ELSEVIER

Psychiatry Research 113 (2002) 139–149

PSYCHIATRY RESEARCH

www.elsevier.com/locate/psychres

Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment

Marcus W. Agelink[a,*], Cavit Boz[b], Heiko Ullrich[a], Jürgen Andrich[c]

[a]*Department of Biological Psychiatry and Neuroscience, Evangl. Clinics Gelsenkirchen, Ruhr-University of Bochum, Munckelstr. 27, D-45879 Gelsenkirchen, Germany*
[b]*Department of Neurology, University of Trabzon, Trabzon, Turkey*
[c]*Department of Neurology, St. Josef-Hospital, Ruhr-University of Bochum, Gelsenkirchen, Germany*

Received 12 December 2001; received in revised form 19 July 2002; accepted 26 September 2002

Abstract

A high sympathetic and/or a low cardiovagal activity in patients with major depression (MD) may contribute to the higher cardiac morbidity and mortality of MD patients. Standardized tests of heart rate variability (HRV) allow a quantitative estimation of autonomic nervous system function. However, previous studies on the relationship between HRV and MD have revealed conflicting results. Our study compared time and frequency domain HRV indices (5-min resting study, deep breathing test, Valsalva test) between 32 patients with MD (DSM-III-R) and 64 non-depressed controls. The severity of depressive symptoms was assessed by the Hamilton Depression Scale (HAM-D); patients were divided into subgroups with moderate (M-HAM-D <25) or severe depressive symptoms (S-HAM-D $\geqslant 25$). After controlling for age, gender and smoking, S-HAM-D patients showed a higher heart rate and a significantly lower modulation of cardiovagal activity compared to controls. Although some of the HRV indices of the M-HAM-D group did not differ significantly from controls, they were in the expected direction. There was a significantly negative correlation between the HAM-D scores and the vagal HRV indices, suggesting a direct association between the severity of depressive symptoms and the modulation of cardiovagal activity. Clinical consequences arising from these findings and possible implications for treatment are discussed.

Keywords: Major depression; Antidepressive treatment; Autonomic nervous system; Heart rate variability; Mortality, cardiovascular

1. Introduction

There is accumulating clinical evidence indicating that (1) the existence of a depressive disorder is associated with increased cardiovascular morbidity and mortality, and that (2) depression represents an independent predictor for an inferior outcome in patients with a pre-existing cardiovascular disease (summarized in Musselman et al., 1998). A possible explanation for this relationship is that depressive disorders influence autonomic nervous system (ANS) function in a manner characterized

*Corresponding author. Tel.: +49-209-160-1601; fax: +49-209-160-2685.

0165-1781/02/$ - see front matter
PII: S0165-1781(02)00225-1

Table 1
Demographic data of the study population

	Controls total ($n=64$)	Patients with major depression	
		M-HAM-D ($n=16$)	S-HAM-D ($n=16$)
Mean age (years)	46.6±11.9	44.3±12.6	53.5±15.8
(Range)	(29–76)	(30–74)	(29–74)
Gender (m/w)	22/42	5/11	6/10
Smokers/non-smokers	21/43	5/11	4/12

Patients with MD were divided into two subgroups according to the severity of depressive symptoms assessed by the HAM-D score (group M-HAM-D < 25 points, group S-HAM-D ⩾ 25 points).

by a reduced parasympathetic and/or increased sympathetic tone. Accepting on the one hand that a raised sympathetic activity is related to a higher susceptibility towards life-threatening cardiac arrhythmias and the development of coronary heart disease (Schwartz et al., 1992), and on the other that vagal activity exerts a cardioprotective effect (Lown and Verrier, 1976; Ben-David and Zipes, 1988), it is tempting to speculate that a higher sympathetic and a lower parasympathetic activity in patients with depressive disorders are related to the high cardiac morbidity and mortality of these patients.

Standardized measurements of heart rate variability (HRV) represent a cost-effective, non-invasive procedure for investigating cardiac ANS function (Task Force Report, 1996). However, experts disagree as to whether a depressive mood can affect HRV: depressive patients show a reduction of HRV (Dalack and Roose, 1990; Rechlin et al., 1994; Guinjoan et al., 1995; Tulen et al., 1996; Stein et al., 2000) or no difference compared to non-depressed controls (Yeragani et al., 1991; Moser et al., 1998). These divergent results might, on the one hand, be explained by methodological differences in measuring HRV (e.g. application of various HRV tests at rest or with various provocation maneuvers) and, on the other hand, by differences in the patient samples (e.g. age, sex and severity of depressive symptoms). This problem was addressed in our study by applying strict inclusion criteria, a standardized diagnostic procedure, an adequate statistical analysis of HRV considering age, sex and the severity of depressive symptoms, and by comparing patient data with those obtained from a large group of healthy controls. Our study compared HRV between untreated patients with DSM-III-R major depression (MD) and healthy controls. The study was undertaken to clarify whether (1) MD patients compared to healthy controls show a reduction in HRV as an expression of a reduced modulation of vagal activity to the heart, and (2) whether a correlation exists between the severity of depressive symptoms and the cardiovagal modulation of heart rate.

