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Research report

Increased heart rate in depressed subjects in spite of unchanged autonomic balance?

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Abstract

A clinical study was conducted to examine the effects of depression on cardiac autonomic control. Cardiac autonomic control was measured in 26 nonmedicated patients (19 females) suffering from Major Depression, melancholic type, and in 26 age- and sex-matched normal controls. We measured heart rate and high frequency heart rate variability (respiratory sinus arrhythmia), pulsewave velocity and blood pressure, during 10 min of supine rest under controlled conditions. Using a log transformed time domain measure of respiratory sinus arrhythmia (logRSA), we found an inverse linear dependence between cardiac vagal tone and age in the healthy subjects as well as the depressed patients. logRSA was 0.22 ± 0.25 in the patients and 0.25 ± 0.16 in the control group. While this difference was not significant ($P > 0.1$), the deviations from the regression line were significantly ($P < 0.0005$) greater in the patients (0.21 ± 0.12) than in the control group (0.09 ± 0.07), indicating a more heterogenous vagal tone in the depressed patients. Heart rate was also significantly ($P < 0.03$) greater in the depressed patients (76.6 ± 12.4) than in the control group (69.5 ± 6.9). No between-group differences were found in pulsewave velocity or systolic blood pressure, but diastolic blood pressure was lower in depressed patients (73.5 ± 8.7 vs. 80.8 ± 9.1). We discuss the possibility that the increased heart rate seen in the absence of vagal tone changes may not be due to altered vagal or sympathetic tone, as measured in this study. Other factors, including altered autonomous heart rate, may be responsible for the higher heart rate in the depressed group.

Keywords: Cardiac vagal tone; Respiratory sinus arrhythmia; Major depression; Age; Pulse wave velocity; Blood pressure; Autonomous heart rate

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1. Introduction

Autonomic dysfunctions in psychiatric disorders have gained increased interest during recent years (e.g. Fahrenberg, 1980; Hoehn-Saric and McLeod, 1993; Lehofer et al., 1997; Liebmann et al., 1994). In Major Depression, autonomic dysfunctions play an important role in diagnosis and in assessment of the recovery process. In particular, sleep disturbances, as well as changes in appetite and chronobiological structure, indicate an important dysregulation of the autonomic system in these patients (e.g. Bicakova-Rocher et al., 1996; Davidson and Turnbull, 1986; Zapotoczky, 1994). Symptoms such as dry mouth or constipation suggest that parasympathetic activity is decreased in drugfree patients (Davidson and Turnbull, 1986), whereas diarrhoea points to increased sympathetic tone.

Recent results from biological studies support the hypothesis of increased sympathetic tone in patients suffering from Major Depression. Veith et al. (1994) and Lechin et al. (1995) found an elevated norepinephrine appearance in depressed patients when compared with controls. The latter group also found increased free-serotonin values, leading the authors to conclude that parasympathetic activity was elevated as well.

Results of psychophysiological studies with depressed patients are inconsistent. Some authors have reported decreased phasic and tonic skin conductance in depressed patients (Christie et al., 1980; Guinjoan et al., 1995; Iacono et al., 1983; Williams et al., 1985), suggesting lowered sympathetic tone. On the other hand, Noble and Lader (1971) found that salivary flow was reduced in these patients and Guinjoan et al. (1995) reported poorer performance in the Valsalva experiment and lying-to-standing manoeuvres. These results indicate a state of reduced parasympathetic tone. Results of four studies measuring heart rate variability also suggest decreased parasympathetic tone in depressed patients (Balogh et al., 1992; Dalack and Roose, 1990; Rechlin et al., 1994a; Roose et al., 1989), but only a non-significant trend in this direction was found by others (Jacobsen et al., 1984; Yeragani et al., 1991). Most studies have found an increased heart rate in depressed patients (Lahmeyer and Bellur, 1987; Carney et al., 1988; Dawson et al., 1977; Gotthardt et al., 1995; Lechin et al., 1995), but this has not always been the case (Lader and Wing, 1969). Gotthardt et al. (1995) found that blood pressure was elevated in depressed patients but Lechin et al. (1995) did not. To our knowledge, pulse wave velocity has never been investigated in depressed subjects.

Different diagnostic criteria, the presence or absence of medication, or possibly a failure in matching the control groups might be responsible for the inconsistencies found in the above studies. Age (DeMeersman, 1993; Hellman and Stacy, 1976) and sex (Moser et al., 1996), in particular, have been found to influence parasympathetic tone and hence respiratory sinus arrhythmia. Peripheral cardiac vagal tone is known to decrease with age in healthy subjects (DeMeersman, 1993; Hellman and Stacy, 1976). Whether a patient is taking medication is another important variable. Tricyclic antidepressants have anticholinergic effects, one of which is to lower cardiac vagal tone (McLeod et al., 1992; Rechlin et al., 1994b; Walsh et al., 1994). Thus, there are physiological differences between medicated and unmedicated patients which should, but have not always been, separated in some studies (Dalack and Roose, 1990; Dawson et al., 1977, 1985).

