Autonomic nervous system functioning in major depression and anxiety disorders

Licht, C.M.M.

2010

document version
Publisher's PDF, also known as Version of record

3.

Association Between Anxiety Disorders and Heart Rate Variability in the Netherlands Study of Depression and Anxiety (NESDA)

Carmilla M. M. Licht
Eco J. C. de Geus
Richard van Dyck
Brenda W. J. H. Penninx

Psychosomatic Medicine 2009;71:508-518

ABSTRACT

Objective: To determine whether patients with different types of anxiety disorder (panic disorder, social phobia, generalized anxiety disorder) have higher heart rate and lower heart rate variability compared with healthy controls in a sample that was sufficiently powered to examine the confounding effects of lifestyle and antidepressants.

Methods: The standard deviation of the normal-to-normal intervals (SDNN), heart rate, and respiratory sinus arrhythmia (RSA) were measured in 2195 subjects (mean age = 41.7 years, 66.8% female) participating in the Netherlands Study of Depression and Anxiety (NESDA). Based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and Composite International Diagnostic Interview (CIDI), NESDA participants were classified as healthy controls (n=616), subjects with an anxiety diagnosis earlier in life (n=420), and subjects with current anxiety diagnosis (n=1159).

Results: Current anxious subjects had a significantly lower SDNN and RSA compared with controls. RSA was also significantly lower in remitted anxious subjects compared with controls. These associations were similar across the three different types of anxiety disorders. Adjustment for lifestyle had little impact. However, additional adjustment for antidepressant use reduced all significant associations between anxiety and heart rate variability to nonsignificant. Anxious subjects who used a tricyclic antidepressant, a selective serotonin re-uptake inhibitor, or serotonergic and noradrenergic working antidepressant showed significantly lower mean SDNN and RSA compared with controls (effect sizes = 0.20 – 0.80 for SDNN and 0.42– 0.79 for RSA). Non-medicated anxious subjects did not differ from controls in mean SDNN and RSA.

Conclusion: This study shows that anxiety disorders are associated with significantly lower heart rate variability, but the association seems to be driven by the effects of antidepressants.

INTRODUCTION

Anxiety disorders have been associated with an increased risk of cardiovascular morbidity and mortality[1-10]. One of the hypothesized causes for this association is a dysregulation of the autonomic control of the heart because autonomic nervous system (ANS) activity is associated with cardiovascular disease (CVD) and mortality[11-15] as well as anxiety disorders. Episodic acute "state" anxiety is characterized by an increase in heart rate paired to a decrease in total heart rate variability and respiratory sinus arrhythmia (RSA)[16-18]. The latter is often seen as the best available proxy for cardiac vagal control[19,20]. Lower total heart rate variability and cardiac vagal control are also found in subjects reporting chronic levels of anxiety, as assessed by "trait anxiety" inventories[21,22] and in patients with a clinical anxiety disorder[23-27]. A recent review by Friedman[22] suggested that RSA is lowered most strongly in patients with panic disorder (PD), when compared with social phobia and generalized anxiety disorder. Friedman's review also detected substantial heterogeneity in the outcome across studies.

A potential limitation of the studies in clinical samples so far is that they were relatively small and, consequently, could not take into account potential confounders of the relationship between anxiety and heart rate variability. Specifically, lifestyle factors and the use of psychoactive medication have not been taken into account in most of the studies to date. With regard to the latter, we recently showed that antidepressants had a major lowering impact on standard deviation of the normal-to-normal interval (SDNN) and RSA in depressed patients[28]. The present study examines heart rate, SDNN, and RSA in subjects with a current or remitted anxiety diagnosis and healthy controls. The study was sufficiently powered to examine the extent to which a potential association between anxiety disorder and heart rate and heart rate variability is confounded by a number of lifestyle factors and the use of antidepressants. We also examined whether differences in heart rate, SDNN, and RSA were consistent across different anxiety disorders (PD, social phobia, and generalized anxiety disorder) and whether these differences were larger for anxiety patients with a current diagnosis compared with those with a remitted diagnosis.

METHODS

Subjects

Subjects participating in the present study came from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted among 2981 adult subjects (age range = 18-65 years) to examine the long-term course of depression and anxiety disorders. The rationale, methods, and recruitment strategy have been described elsewhere[29]. The NESDA sample consists of 652 persons without depression or anxiety disorders and 2329 with a (remitted or current) diagnosis of depressive or anxiety disorder. To represent various settings and stages of psychopathology, depressed or anxious subjects were recruited at three different locations in The Netherlands in different settings: community, primary care, and mental healthcare organizations. Community-based subjects had previously been identified in a population-based study, primary care subjects were identified through a three-stage screening procedure (involving the K10[30] and the short-form Composite International Diagnostic Interview (CIDI) psychiatric interview by phone) conducted among patients of 65 General Practitioners; and mental healthcare patients were recruited when newly enrolled at one of the 17 participating mental health organization locations.

NESDA subjects were assessed between September 2004 and February 2007 during a 4-hour visit to one of the seven field centre locations. During this visit, the presence of anxiety disorders was ascertained using the lifetime version of the CIDI psychiatric interview (World Health Organization (WHO) version 2.1). The CIDI establishes diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria[31] and has shown high interrater and test-retest reliability and high validity for anxiety disorders[32]. In addition, the severity of anxiety was measured among all subjects using the Beck Anxiety Inventory (BAI)[33].

To test whether heart rate, SDNN, and RSA differed across persons with and without an anxiety disorder, three clearly distinct anxiety groups were created for the present study. The first group consisted of 616 control subjects with no history of any anxiety disorders, depression, or other psychiatric disorders. The second group consisted of 420 persons with an anxiety disorder-diagnosis (as defined by the CIDI) earlier in life but not in the past six months. This group was referred to as the remitted anxiety group. The third group—referred to as the current anxiety group— consisted of 1159 persons with a CIDI-confirmed anxiety

disorder in the past six months (84% had experienced an anxious episode in the past month). The remaining 786 NESDA subjects were excluded from the analyses: 688 patients had a depressive disorder in absence of an anxiety disorder; 98 subjects had missing physiological data due to equipment failure during assessment or poor electrocardiogram (ECG) quality.

For additional analysis on anxiety subtype, the 1579 anxious subjects (remitted + current) were further classified based on the CIDI data, in three variables assessing the presence or absence of remitted or current PD, remitted or current social phobia (SP), and remitted or current generalized anxiety disorder (GAD).

Measurements

The clinic visit consisted of a blood draw, a medical examination, supine rest with blood pressure recordings, psychiatric interviews, a cognitive computer task, saliva collection, and administration of several written questionnaires concerning mood state, lifestyle, medical history, and actual medication use. Extensive information about psychological, biological, physical, and demographic determinants was collected. The study protocol was approved centrally by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating centre. All subjects signed an informed consent at baseline assessment.