2. Methods

2.1. Study population

The study was approved by the ethical committee of the University of Bochum. Patients and controls gave their written informed consent. The sample comprised 35 patients, who in a structured interview fulfilled the DSM-III-R criteria for a major depressive disorder (Wittchen et al., 1991), and who showed a normal sinus rhythm in the ECG. The patients were neither suffering from nor had a history of any other psychiatric illnesses. Fifteen patients (7 male, 8 female) had received a tricyclic antidepressant (TCA) before the start of the study. Six patients had received doxepine (dosing in 5 cases 100 mg/d, in 1 case 150 mg/d) and six had received amitriptyline (dosing in 4 cases 75 mg/d, in the remaining 2 cases 100 mg/d); the remaining three patients had received imipramine (75 mg/d). For medications with anticholinergic side effects, a washout period of at least 48 h before testing HRV has been recommended (Low and Pfeifer, 1993). We only included patients who had not received any

antidepressant medication for at least 6 days before study entry. Seven of the 15 patients had received no treatment for at least 2 weeks. Twelve patients had received incidental treatment with lorazepam (up to 3 mg/d) during the week before study entry. Patients who had taken medications with very long half-lives (e.g. fluoxetine) within 4 weeks before the start of the study were excluded.

The severity of the depressive symptoms was classified according to the Hamilton Depression Scale (HAM-D). The rating was performed by an experienced psychiatrist (M.A.), who was blind to the results of the autonomic tests. Patients were divided into two subgroups according to the severity of depressive symptoms. As the cut-off level, we chose the median HAM-D score (24.5 points). In this way two groups were formed of equal size for statistical comparisons: patients with a HAM-D score <25 points formed the M-HAM-D group with a moderate severity of depressive symptoms, while the remainder formed the group with severe depressive symptoms (S-HAM-D).

The control group consisted of students, physicians, nurses, office employees and other workers (e.g. warehouse workers, kitchen and cleaning personnel) of the hospitals in Gelsenkirchen and Bochum. None of them had a history of any psychiatric illness and all were free of any medication. Patients and controls were matched according to their socioeconomic background and were comparable in physical state and fitness. Neither controls nor depressed subjects had any history of cardiovascular, respiratory, endocrinological, neurological or other physical illnesses known to affect HRV (including alcohol or drug abuse). Smokers were not excluded.

2.2. Autonomic nervous system function tests

Subjects were asked to take their normal breakfast on the study day, although caffeine-containing drinks and smoking were not allowed before the recording session. Examinations of patients and controls were all performed in the same order and between 8:30 and 10:00 in the morning. We chose three HRV tests to allow an evaluation of HRV under various conditions: during a standardized 5-min resting study (Task Force Report, 1996), HRV is measured with relaxed spontaneous respiration, while with the deep breathing test, forced, controlled, metronomic breathing is employed. The third test, the Valsalva maneuver, involves complex interplays between several populations of afferent autonomic receptors, and between efferents from both the sympathetic and parasympathetic branch of the ANS (Eckberg, 1980). Therefore, the Valsalva ratio depends on a functional integrity between both sides of the ANS, and does not primarily reflect parasympathetic activity alone.

The evaluation and execution of HRV measurements was based on previously published experimental procedures (Task Force Report, 1996; Agelink et al., 2001b) and will only be explained in brief here. For HRV analyses we used the NEURODIAG software program (Lambeck, Munich, update of the ProSciCard). The study started with a 5-min resting examination followed by an HRV measurement during deep respiration and the Valsalva test. The resting heart rate (HRr) was defined as the average heart rate during the 5-min resting examination. In the time domain, the coefficient of variation (CV) and the root mean square of successive differences (RMSSD) both at rest (e.g. CVr; RMSSDr) and during deep respiration (e.g. CVd; RMSSDd) served to describe parasympathetic modulation. Power spectral analysis was calculated by a Fast-Fourier transformation, whereby three frequency bands were automatically separated: VLF band (very low frequency: 0.003–0.04 Hz), LF band (low frequency: 0.04–0.15 Hz), HF band (high frequency: 0.15–0.4 Hz). Due to the short 5-min analysis period, a conclusive interpretation of the VLF power was not possible (Task Force Report, 1996), and for this reason we restricted the evaluation to LF and HF power: the HF band coincides with the respiratory frequency and reflects mainly respiration-linked variations in heart rate resulting from centrally mediated cardiac vagal control (Task Force Report, 1996). The LF band is probably associated with both parasympathetic and sympathetic modulation (Akselrod et al., 1981; Pomeranz et al., 1985; Task Force Report, 1996). The normalised LFnu (HFnu) power was calculated by dividing the absolute power by the total power (defined as the sum of each spectral component) and multiplying by 100. The

LF/HF ratio was calculated from the absolute values of the LF and HF power for each subject and is considered by some (Pagani et al., 1986; Lanza et al., 1997), although not all researchers (Eckberg, 1997), as an indicator of the sympathetic/parasympathetic balance. For the deep respiration test (DBT), probands were instructed to take six deep breaths/min. The coefficient of variation (CVd) and the RMSSDd were calculated from a total of 100 artifact-free R–R intervals (Agelink et al., 2001b). For the Valsalva test the patients rested in a sitting position and were instructed to use a mouthpiece with an air leak to maintain a mercury manometer at 40 mmHg for 15 s. The Valsalva ratio was defined as the quotient of the longest R–R interval in a period of 20 heart beats after stress divided by the shortest interval during stress.

