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2010

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citation for published version (APA)

Licht, C. M. M. (2010). *Autonomic nervous system functioning in major depression and anxiety disorders*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Cardiac Sympathetic Control in Major Depressive and Anxiety Disorders: An Important Role for Antidepressants

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Submitted

ABSTRACT

Objective: Increased sympathetic activity has been hypothesized to play an important role in the increased risk of cardiovascular disease among persons with a depressive or anxiety disorder, but it is not clear whether increased sympathetic activity reflects a direct effect of anxiety and depression or an indirect effect of antidepressant medication. We tested whether cardiac sympathetic control, measured by the pre-ejection period (PEP) was increased in depressed and/or anxious persons compared to healthy controls, while addressing the possible effects of antidepressants.

Methods: From the Netherlands Study of Depression and Anxiety (NESDA) data were available of 540 control subjects, 1319 subjects with a diagnosis of major depressive (MDD) and/or anxiety disorder of whom 583 subjects used an antidepressant (mean age of total sample 39.9 years, 66.6% female). The PEP was measured non-invasively by ± 1.5 hour of ambulatory impedance cardiography.

Results: Analyses showed that depressed/anxious participants not taking antidepressants did not have shorter PEP than controls. However, subjects with depression/anxiety disorders using tricyclic antidepressants (TCAs) or combined serotonergic/noradrenergic antidepressants (SNRIs) had a significantly shorter PEP compared to controls (12.1ms and 4.9ms shorter, effect sizes of $d=0.726$ and $d=0.203$, respectively). In contrast, subjects with a depression and/or anxiety disorder using selective serotonin re-uptake inhibitors (SSRIs) had a longer PEP than control subjects did (6.6ms longer, effect size $d=0.495$).

Conclusions: This study suggests that MDD and/or anxiety disorders are not associated with increased cardiac sympathetic control, but that TCAs and SNRIs are associated with increased sympathetic control, whereas SSRIs are associated with decreased sympathetic control.

INTRODUCTION

Increased activity of the sympathetic nervous system (SNS) may play an important role in the well established increase in risk for cardiovascular disease in patients with major depressive disorder (MDD) and anxiety disorders¹⁻⁴. Various studies reported increased sympathetic activity in depressed and anxious subjects compared to healthy controls, measured by different indices such as spillover of norepinephrine (NE) and epinephrine (EPI), skin conductance levels, QT interval variability (QTvi), or the pre-ejection period (PEP)⁵⁻¹⁰. However, other studies report no association between psychopathology and SNS activity or decreased SNS activity in subjects with MDD or anxiety disorders¹¹⁻¹⁴, so findings remain inconclusive. A major source of confounding in studies comparing indices of SNS activity between depressed/anxious subjects and controls might be the high prevalence of antidepressants in the former group.

The potential for confounding of autonomic effects by antidepressants was clearly demonstrated in our own recent research on the association between MDD and anxiety disorders and heart rate variability and blood pressure^{15, 16}. Studying blood pressure and heart rate (variability) we found that the putative effects of depression and anxiety on cardiac (para)sympathetic control were largely due to antidepressant use and that depressive or anxious persons not using antidepressants had similar blood pressure and heart rate (variability) as healthy controls. The three major classes of antidepressants, tricyclic antidepressants (TCAs), serotonergic and noradrenergic reuptake inhibitors (SNRIs) and selective serotonin re-uptake inhibitors (SSRIs) were all associated with decreased parasympathetic activity. Remarkably, the expected parallel increases in heart rate and blood pressure were only found in subjects using TCAs and SNRIs, whereas SSRIs seemed to decrease heart rate and blood pressure¹⁷. A hypothetical explanation for this pattern of findings is that SSRIs lead to a decrease in sympathetic activity whereas TCAs and SNRIs have an opposite effect leading to increase in SNS activity^{10,18,19}.

Here we examined the association between cardiac sympathetic control and depression and/or anxiety disorder, taking effects of different antidepressants into account. In 1319 subjects with MDD and/or anxiety disorder and 540 healthy controls we measured the pre-ejection period (PEP) in impedance cardiograms. PEP is a widely used, valid index of sympathetic effects on cardiac contractility²⁰⁻²² and is free from vagal input, which enabled us to investigate whether the

previously found effects of antidepressant use on blood pressure and heart rate were driven by diminished parasympathetic activity only or by an additional increase in sympathetic control over the heart as well. A shortened PEP signals increased inotropic control, i.e. larger sympathetic drive to the left ventricle. In view of our previous results we expect to find a shorter PEP (reflecting increased SNS control) in subjects with MDD or anxiety disorder compared with healthy controls, an effect that is considerably modulated by antidepressants.

