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Psychiatry Research 85 (1999) 199–207

PSYCHIATRY RESEARCH

Influence of age on the parasympatholytic property of tricyclic antidepressants

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Received 20 July 1998; received in revised form 18 December 1998; accepted 29 December 1998

Abstract

Clinical evidence indicates that parasympatholytic effects of tricyclic antidepressants increase with age. The aim of the present study was to determine the possible physiological reason for this phenomenon. Subjects included 23 patients (14 female) with major depression, melancholic type, and 23 age- and sex-matched healthy control subjects. Cardiac vagal tone was measured at rest using both spectral analysis and a time domain beat-to-beat method. Results of the spectral and time domain methods for the estimation of vagal tone used in this study were highly correlated in control subjects as well as in medicated depressed subjects. Both patients and control subjects showed an age-related decline in cardiac vagal tone. Tricyclic antidepressants decreased vagal tone significantly by 25–49% depending on age (20–60 years), although the age difference was not significant. The greater effect of tricyclic antidepressants on parasympathetic activity typically seen in older age groups may reflect the fact that predrug levels of vagal tone are already low in older patients. Measurement of vagal tone prior to drug administration may therefore be of prognostic value for anticholinergic side effects.

Keywords: Cardiac vagal tone; Respiratory sinus arrhythmia; Major depression; Age; Anticholinergic agents

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0165-1781/99/$ - see front matter
PII: S0165-1781(99)00005-0

1. Introduction

Clinical symptoms like dry mouth and constipation suggest that parasympathetic activity is decreased in some unmedicated depressed patients (Davidson and Turnbull, 1986). Thus far, studies that have assessed parasympathetic activity in depression have produced inconsistent results. Some studies have reported reduced salivary flow, increased heart rate, and decreased cardiac vagal tone indicative of decreased parasympathetic activity (Noble and Lader, 1971; Dawson et al., 1977; Lahmeyer and Bellur, 1987; Carney et al., 1988; Roose et al., 1989; Dalack and Roose, 1990; Balogh et al., 1992), while others have failed to find differences between depressed and normal subjects in heart rate or cardiac vagal tone (Lader and Wing, 1969; Jacobsen et al., 1984; Yeragani et al., 1991). In contrast to these contradictory findings, it is widely accepted that treatment with tricyclic antidepressants reduces parasympathetic tone (e.g. McLeod et al., 1992; Walsh et al., 1994). Although there seems to be a pharmacological basis for this phenomenon (Baldessarini et al., 1991), there is little knowledge about the variables that promote or inhibit parasympathicolysis.

Non-invasive measurement of parasympathetic control has gained increasing scientific interest since it became clear that respiratory sinus arrhythmia (RSA) mirrors cardiac vagal tone (Akselrod et al., 1981; Porges et al., 1981; Fouad et al., 1984; Billman and Dujardin, 1990; Hayano et al., 1991). RSA can be calculated 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 RSA (Moser et al., 1994). Depending on respiratory rate, RSA is usually observed in resting subjects in the narrow band of heart rate variations ranging from 2 to 5 s. Sympathetic nervous system activity appears to be too slow to influence heart rate variability in this frequency band (Akselrod et al., 1981).

Peripheral cardiac vagal tone is known to decrease with age in healthy subjects (Hellman and Stacy, 1976; De Meersman, 1993; Moser et al., 1996). In clinical work, it is well known that anticholinergic effects in patients treated with tricyclic agents also increase with age (Peabody et al., 1986; Marcopulos and Graves, 1990; Salzman, 1993). There are three possible explanations for this phenomenon. (i) The anticholinergic response to the medication is higher in older than in younger people, making them also more vulnerable to the side effects. (ii) Due to the age-related decline in cardiac vagal tone (Hellman and Stacy, 1976; De Meersman, 1993; Moser et al., 1996; Lehofer et al., 1996), the vagal tone is reduced below a critical level manifesting itself in clinical symptomatology. In the latter case, the drug effect is superimposed on an already low vagal tone in the elderly. (iii) A combination of (i) and (ii) is conceivable.