Physiological Measurement

Heart rate and SDNN were assessed using a three-lead ECG signal that was measured by the VU-AMS. The VU-AMS is a light-weight ambulatory device that records the ECG and changes in thorax impedance (dZ) from six electrodes placed on the chest and back of the subjects[34,35]. The respiration signal is obtained from the filtered (0.1– 0.4 Hz) dZ signal. An automatic scoring algorithm detects the beginning and end of inspiration and expiration and computes the respiratory rate from these values. RSA was assessed by peak-valley estimation (pvRSA) using the combined ECG and dZ signals. Per breath, estimates of pvRSA were obtained by subtracting the shortest inter-beat-interval (IBI) during heart rate acceleration in the inspirational phase (which was made to include 750 milliseconds from the following expiration to account for phase shifts) from the longest IBI during deceleration in the expirational phase (including 750 milliseconds from the following expiratory pause/inspirational phase). When no phase-related

acceleration or deceleration was found, the breath was assigned a pvRSA score of zero. Automatic scoring of respiration rate and pvRSA was checked by visual inspection of the respiratory signal and IBI time series from the entire recording. Breathing cycles that showed irregularities such as gasps, breath holding, coughing or that had IBI artefacts (ectopic beats or too long beats due to failed R-wave detection) were not considered valid and were rejected and removed from further processing. In the remaining data, the shortest and longest breaths as well as the breaths containing the shortest and longest IBIs (defined by three SD from the mean in either direction) were automatically removed from the entire recording before averaging pvRSA across all remaining breaths to a single mean pvRSA for each of the labelled periods. In total, 74 subjects were removed from the final data set because >25% of their breaths were discarded during automated or visual data cleaning[36,37]. RSA can alternatively be assessed as the high-frequency power of the IBI time series by Fourier or Wavelet-analysis[38] but it has been shown that the time and frequency domain measures essentially pick up the same between-subject variation and can be used interchangeably[37,39]. The advantage of pvRSA assessments is that they additionally yield the respiration rate.

Recording is unobtrusive and subjects, who maintain full freedom of movement, tend to habituate very rapidly to this type of recording. NESDA subjects were wearing the VU-AMS device during a large part of the NESDA clinic visit, at the same time participating in the different assessment parts. The start of the various assessment stages was marked with an event marker to divide the total recording into fixed periods (resting baseline, breaks, interview I, computer task, interview II). Movement registration through vertical accelerometry was used to excise periods where subjects were non-stationary. Removal of breaks and non-stationary parts (about 15 minutes) resulted in the four conditions used in the final analyses: a supine rest condition with three blood pressure measurements (9.7 ± 3.0 minutes), and three conditions with mild cognitive load in which the subjects were sitting upright: interview session I (investigating somatic health; functioning and healthcare utilization; sitting, 38.2 ± 12.7 minutes); interview session II (investigating family and personal history and life events; sitting, 35.6 ± 12.7 minutes); and a computer task (Implicit Association Task; sitting, 16.2 ± 4.0 minutes). The Implicit Association Task is a computerized task designed to measure implicit associations between self-items, on the one hand, and anxiety-related and depression-related items, on the other hand[40].

Covariates

Respiration rate has often been associated with heart rate variability and several studies suggested that research investigating heart rate variability should take respiration rate into account[34,41]. Therefore, we adjusted analyses for respiration rate. Sociodemographics included age, sex, and education in years. In addition, various health indicators were considered as covariates because these have been linked with both anxiety and ANS activity. Body mass index (BMI) was determined as measured weight in kilograms divided by the square of the measured height in meters. Physical activity was measured using the International Physical Activity Questionnaire[42] and expressed in MET-minutes per week (the multiple of one's resting metabolic rate times minutes of physical activity per week). Smoking status was defined as a dichotomous variable; non-smoker versus smokers. Three categories were created for alcohol use: non-drinker, mild-to-moderate drinker (<14 glasses a week), and heavy drinker (≥ 14 glasses a week). Self-reports were used for ascertainment of the presence of heart disease (including coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction) and other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcer). Furthermore, it was determined whether subjects were using heart medication by copying the names of medicines from the containers brought in by the subjects. We classified medication using the WHO Anatomical Therapeutic Chemical (ATC) classification[43]. First, a dichotomous variable for the use of beta-blockers was computed, scoring "yes" if subjects frequently (daily or >50% of the time) used a medication with ATC code starting with: C07 (β-blocking agents). A second variable was made for the use of other heart medication using ATC codes starting with: C01 (cardiac therapy), C02 (antihypertensives), C03 (diuretics), C04 (peripheral vasodilators), C05 (vasoprotectives), or C08 (calcium-channel blockers).

In addition, we conducted additional analyses with covariates that may further explain a potential association between anxiety and heart rate and heart rate variability function. First, because we recently found that antidepressants had a major lowering impact on SDNN and RSA in depressed patients[28], frequent use (daily or >50% of the time) of antidepressant medication was considered as covariate. We distinguished selective serotonin re-uptake inhibitors (SSRIs) (ATC code N06AB), tricyclic antidepressants (TCAs) (ATC code N06AA), and serotonergic and noradrenergic working antidepressants (SNRIs, classified as

N06AX). Second, we explored whether the association between anxiety disorder and heart rate and heart rate variability was explained by the presence of comorbid remitted or current major depressive disorder (MDD) as assessed using the CIDI psychiatric interview. Third, the importance of two indicators of severity of anxiety (BAI score and number of anxiety disorders present) in the association with heart rate and heart rate variability was examined.

Statistical Analyses

Data were analyzed using SPSS 15.0. Characteristics across the three anxiety groups (controls, remitted, and current anxiety) were compared using analysis of variance (ANOVA) and χ^2 statistics. Mixed model analysis showed that differences in ANS measures between anxiety groups were similar for the computer task and interview parts and data during the computer task and interview parts were collapsed to create a single "test" condition to simplify analyses. ANOVAs were conducted separately for the rest and test conditions to compare heart rate, SDNN, and RSA between the anxiety groups. These analyses were repeated with consideration of covariates (respiration rate, age, sex, education, BMI, smoking, alcohol use, physical activity, heart disease, heart medication, and chronic disease count). Subsequently, the role of two main explanatory variables (antidepressant medication and comorbid major depressive disorder) was examined by entering information on these variables in the analyses of covariance.

To examine whether different anxiety disorders had differential associations with heart rate and heart rate variability, we conducted multivariate regression analyses on heart rate, SDNN, and RSA including covariates and anxiety subtype indicators. Finally, we distinguished anxious subjects with and without various types of psychoactive medication and compared their heart rate, SDNN, and RSA with those of controls in fully corrected analyses of covariance (ANCOVAs). Effect sizes were calculated with Cohen's *d* (1988) defined as the difference in the mean RSA, SDNN, and heart rate between two groups, divided by the pooled standard deviation (SD) of these groups.