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=18-65 years) to examine the long-term course of MDD and anxiety disorders. The rationale, methods, and recruitment strategy have been described elsewhere²³. The NESDA sample consists of 652 persons without depressive or anxiety disorders and 2329 with a (remitted or current) diagnosis of depressive or anxiety disorder. In order 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 health care organizations.

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 a MDD and/ or anxiety disorder (social phobia, generalized anxiety disorder, panic disorder) was ascertained using the lifetime version of the Composite International Diagnostic Interview (CIDI) psychiatric interview (WHO version 2.1). The CIDI establishes diagnoses according to the DSM-IV criteria²⁴ and has shown high inter-rater and test-retest reliability and high validity for MDD and anxiety disorders²⁵. In addition, the severity of anxiety was measured among all subjects using the Beck Anxiety Inventory (BAI²⁶), the severity of depression with the 30-item Inventory of Depressive Symptomatology self-report version (IDS-SR²⁷).

For the present analyses, we selected 540 control subjects with no history of any anxiety disorder, depression or other psychiatric disorder. The second, third and fourth group consisted of persons not taking antidepressants: 196 persons with

a current (6-month recency) anxiety disorder, 219 persons with a current MDD, and 321 persons with a current MDD and anxiety disorder. All diagnoses were based on the criteria defined by the CIDI interview and 82% of the participants had a diagnosis in the past month. The final three groups consisted of 583 persons with a CIDI-diagnosis of remitted or current anxiety disorder or MDD currently using an antidepressant for at least one month; 50 subjects were on a TCA, 126 subjects were on an SNRI and 407 subjects used an SSRI. Medication was determined by copying the names of medicines from the containers brought in by respondents and classified according to the WHO Anatomic Therapeutic Chemical (ATC) classification²⁸. The three antidepressants groups were distinguished based on code N06AA (TCA), ATC code N06AB (SSRI), and code N06AX (SNRI). The remaining 1122 NESDA subjects were excluded from the analyses: 550 subjects were excluded because of only lifetime (more than 6 months ago) diagnoses and no antidepressant use, 152 subjects were using beta-blocking agents, 6 were control subjects but were using an antidepressant, 20 subjects were excluded because they simultaneously used two different types of antidepressants and 394 subjects had missing physiological data due to refusal, equipment failure during assessment, or poor physiological signal quality.

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 participants signed informed consent.

Measurements

Main outcome measures

During a large part of the visit to the research centres, NESDA subjects were wearing the VU University Ambulatory Monitoring System (VU-AMS). The VU-AMS is a light-weight device that unobtrusively records the electrocardiogram (ECG) and changes in thorax impedance (dZ) from six surface electrodes placed at the chest and back of the subjects^{29,30}. From the ECG, the R-wave times were extracted from which, after visual inspection of the interbeat interval time series, heart rate was computed. The pre-ejection period (PEP), an index of inotropic drive to the left ventricle²⁰⁻²² was extracted from the dZ/dt (ICG) signal that was ensemble averaged across one-minute periods time-locked to the R-waves in the ECG. Three time points can be scored in ICG ensemble averages: the upstroke or B-point, the dZ/dt(min) point and the incisura or X-point. The PEP is defined as the interval from the upstroke of the ICG (B-point) which is the onset of the left

ventricular electrical activity, to the $dZ/dt(\text{min})$ point that indicates the beginning of blood ejection through the aortic valve. The left ventricular ejection time (LVET) is defined as the interval from the B-point to the X-point, reflecting closure of the aortic valves.