The aim of the present study was to determine which of the explanations seems to be most likely. For this purpose we first investigated if there is a consistent parasympatholytic effect of tricyclic antidepressants and whether this effect on peripheral parasympathetic activity varies with age.

2. Methods

2.1. Subjects

Twenty-three patients (14 female) suffering from major depression, melancholic type, and 23 age- and sex-matched normal control subjects participated in the study. Major depression was diagnosed by means of the Structured Clinical Interview for DSM-III-R (Wittchen et al., 1991), and was both unipolar and non-delusional. The patients all had been treated with a tricyclic antidepressant (TCA), amitriptyline, for at least 7 days. The average dose was 150 mg (range: 125–175 mg). It was administered in two doses, one in the morning and one in the evening. The mean age of the depressed patients was 42 (range: 20–62) years. The mean age of the normal control subjects was 42 (range: 20–63) years. There was no history of psychiatric illness in either the normal control subjects or their first degree relatives. All subjects in both groups were in good physical health.

2.2. Procedures

2.2.1. Measurement of respiratory sinus arrhythmia

To minimize the influences of circadian autonomic variations, all measurements were taken between 15.00 and 19.00 h. After 20 min of supine rest in a quiet air-conditioned room, chest wall ECG was recorded during 10 additional minutes of rest by a data recording system developed by our group (Gallasch et al., 1991; Moser et al., 1992). R–R intervals of the ECG were determined off-line to 1 ms. A computer program using matched filtering of the ECG data was employed to recognize the R-peaks. As a check, all QRS complexes were plotted with the R-peaks synchronized. False R-peaks could easily be recognized visually. ECGs for which false R-peaks made up more than 3% of the record were excluded from further processing. Heart periods containing premature heartbeats and the following delay were replaced by interpolating according to Saul et al. (1988), as were all values greater than 20% below or above the preceding heart period. The interbeat intervals were converted to heart rate. Heart rate variability was computed by spectral estimation as well as by a time domain method.

2.2.1.1. Spectral estimation of heart rate variability. Spectral estimation was performed according to an algorithm first published by Berger et al. (1986) and recommended by Berntson et al. (1997): The interval series of beat-to-beat heart rate was converted to a time series by resampling of the intervals at 4 Hz. After the time series was detrended, a fast Fourier transform was performed using a Hamming window, and the spectral density was computed. Heart rate variability was then computed by integration of the spectrum over the area from 0.15 to 0.5 Hz. Next, logarithms of the resulting values were taken to normalize the log-normal distribution of inter-individual heart rate variability.

2.2.1.2. Time domain computation of vagal tone. For the time domain computation of vagal tone, a method described by Moser et al. (1994, 1998) was used. For each sequence of heartbeats, log RSA was calculated as follows: The median of the absolute heart rate differences between successive heartbeats was taken. The median was chosen because it is less sensitive to outliers than the mean and to the intra-individual log-normal shape of the RSA distribution. Next, the logarithm of the resulting median was taken to normalize the log-normal inter-individual distribution of RSA.

2.2.2. Physiological correlations

Age dependence was assessed by means of linear regression for spectrally derived RSA (high frequency heart rate variability) as well as for log RSA. Regression coefficients and correlation coefficients (r) were calculated separately for each subject group. In addition, log RSA was compared to spectrally estimated heart rate variability for all subjects.

2.2.3. Psychiatric rating instruments

Depression was measured by means of the Beck Depression Inventory (BDI; Beck and Beck, 1972). Anxiety was measured by means of the State–Trait Anxiety Inventory (STAI), State and Trait forms (Spielberger et al., 1970).

2.3. Statistics

Means (± 1 S.D.) of heart rate, high frequency heart rate variability, log RSA, BDI score, and STAI, State and Trait scores, were computed. A paired Student t-test was applied to test the differences of the parameters' means for significance. Slope differences of the regression lines were checked using a test for parallelism (Kleinbaum and Kupper, 1978).