Table 1. Main Sample Characteristics for Controls and Anxious Subjects

Variables	Participants, %			
	Control (n=618)	Remitted Anxiety (n=421)	Current Anxiety (n=1164)	*p*[a]
Age, mean (SD), y	41.1 (14.7)	43.6 (12.6)	40.9 (12.3)	.001
Female sex	61.0	70.5	68.1	.002
Education, mean (SD), y	12.8 (3.2)	12.5 (3.1)	11.6 (3.3)	<.001
Body mass index, mean (SD)	25.1 (4.6)	25.7 (5.0)	25.6 (5.2)	.06
Physical Activity, mean (SD), 1000 METmin/week	3.8 (3.1)	3.6 (2.8)	3.6 (3.1)	.28
Smoking	25.9	32.3	46.6	<.001
Alcohol use				
Non-drinker	11.0	15.2	22.0	<.001
Mild/moderate drinker	71.2	69.8	62.6	
Heavy drinker	17.8	15.0	15.4	
Beta blocking agents	6.5	9.0	8.0	.29
Other heart or blood pressure medication	11.7	11.2	9.7	.40
Heart or coronary disease	4.7	5.5	6.3	.38
Chronic diseases, mean (SD), No.	1.01 (1.1)	1.30 (1.2)	1.37 (1.3)	<.001
Antidepressant use				
TCA	0	2.9	4.2	<.001
SSRI	0	15.9	27.1	<.001
SNRI	0	3.8	9.5	<.001
Comorbid major depressive disorder	0	75.3	79.4	<.001
Panic Disorder[b]				
Remitted	0	35.2	4.4	<.001
Current	0	0	55.4	
Social Phobia[b]				
Remitted	0	41.1	5.1	<.001
Current	0	0	55.5	
Generalized Anxiety Disorder[b]				
Remitted	0	48.7	8.8	<.001
Current	0	0	38.2	
Respiration rate[c], mean (SD), breaths/min	17.2 (1.2)	17.0 (1.1)	17.1 (1.2)	.02
BAI-score, mean (SD)	4.0 (4.8)	9.2 (7.6)	18.9 (10.9)	<.001

BAI, Beck Anxiety Inventory; MET, multiple of the resting metabolic rate; SD, standard deviation.

[a] Comparison using ANOVA analyses (continuous variables) and χ^2-statistics (categorical variable).

[b] Percentages anxiety disorders do not add up to 100% due to comorbidity.

[c] Respiratory rate is averaged over rest and test conditions in this table

RESULTS

The mean age of the study sample (n=2195) was 41.7 years (SD=13.1), 66.8% was female, and 50.9% had <12 years of education. **Table 1** shows the demographic characteristics, disease status, lifestyle habits, and medication use according to anxiety diagnosis. Of the individuals with a current anxiety disorder, 55.4% had a PD, 55.5% had a social phobia, and 38.2% had a generalized anxiety disorder. Compared with the non-anxious subjects, anxious subjects were more likely to be female, had less education, had a higher BMI, were more likely to smoke but less likely to drink, had more chronic diseases, were more likely to use antidepressants, had a lower respiration rate, and had a higher BAI score.

Table 2 presents the results of the unadjusted and adjusted ANOVA analyses on heart rate, SDNN, RSA for anxiety status for the rest and test conditions. Results showed that heart rate did not differ in either condition between current or remitted anxious subjects and healthy controls, independent of covariates. For SDNN, a significant difference was found between the current anxious subjects and the controls in both conditions (in the adjusted model, .002<p<.04 and 0.104<Cohen d<0.156) and for RSA, significant differences were found between the controls and both the current and the remitted anxious subjects for both the rest (p<.001, Cohen d=0.165–0.250) and test condition (.009<p<.03, Cohen d=0.120-0.175) in the fully adjusted model. Additional correction for the BAI score did not change results. Table 2 shows that, in case of SDNN as well as RSA, correction for antidepressant use reduced the differences between the anxiety groups and the control group to nonsignificant.

Table 3 presents the results of the nominal linear regression analyses using the separate anxiety disorders as independent predictors of heart rate, SDNN, and RSA. Model I includes all possible predictors and Model II additionally includes the use of different antidepressants. Heart rate was not significantly different from controls in the rest or test condition in any of the three anxiety disorders. However, current anxiety disorders were associated with significantly lower SDNN and RSA, and RSA was significantly lower in subjects with remitted anxiety disorders as well. Model II shows that all these associations became nonsignificant after adding TCA, SSRI, and SNRI use to the model. The use of especially a TCA had a major effect on both SDNN (for the rest and test conditions, b=-15.340 and b=-16.159, p<.001), and RSA (b=-15.334 and b=-14.943, p<.001). The use of an SSRI or SNRI also showed this effect, although with a more modest effect size (b values

range=-3.638 to -15.263; *p* values range =.004-.001). Significant effects of antidepressant use were also found for heart rate; the use of a TCA or SNRI

Table 2. Mean Heart Rate, Standard Deviation of Normal-to-Normal Beats (SDNN) and Respiratory Sinus Arrhythmia (RSA) in Control and Anxiety Disorders, Unadjusted and Adjusted for Covariates

	Control (n=616)	Remitted anxiety (n=420)	Current anxiety (n=1159)	Control vs. remitted anxiety		Control vs. current anxiety	
				p	Cohen *d*	*p*	Cohen *d*
Rest condition							
			Heart rate, mean (SD), beat-min				
Unadjusted	68.4 (0.4)	68.8 (0.5)	69.3 (0.3)	.61	0.032	.05	0.096
Adjusted[a]	68.5 (0.4)	68.8 (0.5)	69.1 (0.3)	.65	0.029	.22	0.062
Adjusted[b]	68.7 (0.4)	68.8 (0.5)	69.0 (0.3)	.84	0.013	.51	0.033
Adjusted[c]	69.0 (0.4)	69.0 (0.5)	68.8 (0.3)	.95	0.004	.75	0.017
			SDNN, mean (SD), ms				
Unadjusted	79.1 (1.3)	74.3 (1.6)	72.9 (1.0)	.02	0.146	<.001	0.189
Adjusted[a]	78.5 (1.2)	76.3 (1.5)	72.5 (0.9)	.26	0.071	<.001	0.199
Adjusted[b]	77.7 (1.2)	76.3 (1.5)	73.0 (0.9)	.46	0.047	.002	0.156
Adjusted[c]	75.6 (1.3)	75.7 (1.4)	74.2 (0.9)	.94	0.005	.40	0.044
			RSA, mean (SD), ms				
Unadjusted	51.3 (1.3)	45.0 (1.5)	45.4 (0.9)	.002	0.200	<.001	0.188
Adjusted[a]	51.6 (1.1)	46.9 (1.3)	44.5 (0.8)	.005	0.182	<.001	0.273
Adjusted[b]	51.4 (1.1)	47.0 (1.3)	44.7 (0.8)	.009	0.165	<.001	0.250
Adjusted[c]	48.5 (1.1)	46.4 (1.3)	46.3 (0.8)	.21	0.079	.12	0.082
Test condition							
			Heart rate, mean (SD), beats/min				
Unadjusted	73.4 (0.4)	72.6 (0.5)	73.1 (0.3)	.20	0.083	.46	0.037
Adjusted[a]	73.5 (0.4)	72.9 (0.5)	73.0 (0.3)	.31	0.064	.30	0.052
Adjusted[b]	73.5 (0.4)	72.9 (0.5)	72.9 (0.3)	.32	0.062	.24	0.060
Adjusted[c]	73.6 (0.4)	73.0 (0.5)	72.9 (0.3)	.33	0.061	.13	0.079
			SDNN, mean (SD), ms				
Unadjusted	65.6 (0.9)	63.9 (1.1)	62.8 (0.7)	.23	0.077	.02	0.123
Adjusted[a]	65.4 (0.9)	65.1 (1.0)	62.5 (0.6)	.86	0.011	.007	0.138
Adjusted[b]	64.9 (0.9)	65.1 (1.0)	62.7 (0.6)	.91	0.007	.04	0.104
Adjusted[c]	63.4 (0.9)	64.6 (1.0)	63.6 (0.6)	.36	0.058	.85	0.010
			RSA, mean (SD), ms				
Unadjusted	46.6 (1.0)	42.4 (1.3)	43.4 (0.8)	.01	0.168	.01	0.128
Adjusted[a]	47.1 (0.9)	44.2 (1.1)	42.5 (0.6)	.04	0.124	<.001	0.182
Adjusted[b]	47.1 (0.9)	44.2 (1.1)	42.5 (0.7)	.03	0.120	<.001	0.175
Adjusted[c]	45.1 (0.9)	43.6 (1.0)	43.7 (0.7)	.31	0.074	.25	0.062

RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal interval

[a] Adjusted for respiration rate, age, sex and education

[b] Adjustment [a] + additionally adjusted for body mass index, physical activity, smoking, alcohol use, chronic and heart disease, β-blocking agents, other heart medication

[c] Adjustment [b] + additionally adjusted for antidepressant use

increased heart rate (for the rest condition, respectively, b=7.811 and b=3.054, p's≤.001; and for the test condition b=8.101 and b=1.975, p=.02-.001).

Additional correction for comorbid depression did not change these effects, as comorbid depression itself was not significantly associated with SDNN and RSA. Repeating the regression analyses in Table 3 with RSA divided by the IBI (as suggested by Grossman and Kollai)[44] yielded essentially identical results.

Because the regression analyses (Table 3) showed strong effects of antidepressants on the cardiac measures, we decided to further analyze the differences in heart rate, SDNN, and RSA between controls, anxious subject without medication, and anxious subject on TCAs, SSRIs, and SNRIs. Eventually, five groups of anxiety subjects were distinguished: 326 remitted anxious subjects without medication; 701 current anxious subjects without medication; 60 anxious subjects on a TCA; 376 anxious subjects on a SSRI (no TCA users); and 116 anxious subjects on an SNRI (no TCA or SSRI users). ANCOVAs were performed to compare these groups with each other on mean heart rate, SDNN, and RSA.

Table 4 provides the main characteristics of the anxious subjects with and without medication. Medicated anxious individuals were older, had a higher mean BMI, performed less physical activity, drank less, more often used β-blocking agents and other heart or blood pressure medication, had more comorbid MDD and remitted anxiety disorder diagnoses, and had a higher mean BAI score.

Although remitted and current anxious patients without antidepressant medication also differed significantly in BAI score (8.5 and 17.5, respectively), they both did not differ significantly from the controls in terms of heart rate, SDNN, or RSA in rest or test conditions adjusted for covariates (**Table 5; Figure 1**). Addition of the BAI score as a covariate did not change this outcome. In contrast, all anxiety patients on an antidepressant, with BAI scores similar to the current anxious patients without medication, had a significantly lower SDNN and RSA compared with the controls in both conditions (all p≤.003 for SDNN and RSA), with effect sizes ranging between d=0.197 and d=0.799 with the highest effect sizes for TCA users. The antidepressants had parallel effects on heart rate, with the exception of SSRIs. Anxious TCA users had a significantly higher heart rate compared with controls with a large effect size (d=0.802-0.827). Smaller heart rate increases were found in anxious users of SNRIs (p=.09-.001 and d=0.172-0.339).

Table 3. Results of Regression Analyses Predicting Heart Rate, SDNN and RSA among Controls and Anxious Subjects

	Heart rate, beats/min			SDNN, ms			RSA, ms		
	b	*p*	R^2	*b*	*p*	R^2	*b*	*p*	R^2
Rest condition									
Model I			.097			.205			.324
Respiration rate (per 1 breath per minute increase)	.452	<.001		-1.745	<.001		-3.063	<.001	
Age (per 1 year increase)	-.040	.03		-.988	<.001		-1.319	<.001	
Sex (female vs. male)	2.498	<.001		-6.111	<.001		7.706	<.001	
Education (per 1 year increase)	-.068	.29		-.180	.38		-.276	.13	
Physical activity (per 1000 METmin/week increase)	-.171	.07		.370	.07		.159	.39	
BMI (per 1 kg/m^2 increase)	.285	<.001		-.574	<.001		-.405	.001	
Heavy alcohol use vs. no alcohol use	-1.735	.02		5.971	.009		5.690	.005	
Mild/moderate alcohol use vs. no alcohol use	-1.799	.001		7.279	<.001		4.904	.002	
Smoking (yes vs. no)	1.107	.01		-1.435	.30		.377	.76	
Chronic disease (per 1 disease increase)	-.139	.42		-.067	.90		.576	.24	
Heart disease (yes vs. no)	.654	.49		-2.120	.49		-1.936	.47	
Beta-blocking agents (yes vs. no)	-7.341	<.001		.874	.75		2.318	.34	
Other heart medication (yes vs. no)	2.257	.003		-2.095	.39		.468	.83	
Current Panic Disorder (yes vs. no)	-.226	.64		-2.639	.08		-3.066	.02	
Remitted Panic Disorder (yes vs. no)	.306	.67		-4.004	.08		-4.053	.05	
Current Social Phobia(yes vs. no)	.349	.45		-3.071	.04		-4.471	.001	
Remitted Social Phobia (yes vs. no)	-.256	.71		1.352	.53		-2.786	.14	
Current GAD (yes vs. no)	.079	.88		-3.648	.03		-2.242	.13	
Remitted GAD (yes vs. no)	-.148	.80		.660	.73		-.542	.75	
Model II[a]			.118			.222			.349
Current Panic Disorder (yes vs. no)	-.412	.40		-.804	.60		-.234	.86	
Remitted Panic Disorder (yes vs. no)	.209	.77		-2.632	.25		-1.915	.34	
Current Social Phobia(yes vs. no)	.138	.77		-1.882	.20		-.2.777	.03	
Remitted Social Phobia (yes vs. no)	-.359	.59		2.246	.30		-1.245	.51	
Current GAD (yes vs. no)	-.130	.81		-1.837	.27		.122	.93	