Independent of cardiac sympathetic drive, the PEP can be prolonged by increases in afterload or decreases in preload. To account for between-subject differences in afterload, mean arterial blood pressure (MAP) was used as a proxy for mean aortic pressure. Systolic (SBP) and diastolic blood pressure (DBP) were recorded in a supine position by two repeated measurements using the OMRON M4 IntelliSense (HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois, USA). MAP was calculated by $(\text{SBP} + 2 * \text{DBP}) / 3$. No non-invasive measures of between-subject differences in preload that can be applied in large samples are currently available³¹. Within a subject, however, postural changes are the main source of changes in preload. To avoid confounding of PEP by posture, three periods were identified in the total recording period in which subjects did not change posture and were quietly sitting for a prolonged period. Movement registration through vertical accelerometry was used to excise fragments of the recording where subjects were physically active (e.g. bathroom visit). Subjects did not change posture and were sitting for a prolonged period in three assessment parts. Interview session I (investigating somatic health, functioning and health care 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 non-stressful computer task (sitting, 16.2 ± 4.0 minutes) were used in the final analyses.

Exploratory mixed model analysis showed that differences in PEP between our study groups were consistent over these assessment parts. Therefore, data during the computer task and interview parts were collapsed to create one single PEP and LVET value per subject, averaged over 90.2 ± 23 minutes time. The two relevant time points (B-point and X-point) were scored in each of these large-scale ensembles by a single rater (CL). Ensembled ICGs that showed irregularities or had ambiguous B or X points were not considered valid and were rejected and removed from further processing during visual inspection^{32, 33}. A second independent rater (EdG) re-scored 300 random chosen subjects yielding an interrater reliability for PEP scoring of 0.84.

Covariates

Sociodemographics included age, sex, and education in years. In addition, various health indicators were considered as covariates since these have been linked with MDD/anxiety disorder and sympathetic nervous system (SNS) 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 (IPAQ³⁴) 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 non-smoker versus smoker. For regular alcohol use, a continuous variable was computed as mean number of alcoholic consumptions a day. The number of other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcer) ascertained by self-report was computed into a count variable. Self-reports of the presence of heart disease were used for ascertainment of cardiovascular diseases (CVD; including coronary disease, cardiac arrhythmia, angina, heart failure and myocardial infarction), only when confirmed with the use of specific medication. Dichotomous variables for the use of medication were computed, scoring 'yes' if subjects frequently (daily or more than 50% of the time) used a medication. For the confirmation of CVD, cardiac medication (starting with ATC-code C01DA, and C08) was used. In a separate adjustment step, we checked whether results were further influenced by taking individual differences in heart rate and mean arterial pressure into account^{35, 36}.

Statistical analyses

Data was analyzed using SPSS 15.0. Characteristics across groups were compared using ANOVA and χ^2 -statistics. Analyses of variance were conducted to compare PEP across the controls, the unmedicated depressed and/or anxious subjects, and the depressed and/or anxious subjects using different antidepressants. These analyses were repeated with consideration of covariates (age, sex, education, BMI, smoking, alcohol use, physical activity, cardiovascular disease, and chronic disease count). Subsequently, effect sizes were calculated with Cohen *d* (1988) defined as the difference in the mean PEP between groups, divided by the pooled standard deviation of these groups. Because PEP divided by the LVET may better reflect ventricular ejection fraction than PEP by itself according to some sources³⁷ all analyses were repeated using PEP/LVET.

Table 1. Main Sample Characteristics for Controls, Individuals With Major Depressive Disorder and/or Anxiety Disorder not Using Antidepressants and Individuals With Major Depressive Disorder and/or Anxiety Disorder Using Antidepressants