3. Results

The self-ratings and physiological measures of patients and matched control subjects are presented in Table 1. The patients exhibited significantly higher BDI and STAI rating scores than the control subjects. The same was true for heart rate. Both measures of vagal tone, however, were significantly lower in the depressed patients on TCAs than in the control subjects or the unmedicated patients. The age dependence of vagal tone is presented for the time domain method in Fig. 1

and for the frequency domain method in Fig. 2. Both figures show significant, age-related decreases in cardiac vagal tone. This was the case in both medicated depressed patients (T) and normal control subjects (C).

A statistical test for parallelism of the regression lines found no significant between-group differences in the slopes in spite of the significantly different mean values of vagal tone (Table 1). In Fig. 1, regression lines of a different group of untreated patients and their healthy control subjects (taken from Moser et al., 1998) are overlaid for comparison (see Section 4).

The correlation between log RSA, the time domain measure of cardiac vagal tone, and log-high-frequency heart rate variability, the frequency domain measure, is shown in Fig. 3. Regression lines for healthy subjects and patients were calculated separately. Both correlation coefficients are highly significant and the regression lines are almost identical. This indicates that the simple time domain method used in our study yields results comparable to a much more sophisticated frequency domain measure, as has been found in previous studies (Grossman et al., 1990). Fig. 3 also reveals that the correlation between time and frequency domain measures is not altered by medication. It can also be seen that the data points of the healthy subjects tend to cluster at the upper right part of the figure, whereas those of the patients treated with TCAs are located in the lower left quadrant, indicating reduced vagal tone in the depressed patients.

4. Discussion

In this study we compared the age dependence of physiological parameters in a group of patients treated with TCAs with an age- and sex-matched group of healthy subjects without any medication as well as with a group of untreated patients. It would have been advantageous to measure the

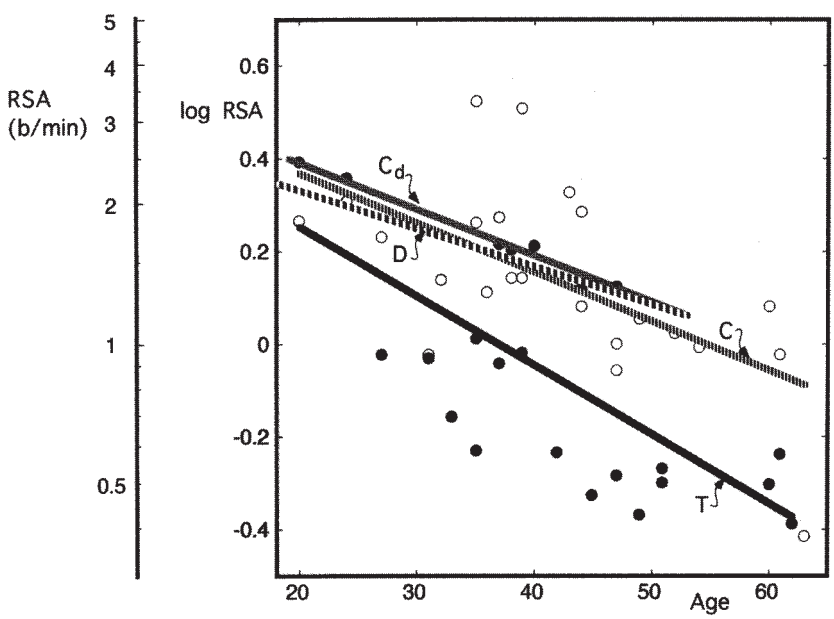

Fig. 1. Age dependence of vagal tone (log RSA) in patients treated with TCA (T) and age- and sex-matched control subjects (C). Both regression lines are significant: −○− C: log RSA = 0.0106 × age + 0.583 $r = -0.61$ ($P < 0.05$); −●− T: log RSA = 0.0149 × age + 0.551 $r = -0.70$ ($P < 0.001$). For comparison, the linear scale for RSA (b.p.m.) is placed next to log RSA. Regression lines D (unmedicated depressed patients) and Cd (their healthy control group) are superimposed from an earlier study of our group (Moser et al., 1998).