1. Cardiac vagal tone, representing parasympathetic nervous activity at the level of the heart, can be calculated from heart rate variability. During the last decade it became clear that respiratory sinus arrhythmia (RSA) mirrors cardiac vagal tone (Akselrod et al., 1981; Billman and Dujardin, 1990; Fouad et al., 1984; Hayano et al., 1991). RSA is the high frequency variability in heart rate mediated by respiration. It can be derived from beat to beat changes in heart rate extracted from the ECG. The short response time typical of the parasympathetic nervous system is responsible for the fact that vagal, but not sympathetic, activity is reflected in RSA (Moser et al., 1994). This is supported and validated by studies which show a dose dependent reduction in RSA by the parasympatholytic atropine (Billman and Dujardin, 1990; Fouad et al., 1984; Hayano et al., 1991). Depending on respiratory rate, RSA is usually observed in the narrow band of heart rate variations ranging from 2–5 s (Moser et al., 1994).
2. Pulse wave velocity is influenced by the stiffness of the arterial system, which is greater when

sympathetic vasomotor control is activated. Increases in pulse wave velocity therefore represent increased sympathetic tone in the cardiovascular system (Busse, 1995; Schandry, 1989).

3. Heart rate is influenced by both branches of the autonomic nervous system in different ways. It is an expression of the balance of the autonomic regulation. Resting heart rate remains stable throughout the ages, whereas the maximal exercise value shows a tendency to decrease, which is described by the equation: 220 minus age (Busse, 1995; Folkow and Svanborg, 1993).

RSA, pulse wave velocity, and heart rate represent a multidimensional description of autonomic activity in the cardiovascular system.

Given the inconsistency in the results of the above mentioned studies, the present study sought to determine whether autonomic regulation of the cardiovascular system differs between patients with major depression, melancholic type, and age-matched, nondepressed control subjects using a multidimensional psychophysiological approach.

2. Methods

2.1. Subjects

The investigation was performed with two groups of subjects. Twenty six subjects (19 female) suffering from Major Depression, melancholic subtype, were diagnosed by the Structured Clinical Interview for DSM-III-R (Wittchen et al., 1991). Their ages ranged from 16–53 years of age, with a mean of 33.7 years. All were physically healthy and remained medication free for at least 3 months before the investigation. Normal controls consisted of 26 healthy subjects (19 female) with a mean age of 34.1 (19–53) years. Major life events and participation in competitive athletic activity within 3 months prior to the study were exclusion criteria for all subjects.

2.2. Physiologic measures

To exclude circadian influences, all measurements were performed between 3 p.m. and 7 p.m. After 20 min of supine rest in a quiet air conditioned room, chest wall ECG was recorded during 10 min of rest, using a small micro-data-logger (Moser et al., 1992). R–R intervals were determined off-line accurately to 1 ms using a moving matched filter algorithm (Moser et al., 1994). Optical inspection of the data revealed some premature beats, which, along with the first heartbeat following each extra systole, were excluded by deleting all values greater than 20% below or above the previous R–R interval (Berger et al., 1986). The resulting R–R time series was used for further processing. Following the resting period, grip force of the dominant hand was measured in the patients. First, maximal voluntary contraction (MVC) force was determined using an electronic hand dynamometer (Gallasch et al., 1991). 70% of MVC was then calculated and the patients had to press the hand dynamometer with the calculated force for 1 minute. The actually achieved force of the 20 stable seconds was than used as a measure for the physical training state of the patients.

Vagal tone was calculated as follows: The interbeat intervals were converted to heart rate and the absolute heart rate differences (in beats-per-min) from one heart beat to the next were calculated for the whole 10 min period. This procedure acts as a high-pass filter that passes the high frequency variations attributed to respiratory sinus arrhythmia but not the slow variations originating from combined sympathetic and parasympathetic activity. The median of the absolute beat-to-beat differences next was transformed by taking its logarithm (Moser et al., in preparation). This method was originally described by Eckoldt (1990) and modified by us (Moser et al., 1994). The logarithm was chosen because the individual median values were not distributed normally, but as a log–normal distribution. The logarithmic transformation of the medians produced a normal distribution. LogRSA was chosen as an indicator of vagal tone because it is easy to calculate and is highly correlated with the spectral estimation of cardiac vagal tone ($r = 0.88$; $n = 220$) (Moser et al., in preparation). Heart rate was calculated as the mean$\pm$1 SD of heart rate during the 10 min rest period.

Pulses from the carotid, finger and heel arteries were recorded by means of optical pulse sensors with high time resolution (Rafolt et al., 1992). Pulse transit time (PTT) to finger and leg was determined off line from the steepest ascent (maximum of first derivative) of the pulse wave in the carotid artery to

the steepest ascent of the pulse wave in the finger and heel arteries (Moser et al., 1992). Pulse wave velocities in arm and leg arteries were calculated from the arterial lengths determined on the body surface, divided by the PTTs (in m/s). Systolic and diastolic blood pressure values were determined at the end of the resting phase in supine position using the Riva Rocci cuff method.

