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A Pilot Study on the Effects of Heart Rate Variability Biofeedback in Patients with Depression and in Healthy Subjects

Martin Siepmann · Volkan Aykac · Jana Unterdörfer · Katja Petrowski · Michael Mueck-Weymann

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Abstract Decreased vagal activity and increased sympathetic arousal have been proposed as major contributors to the increased risk of cardiovascular mortality in patients with depression. It was aim of the present study to assess the feasibility of using heart rate variability (HRV) biofeedback to treat moderate to severe depression. This was an open-label study in which 14 patients with different degrees of depression (13 f, 1 m) aged 30 years (18–47; median; range) and 12 healthy volunteers attended 6 sessions of HRV biofeedback over two weeks. Another 12 healthy subjects were observed under an active control condition. At follow up BDI was found significantly decreased (BDI 6; 2–20; median 25%–75% quartile) as compared to baseline conditions (BDI 22;15–29) in patients with depression. In addition, depressed patients had reduced anxiety, decreased heart rate and increased HRV after conduction of biofeedback ($p < 0.05$). By contrast, no changes were noted in healthy subjects receiving biofeedback nor in normal controls. In conclusion, HRV biofeedback appears to be a useful adjunct for the treatment of depression, associated with increases in HRV.

M. Siepmann · K. Petrowski · M. Mueck-Weymann
Clinic for Psychotherapy and Psychosomatic Medicine, Medical School, Technical University, Dresden, Germany

M. Siepmann (✉) · V. Aykac · J. Unterdörfer
Institute of Clinical Pharmacology, Medical Faculty, Technical University, Fiedlerstr. 27, 01307 Dresden, Germany
e-mail: martin.siepmann@tu-dresden.de

M. Mueck-Weymann
Institute of Behavioural Medicine and Prevention, Medical Informatics and Technology, University for Health Sciences, Hall, Austria

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Introduction

There is clinical evidence that the existence of a depressive disorder is an independent predicator for an inferior outcome in patients with cardiovascular disease (Musselman et al. 1998). A possible explanation for this relationship is that depressive disorders influence autonomic nervous system (ANS) in a manner characterized by a reduced parasympathetic and/or increased sympathetic tone (Mück-Weymann et al. 2002). Heart rate variability (HRV), which is the amount of fluctuation from the mean heart rate, represents the interaction between sympathetic and parasympathetic influences on the cardiac pacemaker in clinical settings. Impaired HRV has been linked to symptoms of depression. A series of studies demonstrated that patients with depression have increased heart rate and attenuated HRV (Rechlin et al. 1994; Agelink et al. 2002; Mück-Weymann et al. 2002; Nahshoni et al. 2004; Siepmann et al. 2005; Catipovic-Veselica et al. 2007). Additionally, cardiac patients with severe depression were previously found to exhibit less HRV than those with less severe depression (Krittayaphong et al. 1997).

Well controlled studies have documented that biofeedback training to maximize HRV can reverse decrease in HRV and improve symptoms in patients with disorders characterized by autonomic nervous system dysfunction i.e. asthma, hypertension and heart disease (Lehrer et al. 2003; McCraty et al. 2003; Nolan et al. 2005). Case studies have shown that HRV biofeedback may improve depressive symptoms (Hassett et al. 2007; Karavidas et al. 2007). The present study was designed to investigate the effects of

HRV biofeedback on autonomic functions and mood in patients with depression as well as in normals.

Methods

Participants and Study Design

38 participants, aged 18–47 years (mean = 28, SD = 7.3) participated in a 6-session HRV biofeedback protocol conducted over 2 weeks. This sample included 14 patients with depression (13 f, 1 m) and 12 healthy volunteers (6 f, 6 m) of whom all received active treatment. Patients already receiving antidepressant and/or anxiolytic medication and/or psychotherapy were included. The sample further included 12 healthy volunteers (6 f, 6 m) who were randomly assigned to an active control condition. Diagnoses and demographics of depressed patients are given in Table 1. Demographics of healthy subjects are given in Table 2. We excluded volunteers who had a history of psychosis, mental deficiency, coronary artery disease, heart failure, kidney disease, hypertension, chronic low blood pressure, hypoglycaemia or cardiac arrhythmias. Psychiatric diagnoses were assessed according to DSMIV by an experienced psychiatrist and documented by use of the Structured Clinical Interview for DSM-IV. Participants were included after taking medical history, physical examination, routine laboratory tests and 12-lead ECG.

Patients and volunteers assigned to biofeedback treatment underwent 3 sessions of biofeedback training per week over 2 weeks. Subjects randomized as controls underwent 3 sessions of an active control condition per week over 2 weeks.

Table 1 Demographics and diagnoses of depressed patients

Patient	Age (years)	Sex	Diagnosis
01	22	f	Major depression
02	47	f	Recurrent depressive disorder
03	23	f	Mild depressive episode
04	23	f	Moderate depressive episode
05	23	f	Recurrent depressive disorder
06	18	f	Dysthymia
07	41	f	Dysthymia
08	28	m	Dysthymia
09	43	f	Dysthymia
10	30	f	Dysthymia
11	24	f	Dysthymia
12	36	f	Recurrent depressive disorder
13	30	f	Bipolar disorder
14	29	f	Dysthymia

Table 2 Demographics of healthy subjects

Subject	Age (years)	Sex	Intervention
01	24	f	Biofeedback treatment
02	24	f	Active control condition
03	23	f	Active control condition
04	26	f	Biofeedback treatment
05	22	f	Active control condition
06	25	f	Biofeedback treatment
07	19	f	Active control condition
08	20	f	Biofeedback treatment
09	27	f	Active control condition
10	27	f	Biofeedback treatment
11	32	f	Biofeedback treatment
12	30	f	Active control condition
13	25	m	Biofeedback treatment
14	26	m	Active control condition
15	30	m	Active control condition
16	24	m	Biofeedback treatment
17	39	m	Biofeedback treatment
18	41	m	Biofeedback treatment
19	39	m	Active control condition
20	40	m	Active control condition
21	25	m	Biofeedback treatment
22	24	m	Active control condition
23	24	m	Active control condition
24	24	m	Biofeedback treatment

Subjective rating and measurement of heart rate variability were conducted before start of biofeedback treatment or active control condition (baseline), upon completion of them and 2 weeks afterwards. Patients were recruited from the Clinic for Psychotherapy and Psychosomatic Medicine of the University Hospital of Dresden, Germany. Subjects were recruited from a local database most of them being students of the Technical University of Dresden.