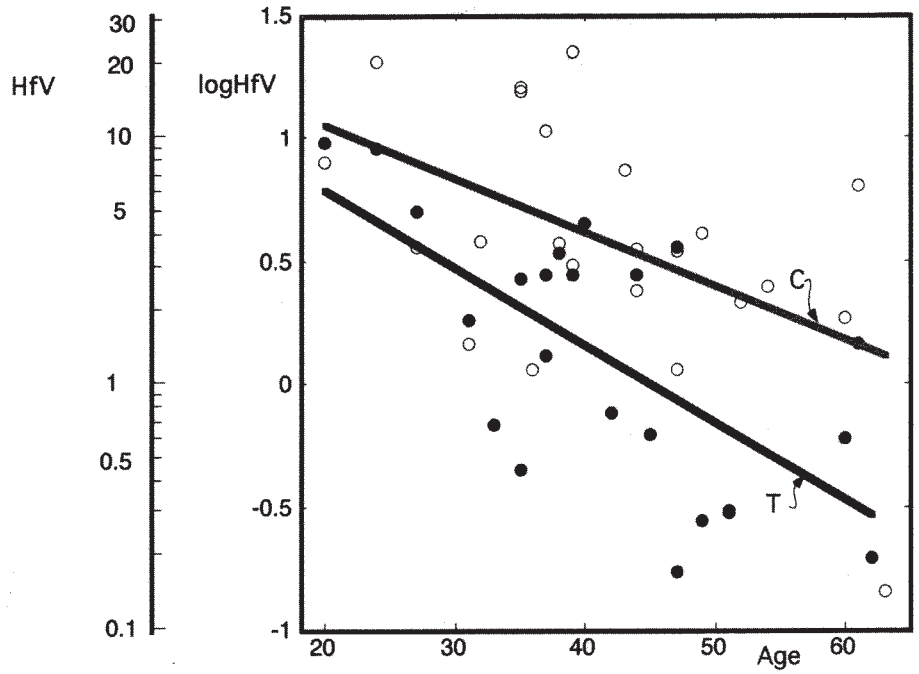

Fig. 2. Age dependence of vagal tone (log HfV) in patients treated with TCA (T) and age- and sex-matched control subjects (C). Both regression lines are significant: −○− C: log HfV = −0.0218 × age + 1.485 $r = -0.51$ ($P < 0.05$); −●− T: log HfV = −0.0314 × age + 1.414 $r = -0.66$ ($P < 0.001$). For comparison, the linear scale for HfV is placed next to log HfV.

Table 1
Psychiatric and physiological differences between depressed subjects medicated with TCA and their age- and sex-matched control subjects

	Depressed patients on TCA $N = 23$ (14 females)	Matched control subjects $N = 23$ (14 females)	Significance of difference between groups (P)*
Age and self-ratings			
Age	41.5 ± 11.2	41.6 ± 11.5	n.s.
BDI	18.0 ± 4.17	1.3 ± 1.22	< 0.001
STAI-S	47.0 ± 7.44	31.0 ± 5.17	< 0.01
STAI-T	46.0 ± 9.4	29.0 ± 6.9	< 0.001
Physiological measures			
Heart rate (b.p.m.)	81.1 ± 8.9	67.4 ± 8.2	< 0.0002
log RSA [log (b.p.m.)]	−0.068 ± 0.239	0.140 ± 0.201	< 0.0002
log HfV	0.109 ± 0.530	0.578 ± 0.492	< 0.0004

Values represent means and standard deviations. * Paired Student t-tests, two-tailed.
Abbreviations: TCA, tricyclic antidepressants; BDI, Beck Depression Inventory; STAT-S and -T, State Trait Anxiety Inventory, State and Trait forms; log RSA, cardiac vagal tone estimate in the time domain; log HfV, cardiac vagal tone estimate in the frequency domain.