2.3. Self ratings

To determine the severity of depression; patients rated themselves on the Beck Depression Inventory (Beck and Beck, 1972). Anxiety was measured with the State Trait Anxiety Inventory (Spielberger et al., 1970).

2.4. Epidemiological data

Durations of the recent depressive episodes were collected by asking the patients during the SCID interview.

2.5. Statistics

Slopes, intercepts, regression lines and correlation coefficients (r) were calculated separately for both groups. A Student t-test was applied to test the niveau differences of the regression lines for significance. Slope differences were checked using a test for parallelism (Kleinbaum and Kupper, 1978). Correlation coefficients were calculated separately for both groups and the significance of differences was tested. Since all patients had a matched control subject, significance was calculated by paired Student t-tests.

3. Results

Table 1 summarizes the group means±1 S.D., as well as the significance of differences between the groups. Scores on the BDI, the STAI-S, and the STAI-T were significantly different between patients and controls. Physiologically, heart rate was significantly higher in patients and diastolic blood

Table 1
Age and self-ratings as well as physiologic measures of unmedicated depressed patients

	Depressed Patients unmedicated $N=26$ (19 female) D	Matched Controls $N=26$ (19 female) C	Significance of Difference between Groups D:C	Deviation from Regression Line		Significance of Difference between Groups d:c
				Depressed Patients d	Matched Controls c	
Age and self-ratings						
Age	33.7±11.05	34.1±10.5	N.S.			
BDI	23.5±9.6	1.5±1.7	<0.001			
STAI-S	57.5±10.7	29.6±4.7	<0.01			
STAI-T	57.3±9.6	30.0±4.7	<0.001			
Physiologic Measures						
Heart rate/min.	76.6±12.4	69.5±6.9	<0.03	9.7±7.3	5.0±4.6	<0.01
High frequency band	6.50±6.56	6.83±4.57	N.S.	0.40±0.20	0.24±0.17	<0.006
LogRSA	0.22±0.25	0.25±0.16	N.S.	0.21±0.12	0.09±0.07	<0.0005
Pulse wave velocity arm	4.67±0.77	4.85±0.705	N.S.	0.58±0.48	0.51±0.46	N.S.
Pulse wave velocity foot	4.07±1.01	3.98±0.88	N.S.	0.74±0.56	0.56±0.61	N.S.
Diast. blood pressure	73.5±8.7	80.8±9.1	<0.02	7.4±4.0	6.7±6.0	N.S.
Syst. blood pressure	119.1±14.4	123.3±11.9	N.S.	10.3±9.7	9.9±6.5	N.S.
Blood pressure amplitude	45.6±13.0	42.5±10.5	N.S.	10.9±6.6	9.0±5.0	N.S.

Note: D, compared to their age and sex matched controls (mean±1 SD); C, deviation from the regression line between parameter and age in depressed patients; d, compared to their age and sex matched controls; c.

pressure was significantly higher in controls. No other between-group differences in physiologic measures were found. The means±1 S.D. of deviation from the regression lines between the respective physiologic measures and age are listed in the right panel of Table 1. Highly significant differences in this deviation were found for heart rate, high frequency heart rate variability and logRSA. In all cases, depressed patients showed a greater deviation from the regression line than the controls. Although this tendency was present for the other physiological measures as well, none reached statistical significance.

A highly significant correlation ($P < 0.001$) between vagal tone (logRSA) and age was found in healthy subjects (Fig. 1), whereas this correlation was only marginally significant ($P < 0.06$) in the patients. The regression lines were almost identical and no significant differences were found for slopes or y-axis intercepts. Similar results were found for spectral estimation of vagal tone (Fig. not shown, results see Table 1). Heart rate shows no age dependence, neither in patients nor in control subjects (Fig. 2) There is, however, a remarkable increase in heart rate in depressed subjects independent of age indicated by the difference in level of the regression lines (Fig. 2).

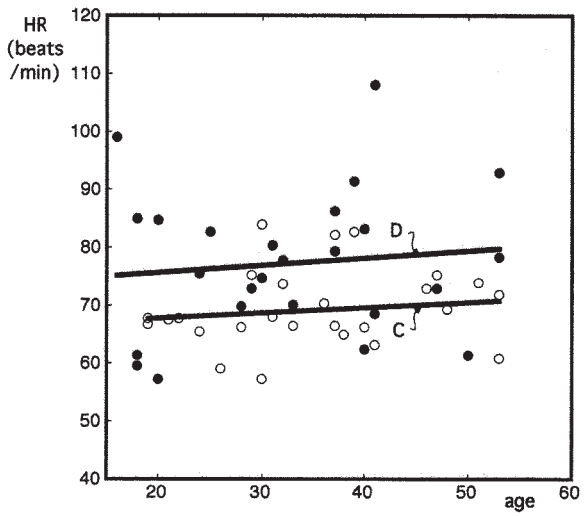

Fig. 2. Age dependence of heart rate in unmedicated depressed patients (D) and age and sex matched control subjects (C).
∘ C: HR = 0.090 × age + 66.1 $r = 0.14$ ($N = 26$, n.s.)
• D: HR = 0.128 × age + 73.0 $r = 0.12$ ($N = 26$, n.s.)

