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Association between Symptoms of Depression and Anxiety with Heart Rate Variability in Patients with Implantable Cardioverter Defibrillators

Jennifer L. Francis, PhD[a], **Ali A. Weinstein, PhD**[a,b], **David S. Krantz, PhD**[a], **Mark C. Haigney, MD**[c], **Phyllis K. Stein, PhD**[d], **Peter H. Stone, MD**[e], **John S. Gottdiener, MD**[f], and **Willem J. Kop, PhD**[f]

[a]Department Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, Bethesda, MD

[b]Center for the Study of Chronic Illness and Disability, George Mason University

[c]Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD

[d]Heart Rate Variability Laboratory, Washington University School of Medicine, St. Louis, MO

[e]Department of Medicine, Brigham and Women's Hospital, Harvard University, Boston, MA

[f]Department of Medicine, University of Maryland Medical Center, Baltimore, MD

Abstract

Objective—Depression and anxiety are associated with autonomic nervous system dysfunction, which may promote the risk of malignant cardiac arrhythmias. This study investigates whether depression and anxiety symptoms are associated with measures of autonomic nervous system dysfunction in patients with implantable cardioverter defibrillators who are at high risk of cardiac rhythm disturbances.

Methods—Patients with an implantable cardioverter defibrillator (ICD) underwent ambulatory electrocardiographic monitoring (n=44, mean age 62.1 ± 9.3 yrs). Depression was assessed using the Beck Depression Inventory and anxiety using the Taylor Manifest Anxiety Scale. Heart rate variability (HRV) was assessed using time (RMSSD, pNN50 and SDNN) and frequency domain measures derived from 24 hour R-R intervals. Multivariate models were adjusted for age, sex, hypertension, diabetes and smoking status.

Results—Defibrillator patients with elevated depression symptoms (n=12) had significantly lower RMSSD (15.25 ± 1.66 ms, vs. 24.97 ± 2.44, p = 0.002) and pNN50 (1.83 ± 0.77 vs. 5.61 ± 1.04, p = 0.006) than defibrillator patients with low depression symptoms (n=32). These associations remained significant after multivariate adjustment for covariates. ICD patients with high anxiety levels (n=10) displayed lower RMSSD (p = 0.013), which became marginally significant when adjusting for covariates (p = 0.069).

Conclusion—Depression and anxiety in defibrillator patients are associated with autonomic nervous system dysfunction indices of reduced parasympathetic control. Autonomic nervous system

Corresponding author: Willem J. Kop, Ph.D., Division of Cardiology, University of Maryland Medical Center, 22 South Greene Street – S3B04, Baltimore, MD 21201. wkop@medicine.umaryland.edu, Phone: 410-328-2063, Fax: 410-328-3530.

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dysfunction may partially explain the association between depression and anxiety with life-threatening cardiac outcomes in vulnerable patients.

Keywords

depression; anxiety; autonomic nervous system; heart rate variability; implantable cardioverter defibrillator

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Epidemiological and clinical research has documented that depression and anxiety are associated with increased risk of coronary artery disease and sudden cardiac death [1–3]. Biobehavioral pathways involved in the increased cardiovascular risk associated with depression have been studied extensively [4], and evidence about mechanisms accounting for the elevated cardiovascular risk associated with anxiety is accumulating [5, 6]. Depression and anxiety are common in patients with implantable cardioverter defibrillators (ICD) [7–11]. Anxiety in ICD patients is associated with impaired quality of life [12, 13] and reduced treatment satisfaction [14], increased pain perception of ICD shocks [15], and possibly with increased risk of ICD discharges [16, 17]. Psychological characteristics, such as depression and anger, predict ventricular arrhythmia in ICD patients [17, 18]. Autonomic nervous system dysfunction is a plausible common pathway involved in the association between psychological factors and adverse cardiovascular events [19, 20]. The present study investigates whether depression and anxiety are associated with altered autonomic nervous system control in coronary artery disease patients with implantable cardioverter defibrillators, who are at high risk of developing malignant cardiac arrhythmias.