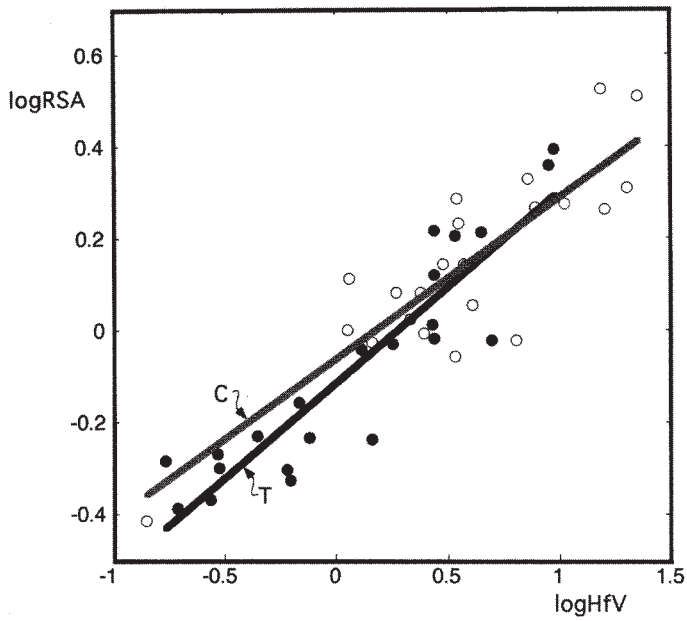

Fig. 3. Correlation between log RSA, a time domain estimate of vagal tone, and log HfV, a measure computed by spectral analysis of HRV, in patients treated with TCA (T) and age- and sex-matched control subjects (C). Both regression lines are highly significant: –○– C: log RSA = 0.350 × log HfV – 0.062 $r = 0.85$ ($P < 0.0001$). –●– T: log RSA = 0.414 × log HfV – 0.114 $r = 0.92$ ($P < 0.0001$).

physiological parameters in the same group of patients before and after treatment. In a clinical study this is not an easy task. Most patients come to psychiatrists already pretreated and it would be ethically inacceptable to take them off an antidepressant for a longer washout period just to obtain data in an unmedicated state. In this study we therefore present data of groups of medicated depressed patients as well as their healthy control subjects. Additionally we present data from an earlier study, which investigated different unmedicated depressed patients and different healthy control subjects. In Fig. 1 the regression lines of these groups are superimposed on the data of this study. Similarities of the control groups as well as differences between medicated and unmedicated patients can be seen.

We found a significantly increased heart rate and decreased cardiac vagal tone in the medicated patient group (see Table 1). Increased heart rate seems to be rather consistently related to depression (for a literature review see Moser et al., 1998) and is found in the unmedicated patients as well. In a previous study we hypothesized that increased sinus node beat frequency void of autonomic influences (autonomous heart rate) is responsible for these observations in unmedicated depressed patients (Moser et al., 1998), and not a change of autonomic tone.

To decide whether the decreased cardiac vagal tone derives from medication or from the disorder itself, we compared heart rate and vagal tone of the medicated patients to the same parameters measured in a group of unmedicated depressed patients of an earlier study (Moser et al., 1998). The latter data were obtained from a group of 26 patients (19 females) that had not been treated with any psychopharmacologic medication for at least 3 months prior to the investigation. We found a significantly decreased vagal tone in the medicated patients (compared to the unmedicated patients for the time domain measure of vagal tone (log RSA; $P < 0.0002$; see also Fig. 1) as well as for the spectral estimate of vagal

tone (log HfV; $P < 0.003$). Heart rate was higher in the treated group as well, although this difference was not significant. It has to be considered that the data derived from different studies and the compared groups were not completely matched. In spite of that, the two linear regression lines of control subjects as well as unmedicated depressed patients are nearly identical (Fig. 1).

We conclude from these results that vagal tone is decreased by the anticholinergic medication, but that lowered vagal tone is not a trait marker of depression itself. The prior finding is also in accordance with the work of McLeod et al. (1992) and Walsh et al. (1994), who found cardiac vagal tone to be decreased by TCAs.