No significant age dependencies were found for pulse wave velocities in the arm (Fig. 3) or leg

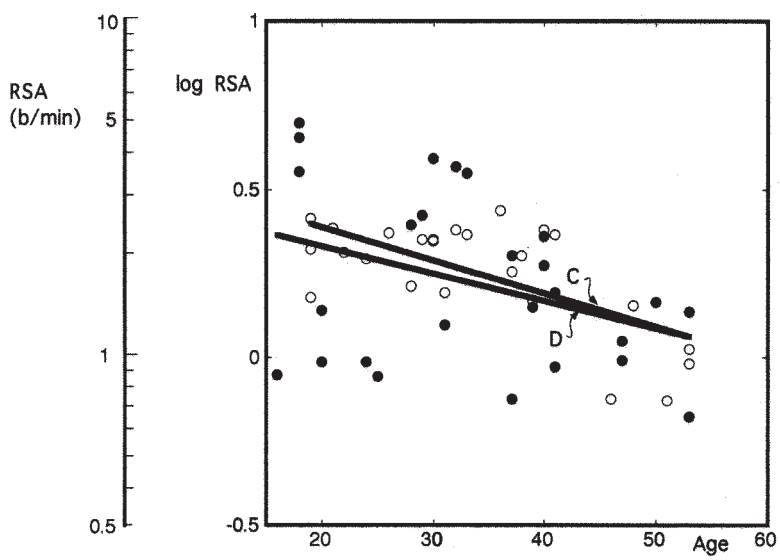

Fig. 1. Age dependence of vagal tone (logRSA) in unmedicated depressed patients (D) and age and sex matched control subjects (C).
∘ C: logRSA = −0.0100 × age + 0.591 $r = -0.66$ ($N = 26$, $P < 0.001$)
• D: logRSA = −0.0083 × age + 0.500 $r = -0.36$ ($N = 26$, $P < 0.06$)
For comparison, the linear scale for RSA (b/min) is placed next to logRSA.

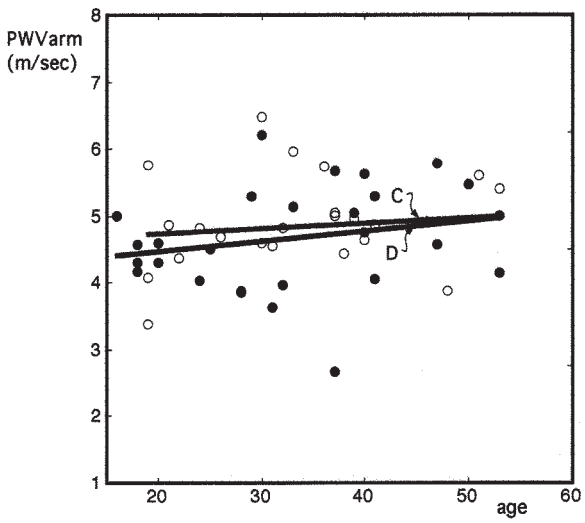

Fig. 3. Age dependence of pulsewave velocity in the arm arteries in unmedicated depressed patients (D) and age and sex matched control subjects (C).
∘ C: PWVa = 0.008 × age + 4.575 $r = 0.12$ ($N = 26$, n.s.)
· D: PWVa = 0.0156 × age + 4.156 $r = 0.23$ ($N = 26$, n.s.)

arteries (Fig. 4), although there was a slight tendency for an increase in pulse wave velocity with age in the leg artery. No significant differences were found between the regression lines for depressed and control subjects.

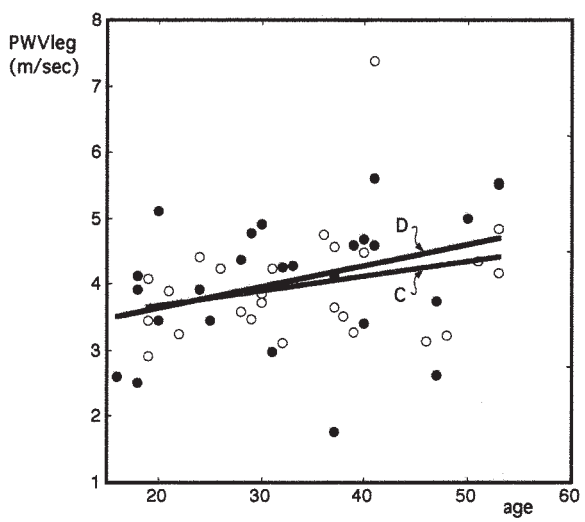

Fig. 4. Age dependence of pulsewave velocity in the leg arteries in unmedicated depressed patients (D) and age and sex matched control subjects (C).
∘ C: PWVl = 0.0226 × age + 3.213 $r = 0.27$ ($N = 26$, n.s.)
· D: PWVl = 0.0324 × age + 2.989 $r = 0.37$ ($N = 0.26$, n.s.)