Autonomic nervous system dysregulation plays an important role in arrhythmias [21]. Heart rate variability (HRV) analysis provides non-invasive markers of autonomic activity [22] and reduced HRV predicts arrhythmia and mortality in post-myocardial infarction patients [23, 24] and malignant arrhythmia in patients with implantable cardioverter defibrillators [25]. Depression is associated with reduced HRV in patients with cardiovascular disease [19, 26] and in healthy populations [27–30], although negative findings have also been reported [31, 32]. Anxiety disorders such as panic disorder [33] and post-traumatic stress disorder [34] have also been associated with reduced HRV, in addition to trait anxiety [35], phobic anxiety symptoms [36], and worry [37]. In contrast to research on depression, very few studies have examined HRV and anxiety in patients with cardiovascular disease [38]. Ambulatory ECG monitoring enables investigation of the relationships between psychosocial measures and autonomic nervous system dysfunction in naturalistic conditions. The present study investigates the hypothesis that elevated depression and anxiety levels are related to reduced HRV in defibrillator patients.

METHODS

Participants

Patients with implantable cardioverter defibrillators with documented coronary artery disease (n = 44) were recruited from three clinics in northeastern USA (Arrhythmia Associates, Fairfax, VA; the Veterans Affairs Medical Center, Washington DC, and St. Francis Hospital, Roslyn, NY) between 1998 and 2004. Exclusion criteria for patients were: atrioventricular conduction defects, left bundle-branch block, chronic atrial fibrillation, myocardial infarction < 1 month, unstable angina, class IV heart failure, critical valve pathology, primary cardiomyopathy, use of amiodarone, and age > 80 years. To optimize electrocardiographic assessments beta-adrenergic blocking agents were withheld for ≥ 48 hours when clinically safe. The study was approved by the participating institutional review boards, and all patients gave written informed consent. Power analyses indicate that the present sample of 44 participants is sufficient for the detection of a correlation coefficient of r = 0.40 and a moderate effect size difference ($\Delta = V^2 / \sigma^2$) = 0.19) between individuals with high versus low levels of psychological variables.

Demographic and clinical information included age, sex, race, cardiovascular disease risk factors (body mass index (BMI), smoking status, hypertension, diabetes mellitus), cardiac history (myocardial infarction, coronary artery bypass surgery, left ventricular ejection fraction), and ICD characteristics (reason for implantation, duration since device implantation, number of discharges since implantation).

Psychological Measures

Depression—Symptoms of depression were assessed using the original version of the Beck Depression Inventory (BDI) [39, 40]. The BDI has been used in a wide range of patients with cardiovascular disorders to assess symptoms of depression [41]. Scores range from 0 – 63 with higher scores indicating increased depression severity, with scores ≥10 indicative of the possible presence of depression based on previous validation studies [41, 42].

Anxiety—The Taylor Manifest Anxiety Scale (20 item version) was administered to assess trait anxiety symptoms [43]. The Manifest Anxiety Scale is a true-false questionnaire derived from the Minnesota Multiphasic Personality Inventory and includes items such as "I am a high-strung person" and "I work under a great deal of tension". Scores range from 0–20 with higher scores indicating increased anxiety. For the purposes of this study, the clinical cut-point for elevated anxiety levels was set at ≥ 9, as reported previously [44].

HRV analysis

Patients were monitored for 48 hours using a three-channel electrocardiographic recorder. Analogue signals were digitized at a sampling rate of 1000 Hz (Marquette Medical Systems). Heart rate was continuously assessed over the course of the 48 hour period. HRV was assessed using the General Electric Medical System MARS Personal Computer Workstation with standard electrocardiographic analysis to accurately label ectopic beats and artifact. Tapes were analyzed by trained reviewers who were blinded to clinical and psychological data. If patients had > 20% missing data because of ectopy or artifacts, then they were excluded from analyses. Two patients were excluded from analyses because of excess supraventricular ectopy.

Time domain indices—Time domain indices of HRV included the following measures: the root mean square successive difference of RR intervals (RMSSD), in milliseconds (ms), the percent of successive RR interval differences > 50 ms (pNN50), in percent, and the standard deviation of RR intervals (SDNN) in ms [45]. RMSSD and pNN50 primarily reflect parasympathetic influence on the heart and the SDNN reflects all sources of variability in heart rate [45].