The age dependence of cardiac vagal tone was compared using two different methods of vagal tone estimation: whereas log RSA is a time domain measure of vagal tone, the spectral estimate of high frequency heart rate variability estimates vagal tone in the frequency domain and needs a sophisticated preparation of the data before the analysis can be performed. The results (Fig. 2) are comparable to the regression lines produced by the time domain method (log RSA) seen in Fig. 1, with similar correlation coefficients and significance levels. Fig. 3 also shows a high correlation between the two estimators of cardiac vagal tone, independent of medication. We conclude from these findings that the time domain measure (log RSA) and the frequency domain method are equally suitable as non-invasive indicators of cardiac vagal tone.

The aim of the present study was to determine whether the parasympatholytic effects of tricyclic antidepressants vary with age, resulting in a greater reduction in vagal tone in the elderly. In this study, we found a significant age-related reduction in vagal tone for patients with major depression, melancholic type, who were taking amitriptyline, as well as for normal control subjects. In the normal control subjects, vagal tone at the age of 60 was reduced by 62% compared to vagal tone at the age of 20. In the group treated with TCAs, a slightly higher aging effect was found (−74%), although the difference was not significant.

As seen in the captions of Figs. 1 and 2, the regression lines of the unmedicated patients did not deviate significantly from that of the healthy control subjects in either slope or intercept. On the other hand, a marked effect of TCAs on cardiac vagal tone was found and this is depicted in the lower regression lines of Figs. 1 and 2. Tricyclic medication reduced vagal activity in all age groups.

The results of the present study lead us to conclude that the anticholinergic effects of TCAs cannot be considered significantly different across ages. The differences seen in the clinical effects of TCAs in the elderly probably reflect the results of the age-related decline in cardiac vagal tone. The resulting reduced vagal tone apparently makes older subject more vulnerable to the parasympatholytic effects of TCAs.

The results discussed above came from the analyses of group data. However, we must point out that cardiac vagal tone varies considerably within and between subjects, even in the same age group. It is conceivable that a patient with relatively high cardiac vagal tone would be more tolerant to a given dose of medication with anticholinergic effects than a patient of the same age who has lower vagal tone. Therefore, the assessment of vagal tone prior to administering medication might be helpful in determining a patient's tolerance to medications with anticholinergic effects. Especially in the elderly a cautious use of anticholinergic medications is recommended, according to clinical practice.

Acknowledgements

This investigation was supported by the Austrian Ministry for Science and Traffic (Projects: Autonomic Monitoring) and the Austrian Research Fund (SFB — Modelling and Control: Project 312). We would like to thank Manfred Lux, Ph.D., for his help.

References

Akselrod, S., Gordon, D., Ubel, F.A., Shannon, D., Barger, A.C., Cohen, R.J., 1981. Power spectrum analysis of heart

rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 231, 220–222.

Baldessarini, R.J., Fleischhacker, W.W., Sperk, G., 1991. Pharmakotherapie in der Psychiatrie. Georg Thieme Verlag Stuttgart-New York, p. 103.

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. Psychopharmacology Bulletin 29, 201–206.

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

Berger, R.D., Akselrod, S., Gordon, D., Cohen, R.J., 1986. An efficient algorithm for spectral analysis of heart rate variability. IEEE Transactions on Biomedical Engineering 9, 900–904.

Berntson, G.G., Bigger, J.T., Eckberg, D.L., Grossmann, P., Kaufmann, P.G., Malik, M., Nagaraja, H.N., Porges, S.W., Saul, J.P., Stone, P.H., Van der Molen, M.W., 1997. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 34, 623–648.

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

Carney, R., Rich, M., TeVelde, A., Saini, J., Clark, K., Freeland, K., 1988. The relationship between heart rate, heart rate variability and depression in patients with coronary artery disease. Journal of Psychosomatic Research 32, 159–164.

Dalack, G.W., Roose, S.P., 1990. Perspectives on the relationship between cardiovascular disease and affective disorder. Journal of Clinical Psychiatry 51, 4–11.

Davidson, J., Turnbull, C.D., 1986. Diagnostic significance of vegetative symptoms in depression. British Journal of Psychiatry 148, 442–446.

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

De Meersman, R.E., 1993. Aging as a modulator of respiratory sinus arrhythmia. Biological Sciences 48, B74–B78.