Blood pressure was measured manually using a cuff fixed on the left arm. The average arterial resting blood pressure was defined as the mean of two consecutive measurements made at 2-min intervals, after the patients had been lying at rest for at least 10 min on an examination bench.

2.3. Statistics

Demographic data of patients and controls were compared using the Mann–Whitney *U*-test and χ^2-test, wherever appropriate. Because the HRV indices were skewed, all HRV indices (except the LF/HF ratio) were log-transformed; after logarithmic transformation, the HRV indices showed a normal distribution. To compare the HRV between patients and controls, a multivariate analysis was used employing group (controls, M-HAM-D, S-HAM-D) and gender as independent factors, HRV indices as dependent variables, and age and smoking as covariates. Statistical significances of group differences were re-evaluated using a one-way ANOVA with a post hoc comparison of means using Duncan's multiple range test. Correlations between variables were calculated using Pearson correlation coefficients.

3. Results

3.1. Clinical data

In order to guarantee a high quality of HRV recordings, only patients who showed at least 98% artifact-free and correctly identified QRS complexes within the measuring period of all three HRV tests were considered for statistical evaluation; this criterion was fulfilled in 32 patients. As expected, patients of the M-HAM-D group showed a lower mean HAM-D score ($P<0.001$): on average it was 22.1 (S.D. 1.3 points; range 20–24) in the M-HAM-D group and 28.5 (S.D. 3.0 points, range 25–34) in the S-HAM-D group. Seven patients of the M-HAM-D group and eight patients of the S-HAM-D group had received a TCA before the start of the study, which in all cases had already been discontinued at least 6 days prior to HRV measurement. Significant differences were not found regarding the demographic variables (age, sex, smoking) when comparing the two patient subgroups, and when comparing each of the two subgroups with non-depressed controls (Table 1).

3.2. Heart rate variability and blood pressure

With all patients, resting blood pressure was within normal ranges; there were no significant differences in blood pressure between healthy controls and MD patients (data not shown). Multivariate analysis (covariates age and smoking), with the independent factor 'group' (controls, M-HAM-D, S-HAM-D) and the HRV indices as dependent variables (MANCOVA, d.f.=2,91), showed a significant effect for the factor 'group' on the resting heart rate ($F=3.96$, $P=0.022$), the CV, and the RMSSD both at rest (CVr, $F=3.01$, $P=0.050$; RMSSDr, $F=3.20$, $P=0.045$) and during deep respiration (CVd, $F=3.31$, $P=0.041$; RMSSDd, $F=4.34$, $P=0.016$), the spectral HF power ($F=3.70$, $P=0.029$) and on the Valsalva ratio ($F=5.49$, $P=0.006$). All these significant group effects remained when gender was considered as a second independent factor (MANCOVA, d.f.=2,88) in addition to group, although there was only a trend regarding the resting heart rate ($F=2.48$, $P=0.09$). Since some patients had already received TCAs (which are known to reduce HRV), we repeated the statistical calculation on untreated MD patients alone ($n=17$). This process produced no new findings: multivariate analysis (covariates age and smoking) showed either a clear trend or a significant effect for the factor 'group' (controls,

Table 2
Summary of the time and frequency domain HRV indices in patients with MD and non-depressed controls

	Controls total ($n=64$)	Patients with major depression	
		M-HAM-D ($n=16$)	S-HAM-D ($n=16$)
5-min resting			
HRr (bpm)	71.4±9.0	78.2±14.0*	76.7±13.6*
log CVr (%)	0.61±0.17	0.59±0.15	0.45±0.20*,**
log RMSSDr (ms)	1.36±0.24	1.30±0.24	1.15±0.26*
log LF power (ms^2)	2.80±0.42	2.76±0.36	2.58±0.53
LF power (nu)[a]	34.0±13.9	31.7±11.1	35.7±10.5
log HF power (ms^2)	2.58±0.47	2.45±0.55	2.13±0.52*
HF power (nu)[a]	22.5±13.5	20.7±16.7	15.7±10.8
LF/HF ratio	2.33±2.07	3.03±2.62	3.86±3.22*
Deep respiration			
log CVd (%)	0.80±0.21	0.81±0.23	0.59±0.28*,**
log RMSSDd (ms)	1.49±0.25	1.43±0.35	1.22±0.34*,**
Valsalva			
Valsalva ratio	1.41±0.23	1.27±0.22*	1.20±0.20*

The values given are means (±S.D.). *List of abbreviations:* resting heart rate (HRr); nu, normalized units; time domain HRV indices included the coefficient of variation (CV) and the root mean square of successive differences (RMSSD); frequency domain HRV indices included the low frequency (LF) power (0.04–0.15 Hz) and the high frequency (HF) power (0.15–0.4 Hz); the LF/HF ratio serves to describe the sympathovagal balance. Statistical comparisons involved a one-way ANOVA with a post hoc comparison of means by Duncan's multiple range test.