Characteristics	Participants, %					<i>p</i> ^a
	Control (n=540)	No antidepressant (n=736)	On TCA (n=50)	On SNRI (n=126)	On SSRI (n=407)	
Demographics						
Age, mean (SD), years	39.7 (14.6)	38.7 (12.5)	46.5 (10.3)	43.0 (10.7)	40.5 (11.6)	<.001
Female Sex	61.7	68.3	74.0	63.5	70.3	.03
Education, mean (SD), years	12.9 (3.2)	11.9 (3.2)	11.0 (3.3)	11.8 (3.3)	11.7 (3.4)	<.001
Lifestyle and health factors						
Body Mass Index, mean (SD), kg/m ²				25.7 (5.5)	25.8 (5.6)	.002
Physical Activity, mean (SD), 1000 METmin/week	3.9 (3.1)	3.7 (3.1)	3.3 (2.5)	3.1 (3.1)	3.5 (3.3)	.13
Smoking	27.0	42.3	50.0	51.6	46.4	<.001
Alcohol, mean (SD), no./day	1.02 (1.3)	1.01 (1.4)	0.82 (1.8)	0.78 (1.0)	0.91 (1.6)	.31
Chronic diseases, mean (SD), no.	1.04 (1.1)	1.32 (1.2)	1.42 (1.5)	1.32 (1.3)	1.26 (1.2)	<.001
Cardiovascular Disease	7.4	7.7	4.0	6.3	4.7	.001
Psychopathology^b						
Current MDD	0	29.8	16.0	23.0	17.7	<.001
Current anxiety disorder	0	26.6	22.0	20.6	20.1	<.001
Current MDD and anxiety disorder	0	43.6	54.0	50.0	46.6	<.001
IDS score, mean (SD)	8.2 (7.2)	28.2 (11.9)	29.5 (12.7)	32.2 (12.6)	29.9 (13.3)	<.001
BAI score, mean (SD)	10.6 (10.1)	13.8 (11.1)	14.1 (10.7)	14.4 (11.9)	14.2 (11.2)	<.001

BAI, Beck anxiety inventory; IDS, inventory of depressive symptomatology; MDD, major depressive disorder; MET, multiple of the resting metabolic rate; SNRI, noradrenergic and serotonergic working antidepressant; SSRI, Selective serotonin re-uptake inhibitors; TCA, tricyclic antidepressant

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

^b In the groups on antidepressants the percentages do not add up to 100% since subjects with a remitted diagnoses were included but percentages were not presented in this table

RESULTS

Table 1 shows the main characteristics of the control group, the subjects with MDD and/or anxiety disorder not using an antidepressant, and the subjects with MDD and/or anxiety disorder using antidepressants. Compared to healthy controls, depressed or anxious subjects were older (only those using antidepressants), more often female, had fewer years of education, had a higher BMI, performed less physical activity (only true for those taking antidepressants), smoked more often, had more chronic diseases and less CVD (those on antidepressants). As seen in Table 1, the mean severity score for depression (IDS) and anxiety (BAI) are not significantly lower in unmedicated depressed and/or anxious subjects compared to the medicated subjects.

