Major Depression and Cardiac Autonomic Control

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We investigated autonomic control of heart rate in patients with major depression, melancholic type. Twenty-three depressed inpatients who were being treated with tricyclic antidepressants and 23 depressed patients who were taking no medications were compared with age- and sex-matched control groups on resting cardiac vagal tone and heart rate. In unmedicated depressed patients, cardiac vagal tone was comparable to that of control subjects, but heart rate was significantly higher. This increase in heart rate may have been due to sympathetic activation caused by anxiety, since the depressed patients were significantly more anxious than the control subjects. Medicated patients exhibited diminished cardiac vagal tone and higher heart rate than unmedicated patients and controls. This was probably due to the anticholinergic effects of the antidepressants. Our findings suggest that cardiac vagal tone is not lower than normal in patients with depression, melancholic type. © *1997 Society of Biological Psychiatry*

Key Words: Heart rate, respiratory sinus arrhythmia, autonomic nervous system, major depression, tricyclic antidepressants

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Introduction

Symptoms suggesting autonomic imbalance, such as changes in appetite, constipation, diarrhea, reduction of saliva, and sleep disturbances, commonly accompany depressive disorders and play an important role in their diagnosis and prognosis (Gelder et al 1991; Janowsky et al 1972, 1994). Although disturbances in circadian rhythms have been well documented in depression (Heimann and Pflug 1978), studies of peripheral autonomic, including cardiovascular, states have produced inconclusive results. Data from some (Carney et al 1995; Dalack and Roose 1990; Roose et al 1989; Rechlin et al 1994), but not all (Carney et al 1988; Jacobsen et al 1984; Yeragani et al 1991) studies of heart rate variability suggest that depressed patients have significantly decreased parasympathetic tone. Increased heart rate in depressed patients also has been reported in some (Carney et al 1988; Dawson et al 1977; Lahmeyer and Bellur 1987; Lake et al 1982; Rechlin et al 1994), but not all (Lader and Wing 1969) studies. The inconsistencies in these findings may be due to the characteristics of patient and control groups, or

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whether patients were or were not taking antidepressant medications. Precise diagnostic definitions are important because somatic symptoms vary in quality as well as intensity in subgroups of major depression. For example, studies reviewed by Zahn (1986) have found cardiovascular changes in depression to be associated with coexisting levels of anxiety rather than depression. Moreover, control groups have not always been matched for age and sex (Dalack and Roose 1990; Jacobsen et al 1984; Lahmeyer and Bellur 1987; Roose et al 1989). Both of these factors are known to influence autonomic functions, including cardiac vagal tone (Eckoldt 1990; Moser et al, unpublished manuscript). Finally, antidepressants with anticholinergic effects are known to decrease cardiac vagal tone (McLeod et al 1992; Walsh et al 1994). Therefore, medicated patients are not physiologically comparable to unmedicated patients (Jacobsen et al 1984; Carney et al 1988), although medicated and unmedicated patients were mixed together in some of the above studies (Dalack and Roose 1990; Dawson et al 1977, 1985).

The aim of the present study was to compare cardiac vagal tone and heart rate in patients diagnosed with major depression, melancholic type, with those of a healthy control group matched for age and sex. Further, within the group of depressed patients, those taking tricyclic antidepressants were compared with those who were medication free. Previous studies have reported decreased phasic and tonic skin conductance (Christie et al 1980; Iacono et al 1983; Williams et al 1985) and reduced salivary flow (Noble and Lader 1971) in depressed patients, suggesting an attenuation of autonomic function. We predicted, therefore, that cardiac vagal tone would be reduced in both patient groups. Because of the anticholinergic effects of antidepressants, however, we also predicted that cardiac vagal tone would be reduced to a greater extent in the medicated group.

Methods

Subjects

Patients consisted of 46 medically healthy inpatients with major depression, melancholic type, who were recruited from the Department of Psychiatry, University of Graz. The diagnosis was confirmed by means of the Structured Clinical Interview for DSM-III-R (SCID; Wittchen et al 1991). In addition, all patients completed the Beck Depression Inventory (BDI; Beck and Beck 1972) and the State–Trait Anxiety Inventory (STAI; Spielberger et al 1970). Half of the patients had been drug free for at least 3 months (either in connection with the first onset of depression or because patients did not receive phase prophylaxis), whereas the other half were currently being treated with imipramine, 150 mg per day, or an equivalent dose of another tricyclic antidepressant (16 received amitryptiline, 4 imipramine, and the rest clomipramine). The duration of treatment ranged from 3 weeks to 6 months. Control subjects consisted of 46 medically and psychiatrically healthy volunteers who were screened with the help of the SCID. The control subjects were matched for sex and, within a 2-year range, for age with the depressed patients.