[a] The normalised LFnu (HFnu) power was calculated by dividing the absolute LF (HF) power by the total power (defined as the sum of each spectral component) and multiplying by 100.

* $P<0.05$ compared to healthy controls.

** $P<0.05$ compared to the M-HAM-D group.

M-HAM-D, S-HAM-D) on resting heart rate ($F=2.86$, $P=0.064$), the CV and the RMSSD both at rest (CVr, $F=2.90$, $P=0.061$; RMSSDr, $F=2.64$, $P=0.068$) and during deep respiration (CVd, $F=4.69$, $P=0.012$; RMSSDd, $F=5.94$, $P=0.004$), the spectral HF power ($F=3.13$, $P=0.049$) and the Valsalva ratio ($F=5.29$, $P=0.007$). All these significant group effects also remained when gender was considered as a second independent factor (MANCOVA, d.f.=2,75) in addition to group.

Table 2 shows the mean values of the HRV indices between the patient sub-groups and controls. Post hoc comparison of means demonstrated that patients of the S-HAM-D group had the lowest HRV indices; significant differences compared to non-depressed controls resulted for all the HRV indices studied except spectral LF power. Analysis of only untreated patients revealed the same result ($n=17$). The mean CV and the RMSSDd in the S-HAM-D group were significantly lower not just in comparison to healthy controls, but also compared to the M-HAM-D group (ANOVA with Duncan's multiple range test, $P<0.05$). This result was confirmed also when untreated patients were analyzed alone. The only significant differences between patients of the M-HAM-D group and healthy controls related to the resting heart rate and the Valsalva ratio (Table 2).

With the exception of the LF power and the LF/HF ratio, the remaining HRV indices mainly reflect modulation of vagal activity to the heart. Overall, therefore, the described pattern of findings illustrates that vagal modulation is lowered under both conditions, i.e. at rest and during deep breathing, amongst S-HAM-D patients compared to non-depressed controls. The reduced modulation of vagal activity is accompanied by a subsequent displacement of the sympathovagal balance in favour of sympathetic modulation (expressed as a higher LF/HF ratio) and a higher resting heart rate amongst patients of the S-HAM-D group compared to healthy controls.

There was a significantly negative correlation ($P<0.05$) between the severity of depressive symptoms (assessed by the HAM-D score) and vagal HRV indices; this concerned the variation coefficients (CVr, $r=-0.42$; CVd, $r=-0.48$), the root mean square of successive differences (RMSSDr, $r=-0.44$; RMSSDd, $r=-0.39$) as well as the absolute spectral HF power ($r=-0.40$). For the HF power expressed in normalised units (HFnu), statistical analysis only revealed a trend ($r=-0.31$). When untreated patients were considered alone, a similar picture was seen with correlation coefficients ranging from -0.41 (e.g. CVr) to -0.55 (e.g. RMSSDr); for the spectral HFnu there was now a significant effect ($r=-0.50$). No correlation existed between the Valsalva ratio, the resting heart rate and the HAM-D scores.

4. Discussion

4.1. Reduced HRV in patients with major depression

This study compared cardiac ANS function assessed by standardized tests of HRV between untreated MD patients and healthy controls. We found that MD patients had a higher resting heart rate and a lower Valsalva ratio compared to non-depressed controls. This finding replicates the results of our earlier study (Agelink et al., 2001a). However, in the current study, we also compared HRV between patient subgroups with a moderate and severe expression of depressive symptoms (measured by their HAM-D scores): we found that only severely depressive patients (HAM-D score $\geqslant 25$ points) showed a reduced HRV, and more precisely, a significantly lower modulation of cardiac vagal activity compared to non-depressed controls. Associations between a reduced HRV and a higher risk of cardiovascular morbidity and/or mortality have been shown for a number of clinical conditions such as alcoholism, diabetes mellitus, myocardial infarction and chronic congestive heart failure (Johnson and Robinson, 1988; Ewing and Clarke, 1986; Multicenter Post-infarction Research Group, 1987; La Rovere et al., 1998; Szabo et al., 1987). Moreover, an imbalance in cardiac ANS function in favour of sympathetic activity (measured as a high LF/HF ratio) increases the risk for cardiac morbidity or mortality in patients with pre-existing cardiac diseases such as unstable angina or myocardial infarction (Lanza et al., 1997), and even in apparently healthy subjects without structural heart disease (Molgaard et al., 1991). For this reason it seems plausible that the pattern of findings consisting of a reduced HRV and a displacement of sympathovagal balance in favour of sympathetic modulation, which we found here amongst severely depressive patients, is at least partly responsible (together with other potential factors; for a summary, see Musselman et al., 1998) for the higher cardiovascular mortality seen in severely depressive patients. However, epidemiological studies have found that even mildly depressed patients are at increased risk for mortality, although less so than more severely depressed patients (Barefoot and Schroll, 1996; Lesperance et al., 1996). Although in our study some of the HRV indices of the M-HAM-D group did not differ significantly from the HRV indices in non-depressed controls, they were in the expected direction. Thus, the results of our study are consistent with previous findings from prognostic studies. The present study, together with our earlier results (Agelink et al., 2001a), allows even a direct correlation to be assumed between the degree of severity of depressive symptoms and modulation of cardiovagal activity; the more severe the depressive symptoms, the lower is the cardiovagal activity (measured according to time and frequency domain HRV indices at rest and with deep metronomic breathing).