Frequency domain indices—Fast Fourier Transformation was used to determine HRV components in the following frequency bands: high frequency (HF; 0.15 – 0.40 Hz, in $ln.ms^2$) and low frequency (LF; 0.04 – 0.15 Hz, in $ln.ms^2$). High frequency HRV primarily reflects parasympathetic modulation of heart rate, whereas LF-HRV reflects both sympathetic and parasympathetic modulation of heart rate [45]. The ratio of low frequency to high frequency power was also examined (LF/HF) as an index of sympathovagal balance [45], although this index is associated with some validity concerns [22].

Patients were monitored for 48 hours and HRV was assessed for each of the two consecutive 24-hour observation periods. HRV analyses were based on the minimum value of the two 24-hour periods. Consistent with prior studies [46] correlations between the two days of assessment were high (r-values ranging from 0.59 to 0.92) and no differences in the mean HRV indices over the two days of observation were observed (p-values > 0.10).

Statistical Analysis

Clinical and demographic data are presented as mean ± standard deviation or percentages and HRV data as mean ± standard error of the mean. Comparisons among defibrillator patients were conducted using *t*-tests or χ^2 test as appropriate. Logarithmic transformations were applied to frequency domain HRV data to obtain normal distributions. Associations between depression and anxiety with HRV outcome measures were examined using dichotomized and continuous questionnaire scores. T-tests were used to examine differences between patients with elevated levels of depression symptoms versus patients with low depression levels. Variances were pooled only when equality of variance could be assumed based on Levene's test of equality. Analyses of covariance were used to adjust for potentially confounding factors (age, sex, hypertension, diabetes mellitus, and smoking status). Analyses for elevated versus low anxiety levels were conducted in the same manner. Associations of continuous depression and anxiety symptoms with HRV indices were examined using Pearson product-moment correlation coefficients and multivariate regression analysis. Two-tailed probabilities were examined and because 5 HRV measures were examined, the Bonferroni-corrected alpha level was set at 0.05 / 5 = 0.01.

RESULTS

Participants

Demographic and clinical characteristics are presented in the left data column of Table 1. Twelve (27.3%) patients had Beck Depression Inventory scores indicative of elevated depression (≥ 10) and 10 patients (22.7%) had Manifest Anxiety Scores suggesting elevated anxiety levels (≥ 9).

Patients with low versus elevated depression levels did not significantly differ on demographic or clinical measures, including cardiovascular risk factors, cardiac disease markers, and ICD characteristics (Table 1). Table 2 displays group comparisons related to the presence or absence of anxiety. Anxiety was associated with a history of sudden death reanimation (p = 0.033) and higher left ventricular ejection fraction (p = 0.029).

Table 3 displays the interrelationships between the HRV indices, documenting significant interrelationships consistent with the parasympathetic component of these indices. Mean HRV data for this sample were as follows: RMSSD 22.2 ± 12.4 ms, pNN50 = 4.5 ± 5.3 %, SDNN = 102.9 ± 32.7 ms, HF = 4.1 ± 0.9 ln.ms^2, LF = 5.2 ± 1.1 ln.ms^2, and LF/HF 1.3 ± 0.2.

Depression and HRV in defibrillator patients

Associations between depression and HRV indices are shown in Table 4. Patients with elevated depression levels (i.e., BDI score ≥ 10; n= 12) had significantly lower RMSSD (p = 0.002) and pNN50 (0.006) than patients with low depression levels (n = 32). No associations were found between depression status and SDNN. When adjusting for age, sex, hypertension, diabetes and current smoking status, the associations remained significant (RMSSD p = 0.047, PNN50 p = 0.040). Continuous depression scores were also correlated with decreased RMSSD (r = −0.31, p = 0.049, covariate adjusted p = 0.065) and similar associations were found for pNN50 (r = −0.29, p = 0.064, covariate adjusted p = 0.037),

HF-HRV tended to be lower in patients with elevated depression symptoms compared to patients with low levels of depressive symptoms (3.7 ± 0.7 ln.ms^2 vs. 4.4 ± 1.0 ln.ms^2; p = 0.087). LF-HRV did not differ between patients with versus without elevated depression (5.1 ± 1.0 ln.ms^2 vs. 5.3 ± 1.2 ln.ms^2; p = 0.62), and the LF/HF ratio was marginally higher in ICD patients with elevated depression levels (p = 0.061). Continuous depression levels were not associated with HF-HRV or LF-HRV (r = −0.14 and r = −0.31, respectively, p-values > 0.20).