Table 3. Continued

	Heart rate, beats/min			SDNN, ms			RSA, ms		
	b	*p*	R^2	*b*	*p*	R^2	*b*	*p*	R^2
Remitted GAD (yes vs. no)	-.257	.59		1.513	.42		.669	.68	
Use of a tricyclic antidepressant (yes vs. no)	7.811	<.001		-15.340	<.001		-15.334	<.001	
Use of an SSRI (yes vs. no)	-.182	.75		-5.191	.004		-10.500	<.001	
Use of an SNRI (yes vs. no)	3.054	.001		-15.263	<.001		-14.284	<.001	
Test condition									
Model I			.123			.191			.313
Respiration rate (per 1 breath per minute increase)	1.098	<.001		-2.750	<.001		-3.770	<.001	
Age (per 1 year increase)	-.085	<.001		-.647	<.001		-1.045	<.001	
Sex (female vs. male)	2.306	<.001		-3.575	<.001		6.906	<.001	
Education (per 1 year increase)	-.059	.36		.117	.41		-.038	.80	
Physical activity (per 1000 METmin/week increase)	-.185	.005		.272	.06		.098	.52	
BMI (per 1 kg/m^2 increase)	.179	<.001		-.397	<.001		-.174	.09	
No alcohol use vs. heavy alcohol use	-.926	.20		2.611	.10		2.242	.19	
No alcohol use vs. mild/moderate alcohol use	-1.271	.02		3.022	.01		2.991	.02	
Smoking (yes vs. no)	.111	.80		-1.399	.15		1.410	.16	
Chronic disease (per 1 disease increase)	-.040	.82		.103	.79		.366	.37	
Heart disease (yes vs. no)	.562	.56		-.821	.71		-.663	.77	
Beta-blocking agents (yes vs. no)	-9.180	<.001		2.526	.19		2.123	.30	
Other heart medication (yes vs. no)	2.207	.004		-2.745	.11		-.797	.66	
Current Panic Disorder (yes vs. no)	-.784	.10		-.968	.36		-2.345	.04	
Remitted Panic Disorder (yes vs. no)	-.083	.91		-.865	.59		-2.400	.15	
Current Social Phobia(yes vs. no)	.094	.84		-1.092	.29		-2.222	.04	
Remitted Social Phobia (yes vs. no)	.061	.93		-1.767	.24		-3.158	.05	
Current GAD (yes vs. no)	.233	.65		-3.177	.007		-3.516	.004	
Remitted GAD (yes vs. no)	-1.020	.08		1.573	.23		-.833	.55	

Table 3. Continued

	Heart rate, beats/min			SDNN, ms			RSA, ms		
	b	*p*	R^2	*b*	*p*	R^2	*b*	*p*	R^2
Model II[a]			.145			.213			.333
Current Panic Disorder (yes vs. no)	-.732	.13		.261	.81		-.433	.70	
Remitted Panic Disorder (yes vs. no)	.003	.99		.059	.97		-.970	.56	
Current Social Phobia(yes vs. no)	-.005	.99		-.186	.86		-1.003	.36	
Remitted Social Phobia (yes vs. no)	.068	.92		-1.106	.46		-2.092	.18	
Current GAD (yes vs. no)	.217	.68		-1.995	.09		-1.906	.12	
Remitted GAD (yes vs. no)	-1.038	.08		2.192	.09		.028	.98	
Use of a TCA (yes vs. no)	8.101	<.001		-16.159	<.001		-14.943	<.001	
Use of an SSRI (yes vs. no)	-1.163	.04		-3.638	.004		-6.937	<.001	
Use of an SNRI (yes vs. no)	1.975	.02		-9.286	<.001		-9.873	<.001	

[a] Model II included all covariates of Model I as well as antidepressant use variables. Regression coefficients are only shown for anxiety and antidepressant use variables

In anxious SSRI users, the opposite effect was found such that heart rate was lower than in anxious subjects without medication, although only in the test condition (p=.005 and d=0.185).

Table 4. Main Sample Characteristics for Anxious Subjects Taking and not Taking Antidepressants

	Participants, %				
	Current anxiety	Any Anxiety Disorder			
Variable	No use (n=701)	On TCA (n=60)	On SSRI (n=376)	On SNRI (n=116)	p[a]
Age, mean (SD), years	40.2 (12.8)	47.2 (10.4)	41.4 (11.6)	43.2 (10.9)	<.001
Female Sex	69.5	73.8	69.7	60.2	.16
Education, mean (SD), years	11.7 (3.3)	11.2 (3.5)	11.7 (3.3)	11.7 (3.2)	.73
BMI, mean (SD), kg/m^2	25.2 (4.9)	27.4 (6.2)	26.3 (5.7)	25.9 (5.5)	<.001
Physical Activity, mean (SD), 1000 METmin/week	3.8 (3.2)	2.8 (2.5)	3.5 (3.2)	3.1 (3.1)	.03
Smoking	43.7	52.5	45.5	52.5	.22
Alcohol use					
Non-drinker	18.3	37.7	25.8	26.3	<.001
Mild/moderate drinker	64.9	49.2	59.5	65.3	
Heavy drinker	16.8	13.1	14.7	8.5	
Beta blocking agents	7.2	14.8	7.4	12.7	.05
Other heart or blood pressure medication	8.3	21.3	8.9	15.3	.002
Heart or coronary disease	5.4	6.6	6.6	5.1	.86
Chronic diseases, mean (SD), No.	1.35 (1.2)	1.64 (1.6)	1.33 (1.3)	1.47 (1.4)	.28
Antidepressant use					
TCA	0	100	0	0	<.001
SSRI	0	6.6	100	0	<.001
SNRI	0	3.3	2.1	100	<.001
Comorbid MDD	72.6	88.5	89.7	91.5	<.001
Panic Disorder[b]					
Remitted	4.2	9.8	13.7	11.0	<.001
Current	50.7	42.6	53.4	51.7	.45
Social Phobia[b]					
Remitted	4.2	13.1	14.5	7.6	<.001
Current	56.0	47.5	45.5	44.9	.004
GAD[b]					
Remitted	8.9	16.4	15.3	14.4	.007
Current	35.4	24.6	33.7	44.9	.04
BAI-score, mean (SD)	17.6 (10.7)	20.0 (12.4)	19.4 (11.4)	19.7 (10.4)	.02

AD, antidepressant; BAI, Beck Anxiety Inventory; MET, multiple of the resting metabolic rate.
[a] Comparison using ANOVA analyses (continuous variables) and χ^2-statistics (categorical variable).
[b] Percentages anxiety disorders do not add up to 100% due to comorbidity

DISCUSSION

This large-scale cohort study showed that, when compared with healthy controls, subjects with an anxiety disorder have a significantly lower total heart rate variability, an established risk factor for CVD[11,15,45], and significantly lower RSA, which is considered to reflect the lower cardiac vagal control[46,47] that might underlie this increased risk.[48] The lower heart rate variability was not specific to PD, but was found for all anxious individuals, whether afflicted with PD, SP, or GAD. Lower heart rate variability, especially lower cardiac vagal control, was not only observed among current anxiety patients but also among those with a remitted diagnosis. In all instances, the effect sizes were very modest, with *d* values between 0.10 and 0.25. Very similar results were found in the supine rest condition and the (much longer) active test condition.