4.2. Clinical consequences and implications for antidepressive treatment

In overview, our study showed that MD patients have disturbed cardiac ANS function, manifested clinically as an increase in resting heart rate and a reduction in HRV. What are the consequences of these findings? If there is indeed a correlation between the raised cardiovascular mortality of MD patients and an MD-associated disruption of neurocardiac regulation, two questions are of particular interest: (1) Are these disruptions of autonomic neurocardiac regulation reversible after remission

of the depressive disorder (e.g. after successful antidepressive therapy), or do they persist despite remission (which would mean that they represent practically a marker for MD)? (2) What influence does antidepressive therapy itself have on an MD-associated disruption of autonomic neurocardiac regulation?

The fact that we and others (Kittayaphong et al., 1997; Stein et al., 2000) found an association between the severity of depressive symptoms and diverse vagal HRV indices leads to the hypothesis that a reduction of depressive symptoms might result in an increase in cardiovagal modulation of heart rate. Even though the few studies until now allow no definitive conclusions to be made regarding this, a number of notable findings have been produced; an increase in HRV has indeed been seen after successful treatment of depression involving electroconvulsive therapy (Nahshoni et al., 2001; Agelink et al., 1998), although contradictory findings have also been reported (Schultz et al., 1997). Only recently, an extensive study showed that successful antidepressive behaviour therapy of patients with coronary artery heart disease results in a reduction of heart rate and an increase in short term HRV (RMSSD) (Carney et al., 2000). Since the RMSSD, unlike the frequency-dependent HRV indices, is linearly dependent on heart rate (Agelink et al., 2001b), and since no untreated control group was studied, this study still allows no definitive conclusions to be drawn on the effects of a successful behaviour therapy on short-term HRV. In the cited study, successfully treated MD patients showed an improvement, but not a normalisation, of heart rate and RMSSD compared to non-depressed controls. This finding is consistent with the hypothesis that depression, even when successfully treated, may have residual neurophysiological effects that will never normalise (Post, 1992). This hypothesis implies that in MD patients at least a proportion of the pathology in cardiac ANS function is clearly independent of the existence (and therefore also of the severity) of depressive symptoms. Considering this, it seems remarkable that in our study MD patients had a reduced Valsalva ratio independent of the severity of depressive symptoms. This pattern of findings corresponds well with our earlier study showing that MD patients had a lowered Valsalva ratio compared to healthy individuals independent of the severity of depressive symptoms (Agelink et al., 2001a). Although the Valsalva ratio is usually interpreted as an index of parasympathetic function (since the bradycardiac phase can be altered to a large extent by atropine), it does in fact involve complex interplays between several populations of afferent autonomic receptors, and between efferents from both sides of the ANS (Eckberg, 1980). Considering the physiological processes underlying the Valsalva maneuver, our findings suggest the presence of functional disturbances in the interaction between the sympathetic and parasympathetic system, affecting patients who suffer from MD (independent of the severity of depressive symptoms). Following from this, our results lead us to ask whether such disruptions of autonomic neurocardiac regulation may represent a trait marker for MD.

The effects of psychotropic drugs on HRV appear to be dependent mainly on the receptor profiles of each of the substances. The best-replicated finding in the literature is that classical TCAs reduce HRV; this has been attributed to an anticholinergic activity of TCAs (Rechlin, 1994). The effects of another class of antidepressants, the serotonin reuptake inhibitors (SSRIs), is not clear: three studies from independent researchers found evidence that treatment with paroxetine or fluoxetine increased HRV in healthy heart patients (Balogh et al., 1993), and at least transiently increased HRV in coronary heart disease patients (Roose et al., 1998b), or shifted and even normalised the sympathovagal balance in favour of cardiovagal modulation amongst patients with panic disorders and dysthymia (measured as a reduction in the LF/HF ratio) (Tucker et al., 1997). However, other investigators failed to confirm these findings (Rechlin, 1994; Lederbogen et al., 2001). None of the studies mentioned investigated an untreated control group. Directly compared to TCAs, SSRIs appear to be better tolerated especially amongst patients with a pre-existing cardiac disease (Roose et al., 1998a,b); whether this clinical observation occurs simultaneously with a favourable effect of SSRIs on HRV needs to be clarified in controlled studies. Another class of substances which are

known to reduce heart rate and increase HRV are the beta-blockers. According to our knowledge, there is no information available in the literature showing whether beta-blockers exert a favourable effect on the modulation of cardiovagal activity in MD patients, and whether on the basis of such an effect this might contribute to a reduction in cardiovascular mortality.