Experimental Procedures

All experimental sessions were performed between the hours of 3 PM and 7 PM. Subjects rested in the supine position in a quiet room under constant conditions for 25 min. During the last 5 min of the rest period, an electrocardiogram (ECG) was recorded from bipolar chest wall leads using a small data acquisition computer (Moser et al 1992).

R-R intervals were determined off-line to 1 msec. A computer program was employed that used matched filtering of the ECG data to recognize the R-peaks. As a check, all QRS-complexes were plotted and synchronized for the R-peak. False R-peaks could readily be detected visually. Experimental data containing more than 3% false R-peaks were excluded from further processing.

Respiratory sinus arrhythmia (RSA) was calculated as shown in Figure 1 by means of a method based on the work of Eckoldt (Eckoldt 1990) and further developed in our laboratory (Moser et al 1994): R-R intervals were converted to heart rate and the absolute heart rate differences (in beats per minute) from one heart beat to the next were calculated for the whole 5-min period. This procedure acts as a simple 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. 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 = .87; Moser, unpublished manuscript).

Statistics

The following calculations were performed with a standard computer package (Matlab, The Mathworks, Inc): mean ± 1 SD of age, heart rate, logRSA, anxiety rating score (STAI State and Trait), and depression rating score

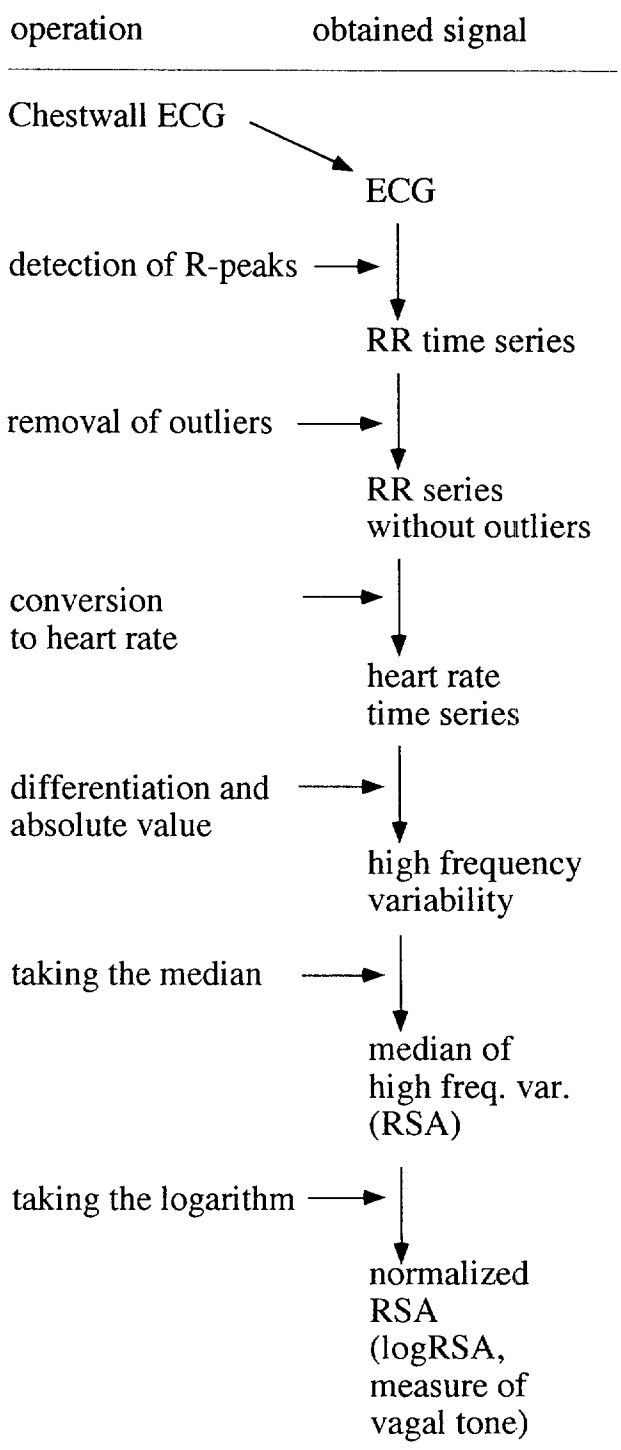

Figure 1. Processing of ECG data to obtain the time-domain measure of cardiac vagal tone (logRSA).

(BDI). Two-tailed, paired Student's t tests were used to examine differences between the subject groups. Linear regression and Pearson correlation coefficients were calculated to assess the relationship between logRSA and heart rate. The regression lines were tested for parallelism of the slopes as well as for differences in intercepts and correlation coefficients (Kleinbaum and Kupper 1978).