Anxiety and HRV indices

As shown in Table 5, elevated anxiety was associated with lower RMSSD ($p = 0.013$). Adjusting for covariates attenuated the significance of this relationship (adjusted $p = 0.069$). Results were not significant for pNN50 ($p = 0.19$) and there were no differences in frequency domain indices between the high versus low anxiety groups (p-values > 0.5). The associations of continuous anxiety scores with HRV were in the expected direction but did not reach statistical significance (r-values > − 0.22, p-values > 0.2).

Combined Effects of Depression and Anxiety

Depression and anxiety levels were significantly correlated ($r = 0.49$, $p < 0.001$). When examining depression and anxiety scores simultaneously as continuous variables using multivariate regression analyses, it was found that depression was more strongly associated with RMSSD (beta = −0.33, $p = 0.071$) then anxiety (beta = 0.03, $p = 0.80$). Data for PNN50 revealed a similar pattern (beta depression = −0.32, $p = 0.077$; beta anxiety = 0.03, $p = 0.86$).

Exploratory analyses were conducted examining the combined effect of depression and anxiety on HRV indices that displayed associations. Six patients displayed elevated depression levels combined with elevated anxiety levels (≥10 on Beck Depression Inventory and ≥ 9 on the Manifest Anxiety Scale), 6 patients had elevated depression and low anxiety, 4 had elevated anxiety and low depression levels, and 28 had low scores on both depression and anxiety scales. Patients with combined elevated depression and anxiety had significantly lower RMSSD ($p < 0.001$) compared to those with low depression and low anxiety (Figure 1). The ANOVA analyses for linear trend across the 4 groups was also significant ($p = 0.047$). Results for pNN50 showed the same pattern (group comparison $p < 0.001$, p trend = 0.042). None of the other subgroup comparisons were significant and differences in SDNN or frequency domain variables were also not significant. Levels of depression in the combined high depression and high anxiety subgroup (12.5 ± 4.6) were not significantly higher than depression levels in the group with elevated depression and low anxiety levels (BDI = 12.2 ± 2.6). The effects of depression and anxiety on RMSSD and PNN50 were additive, and the depression by anxiety interactions on HRV indices were not significant (p-values > 0.20).

DISCUSSION

This study demonstrates that elevated levels of depression and anxiety are related to HRV-based indices of autonomic nervous system dysfunction in patients with implantable cardioverter defibrillators. A shift towards increased sympathetic and reduced parasympathetic nervous system activity may provide a pathophysiological mechanism accounting for the elevated arrhythmic risk in patients with psychological factors associated with elevated cardiovascular risk.

The association between psychological factors and HRV has not previously been examined in patients with high risk of malignant arrhythmias. Associations between depression and HRV tended to be stronger than associations between anxiety and HRV measures. Data analyses based on categorical data identifying relatively high levels of depression and anxiety versus low levels using previously published cut-off values revealed stronger associations with HRV then analyses examining depression and anxiety as continuous variables. These results suggest that psychosocial factors may adversely affect autonomic function only at levels above a certain critical threshold. Further research is needed to examine whether a formal clinical diagnosis of Major Depressive Disorder or specific anxiety disorders better identify cardiac patients at high risk of abnormal autonomic control.

Depression and anxiety often occur in the same patient and exploratory analyses indicate that the combination of high depression with high anxiety was associated with the most pronounced parasympathetic withdrawal as measured by the RMSSD and pNN50 indices. Reduced HRV in the group with elevated levels of both depression and anxiety levels was not merely a function of more severe depression symptoms because depression levels were not higher between the elevated depression subgroups with versus without elevated anxiety levels. These results raise the possibility that anxiety may exacerbate the relationship between depression and reduced HRV. Consistent with these findings are observations in physically healthy depressed individuals, documenting low vagal control during laboratory conditions in the subset of individuals with high state anxiety [35]. Furthermore, some evidence suggests that high anxiety and not depression is associated with reduced vagal control among post myocardial infarction patients [47]. Symptomatic heterogeneity of HRV within depression [48] and evidence that worry episodes are associated with decreased HRV [49] indicates that attention to individual symptom profiles rather than diagnostic categories may be important. Additional research examining depression and anxiety symptoms is necessary to establish the neurobehavioral mechanisms that integrate central and autonomic nervous system activity.