Finally, newer studies suggesting that vagal nerve stimulation (VNS) has an antidepressive effect (George et al., 2000; Elger et al., 2000; Rush et al., 2002) have fed further speculation on the role of vagal dysfunction in the pathophysiology of MD. Considering this, it would be interesting to study whether, and if so, what influence the VNS has on autonomic regulation in afflicted patients. Because surgical intervention is required to institute VNS, a predictable outcome of therapeutic success would be more desirable than would be the case when applying medication. Before implantation of the stimulator, it would certainly be interesting to determine whether autonomic regulation differs between responders and non-responders to VNS.

4.3. Study limitations

Some limitations need to be considered when interpreting the results of this study. Firstly, MD is an episodic phenomenon. Since no standardized guidelines currently exist for measuring HRV in MD patients (e.g. timepoint of measurement during the course of a depressive episode), comparison of results between different studies is complicated. Moreover, there is no consensus on the criteria for describing the severity of depression. In our study we used a practical, although arbitrary, classification of patients according to their HAM-D scores. The cut-off level was defined as the median HAM-D score for moderately or severely depressed patients, so that two subgroups of equal size could be compared. Secondly, the washout phase for TCAs (some of our patients had been undergoing such therapy before the study) was at least 6 days, and in this way was relatively short in some cases. There are two reasons why we consider it unlikely that this condition may have falsified our results: a separate statistical calculation including only non-pretreated MD patients also disclosed a reduction of vagal HRV indices in severely depressed patients compared to healthy individuals. Moreover, our results as well as those of other groups (Kittayaphong et al., 1997; Stein et al., 2000) allow us to assume a direct association between the severity of depressive symptoms and modulation of cardiovagal activity. Thirdly, HRV decreases with increasing age. Since the age range of the population sample was wide (29–74 years), it is conceivable that the statistical difference in the HRV indices may at least in part be due to age differences. For this reason, and despite the fact that age differences between patient subgroups and controls were not significant, age was always considered as a covariate for all multivariate analyses. Moreover, the patient collective was also subdivided into two equally sized groups around the median patient age, from which it was found that an inverse correlation existed between the severity of depressive symptoms (assessed by the HAM-D score) and vagally mediated HRV indices both in the younger and older patient groups. Fourthly, even though published guidelines for measuring and interpreting HRV have been considered (Task Force Report, 1996), the interpretation of the results given here (reduction of cardiovagal modulation of heart rate and displacement of sympathovagal balance in favour of sympathetic nerve activity in patients with MD) should not lead to an oversimplification in understanding of the extremely complicated regulatory cycle of autonomic neurocardiac regulation, since the measured HRV represents the outcome of an end-organ response, determined by the nerve firing rates, electrochemical coupling, cardiac adrenergic receptor sensitivity, postsynaptic signal transduction, and multiple neural reflexes (Kingwell et al., 1994). Thus, studies on HRV allow no statements to be made regarding the type and topographical classification of damage to the autonomic regulatory cycle that underlies the autonomic dysregulation. For this reason our study can not definitively differentiate whether the vagal dysregulation found in MD patients underlies an alteration in function of either the central or peripheral nervous system. However, we did exclude patients

with diseases that might be associated with a peripheral autonomic neuropathy (e.g. diabetes mellitus). Considering on the one hand that HRV studies were used originally to detect peripheral neuropathy, and on the other that the presence of MD is probably associated with a central autonomic regulatory disorder (e.g. hyperactivity of the HPA system), the results of our study allow us to assume the presence of a central autonomic regulatory disturbance in MD, which can be clearly detected using standardized investigations of HRV. Finally, a number of methodologically sound studies have not been able to find any relationship between sympathetic nerve activity (measured as muscle sympathetic nerve activity or catecholamine concentrations) and spectral estimates of sympathetic activity (e.g. LF, LFnu, LF/HF ratio) (Kingwell et al., 1994; Sloan et al., 1996). The study presented here focused on cardiovagal modulation in MD patients; for adequately assessing sympathetic nerve activity, additional studies are urgently recommended (e.g. MSNA, cardiac noradrenaline spillover).

Acknowledgments

The authors thank T. Majewski (Department of Cardiology, Gelsenkirchen) for evaluating the electrocardiograms and J.P. Keogh (Ph.D.) for his assistance in translating the manuscript.