4. Discussion

In this study, different aspects of autonomic circulatory regulation were investigated in unmedicated depressed patients compared to age- and sex-matched controls. All measurements were performed during rest in a supine relaxed state. This measurement condition was considered to be reproducible and similar for patients and control subjects. The data recording system used was originally developed for space application in cosmonauts and was optimized in terms of reducing patient load due to the measurements (Moser et al., 1992). The measurement room was calm and the least possible stress was exerted on the patients. The results obtained therefore are representative for the resting state and do not offer information about conditions of emotional or physical load.

Vagal tone was calculated using a time domain method (logRSA) as well as a frequency domain method (high frequency HRV). Although the numerical values of the results are not identical (Fig. 1, Table 1) due to different calculation procedures, similar group differences appear in both vagal estimates. The depressed patients showed slightly lower mean vagal tone, regardless of the method used, although this difference was not significant. This result is consistent with those of Jacobsen et al. (1984) and Yeragani et al. (1991), but not with those of others, who found decreased vagal tone in depressed patients (Balogh et al., 1992; Dalack and Roose, 1990; Rechlin et al., 1994a; Roose et al., 1989). This discrepancy might be explained by the different criteria used for recruiting patients. In the present study, patients were included only if they had not been taking psychotropic medications for at least 3 months prior to study participation. Our patients thus consisted mainly of newly admitted depressed patients and patients who suffered a relapse following a symptom-free period of at least 3 months. Other studies reported washout periods of only 1 week for their drug free patients or included patients who were still taking medication at the time of the study (e.g. Dalack and Roose, 1990; Dawson et al.,

1977, 1985). Several studies have shown that medications, especially tricyclic antidepressants, produce a severe vagal depression (McLeod et al., 1992; Lehofer et al., 1996, 1997; Moser et al., 1996). It is quite possible that vagal tone was influenced by medication in studies that did not carefully separate medicated and unmedicated patients.

Although we have investigated only patients between 17 and 53 years of age, the age dependency of vagal tone is quite pronounced and does not differ between patients and control subjects (Fig. 1). There was one difference between patients and control subjects that can be found in heart rate as well as in vagal tone (Table 1): The mean deviation of the single measurements from the regression line between the parameter and age is significantly greater for the patients in all cases. This can be also seen in Figs. 1 and 2, in which the scatter around the regression line is remarkably higher in the patients than in the control group. Whether this is an indication that diagnosis according to DSM III R does not yield a completely homogenous group of patients suffering from Major Depression, or that this disease is characterized by increased scatter in physiologic parameters, is not clear. Given the small degree of stress created by the experimental situation (for the reasons given above), it is remarkable that some patients displayed relatively high vagal tone (Fig. 1), indicating a relaxed state, whereas others showed reduced vagal tone, indicating either some sort of stress or simply lower tonic vagal levels. Control subjects usually were found in the middle between these extremes (Fig. 1).

To test the hypothesis, that confounding variables might be responsible for the higher scatter around the regression line found in depressed patients, we investigated the influence of state and trait anxiety, depression rating and duration of episode upon vagal tone versus age residuals. We found no significant correlation between the vagal tone residuals and state ($r = -0.25$, n.s.) and trait anxiety ($r = 0.03$, n.s.) nor depression rating ($r = 0.22$, n.s.). We therefore conclude, that neither the intensity of depression nor of anxiety significantly influence vagal tone.

Yet there was a significant negative correlation between vagal tone residuals and duration of the recent depressive episode (Fig. 5). This was true for both measures of vagal tone, logRSA ($r = -0.53$, $P < 0.01$) as well as high frequency HRV ($r = 0.48$, $P < 0.02$). It is known from other studies (Eckoldt, 1990) that vagal tone also depends on physical state of the subject. It seemed therefore possible, that the immobilisation caused by the disorder leads to the observed dependence of vagal tone on duration of depressive episode. To clarify this question, we investigated a possible correlation between the handgrip strength (as an indicator of physical state) and the vagal tone residuals. There was a non-significant negative correlation ($r = -0.27$, P: n.s.) instead of the expected positive correlation, which indicates that vagal tone was not positively influenced by physical state in our patients.

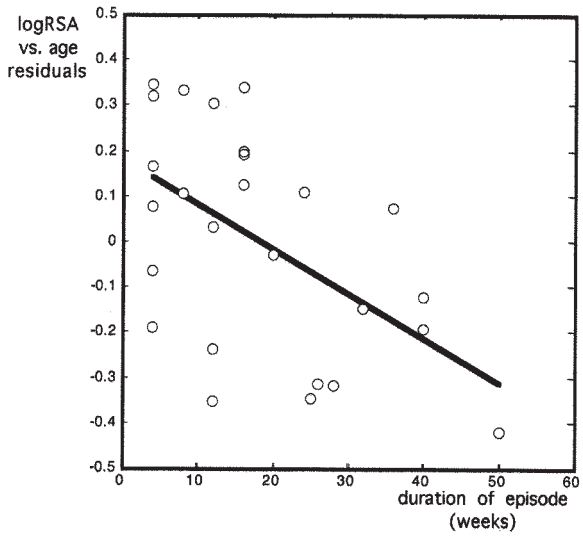

Fig. 5. Dependence of vagal tone vs. age residuals in unmedicated depressed patients upon duration of depression episode.
∘ Vagal tone (logRSA) = 0.00986 × duration + 0.1795 $r = -0.53$ ($N = 26$, $P < 0.01$)

We therefore conclude from this part of the investigation that the duration of the depressive episode is the most important confounding variable influencing vagal tone besides age and that the correlation shown in Fig. 5 is not caused by the physical state of the patients.