A major aim of the study was to examine the extent to which the potential association between the presence of anxiety disorders and heart rate variability is confounded by lifestyle and use of antidepressants, and this may have been the first study sufficiently powered to do so. Compared with all previous studies, we used a large sample of patients with remitted or current anxiety, both medicated and non-medicated, who were ascertained in multiple ways to obtain a representative population sample of patients. In addition, the availability of prolonged ambulatory recordings of SDNN and RSA in the nearly complete sample provided us with stable and reliable indicators. Our findings showed that lower heart rate variability in anxious subjects survived adjustment for possible confounding factors as health indicators and lifestyle, but further adjustment for antidepressant use rendered all associations nonsignificant.

Considering the effects of age on the cardiac indices, our results are in line with other studies reporting significant decreases in heart rate and heart rate variability with age[49-52]. In our study, females had a significantly higher heart rate and RSA, but lower SDNN compared with males, which is in accordance with earlier findings[50-52]. Although several papers have been published on heart rate variability and obesity, few studies have addressed the relationship between heart rate variability and continuous BMI, and findings have been inconsistent[50,53-55]. In line with Kageyama *et al*.[55] and Britton *et al*.[53], we found that an increase in BMI was significantly associated with an increase in heart rate and a decrease in SDNN, but the effect of BMI on RSA was not significant. We found no significant effect of smoking on heart rate and heart rate variability, which concurs with some[55] but

Table 5. Heart Rate, SDNN and RSA per Medication Group[a]

			Heart rate, beats/min			SDNN, ms			RSA, ms		
	N	BAI-score	mean (SE)	*p*	Cohen *d*	mean (SE)	*p*	Cohen *d*	mean (SE)	*p*	Cohen *d*
Rest condition											
Control	616	4.0	68.7 (0.4)	REF[b]	REF[b]	77.9 (1.2)	REF[b]	REF[b]	51.6 (1.1)	REF[b]	REF[b]
Participants with anxiety not taking antidepressants											
Remitted diagnosis	326	8.5	68.7 (0.5)	.95	0.005	77.7 (1.6)	.91	0.008	49.5 (1.4)	.24	0.080
Current diagnosis	701	17.5	68.3 (0.4)	.54	0.035	77.0 (1.1)	.59	0.031	49.7 (1.0)	.19	0.074
Participants with anxiety taking antidepressants											
TCA	60	19.9	76.4 (1.2)	<.001	0.827	60.5 (3.8)	<.001	0.590	32.9 (3.3)	<.001	0.719
SSRI	376	19.1	68.5 (0.5)	.74	0.022	70.6 (1.5)	<.001	0.246	38.5 (1.3)	<.001	0.505
SNRI	116	19.9	71.8 (0.9)	.001	0.339	60.3 (2.7)	<.001	0.596	33.9 (2.4)	<.001	0.680
Test condition											
Control	616	4.0	73.5 (0.4)	REF[b]	REF[b]	65.1 (0.8)	REF[b]	REF[b]	47.6 (0.9)	REF[b]	REF[b]
Participants with anxiety not taking antidepressants											
Remitted diagnosis	326	8.5	73.1 (0.5)	.58	0.038	65.8 (1.1)	.62	0.034	45.6 (1.2)	.18	0.091
Current diagnosis	701	17.5	72.5 (0.3)	.07	0.103	65.8 (0.8)	.56	0.033	46.7 (0.8)	.43	0.045
Participants with anxiety taking antidepressants											
TCA	60	19.9	80.9 (1.2)	<.001	0.802	48.6 (2.7)	<.001	0.799	30.4 (2.8)	<.001	0.790
SSRI	376	19.1	71.7 (0.5)	.005	0.185	61.0 (1.1)	.003	0.197	38.5 (1.1)	<.001	0.417
SNRI	116	19.9	75.1 (0.9)	.09	0.172	55.6 (1.9)	<.001	0.463	34.8 (2.0)	<.001	0.586

[a] Adjusted for respiration rate, age, sex and education, BMI, physical activity, smoking, alcohol use, chronic and heart disease and heart medication
[b] Control is the reference group. All *p* values and effect sizes are for comparison of the group in that specific line and control subjects

contrasts with other previous reports[56]. In contrast to many smaller studies reporting no effect or a detrimental effect of acute or chronic alcohol use on ANS functioning[55,57-61], we found that moderate and mild drinkers had a significantly higher heart rate variability and lower heart rate compared with non-drinking individuals. Our results show that physically active subjects have a lower heart rate and higher SDNN, as observed previously[14,62,63]. RSA, however, was not significantly higher in the more active individuals.Although these lifestyle factors may act as potential confounders, multivariate analyses showed that they did not explain the lower SDNN and RSA in patients with anxiety disorders. Instead, this association seemed to be mainly driven by the effects of antidepressants. Anxious subjects receiving antidepressants showed significantly lower RSA (effect sizes between d=0.415 and d=0.783) and SDNN (effect sizes between d=0.195 and d=0.792), whereas differences between controls and anxious subjects without antidepressants were nonsignificant independent of present or past diagnosis. This effect was also independent of anxiety severity because current anxious subjects without and with medication hardly differed in BAI severity score, whereas they significantly differed in terms of heart rate,

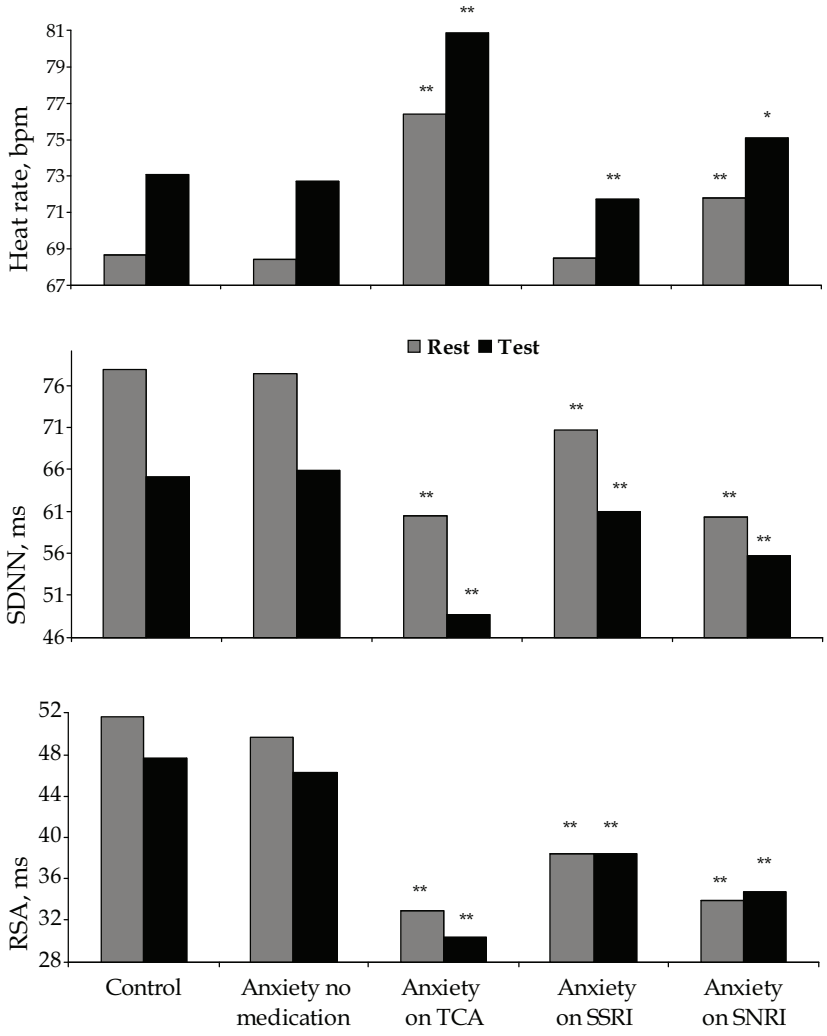

Figure 1. *Mean heart rate, SDNN, and RSA in resting and test conditions of controls, anxious persons not taking antidepressants and anxious persons on antidepressants. *.05≤p<.10, ** p≤005; all p-values compare anxious subjects with controls.*

