusted O.R.	p-Value	Adjusted** O.R.	p-Value	Adjusted OR (95% CI)
Any ECG Abnormality	648	14.5	40	21.5	1.65	<0.01	1.51	<0.05	(1.03–2.22)
Ventricular Conduction Defect	142	3.2	6	3.2	1.02	NS	0.99	NS	(0.42–2.30)
AV Conduction Defect	147	3.3	7	3.8	1.16	NS	1.02	NS	(0.46–2.27)
Arrhythmias	381	8.5	20	10.8	1.31	NS	1.41	NS	(0.86–2.33)
ST Wave Junction/Segment Abnormality	49	1.1	2	1.1	0.98	NS	1.04	NS	(0.24–4.48)
Infarction	51	1.1	4	2.2	1.98	NS	1.48	NS	(0.51–4.30)
ST/T Wave Abnormality	247	5.5	17	9.1	1.77	<0.05	1.41	NS	(0.79–2.53)
QTc (ms)	13	0.3	1	0.5	1.92	NS	1.60	NS	(0.19–13.36)

* ECG classifications based on *The Minnesota Code Manual of Electrocardiographic Findings* (44).

** All results are adjusted for race, age, education, income, place of military service, alcohol consumption in the past month, body mass index, current illicit drug use, current use of cardiovascular drugs, pack-years of cigarette smoking, and current use of central nervous system drugs using logistic regression.

OR = Odds Ratio; CI = Confidence Interval; ECG = Electrocardiogram.

TABLE 2C

Electrocardiographic Abnormalities by Current Psychiatric Status

Abnormal ECG Results*	Total Population (N = 4,462) No.	%	Total with Depression Disorder in Past Month (n = 157) No.	%	Unadjusted O.R.	p-Value	Adjusted** O.R.	p-Value	Adjusted OR (95% CI)
Any ECG Abnormality	648	14.5	37	23.6	1.86	<0.01	1.71	<0.01	(1.13–2.58)
Ventricular Conduction Defect	142	3.2	7	4.5	1.44	NS	1.56	NS	(0.70–3.50)
AV Conduction Defect	147	3.3	6	3.8	1.17	NS	0.95	NS	(0.40–2.29)
Arrhythmias	381	8.5	23	14.6	1.89	<0.01	1.98	<0.01	(1.22–3.23)
ST Wave Junction/Segment Abnormality	49	1.1	2	1.3	1.17	NS	1.00	NS	(0.23–4.41)
Infarction	51	1.1	2	1.3	1.12	NS	0.78	NS	(0.18–3.46)
ST/T Wave Abnormality	247	5.5	13	8.3	1.57	NS	1.17	NS	(0.60–2.28)
QTc (ms)	13	0.3	0	0.0	***	***	***	***	***

* ECG classifications based on *The Minnesota Code Manual of Electrocardiographic Findings* (44).

** All results are adjusted for race, age, education, income, place of military service, alcohol consumption in the past month, body mass index, current illicit drug use, current use of cardiovascular drugs, pack-years of cigarette smoking, and current use of central nervous system drugs using logistic regression.

*** Could not calculate ORs because of missing data. OR = Odds Ratio; CI = Confidence Interval; ECG = Electrocardiogram.

more, it is known that some higher-order cognitive outcomes, such as emotional distress, can activate lower-order neurological states, via the sympathoadrenal system and, hence, amplify the pathogenetic effects of psychological distress (12,15,59,60). This "negative feedback loop" is thought responsible for the development of secondary mental disorders associated with PTSD, particularly anxiety and phobic disorders (15,27). These complex psychobiological interactions clearly complicate assessing the effects of stress exposures on disease outcomes, but provide a basic psychophysiological mechanism to explain the persistence and the long-term consequences of sympathoadrenal–neuroendocrine system arousal associated with severe stress. Second, combat exposure in Vietnam appears to be the principal reason for the prevalence of current posttraumatic stress, anxiety, and depression disorders among these men (26,27). Third, because the average age of PTSD symptom onset was 21.2 years of age among our subjects, it is unlikely that heart disease preceded PTSD in this situation, since these men were found disease-free at military induction a few years earlier. Given the above three factors, we believe that our results should not be confounded by the fact that the onset of cardiovascular disease could have caused some psychiatric disorders (57).