Heart rate values were found to be significantly increased by about 10% (7 beats/min) in the patient group (Table 1) and displayed no significant age dependency (Fig. 2). The regression lines are parallel for both patients and controls, so the difference is independent of age. Heart rate is determined by three

components: (1.) The "autonomous" rate of the heart, which is known to be around 100 beats/min. This can be found in transplanted hearts that are not yet reinnervated (Shapiro, 1996) or in subjects with experimentally produced total autonomic blockade (Fouad et al., 1984). (2.) The vagal innervation, which reduces "autonomous heart rate" to normal values of around 70 beats/min and can even halt the heart if strong emotions (fear) increase the vagal drive. (3.) The sympathetic innervation which increases and determines the long time level of heart rate.

In this study we found a significant increase in heart rate (Fig. 2) but at the same time found no differences in cardiac vagal tone (Fig. 1). An increased sympathetic tone or an increased autonomous heart rate in depressed patients both could be responsible for this observation. To find out which of the possibilities is more likely we investigated pulse wave velocity, which is considered to be an indicator of vascular sympathetic tone due to the purely sympathetic innervation of peripheral arterial vessels (Kirchheim, 1982). No significant differences between patients and control subjects were found in pulse wave velocity, either in the arm or in the leg arteries. (Table 1, Fig. 3, Fig. 4).

Systolic and diastolic blood pressure were also measured in this study, using the Riva Rocci cuff method. Depressed patients showed slightly decreased blood pressure values, with diastolic blood pressure significantly lowered by 10%, suggesting reduced peripheral resistance. If morphological differences in the arterial system can be excluded, decreased blood pressure can be attributed to low sympathetic tone, even though heart rate is higher.

Higher heart rates in depressed patients are found consistently in literature (Lahmeyer and Bellur, 1987; Carney et al., 1988; Dawson et al., 1977; Gotthardt et al., 1995; Lechin et al., 1995), whereas the status of vagal tone is less clear (Balogh et al., 1992; Dalack and Roose, 1990; Jacobsen et al., 1984; Rechlin et al., 1994a; Roose et al., 1989; Yeragani et al., 1991). To our knowledge, pulse wave velocity has not been systematically investigated in depressed patients. In this study, we found an increased heart rate in the absence of reduced vagal tone in depressed patients. Pulse wave velocity in leg and arm arteries and systolic blood pressure were similar in patients and control subjects. Diastolic blood pressure was decreased, further indicating decreased rather than increased sympathetic tone.

Taken together (Fig. 6), our results suggest that autonomous heart rate is higher in depressed patients than in age and sex matched nondepressed controls. Also, since all regression lines involving age were similar for patients and controls, we can conclude that this difference in the autonomous heart rate is independent of age. Interestingly several studies have revealed an up to six times higher incidence of cardiovascular diseases (for overview: Dalack and Roose, 1990) in depressed compared to nondepressed subjects.

The alternative explanation, that increased sympathetic drive is responsible for the observed increased heart rate, is inconsistent with our pulse wave velocity and blood pressure findings. It is not clear yet whether our findings reflect the fact that depressed patients have less well trained hearts resulting from a history of reduced physical exercise or that higher autonomous heart rate is actually a physiological state or trait marker of depression.

Finally, we found a significantly increased scatter in vagal tone in depressed subjects which is highly correlated to the duration of the recent depressive episode but not to anxiety or depression measures. There was a nonsignificant negative correlation between vagal tone and handgrip strength. We therefore conclude that it is not the physical fitness which

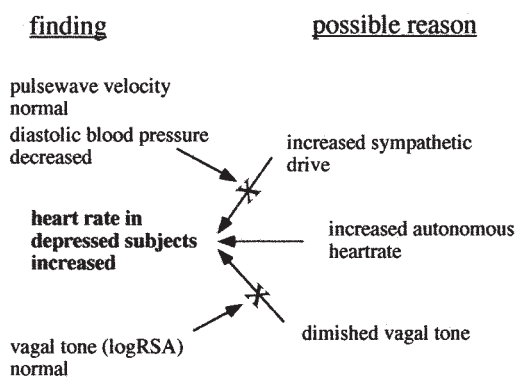

Fig. 6. Possible physiological factors determining heart rate (right) and findings of this study (left) indicating, that increased autonomous heart rate is most likely the reason for the significantly increased heartrate in depressed subjects.

is responsible for the scatter in vagal tone in depressed subjects.