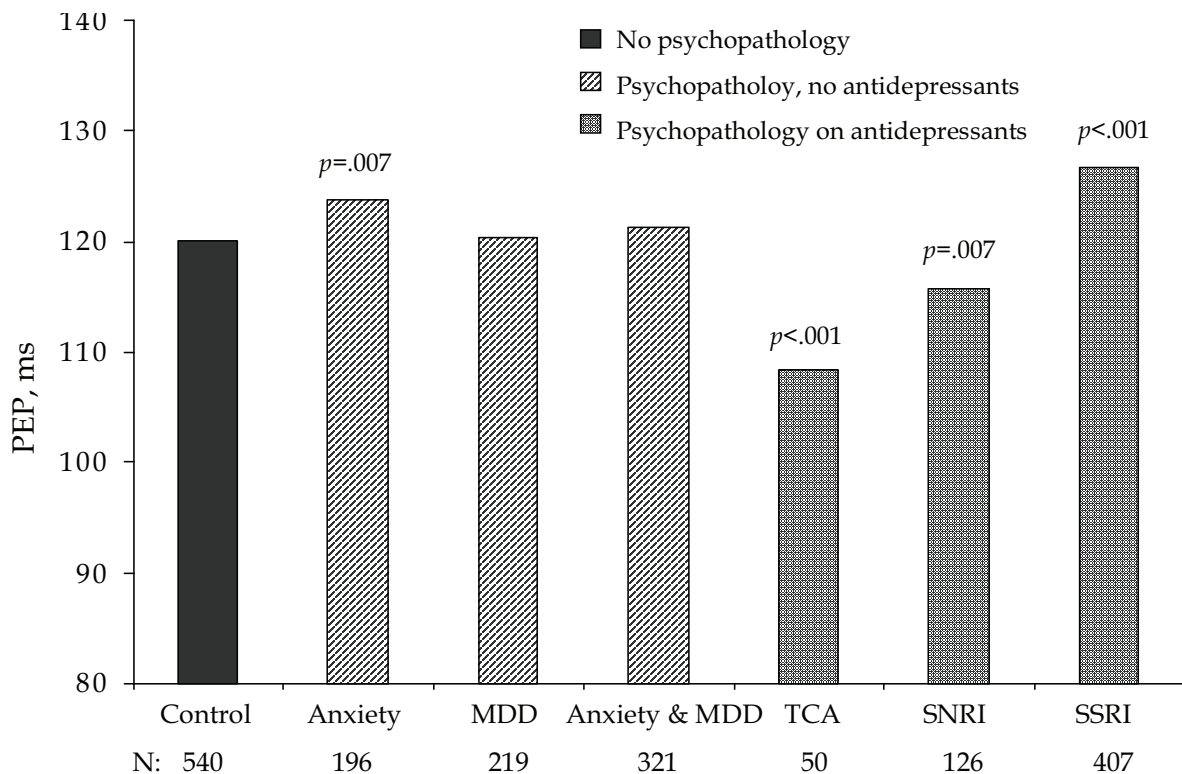


Figure 1. Mean unadjusted pre-ejection period (ms) of controls, unmedicated patients with MDD and/or anxiety and medicated persons with MDD and/or anxiety. P-values are in comparison with control group.

Figure 1 represents the mean unadjusted PEP for the control, the anxious, the MDD and the comorbid group not taking antidepressants and the MDD and anxiety disorder group taking different antidepressants. Depressed and anxious subjects using TCAs had a 10% shorter PEP compared to the healthy controls

($p < .001$) and subjects using SNRIs had a 4% shorter PEP compared to the healthy controls ($p = .007$). In contrast, subjects using SSRIs had a 6% longer PEP compared to the healthy controls ($p < .001$). The PEP in MDD subjects not taking antidepressants or MDD/anxiety comorbid subjects not taking antidepressants was not different from the PEP in healthy controls. Current anxious subjects not taking antidepressants had a 2.5% longer PEP compared to healthy controls ($p = .007$) which suggests lower sympathetic drive in these subjects, in contrast to the expected direction of the effect.

Table 2. The Pre-ejection Period (PEP) by Medication Group^a (n=1859)

	N	IDS score, mean	BAI score, mean	PEP, mean (SE), ms	<i>p</i>	Cohen <i>d</i>
Control	540	8.2	10.6	120.2 (0.7)	REF ^b	REF ^b
Current anxiety disorder, no antidepressant	196	21.9	13.5	123.5 (1.2)	.02	0.197
Current MDD, no antidepressant	219	26.2	14.5	120.3 (1.1)	.93	0.007
Current anxiety and MDD, no antidepressant	321	33.3	13.4	121.2 (0.9)	.39	0.061
MDD/Anxiety on TCA	50	29.5	14.1	108.1 (2.3)	<.001	0.726
MDD/Anxiety on SNRI	126	32.2	14.4	115.3 (1.5)	.003	0.203
MDD/Anxiety on SSRI	407	29.9	14.2	126.8 (0.8)	<.001	0.495

^a Adjusted for age, sex, education, BMI, physical activity, smoking, alcohol use, chronic disease & CVD

^b Control is the reference group. All *p* values and effect sizes are for comparison with the control subjects

Table 2 shows the results of two ANCOVA analyses. The PEP of the anxious, depressive, comorbid and antidepressant groups was compared with the PEP of the control group, corrected for age, sex, education, lifestyle and health factors. Results show that these covariates did not influence the group differences in PEP: PEP remained significantly shorter in TCA users, SNRI users and significantly longer in SSRI users and non-medicated persons with pure anxiety disorder as compared to controls. Additional adjustment for heart rate and mean arterial pressure (data not shown) also did not influence the results for the comparison between medicated subjects and controls. However, the difference in PEP between unmedicated anxious and healthy control persons was reduced to non-significant ($p = .13$, effect size $d = 0.118$). Repeating all these analyses using PEP divided by the left ventricular ejection time yielded very similar findings, in line with the high correlation between PEP and PEP/LVET ($r = .80$).

DISCUSSION

This large-scale cohort study showed that cardiac sympathetic drive, as measured by the PEP, is not increased in subjects with a current MDD and/or anxiety disorder compared with healthy controls, as long as subjects are not using antidepressant medication. Subjects using TCAs or SNRIs had significantly shorter PEP, which suggests increased cardiac sympathetic control, and users of SSRIs had a significantly longer PEP, indicative of decreased cardiac sympathetic control, compared with healthy controls and non-medicated subjects. Since IDS and BAI-scores were similar in depressed and anxious subjects taking and not taking antidepressants, severity of the anxiety or depressive disorder does not seem to explain the differences in PEP between the unmedicated subjects and the TCA and SNRI users.