References

Agelink, M.W., Lemmer, W., Malessa, R., Zeit, T., Klieser, E., 1998. Improvement of neurocardial vagal dysfunction after successful antidepressive treatment with electro-convulsive therapy. European Psychiatry 13, 259S.

Agelink, M.W., Majewski, T., Wurthmann, C., Postert, T., Linka, T., Rotterdam, S., Klieser, E., 2001. Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. Journal of Affective Disorders 62, 187–198.

Agelink, M.W., Malessa, R., Baumann, B., Majewski, T., Akila, F., Zeit, T., Ziegler, D., 2001. Standardised tests of heart rate variability (HRV): normal ranges obtained from 309 healthy humans and effects of age, gender and heart rate. Clinical Autonomic Research 11, 99–108.

Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D.C., Barger, A.C., Cohen, R.J., 1981. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. Science 213, 220–222.

Balogh, S., Fitzpatrick, D.F., Shelton, D.G.S., Hendricks, E., Paige, S.R., 1993. Increases in heart rate variability with successful treatment in patients with major depressive disorder. Psychopharmacology Bulletin 29, 201–206.

Barefoot, J.C., Schroll, M., 1996. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation 93, 1976–1980.

Ben-David, J., Zipes, D.P., 1988. Autonomic neural modulation of cardiac rhythm: Part I. Basic concepts. Modern Concepts of Cardiovascular Disease 57, 41–46.

Carney, R.M., Freedland, K.E., Stein, P.K., Skala, J.A., Hoffmann, P., Jaffe, A.S., 2000. Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. Psychosomatic Medicine 62, 639–647.

Dalack, G.W., Roose, S.P., 1990. Perspectives on the relationship between cardiovascular disease and affective disorder. Journal of Clinical Psychiatry 51, 4–9.

Eckberg, D.L., 1980. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. American Journal of Physiology 239, H581–H593.

Eckberg, D.L., 1997. Sympathovagal balance: a critical appraisal. Circulation 96, 3224–3232.

Elger, G., Hoppe, C., Falkai, P., Rush, A.J., Elger, C.E., 2000. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Research 42, 203–210.

Ewing, D.J., Clarke, B.F., 1986. Autonomic neuropathy: its diagnosis and prognosis. Journal of Clinical Endocrinology and Metabolism 15, 855–889.

George, M.S., Sackeim, H.A., Rush, A.J., Marangell, L.B., Nahas, Z., Husain, M.M., Lisanby, S., Burt, T., Goldman, J., Ballenger, J.C., 2000. Vagus nerve stimulation: a new tool for brain research and therapy. Biological Psychiatry 47, 287–295.

Guinjoan, S.M., Bernabo, J.L., Cardinali, D.P., 1995. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. Journal of Neurology, Neurosurgery and Psychiatry 58, 299–302.

Johnson, R.H., Robinson, B.J., 1988. Mortality in alcoholics with autonomic neuropathy. Journal of Neurology, Neurosurgery and Psychiatry 51, 476–480.

Kingwell, B.A., Thompson, J.M., Kaye, D.M., McPherson, G.A., Jennings, G.L., Esler, M.D., 1994. Heart rate spectral analysis, cardiac norepinephrine spillover and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 90, 234–240.

Kittayaphong, R., Cascio, W.E., Light, K.C., Sheffield, D., Golden, R.N., Finkel, J.B., Glekas, G., Koch, G.G., Sheps, D.S., 1997. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. Psychosomatic Medicine 59, 231–235.

Multicenter Postinfarction Research Group, Kleiger, R.E., Miller, I.P., Bigger, J.T., Moss, A.J., 1987. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. American Journal of Cardiology 59, 256–262.

La Rovere, M.T., Bigger, J.T., Marcus, F.I., Mortara, A., Schwartz, P.J., 1998. Baro-reflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 351, 478–484.

Lanza, G.A., Pedrotti, P., Rebuzzi, A.G., Pasceri, V., Quaranta, G., Maseri, A., 1997. Usefulness of the addition of heart rate variability to Holter monitoring in predicting in-hospital cardiac events in patients with unstable angina pectoris. American Journal of Cardiology 80, 263–267.

Lederbogen, F., Gernoth, C., Weber, B., Colla, M., Kniest, A., Heuser, I., Deuschle, M., 2001. Antidepressive treatment with amitriptyline and paroxetine: comparable effects on heart rate variability. Journal of Clinical Psychopharmacology 21, 238–239.

Lesperance, F., Frasure-Smith, N., Talajic, M., 1996. Major depression before and after myocardial infarction: its nature and consequences. Psychosomatic Medicine 58, 99–110.

Low, P.A., Pfeifer, M.A., 1993. Standardization of clinical tests for practice and clinical trials. In: Low, P.A. (Ed.), Clinical Autonomic Disorders. Little Brown and Co, Boston.

Lown, B., Verrier, R.L., 1976. Neural activity and ventricular fibrillation. New England Journal of Medicine 294, 1165–1170.