Results

Table 1 shows the means ± standard deviations for the investigated variables across subject groups. Significant differences were found in heart rate and logRSA between healthy subjects and depressed patients treated with tricyclic antidepressants. Significant differences in heart rate and logRSA were found also between medicated and unmedicated depressed patients. Heart rate was highest and logRSA was lowest in the medicated group of depressed patients. No differences in logRSA were found between the unmedicated depressed patients and the matched control subjects. Heart rate, however, was higher in both groups of depressed patients than in the controls.

In Figure 2, heart rate is plotted as a function of logRSA. Linear regressions were fitted to the data of each subject group. For the sake of simplicity, data from the two control groups were pooled and only one regression line for all healthy subjects was computed. Vagal tone had a strong decelerating influence on heart rate only in the group of untreated depressed patients ($r = -.49$; $p < .05$). There was no significant correlation between heart rate and vagal tone in the healthy subjects or in the group of medicated depressed patients. Tricyclic antidepressants significantly decreased logRSA and increased heart rate.

Discussion

In this study, a new measure, logRSA, was used to assess cardiac parasympathetic tone in patients with major depression, melancholic type. This measure uses the median absolute beat-to-beat heart rate variability to estimate vagal tone. The median was chosen over the mean because it is influenced very little by outliers or ectopic heart beats. A logarithmic transformation of the within-group medians produced a normal distribution of medians for each subject group. Recently, this method was compared with other measures of vagal tone on a sample of 200 healthy subjects (Moser et al, unpublished manuscript). In that study, we used the decline in vagal tone with age as an indirect validation of methods determining vagal tone, and found logRSA to yield the highest correlation with age.

In this present study, we found that patients taking tricyclic antidepressants showed a tendency toward lower scores on the Beck Depression Inventory than unmedicated depressed patients, but the difference between the two groups was not significant. Thus, patients taking medication only responded partially to treatment and continued to exhibit pathological levels of depression. On

Table 1. Comparison between Patients with Major Depression, Melancholic Type, Unmedicated (A) and Matched Healthy Controls (B), Patients with Major Depression, Melancholic Type on Tricyclic Antidepressants (C) and Matched Controls (D), and between the Unmedicated (A) and Medicated (C) Depressed Groups

	(A) Depressed patients, unmedicated (n = 23) (14 female)	(B) Matched controls (n = 23) (14 female)	(C) Depressed patients on TCA (n = 23) (14 female)	(D) Matched controls (n = 23) (14 female)	Significance of difference between groups		
					A:B	C:D	A:C
Age and self-ratings							
Age	36.3 ± 10.9	35.6 ± 11.3	40.2 ± 9.6	41.0 ± 10.4	ns	ns	ns
BDI	23.2 ± 12.2	4.8 ± 4.6	16.7 ± 6.3	2.7 ± 2.7	<.001	<.001	<.003
STAI-S	54.1 ± 13.9	37.0 ± 10.0	46.5 ± 9.6	37.0 ± 7.2	<.001	<.001	<.004
STAI-T	54.2 ± 11.4	37.0 ± 9.9	50.5 ± 8.6	34.3 ± 6.1	<.001	<.001	ns
Physiologic measures							
Heart rate/min	74.2 ± 13.7	66.8 ± 8.3	82.2 ± 8.9	68.2 ± 9.6	<.05	<.0001	<.03
logRSA	0.204 ± 0.256	0.216 ± 0.237	0.048 ± 0.23	0.185 ± 0.186	ns	<.0005	<.001

Means and ± 1 standard deviations, Student's t tests, two tailed.

TCA, tricyclic antidepressants; BID, Beck Depression Inventory; STAI-S and -T, State Trait Anxiety Inventory, State and Trait form; logRSA, vagal tone as computed from logarithm of beat-to-beat heart rate variability.

the STAI, both patient groups rated their anxiety levels within a range commonly seen in generalized anxiety disorder patients (McLeod and Hoehn-Saric 1993). Therefore, the medicated and unmedicated patients had comparable levels of depression and anxiety. In spite of increased levels of anxiety, our unmedicated depressed patients did not appear to be agitated, although they did exhibit the elevated heart rate characteristic of the agitated depression described by other investigators (Lader and Wing 1969).