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References

Akselrod, S., Gordon, D., Ubel, F.A. et al., 1981. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. Science 231, 220–222.

Balogh, S., Fitzpatrick, D.F., Hendricks, S.E., Paige, S.R., 1992. Increases in heart-rate-variability with successful treatment in patients with major depressive disorder. Psychopharmacol. Bull. 29 (2), 201–206.

Beck, A.T., Beck, R.W., 1972. Screening depressed patients in family practice. Postgrad. Med. 52, 81–85.

Berger, R., Akselrod, S., Gordon, D., Cohen, R., 1986. An efficient algorithm for spectral analysis of heart rate variability. IEEE Trans. biomed. Eng. BME-33 9, 900–904.

Bicakova-Rocher, A., Gorceix, A., Reinberg, A., Ashkenazi, I.I., Ticher, A., 1996. Temperature rhythm of patients with Major Depressive Disorders. Reduced circadian period length. Chronobiol. Int. 13 (1), 47–58.

Billman, G.E., Dujardin, J.P., 1990. Dynamic changes in cardiac vagal tone as measured by time series analysis. Am. J. Physiol. 258, H896–H902.

Busse, R., 1995. Gefäßsystem und Kreislaufregulation. In: Schmidt, R.F., Thews, G. (Eds.), Physiologie des Menschen. Springer-Verlag, Berlin Heidelberg New York, pp. 498–564.

Carney, R.M., Rich, M.W., TeVelde, A., Saini, J., Clark, K., Freeland, E., 1988. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. J. Psychosom. Res. 32 (2), 159–164.

Christie, M.J., Little, B.C., Gordon, A.M., 1980. Peripheral indices of depressive states. In: van Praag, H.M. et al. (Eds.), Handbook of Biological Psychiatry Part II: Brain Mechanism and Abnormal Behavior Psychophysiology. Marcel Decker, New York. pp. 145–182.

Dalack, G.W., Roose, S.P., 1990. Perspectives on the relationship between cardiovascular disease and affective disorder. J. Clin. Psychiatry 51 (Suppl), 4–11.

Davidson, J., Turnbull, C.D., 1986. Diagnostic significance of vegetative symptoms in depression. Br. J. Psychiat. 148, 442–446.

Dawson, M.E., Schell, A.M., Braaten, J.R., Catania, J.J., 1985. Diagnostic utility of autonomic measures for major depressive disorders. Psychiatry Res. 15, 261–270.

Dawson, M.E., Schell, A.M., Catania, J.J., 1977. Autonomic correlates of depression and clinical improvement following electroconvulsive shock therapy. Psychophysiology 14 (6), 569–578.

DeMeersman, R.E., 1993. Aging as a modulator of respiratory sinus arrhythmia. Biol. Sci. 48 (2), B74–B78.

Eckoldt, K., 1990. Probleme und Ergebnisse der Analyse des Sinusrhythmus. Psychiatr. Neurol. Med. Psychol. Beih. 43, 53–63.

Fahrenberg, J., 1980. Empirische Beiträge zur multivarianten Aktivierungstheorie. Med. Psychol. 6 (1/2), 95–102.

Folkow, B., Svanborg, A., 1993. Physiology of cardiovascular aging. Physiol. Rev. 73, 725–762.

Fouad, F., Tarazi, R., Ferrario, C., Fighaly, S., Alicandri, C., 1984. Assessment of parasympathetic control of heart rate by a noninvasive method. Am. J. Physiol. 246, H838–H842.

Gallasch, E., Moser, M., Hindinger, J. et al., 1991. An interactive hand-held measurement system for biomedical applications. Forum der Meßtechnik, Bd. 5, 540–545.

Gotthardt, U., Schweiger, U., Fahrenberg, J., Lauer, C.J., Holsboer, F., Heuser, I., 1995. Cortisol, ACTH, and cardiovascular response to a cognitive challenge paradigm in aging and depression. Am. J. Physiol. 268, R865–73.

Guinjoan, S.M., Bernabo, J.L., Cardinali, D.P., 1995. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J. Neurol. Neurosurg. Psychiatry 59, 299–302.

Hayano, J., Sakakibara, Y., Yamada, A. et al., 1991. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. Am. J. Cardiol. 67, 199–204.

Hellman, J.B., Stacy, R.W., 1976. Variation of respiratory sinus arrhythmia with age. J. Appl. Physiol. 41 (5), 734–738.

Hoehn-Saric, R., McLeod, D., 1993. Somatic manifestation of normal and pathological anxiety. In: Hoehn-Saric, R., McLeod, D. (Eds.), Biology of Anxiety Disorders. American Psychiatric Press, Washington DC. pp. 177–222.

Iacono, W.G., Lykken, P.T., Peloquin, L.J., Lumry, A.E., Valentine, R.H., Tuason, V.B., 1983. Electrodermal activity in euthymic unipolar and bipolar affective disorders: A possible marker for depression. Arch. Gen. Psychiatry. 40, 557–565.