Clinical variables were not strongly predictive of depression or anxiety. Some support was found for an association between the precipitating circumstances leading to ICD implantation (i.e., sudden death reanimation) with trait anxiety. Other studies have found that increased psychological distress in ICD patients occurs in response to defibrillator shocks [52]53 which was not confirmed in the present study. Somatic symptoms of depression (e.g., fatigue) and anxiety (e.g., palpitations) may occur more frequently in defibrillator patients, and the present data may in part reflect cardiac symptom severity. However, indices of cardiac disease severity such as history of bypass surgery or history of myocardial infarction were not related to psychological measures, and anxiety was unexpectedly associated with better cardiac pump function. Current guidelines for the assessment of depression in patients with cardiac disease indicate that somatic depressive symptoms need to be included in the diagnosis of depression in cardiac patients [54], which is consistent with the present findings suggesting that underlying cardiac disease severity is not likely to be a primary explanatory factor of depression and anxiety in ICD patients.

Time domain HRV measures showed stronger associations with psychological measures than frequency domain measures. One explanation is that time domain assessments collected over several hours are less vulnerable to ECG artifacts and ectopy than frequency domain measures, despite the exclusion of these episodes from the HRV analyses. Breathing frequency may also have affected the results, and some evidence indicates that time domain HRV indices (RMSSD) are less influenced by breathing than frequency domain measures (HF-HRV) [50]. It is also possible that frequency domain measures are better tools to document short-term (< 10 min) HRV changes than sustained (8 > hours) markers of autonomic dysfunction. We have previously documented such short-term frequency domain HRV changes precede ambulatory ischemia with mental stress during daily life [51]. Future studies may investigate HRV changes to acute psychological challenges during daily life using ambulatory monitoring techniques in ICD patients.

The study has limitations that merit discussion. The present findings are based on cross-sectional analyses in a relatively small sample, thus limiting causal inference. Beta-adrenergic blocking agents were used by 61% of the patients which may have increased the HRV measures [55]. This is not a likely explanation because no significant differences in HRV were found between ICD patients taking beta blocking agents versus those who were not on such medications (p-values > 0.2). Prospective examination of psychological factors and HRV in larger samples including a broader range of cardiac patients would be beneficial to precisely determine the magnitude and time-trajectories of depression and anxiety as related to

autonomic nervous system indices while adjusting for potentially confounding factors such as cardiac symptom severity and other clinical characteristics.

Psychological characteristics, such as depression and anger, predict ventricular arrhythmia in general coronary artery disease populations and defibrillator patients [17, 18]. The present data suggest that assessment of multiple psychological risk factors may improve risk stratification of cardiac patients. This is particularly important in defibrillator patients where high levels of distress are common after implantation and can act as triggers of arrhythmias resulting in device discharges that pose recurrent transient risks [56]. The levels of depression and anxiety were relatively low in the present study, and associations with autonomic dysfunction are expected to be even stronger in patients with clinical major depressive disorder and those with anxiety disorders such as panic attacks and post-traumatic stress disorder.

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Abbreviations

ICD	implantable cardioverter defibrillators
HRV	heart rate variability
BDI	Beck Depression Inventory
BMI	body mass index