Molgaard, H., Sorensen, K.E., Bjerregaard, P., 1991. Attenuated 24-h heart rate variability in apparently healthy subjects, subsequently suffering sudden cardiac death. Clinical Autonomic Research 1, 233–237.

Moser, M., Lehofer, M., Hoehn-Saric, R., McLeod, D.R., Hildebrandt, G., Steinbrenner, B., Voica, M., Liebmann, P., Zapotoczky, G., 1998. Increased heart rate in depressed subjects in spite of unchanged autonomic balance. Journal of Affective Disorders 48, 115–124.

Musselman, D.L., Evans, D.L., Nemeroff, C.B., 1998. The relationship of depression to cardiovascular disease. Epidemiology, biology and treatment. Archives of General Psychiatry 55, 580–592.

Nahshoni, E., Aizenberg, D., Sigler, M., Zalsman, G., Strasberg, B., Imbar, S., Weizman, A., 2001. Heart rate variability in elderly patients before and after electroconvulsive therapy. American Journal of Geriatric Psychiatry 9, 255–260.

Pagani, M., Lombardi, F., Guzzetti, S., Rimoldi, O., Furlan, R., Pizzinelli, P., Sandrone, G., Malfatto, G., Dell'Orto, S., Piccaluga, E., Turiel, M., Baselli, G., Cerutti, S., Malliani, A., 1986. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympathovagal interaction in man and conscious dog. Circulation Research 59, 178–193.

Pomeranz, B., Macauley, R.J.B., Caudill, M.A., Kutz, I., Adam, D., Gordon, D., 1985. Assessment of autonomic function in humans by heart rate spectral analysis. American Journal of Physiology 248, H151–H153.

Post, R.M., 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. American Journal of Psychiatry 149, 999–1010.

Rechlin, T., 1994. The effects of amitriptyline, doxepine, fluvoxamine and paroxetine treatment on heart rate variability. Journal of Clinical Psychopharmacology 14, 392–395.

Rechlin, T., Weis, M., Spitzer, A., Kaschka, W.P., 1994. Are affective disorders associated with alterations of heart rate variability? Journal of Affective Disorders 32, 271–275.

Roose, S.P., Glassman, A.H., Attia, E., Woodring, S., Giardian, E.G., Bigger, J.T., 1998. Cardiovascular effects of fluoxetine in depressed patients with heart disease. American Journal of Psychiatry 155, 660–665.

Roose, S.P., Laghrissi-Thode, F., Kennedy, J.S., Nelson, J.C., Bigger, J.T., Pollock, B.G., Gaffney, A., Narayan, M., Finkel, M.S., McCafferty, J., Gergel, I., 1998. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 279, 287–291.

Rush, A.J., Linden, M., Zobel, A., 2002. Vagusstimulation. Eine neue Behandlungsoption für chronifiziert depressive Erkrankungen. Fortschritte für Neurologie und Psychiatrie 70, 297–302.

Schultz, S.K., Anderson, E.A., van de Borne, P., 1997. Heart rate variability before and after treatment with electroconvulsive therapy. Journal of Affective Disorders 44, 13–20.

Schwartz, P.J., La Rovere, M.T., Vanoli, E., 1992. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post myocardial infarction risk stratification. Circulation 85, 177–191.

Sloan, R.P., Shapiro, P.A., Bagiella, E., Bigger, J.T., Lo, E.S., Gorman, J.M., 1996. Relationship between circulation catecholamines and low frequency heart period variability as indices of cardiac sympathetic activity during mental stress. Psychosomatic Medicine 58, 25–31.

Stein, P.K., Carney, R.M., Freedland, K.E., Skala, J.A., Jaffe, A.S., Kleiger, R.E., Rottman, J.N., 2000. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. Journal of Psychosomatic Research 48, 493–500.

Szabo, B.M., van Veldhuisen, D.J., van der Veer, N., Brouwer, J., De Graeff, P.A., Crijns, H.J., 1987. Prognostic value of heart rate variability in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. American Journal of Cardiology 79, 978–980.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Circulation 93, 1043–1065.

Tucker, P., Adamson, P., Miranda, R., Scarborough, A., Williams, D., Groff, J., McLean, H., 1997. Paroxetine increases heart rate variability in panic disorders. Journal of Clinical Psychopharmacology 17, 370–376.

Tulen, J.H.M., Bruijn, J.A., de Man, K.J., Pepplinkhuizen, L., van den Meiracker, A.H., Man in't Veld, A.J., 1996. Cardiovascular variability in major depressive disorder and effects

of imipramine and mirtazapine. Journal of Clinical Psychopharmacology 16, 135–145.
Wittchen, H.U., Zaudig, M., Schramm, E., 1991. Strukturiertes klinisches Interview für DSM-III-R. second ed. Beltz Test GmbH, Weinheim.
Yeragani, K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Jung, I., Sherwood, P., 1991. Heart rate variability in patients with major depression. Psychiatry Research 37, 35–46.