SDNN, and RSA. Also, additional correction for anxiety severity and comorbid MDD did not change the results. Although the effects of TCAs, which have previously been reported to have a powerful tachycardiac effect[64-66], were the most prominent (effect sizes = around 0.8), the antidepressant effects were not limited to TCAs. Consistently lower SDNN and RSA were also found in anxious patients using SSRIs (effect sizes = between 0.2 and 0.4) and SNRIs (effect sizes = between 0.5 and 0.6).

The above results and conclusions must be weighed by some limitations of this study. First, this study was performed during a clinic visit involving uncommon procedures, unfamiliar research assistants, and interviews with questions of a personal nature. Anxious patients may be more inclined to respond to such challenges with decreased cardiac vagal tone, and our results may have partially reflected this. It is unclear, however, how this "laboratory anxiety" can account for the observed effects of antidepressant medication on RSA and SDNN. Nonetheless, generalizability to a more familiar and less stressful real life setting cannot be assumed without actual ambulatory recording. Second, the demands of the already vulnerable participants of this large longitudinal cohort study did not allow us to add a true stress condition to the design. The test condition was not intended to be stressful and the mild decrease in heart rate variability levels compared with supine rest should be attributed mainly to the change in posture. Therefore, we could not test the idea that ANS reactivity to stressors differs between anxious subjects and healthy controls as is implied by theoretical models like the polyvagal theory and the autonomic flexibility-neurovisceral integration model[67,68]. Finally, we cannot exclude systematic differences in cardiac sympathetic control or intrinsic heart rate between the various groups in this study, which may have affected our measures of heart rate variability and cardiac vagal control. Medication-specific effects on sympathetic nervous system activity, for instance, might explain why we find lower heart rate variability but not the higher heart rate in anxious subjects using SSRIs. To resolve this, additional measures of cardiac sympathetic control would have been needed.

In sum, our findings demonstrate that subjects with an anxiety disorder have a lower SDNN and RSA. The major part of this association was due to the effect of antidepressant use because the use of TCAs and SSRIs as well as SNRIs had a pronounced effect on heart rate variability. As it has been widely established that lowered heart rate variability is a risk factor for cardiovascular morbidity and mortality[11,15,45,48], our findings of lower SDNN and RSA in antidepressant users

could be of importance for clinical practice. However, cause and effect remain to be established. Before longitudinal follow-up data are available, we do not know whether the lower SDNN and RSA are caused by antidepressants and whether the low SDNN and RSA found in medicated subjects is reversed when subjects cease their medication. It is also an open question whether lower heart rate variability found in antidepressant users is outweighed by the beneficial effects of antidepressant medication on anxiety and future heart disease.

REFERENCES

1. Albert CM, Chae CU, Rexrode KM, Manson JE, Kawachi I. Phobic anxiety and risk of coronary heart disease and sudden cardiac death among women. *Circulation.* 2005;111:480-487.
2. Dunner DL. Anxiety and panic: relationship to depression and cardiac disorders. *Psychosomatics.* 1985;26:18-22.
3. Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Tension and anxiety and the prediction of the 10-year incidence of coronary heart disease, atrial fibrillation, and total mortality: the Framingham Offspring Study. *Psychosom Med.* 2005;67:692-696.
4. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry.* 2008;65:62-71.
5. Friedman S. Cardiac disease, anxiety, and sexual functioning. *Am J Cardiol.* 2000;86:46F-50F.
6. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS. Relationship of depression, anxiety, and social isolation to cheart rateonic heart failure outpatient mortality. *Am Heart J.* 2006;152:940-948.
7. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: the HUNT study. *Psychosom Med.* 2007;69:323-331.
8. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. *J Am Coll Cardiol.* 2003;42:1801-1807.
9. Szekely A, Balog P, Benko E, Breuer T, Szekely J, Kertai MD, Horkay F, Kopp MS, Thayer JF. Anxiety predicts mortality and morbidity after coronary artery and valve surgery—a 4-year follow-up study. *Psychosom Med.* 2007;69:625-631.
10. Tully PJ, Baker RA, Knight JL. Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. *J Psychosom Res.* 2008;64:285-290.
11. Dekker JM, Crow RS, Folsom AR, Hannan PJ, Liao D, Swenne CA, Schouten EG. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis risk in communities. *Circulation.* 2000;102:1239-1244.
12. Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, Rautaharju P, Heiss G. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC study. Atherosclerosis risk in communities study. *Am J Epidemiol.* 1997;145:696-706.
13. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. *Clin Exp Hypertens.* 2004;26:637-644.
14. Rosenwinkel ET, Bloomfield DM, Arwady MA, Goldsmith RL. Exercise and autonomic function in health and cardiovascular disease. *Cardiol Clin.* 2001;19:369-387.

15. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham heart study. *Circulation.* 1996;94:2850-2855.
16. Fuller BF. The effects of stress-anxiety and coping styles on heart rate variability. *Int J Psychophysiol.* 1992;12:81-86.
17. Jonsson P. Respiratory sinus arrhythmia as a function of state anxiety in healthy individuals. *Int J Psychophysiol.* 2007;63:48-54.
18. Watkins LL, Grossman P, Krishnan R, Sherwood A. Anxiety and vagal control of heart rate. *Psychosom Med.* 1998;60:498-502.
19. Berntson GG, Cacioppo JT, Grossman P. Whither vagal tone. *Biol Psychol.* 2007;74:295-300.
20. Houtveen JH, Rietveld S, de Geus EJ. Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. *Psychophysiology.* 2002;39:427-436.
21. Brown HN, Kemble SB. Episodic anxiety and cardiac arrhythmias. *Psychosomatics*. 1981;22:907-915.
22. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. *Biol Psychol.* 2007;74:185-199.
23. Cohen H, Benjamin J, Geva AB, Matar MA, Kaplan Z, Kotler M. Autonomic dysregulation in panic disorder and in post-traumatic stress disorder: application of power spectrum analysis of heart rate variability at rest and in response to recollection of trauma or panic attacks. *Psychiatry Res.* 2000;96:1-13.
24. Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA. Altered heart rate variability in panic disorder patients. *Biol Psychiatry.* 1995;37:18-24.
25. McCraty R, Atkinson M, Tomasino D, Stuppy WP. Analysis of twentyfour hour heart rate variability in patients with panic disorder. *Biol Psychol.* 2001;56:131-150.
26. Yeragani VK, Balon R, Pohl R, Ramesh C, Glitz D, Weinberg P, Merlos B. Decreased R-R variance in panic disorder patients. *Acta Psychiatr Scand.* 1990;81:554-559.
27. Cohen H, Benjamin J. Power spectrum analysis and cardiovascular morbidity in anxiety disorders. *Auton Neurosci*. 2006;128:1-8.
28. Licht CMM, de Geus JCN, Zitman FG, Hoogendijk WJG, van Dyck R, Pennix BWJH. Association between major depressive disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA). *Arch Gen Psychiatry.* 2008;65:1358-1367.
29. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, Cuijpers P, de Jong PJ, van Marwijk HWJ, Assendelft WJJ, van der Meer K, Verhaak P, Wensing M, de Graaf R, Hoogendijk WJ, Ormel J, van Dyck R. The Netherlands study of depression and anxiety (NESDA): rationale, objectives and methods. *Int J Meth Psychiatr Res.* 2008;17:121-140.
30. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, Walters EE, Zaslavsky AM. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med.* 2002;32:959-976.
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 2001.
32. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res.* 1994;28:57-84.
33. Steer RA, Kumar G, Ranieri WF, Beck AT. Use of the Beck anxiety inventory with adolescent psychiatric outpatients. *Psychol Rep*. 1995;76:459-465.
34. de Geus EJ, Willemsen GH, Klaver CH, van Doornen LJ. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. *Biol Psychol.* 1995;41:205-227.
35. Willemsen GH, de Geus EJ, Klaver CH, van Doornen LJ, Carroll D. Ambulatory monitoring of the impedance cardiogram. *Psychophysiology.* 1996;33:184-193.
36. Eckberg DL. The human respiratory gate. *J Physiol.* 2003;548:339-352.
37. Grossman P, van BJ, Wientjes C. A comparison of theart rateee quantification methods for estimation of respiratory sinus arrhythmia. *Psychophysiology.* 1990;27:702-714.
38. Houtveen JH, Molenaar PC. Comparison between the Fourier and Wavelet methods of spectral analysis applied to stationary and nonstationary heart period data. *Psychophysiology.* 2001;38:729-735.

39. Goedhart AD, van der SS, Houtveen JH, Willemsen G, de Geus EJ. Comparison of time and frequency domain measures of RSA in ambulatory recordings. *Psychophysiology* 2007;44:203-215.
40. Greenwald AG, McGhee DE, Schwartz JL. Measuring individual differences in implicit cognition: the implicit association test. *J Pers Soc Psychol.* 1998;74:1464-1480.
41. Grossman P, Karemaker J, Wieling W. Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: the need for respiratory control. *Psychophysiology* 1991;28:201-216.
42. Booth M. Assessment of physical activity: an international perspective. *Res Q Exerc Sport.* 2000;71:S114-S120.
43. World Health Organization, Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification. 2008. www.whocc.no/atc Accessed December 2008.
44. Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. *Psychophysiology.* 1993;30:486-495.
45. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation.* 1993;88:927-934.
46. Berntson GG, Cacioppo JT, Quigley KS. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology.* 1993;30:183-196.
47. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation.* 1996;93:1043-1065.
48. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol.* 2007;74:224-242.
49. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, Ziegler D. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. *Clin Auton Res.* 2001;11:99-108.
50. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, Grupi CJ. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. *Am J Cardiol.* 2004;93:381-385.
51. Kupper NH, Willemsen G, van den Berg M, de Boer D, Posthuma D, Boomsma DI, de Geus EJ. Heritability of ambulatory heart rate variability. *Circulation.* 2004;110:2792-2796.
52. Zhang J. Effect of age and sex on heart rate variability in healthy subjects. *J Manipulative Physiol Ther.* 2007;30:374-379.
53. Britton A, Shipley M, Malik M, Hnatkova K, Hemingway H, Marmot M. Changes in heart rate and heart rate variability over time in middle-aged men and women in the general population (from the Whitehall II cohort study). *Am J Cardiol.* 2007;100:524-527.
54. Wu JS, Lu FH, Yang YC, Lin TS, Huang YH, Wu CH, Chen JJ, Chang CJ. Epidemiological evidence of altered cardiac autonomic function in overweight but not underweight subjects. *Int J Obes (Lond).* 2008;32:788-794.
55. Kageyama T, Nishikido N, Honda Y, Kurokawa Y, Imai H, Kobayashi T, Kaneko T, Kabuto M. Effects of obesity, current smoking status, and alcohol consumption on heart rate variability in male white-collar workers. *Int Arch Occup Environ Health.* 1997;69:447-454.
56. Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Short- and long-term effects of cigarette smoking on heart rate variability. *Am J Cardiol.* 1990;65:84-88.
57. Malpas SC, Whiteside EA, Maling TJ. Heart rate variability and cardiac autonomic function in men with cheart rateonic alcohol dependence. *Br Heart J.* 1991;65:84-88.
58. Murata K, Landrigan PJ, Araki S. Effects of age, heart rate, gender, tobacco and alcohol ingestion on R-R interval variability in human ECG. *J Auton Nerv Syst.* 1992;37:199-206.
59. Murata K, Araki S, Yokoyama K, Sata F, Yamashita K, Ono Y. Autonomic neurotoxicity of alcohol assessed by heart rate variability. *J Auton Nerv Syst.* 1994;48:105-111.
60. Ryan JM, Howes LG. Relations between alcohol consumption, heart rate, and heart rate variability in men. *Heart.* 2002;88:641-642.
61. Thayer JF, Hall M, Sollers JJ III, Fischer JE. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *Int J Psychophysiol.* 2006;59:244-50.

62. Goldsmith RL, Bigger JT Jr, Bloomfield DM, Steinman RC. Physical fitness as a determinant of vagal modulation. *Med Sci Sports Exerc.* 1997;29:812-817.
63. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am J Epidemiol.* 2003;158:135-143.
64. Glassman AH, Roose SP, Bigger JT Jr. The safety of tricyclic antidepressants in cardiac patients. Risk-benefit reconsidered. *JAMA.* 1993;269:2673-2675.
65. Pacher P, Ungvari Z, Nanasi PP, Furst S, Kecskemeti V. Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any? *Curr Med Chem.* 1999;6:469-480.
66. Slavicek J, Paclt I, Hamplova J, Kittnar O, Trefny Z, Horacek BM. Antidepressant drugs and heart electrical field. *Physiol Res*. 1998;47:297-300.
67. Friedman BH. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. *Biol Psychol.* 2007;74:185-199.
68. Porges SW. The polyvagal theory: phylogenetic substrates of a social nervous system. *Int J Psychophysiol.* 2001;42:123-146.