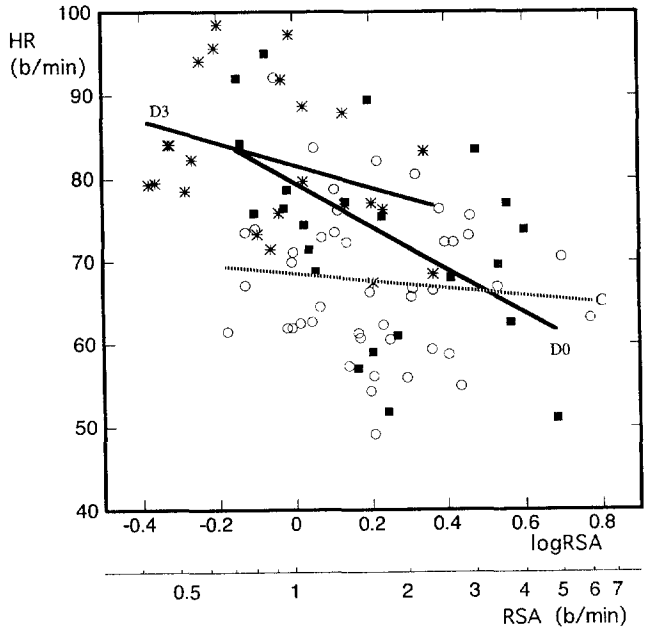

Figure 2. Dependence of heart rate on vagal tone in healthy subjects (C), untreated depressives (D0), and depressives treated with TCA (D3). The regression lines are as follows. C: heart rate (HR) = −4.39 × logRSA + 68.39, r = −.10, ns; D0: HR = −26.12 × logRSA + 79.53, r = −.49, p < .05; D3: HR = −13.45 × logRSA + 81.51, r = −.35, ns.

Contrary to our prediction, unmedicated depressed patients did not differ from control subjects on cardiac vagal tone (Table 1, Figure 2), in spite of the fact that patients with major depression, melancholic type, generally tend to exhibit symptoms that suggest lowered parasympathetic activity. Since patients and controls were carefully matched for age and sex, and patients were diagnostically homogenous, we have to conclude that cardiac vagal tone is not altered by depression, melancholic type.

Some of the earlier studies used a 24-hour ECG monitoring and found nonsignificant (Carney et al 1988), versus significantly diminished (Dalack and Roose 1990; Carney et al 1995) vagal tone. Others performed a short-term measurement of heart rate variability (few minutes) and found no significant difference (Yeragani et al 1991). Possible influence of psychotropic drugs on vagal tone due to medication during measurements (Dalack and Roose 1990) or due to the influence of an additional coronary artery disease of the investigated groups (Carney et al 1995) might be responsible for contradicting results.

Differences concerning the level of vagal tone in depressed subjects between our findings and those of earlier studies may be explained by the fact that the influence of age and sex on cardiac vagal tone was not taken into account by two of the earlier studies (Dalack and Roose 1990; Roose et al 1989). It is known that vagal tone diminishes with age and is higher in women (DeMeersman 1993; Hellman and Stacy 1976; Moser et al, unpublished manuscript).

Rechlin et al (1994) investigated 16 patients with major depression, melancholic type, treated with tricyclic anti-

depressants (TCA), and found a significantly diminished vagal tone using 5-min recordings of heart rate variability. This is in accordance with our observation of diminished cardiac vagal tone in the TCA group (Figure 2, Table 1).

In this study, we found a significantly increased heart rate in both the unmedicated and the medicated depressed patients (Table 1). Several other studies have found increased heart rate in depressed subjects (Carney et al 1988; Dawson et al 1977; Lahmeyer and Bellur 1987; Lake et al 1982; Rechlin et al 1994), whereas one study has not (Lader and Wing 1969).

Three variables determine heart rate. The "autonomous" heart rate that lacks any autonomic nervous system control is known to be about 100 beats per minute and is found in transplanted heart patients (Bernardi et al 1989). Tonic vagal activity lowers this rate to normal values of about 65 beats per minute, whereas sympathetic activity increases heart rate. Both branches of the autonomic nervous system normally contribute to the resting heart rate. In the present study, we found vagal tone to be similar in unmedicated depressed patients and control subjects. Heart rate, on the other hand, was higher in unmedicated depressed patients. One can conclude from this that either higher sympathetic tone or possibly increased autonomous heart rate could be the reason for the higher heart rate observed in depressed patients. In patients treated with TCAs, pharmacologically induced reduction of vagal tone was observed. This reduction of vagal tone in the medicated group can be attributed to the anticholinergic effects of tricyclic antidepressants (McLeod et al 1992; Walsh et al 1994). Heart rate was highest in this group. Interestingly, heart rate was correlated with vagal tone only in the unmedicated patient group (Figure 2); no significant correlations were found in either the control subjects or the TCA-treated patients. It is possible that resting heart rate is under stronger sympathetic influence in healthy subjects and in TCA-treated depressed patients, but under stronger vagal control in untreated depressed patients.

The findings of the present study emphasize the importance of an adequate washout period for medications affecting the autonomic nervous system prior to conducting physiological assessment studies. These findings are limited, however, to resting cardiac vagal tone and heart rate measures in patients with major depression, melancholic type. A more complete picture of autonomic states in depression would require physiological recordings of cardiovascular as well as other autonomic systems in response to standardized laboratory stressors, as well as ambulatory monitor recordings that measure physiological responses to everyday stressors in different subgroups of depression.

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