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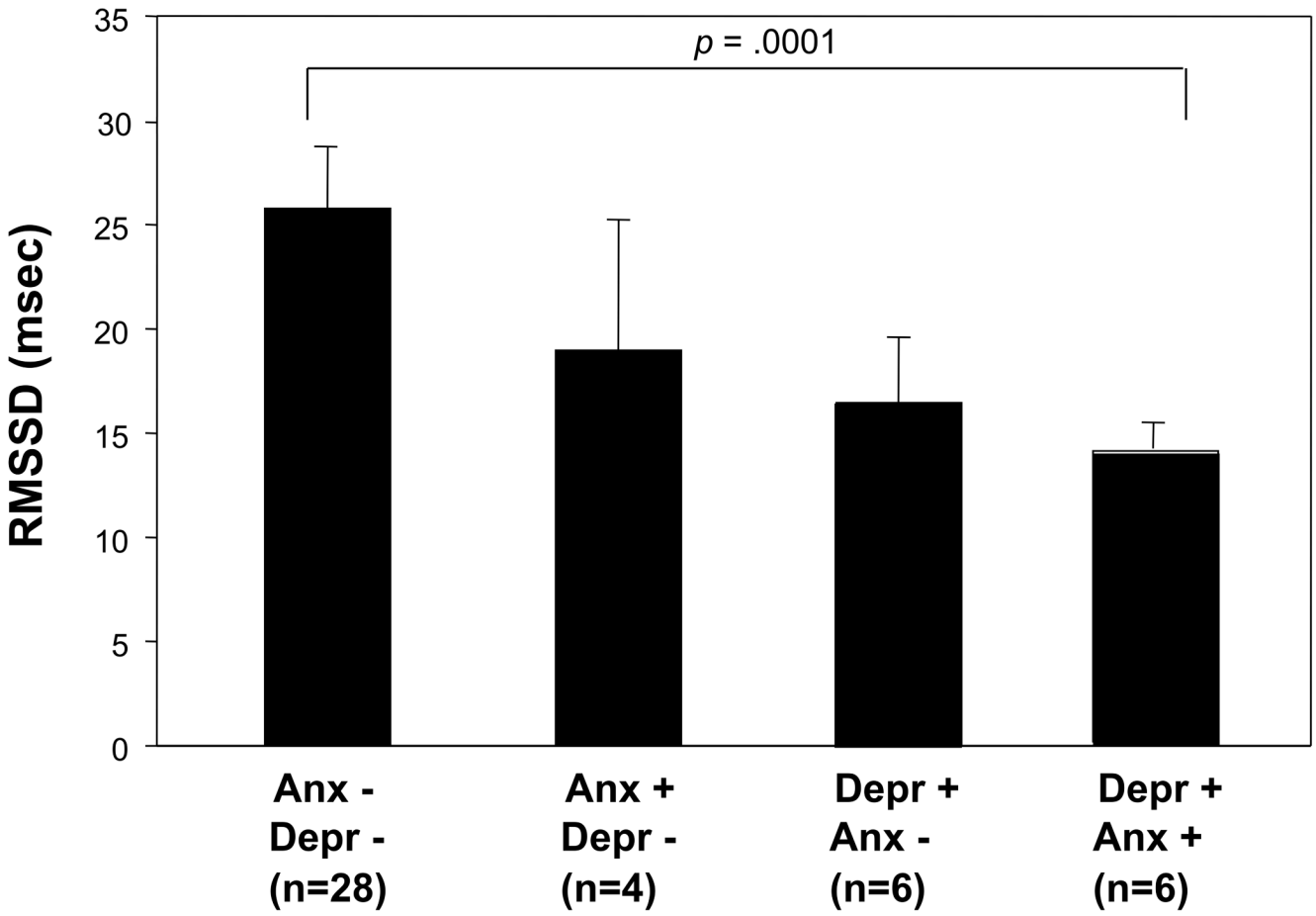

Figure 1.

The combined effect of depression and anxiety on HRV indices. Depression and anxiety status was based on previously validated cut-off scores (≥10 for the Beck Depression Inventory and ≥ 9 on the Manifest Anxiety Scale). Patients with combined positive status for both depression and anxiety scores had significantly lower RMSSD ($p < 0.001$) compared to those with low depression and low anxiety. The ANOVA analyses for trend across the 4 groups was also significant ($p = 0.047$). Depr = depression, Anx = anxiety; RMSSD = root mean square of successive differences.

Table 1

Demographic and clinical characteristics of patients with and without symptoms of depression