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

Gallasch, E., Moser, M., Hindinger, J., Rafolt, D., Jernej, G., Eder, H., Grießmayer, G., Wronski, B., Ansperger, A., Kenner, T., 1991. An interactive hand-held measurement system for biomedical applications. Forum der Meßtechnik 5, 540–545.

Grossman, P., van Beek, J., Wientjes, C., 1990. A comparison of three quantification methods for estimation of respiratory sinus arrhythmia. Psychophysiology 27, 702–714.

Hayano, J., Sakakibara, Y., Yamada, A., Yamada, M., Mukai, S., Fujinami, T., Yokoyama, K., Watanabe, Y., Takata, K., 1991. Accuracy of assessment of cardiac vagal tone by heart rate variability by normal subjects. American Journal of Cardiology 67, 199–204.

Hellman, J.B., Stacy, R.W., 1976. Variation of respiratory sinus arrhythmia with age. Journal of Applied Physiology 41, 734–738.

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

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

Lader, M.H., Wing, L., 1969. Physiological measures in agitated and retarded depressed patients. Journal of Psychiatric Research 7, 89–100.

Lahmeyer, H.W., Bellur, S.N., 1987. Cardiac regulation and depression. Journal of Psychiatry Research 21, 1–6.

Lehofer, M., Moser, M., Hoehn-Saric, R., Hildebrandt, G., Drnovsek, B., Niederl, T., Zapotoczky, H.G., 1996. Diminished pulse respiration coupling in depressed patients. Biological Psychiatry 39, 526.

Marcopulos, B.A., Graves, R.E., 1990. Antidepressant effect on memory in depressed older persons. Journal of Clinical and Experimental Neuropsychology 12, 655–663.

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

Moser, M., Gallasch, E., Rafolt, D., Jernej, G., Kemp, C., Moser-Kneffel, E., Kenner, T., Baevskij, R., Funtowa, I., 1992. Cardiovascular Monitoring in Microgravity — The Experiments PULSTRANS and SLEEP. Springer-Verlag, Wien, New York.

Moser, M., Lehofer, M., Sedminek, A., Lux, M., Zapotoczky, H.G., Kenner, T., 1994. Heart rate variability as a prognostic tool in cardiology. Circulation 9, 1078–1082.

Moser, M., Lehofer, M., Hoehn-Saric, R., Egner, S., Voica, M., Messerschmidt, D., Zeiringer, H., Kenner, T., 1996. Factors influencing cardiac vagal tone in depressed patients. Biological Psychiatry 39, 526.

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

Noble, P.E., Lader, M.H., 1971. Salivary secretion in depressive illness: a physiological and psychometric study. Psychological Medicine 1, 372–376.

Peabody, C.A., Whiteford, H.A., Hollister, L.E., 1986. Antidepressants and the elderly. Journal of the American Geriatric Society 34, 869–874.

Porges, S.W., Bohrer, R.E., Keren, G., Cheung, M.N., Franks, G.J., Drasgow, F., 1981. The influence of methylphenidate on spontaneous autonomic activity and behavior in children diagnosed as hyperactive. Psychophysiology 18, 42–48.

Roose, S.P., Glassman, A.H., Dalack, G.W., 1989. Depression, heart disease, and tricyclic antidepressants. Journal of Clinical Psychiatry 50, 12–16.

Salzman, C., 1993. Pharmacologic treatment of depression in the elderly. Journal of Clinical Psychiatry 54, 23–28.

Saul, J.P., Arai, Y., Berger, R.D., Lilly, L.S., Colucci, W.S., Cohen, R.J., 1988. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. American Journal of Cardiology 61, 1292–1299.

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

Walsh, B., Giardina, E., Gloan, R., Greenhill, L., Goldfein, J., 1994. Effects of desipramine on autonomic control of the heart. Journal of the American Academy for Child and Adolescent Psychiatry 33, 191–197.

Wittchen, H.U., Zaudig, M., Schramm, E., Spengler, P., Mombour, W., Klug, E., Horn, R., 1991. Stukturiertes Klinisches Interview for DSM III R, 2nd ed. Beltz-Test GmbH, Weinheim.

Yeragani, V.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.