Jacobsen, J., Hauksson, P., Vestergaard, P., 1984. Heart rate variation in patients treated with antidepressants. An index of anticholinergic effects?. Psychopharmacol. 84, 544–548.

Kirchheim, H., 1982. Kreislaufregulation. In: Busse, R. (Ed), Kreislaufphysiologie. Georg Thieme Verlag Stuttgart New York, pp 167–210.

Kleinbaum, D.G., Kupper, L.L., 1978. Applied Regression Analysis and Other Multivariable Methods. Duxbury Press, Massachusetts.

Lader, M.H., Wing, L., 1969. Physiological measures in agitated and retarded depressed patients. J. Psychiatr. Res. 7, 89–100.

Lahmeyer, H.W., Bellur, S.N., 1987. Cardiac regulation and depression. J. Psychiatr. Res. 21, 1–6.

Lechin, F., van der Dijs, B., Orozco, B. et al., 1995. Plasma neurotransmitters, blood pressure, and heart rate during supine

resting, orthostasis, and moderate exercise conditions in major depressed patients. Biol. Psychiatry 38, 166–173.

Lehofer, M., Moser, M., Hoehn-Saric, R. et al., 1997. Major Depression and cardiac autonomic control. Biol. Psychiatry, in print.

Lehofer, M., Moser, M., Hoehn-Saric, R. et al., 1996. Diminished pulse respiration coupling in depressed patients. Biol. Psychiatry 39, 526.

Liebmann, P.M., Lehofer, M., Schönauer-Cejpek, M. et al., 1994. Pain sensitivity in former opiod addicts. Lancet 34, 1031–1032.

McLeod, D., Hoehn-Saric, R., Porges, S.W., Zimmerli, W.D., 1992. Effects of alprazolam and impramine on parasympathetic cardiac control in patients with generalized anxiety disorder. Psychopharmacol. 107, 535–540.

Moser, M., Lehofer, M., Hoehn-Saric, R. et al., 1996. Factors influencing cardiac vagal tone in depressed patients. Biol. Psychiatry 39, 526.

Moser, M., Lehofer, M., Sedminek, A., Lux, M., Zapotoczky, H.G., Kenner, T., 1994. Heart rate variability as a prognostic tool in cardiology: A contribution to the problem from a theoretical point of view. Circulation 90, 1078–1082.

Moser, M., Gallasch, E., Rafolt, D. et al., 1992. Monitoring of cardiovascular parameters during the Austromir space flight. Proceedings of Satellite Symposium 4: Columbus Eight (Cosy-8) Utilisation of Earth Orbiting Laboratories, from the International Space Year Conference, held in Munich, Germany, 30 March-4 April 1992 (ESA ISY-4, July 1992), pp. 169–174.

Noble, P.E., Lader, M.H., 1971. Salivary secretion in depressive illness: A physiological and psychometric study. Psychol. Med. 1, 372–376.

Rafolt, D., Moser, M., Gallasch, E., Kenner, T., 1992. Neue optische, mechanische und optomechanische Pulssensoren für die nichtinvasive Pulskurvenaufzeichnung an den Akren und großen Arterien. Biomedizinische Technik Band 57. Ergänzungsband 1, 167–169.

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

Rechlin, T., Claus, D., Weis, M., 1994. Heart rate analysis in 24 patients treated with 150 mg amitryptiline per day. Psychopharmacology 110, 110–114.

Roose, S.P., Glassman, A.H., Dalack, G.W., 1989. Depression, heart disease, and tricyclic antidepressants. J. Clin. Psychiatry 50 (7(Suppl)), 12–16.

Schandry, R., 1989. Lehrbuch der Psychophysiologie. Psychologie Verlags-Union München-Weinheim.

Shapiro, P.A., 1996. Heart rate reactivity and heart period variability throughout the first year after heart transplantation. Psychophysiology 33, 54–62.

Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. STAI Manual. Consulting Psychologists Press, Palo Alto, CA.

Veith, R.C., Lewis, N., Linares, O.A. et al., 1994. Sympathetic nervous system activity in major depression. Basal and desipramine induced alterations in plasma norepinephrine kinetics. Arch. Gen. Psychiatry 51, 411–422.

Walsh, B., Giardina, E., Gloan, R., Greenhill, L., Goldfein, J., 1994. Effects of desipramine on autonomic control of the heart. J. Am. Acad. Child Adolesc. Psychiatry 33 (2), 191–197.

Williams, K.M., Iacono, W.G., Remick, R.A., 1985. Electrodermal activity among subtypes of depression. Biol. Psychiatry 20, 158–162.

Wittchen, H.U., Zaudig, M., Schramm, E. et al., 1991. Stukturiertes Klinisches Interview für DSM III R. Weinheim, Beltz-Test GmbH, 2nd ed.

Yeragani, V.K., Pohl, R., Balon, R. et al., 1991. Heart rate variability in patients with major depression. Psychiatry Res. 37, 35–46.

Zapotoczky, H.G., 1994. Depression – wie erkennen, wie behandeln? Hofmann La Roche, Wien, Austria.