	Total (N=44) mean±sd; n(%)	**No Depression BDI < 10 (N=32) mean±sd; n (%)**	**Depression BDI ≥ 10 (N=12) mean±sd; n (%)**
Demographics			
Age (years)	62.1 ± 9.3	63.7 ± 9.2	58.0 ± 8.6
Sex (Female, n (%)	3 (6.8%)	2 (6.2%)	1 (8.3%)
Race African American	5 (11.4%)	4 (12.5%)	1 (8.3%)
European American	39 (88.6)	28 (87.5%)	11 (91.7%)
Cardiovascular disease risk			
BMI (kg/m^2)	29.5 ± 5.4	29.5 ± 5.8	29.4 ± 4.7
Current Smoker	7 (15.9)	5 (15.6%)	2 (16.7%)
Hypertension	31 (70.5)	24 (75.0%)	7 (58.3%)
Diabetes	12 (27.3)	8 (25.0%)	4 (33.3)
Cardiac History			
History of myocardial infarction	37 (82.9%)	28 (86.2%)	9 (75.0%)
History of bypass surgery	23 (52.3)	16 (50.0%)	7 (58.3%)
Ejection fraction (%)	35.9 ± 12.7	34.9 ± (12.8%)	38.5 ± 12.5
Reason for ICD			
Sudden death	3 (6.8%)	1 (3.1%)	2 (16.7%)
Syncope with VT/VF	15 (34.1%)	12 (37.5%)	3 (25.0%)
Symptomatic VT	13 (29.5%)	10 (31.3%)	3 (25.0%)
VT during Holter	10 (22.8%)	8 (25.0%)	2 (16.7%)
Asymptomatic VT	3 (6.8%)	1 (3.1%)	2 (16.7%)
Duration since ICD (months)	13,9 ± 15.4	15.4 ± 17.6	9.9 ± 6.0
Prior ICD discharges (#)	1.7 ± 3.3	1.6 ± 2.3	2.2 ± 5.6
Beta-adrenergic blocking agent			
Not prescribed	7 (15.9)	5 (15.6%)	2 (16.7%)
Withheld	10 (22.7)	7 (21.9%)	3 (25.0%)
Continued	27 (61.4)	20 (62.5%)	7 (58.3%)
Psychological measures			
BDI	6.5 ± 4.4	4.4 ± 2.6	12.3 ± 3.0
Taylor	4,8 ± 3,6	4.0 ± 3.2	7.0 ± 4.1 *

VT = ventricular tachycardia; VF = ventricular fibrillation; ICD = implantable cardioverter defibrillator.
Group comparisons wee not significant (p>0.10) for demographic and clinical variables.

* p = 0.015 (BDI differences were not tested statistically because this variable was used to create the depression groups).

Table 2

Characteristics of patients with and without anxiety symptoms

	No Anxiety Taylor < 9 (N=34) mean±sd; n (%)	**Anxiety Taylor ≥ 9 (N=10) mean±sd; n (%)**
Demographics		
Age (years)	62.6 ± 9.3	60.6 ± 9.8
Sex (Female, n (%)	1 (2.9%)	2 (20.0%)
Race African American	4 (11.8%)	1 (10.0%)
European American	30 (88.2%)	9 (90.0%)
Cardiovascular disease risk factors		
BMI (kg/m^2)	29.4 ± 5.8	29.7 ± 4.2
Current Smoker	6 (17.6%)	1 (10.0%)
Hypertension	23 (67.6%)	8 (80.0%)
Diabetes	10 (29.4%)	2 (20.0)
Cardiac History		
History of myocardial infarction	30 (87.1%)	7 (70.0%)
History of bypass surgery	19 (55.9%)	4 (40.0%)
Ejection fraction (%)	33.5 ± 11.4	43.9 ± 14.1 *
Reason for ICD		
Sudden death	0 (0.0%)	3 (30.0%) *
Syncope with VT/VF	13 (38.2%)	2 (20.0%)
Symptomatic VT	10 (29.4%)	3 (30.0%)
VT during Holter	9 (26.4%)	1 (10.0%)
Asymptomatic VT	2 (5.9%)	1 (10.0%)
Duration since ICD (months)	13.5 ± 16.3	14.9 ± 12.4
Prior ICD discharges (#)	2.1 ± 3.7	0.6 ± 0.9
Beta-adrenergic blocking agent		
Not prescribed	5 (14.7%)	2 (20.0%)
Withheld	6 (17.6%)	4 (40.0%)
Continued	23 (67.6%)	4 (40.0%)
Psychological measures		
Beck Depression Inventory	5.7 ± 4.0	9.7 ± 4.6 *
Taylor Manifest Anxiety Scale	3.2 ± 2.3	10.3 ± 1.1

VT = ventricular tachycardia; VF = ventricular fibrillation; ICD = implantable cardioverter defibrillator.
Group comparisons wee not significant (p>0.10) for demographic and clinical variables.