We recently reported that PTSD-positive Vietnam theater veterans were more likely to have higher white blood, total lymphocyte, T-cell, and CD4 cell counts (61), which was expected since studies indicate PTSD-positive veterans have lower plasma cortisol, an immunosuppressant (15). These immunologic findings are important, because mononuclear leukocytes and endothelial-dependent mechanisms have been implicated in a broad spectrum of diseases, ranging from atherosclerosis to rheumatoid arthritis (62). Thus, it is believed that the chronic disease outcomes associated with PTSD could be wide-ranging (7), especially since PTSD is associated with other psychiatric disorders, such as anxiety and depression (37), which could further accelerate the disease process, as we have alluded.

This study has some limitations. First, this is an observational study. Thus, it is possible that the associations reported could have been related to a third uncontrolled variable. For example, although there is anecdotal evidence to the contrary, it is possible that combat soldiers had greater exposure to toxic chemicals, diseases, and drug abuse in comparison to noncombat soldiers in the rear-area base camps or in other theaters of operations. As a consequence, PTSD-positive veterans could have a higher prevalence of CHD after their military service. Second, it has been suggested that those with mental disorders are less likely to be physically active and to take care of their physical health (57). As a consequence of poor self-care behaviors, then, veterans with mental disorders could be at greater risk for heart disease, but not because of alterations in stress-related neuroendocrine functions, as we hypothesized. To control for this factor, we adjusted our data for body mass index, current education, and current income, with the knowledge that previous research suggested that neither combat exposure nor PTSD was associated with Vietnam veterans' current socioeconomic status (63). Furthermore, our previous research has shown that neither history of alcohol nor drug abuse could account for the prevalence of reported circulatory diseases among these men after military service (7). In addition, as noted above, the AV conduction defect and infarction results for PTSD were still significant after controlling for current anxiety and depression disorders. Third, the overall response rate for this study was 60%. This could have biased our study's findings, although an analysis conducted by Centers for Disease Control (CDC) investigators failed to detect this bias (41). Fourth, since our study included only men, our findings may not be applicable to women. Fifth, controlling for cardiovascular medications may have overadjusted our results, because some men using these medications likely had CHD. Sixth, as noted, some investigators have suggested that the onset of heart disease could have caused the onset of psychiatric disorders (57). We think that the existing evidence cited, plus the fact we controlled for anxiety and depression, helps rule out this "reverse causation" hypothesis, however.

It is believed that, in spite of the limitations noted, the findings reported are significant for several reasons. First, this is one of the few studies that has examined the association between the presence of long-term stress disorders and 12-lead ECG results among a large national sample of at-risk, middle-aged men. Second, these findings are consistent with a growing body of scientific literature related to environmental stress exposures and cardiovascular disease development (1,6,21,51). Third, there is interest among researchers in understanding the mechanisms by which psychosocial factors exacerbate illness, lower resistance, and cause disease (10,11,64). This research suggests a link between severe stress exposures and CHD: Those with current PTSD, as well as depression, show ECG evidence of cardiac arrhythmias, AV conduction defects, and infarctions. Since, as noted, we know that the majority of men studied developed PTSD due to combat exposures in Vietnam (15), we may conclude that exposure to this stressor is likely associated with CHD, although other risk factors also could be involved (65,66).

Overall, we think the results reported are significant, given the average age of the participants noted and the fact we only used resting 12-lead ECG findings—knowing that the latter would clearly underdiagnose CHD (67). Given that about 30% of male Vietnam veterans were found to develop PTSD after Vietnam service (26), the cardiovascular implications for this population could be great and deserves clinical surveillance, especially given the increasing age of these veterans and the association between PTSD and the history of infarction we found (OR = 4.44, 95% CI = 1.20–16.43, $p < 0.05$). Finally, we think our findings also should apply to other occupational groups traditionally exposed to severe environmental stressors too (34), especially if other traditional risk factors also are present (21).

These findings need to be replicated and expanded to further validate this study and to better specify key causal linkages. In particular, we think that better knowledge of the mammalian fear response and human fear conditioning at the biological, physiological, and psychological levels will aid in this endeavor (7,15,58–60). In addition, more research is needed to unravel the role of anxiety and depression in CHD development among those with a history of PTSD. It should be noted that despite major modern developments in cardiovascular medicine, fully half of all patients with CHD appear to have no known risk factors (68). We think that our research suggests the need to further investigate the psychobiological basis of this disease in future studies.

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