Our findings are in contrast with several papers that report increased sympathetic activity in depressed or anxious subjects^{5,7-10}. Explanations for these different results may concern differences in sample size. For example, Gold *et al.* (2005), reported mean NE levels in 10 depressed subjects and 12 healthy controls and Guinjoan *et al.* (1995) described the differences in sympathetic skin response levels between 18 depressed patients and 18 healthy controls. Also, some of these studies did not consider antidepressant medication⁶ or excluded antidepressant use for a relatively short period prior to testing (10 days-2 weeks)^{7,8} and the reported increase in sympathetic activity might largely be caused by the current or persistent effects of TCAs or SNRIs.

Our results suggest potential SNS activity increasing effects of TCAs and SNRIs and lowering effect of SSRIs on cardiac sympathetic drive, which is consistent with most previous studies on the effects of these drugs³⁸⁻⁴³. Differential effects of SNRI and SSRI in MDD patients were also seen by Kotschke *et al* (2009) who reported a larger shift in autonomic balance toward sympathetic modulation in the SNRI medicated patients compared to SSRI medicated patients. Importantly, they used QT variability as the main index of cardiac sympathetic activity rather than the PEP: the striking congruence between the PEP and QT variability results further adds credence to our findings. However, these differential SNS effects of the various classes of antidepressants may critically depend on the dose and duration of medication use and not all studies have found similar results⁴⁴⁻⁴⁶. Our study was a large observational cohort study in which doses varied considerably between patients whom had been on antidepressants from one month through a

maximum of 35 years with an average of 2.9 years. Most studies that find decreased or similar SNS activity in TCA or SNRI users, assessed SNS activity before and after treatment with a single fixed dose for all subjects.

A limitation of our study is that the PEP is a complex measure that does not only reflect cardiac sympathetic drive. Although within-subject differences in preload and afterload were likely to be minimal because all measurements were done in a sitting posture, effects of between-subject differences in afterload and preload may be incompletely captured by the covariates MAP and heart rate. In addition, cardiac adrenoceptor sensitivity, for instance by heart rate responsiveness to beta-adrenergic agonists, was not assessed. The interpretation of PEP as a measure of individual differences in cardiac sympathetic drive may be compromised if the effects of increased sympathetic drive are masked by a strong downregulation of cardiac beta-receptors. We cannot rule out that subjects with MDD or anxiety disorder have decreased beta-receptor sensitivity. To fully falsify the hypothesis that the association between MDD or anxiety disorder and cardiovascular disease derives from an over-active SNS, additional studies are needed that address the cardiac adrenoceptor status of MDD and anxiety patients. We note, however, that downregulation of beta-receptors in subjects with psychopathology would not only have led to an underestimation of the effect of MDD and anxiety but also of the effects of TCAs, SNRIs, and SSRIs which would then have been even larger than found here. A further limitation of our study is that it is based on cross-sectional data only, so further longitudinal analyses are needed to clarify causality of the found associations.

These limitations were balanced by strong points: This is the first study with a large enough sample, including both healthy controls and subjects with MDD and/or anxiety disorders not using antidepressants as well as subjects using different types of antidepressants, to separate antidepressant effects from those of the psychiatric condition per se. Also, prolonged recording of the impedance cardiogram under standardized conditions increased the confidence in the reliability of the PEP assessment.

We conclude that there are rather large differences in cardiac sympathetic control across different antidepressant classes. These results converge with several studies reporting increased occurrence of hypertension and adverse cardiovascular events in patients using TCAs and SNRIs^{10, 17, 47-49}. The detrimental effect of TCAs and SNRIs on the SNS might, therefore, explain a part of the well established relation between MDD/anxiety and cardiovascular disease. This would have

consequences for the optimal pharmacological treatment of depressive and anxiety disorders in patients at increased risk for cardiovascular disease. For these patients, SSRIs may be more appropriate because they do not appear to yield the same adverse effects on sympathetic drive as observed for TCAs and SNRIs.

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