* = $p < 0.05$ (Group differences for the Taylor MAS were not tested statistically because this variable was used to create the anxiety groups).

Table 3

Correlations between HRV indices in ICD patients.

	RMSSD	PNN50	SDNN	HF-HRV	LF-HRV	LF/HF
PNN50	0.89 **					
SDNN	0.60 **	0.56 **				
HF-HRV	0.64 **	0.58 **	0.70 **			
LF-HRV	0.53 **	0.43 *	0.75 **	0.82 **		
LF/HF	−0.34 *	−0.35 *	−0.10	−0.43 **	0.13	
HR (avg)	−.275	−.275	−.502 **	−.305 *	−.207	.214

RMSSD = root mean square successive difference of RR intervals; PNN50 = percent of successive RR interval differences > 50 ms; SDNN = standard deviation of RR intervals (SDNN); LF = low frequency HRV; HF = high frequency HRV; LF/HF = ratio of LF and HF; HR (avg) = Average heart rate during ambulatory monitoring.

Table 4

Association between depression and HRV indices of autonomic nervous system activity

	Unadjusted mean			Adjusted mean*		
	No Depression BDI < 10 mean±s.e.m.	**Depression BDI ≥ 10 mean±s.e,m.**	**p** [a]	**No Depression BDI < 10 mean±s.e,m.**	**Depression BDI ≥ 10 mean±s.e,m.**	**p**
RMSSD (ms)	24.97 ± 2.44	15.25 ± 1.66	0.002	24.72 ± 2,19	15.85 ± 3.57	0.047
pNN50 (%)	5.61 ± 1.04	1.83 ± 0.77	0.006	5.64 ± 0.93	1.75 ± 1.51	0.040
SDNN (ms)	112.0 ± 6.13	107.4 ± 10.50	0.70	110.76 ± 6.27	110.86 ± 10.60	0.99
HF ($ln.ms^2$)	4.27 ± 0.18	3.71 ± 0.21	0.087	4.27 ± 0.16	3.72 ± 0.27	0.092
LF ($ln.ms^2$)	5.28 ± 0.22	5.08 ± 0.31	0.62	5.30 ± 0.21	5.03 ± 0.34	0.51
LF/HF	1.25 ± 0.03	1.37 ± 0.05	0.061	1.26 ± 0.03	1.35 ± 0.05	0.16

*adjusted for age, sex, hypertension and diabetes status.

[a]unadjusted p values were calculated using unpooled variances and adjusted degrees of freedom if homogeneity of variance was not present (i.e., Levene's test for equivalence of variance $p < 0.05$; RMSSD and PNN50).

Table 5

Association between depression and HRV indices of autonomic nervous system activity

	Unadjusted mean			Adjusted mean*		
	No Anxiety Taylor < 9 mean±s.e,m.	**Anxiety Taylor ≥ 9 mean±s.e,m.**	**p** [a]	**No Anxiety Taylor < 9 mean±s.e,m.**	**Anxiety Taylor ≥ 9 mean±s.e,m.**	**p**
RMSSD (ms)	23.97 ± 2.29	15.67 ± 2.15	0.013	24.09 ± 2.09	15.24 ± 4.13	0.069
pNN50 (%)	5.08 ± 0.95	2.48 ± 1.44	0.19	5.17 ± 0.91	2.16 ± 1.79	0.15
SDNN (ms)	111.67 ± 6.19	107.68 ± 9.94	0.75	112.40 ± 6.00	105.29 ± 11.40	0.59
HF ($ln.ms^2$)	4.14 ± 0.16	4.03 ± 0.35	0.74	4.17 ± 0.16	3.93 ± 0.31	0.50
LF ($ln.ms^2$)	5.25 ± 0.20	5.13 ± 0.40	0.78	5.27 ± 0.20	5.06 ± 0.39	0.64
LF/HF	1.28 ± 0.03	1.29 ± 0.07	0.85	1.28 ± 0.03	1.30 ± 0.06	0.77

*adjusted for age, sex, hypertension and diabetes status.

[a]unadjusted p values were calculated using unpooled variances and adjusted degrees of freedom if homogeneity of variance was not present (i.e., Levene's test for equivalence of variance $p < 0.05$; RMSSD and PNN50).