Participants received the evaluations and experimental treatment at no cost, and without other inducements. Written informed consent from the participants and approval from the University Hospital Ethics Committee (Dresden, Germany) were obtained.

HRV Biofeedback

A standardized HRV biofeedback system (Stressball^{TM}, BioSign, Ottenhofen, Germany) was used. The method has been described in detail elsewhere (Mück-Weymann et al. 1996; Mück-Weymann and Beise 2005). Briefly, the participants were taught to breathe at her/his resonant frequency, i.e. the frequency at which maximum amplitudes of HRV are generated voluntarily for each individual.

A pacing stimulus was visualized for this purpose: a balloon that moved up and down on a computer screen at the target respiratory rate. Also, the screen displayed heart rate and a moving HRV analysis of it. The participants were asked to increase the coherence of their heart rate that occurred at approximately resonant frequency. The participants were instructed to breathe in phase with heart rate changes for approximately 25 min, with the goal of maximally increasing amplitude of respiratory sinus arrhythmia. An active control condition was achieved with the subjects sitting infront of the computer screen switched on, but not being instructed to breathe in a paced way or to maximize their HRV.

Measurement of Physiological Variables

Heart Rate Variability

Heart rate analysis was carried out with the computer program Chart® (AD Instruments, Castle Hill, Australia). Details have been described elsewhere (Rechlin et al. 1994). In brief, the ECG signal was digitized at a sample rate of 400 per second. After a resting period of 10 min subjects were instructed to breathe deeply at a frequency of 6 cycles per minute (6 s inspiration, 4 s expiration) as deep respiration was demonstrated to produce maximal HRV in healthy volunteers. This pattern of paced breathing was achieved by asking the participants to synchronize their breathing with breathe-in and breathe- out guiding tones given via head phone. Breathing patterns (paced or unpaced during relaxed rest) were controlled by online registration of respiratory chest movements by means of a respiratory belt transducer containing a piezo-elcetric device that responds linearly to changes in length. It measures changes in thoracic circumference during respiration and indicates inhalation, expiration, breathing strength and rate of respiration. The pNN50, (that is, the fraction of consecutive normal sinus (NN) intervals that differ by more than 50 ms) was calculated from 200 artefact free heart beats. A spectral power analysis was carried out over 3 min recording by means of a Fast Fourier Transformation (FFT). Absolute power values were assessed for three frequency bands: very low frequency (VLF) = 0.01–0.04 Hz, low frequency (LF) = 0.04–0.15 Hz and high frequency (HF) = 0.15–0.4 Hz. The ratio between absolute power values in the LF and HF bands (LF/HF) was then calculated.

Vasoconstrictory Response of Cutaneous Blood Vessels (VR)

The cutaneous blood flux was measured in relative units (rU) with a Periflux laser-Doppler flux meter (Perimed®, Sweden). Details of the methods have been described elsewhere (Mück-Weymann and Rechlin 1996). In brief, the periflux probe which was located on the tip of a middle finger recorded the arterial, capillary and venous erythrocyte flux at a depth of 2 mm. The fall and returning of the laser Doppler flux (LDF) signal provoked by deep respiration is the so called inspiratory gasp response. After a resting period of 10 min subjects were instructed to take a single deep breath. The vasoconstrictory response (VR) was defined as baseline value (finger tip blood flux at baseline; FTBFbase) minus the lowest value within the next 10 after deep inspiration (FTBFmin) over FTBFbase:

$$\mathrm{VR} = \frac{\mathrm{FTBFbase} - \mathrm{FTBFmin}}{\mathrm{FTBFbase}}$$

The time periods needed for 50% constriction (Δt 50% down) and 50% redilation of cutaneous vessels (Δt 50% up) were then calculated.

Questionnaires

Severity of depression was assessed by means of the Beck Depression Inventory (BDI; Beck et al. 1961). Anxiety was measured with the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al. 1970).

Statistical Analysis

The statistical analysis of all data was performed with the Sigma Stat® software package (Jandel, San Rafael, CA, USA). Evaluation of heart rate, pNN50, Δt 50% down and Δt 50% up was done with a one-way ANOVA procedure for repeated measurements following testing for normality and equality of variances of the differences between levels of the repeated measures factor. If significant, Student-Newman-Keuls posthoc tests were used for comparisons between treatment, follow up and baseline conditions. Friedman repeated measures ANOVA on ranks followed by Dunn's posthoc tests were applied for all other parameters as the corresponding values were found not normally distributed. pNN50 was chosen as a primary variable. Statistical significance was accepted at $p < 0.05$.

Results

As it is stated in the method section session comparisons were made separately for conditions of relaxed rest and paced breathing. As it is outlined in Fig. 1 heart rate was found decreased in depressed patients under conditions of relaxed rest at completion of biofeedback as well as 2 weeks afterwards. ($F = 16.7$, $p < 0.0001$). Heart rate was found decreased in depressed patients under conditions

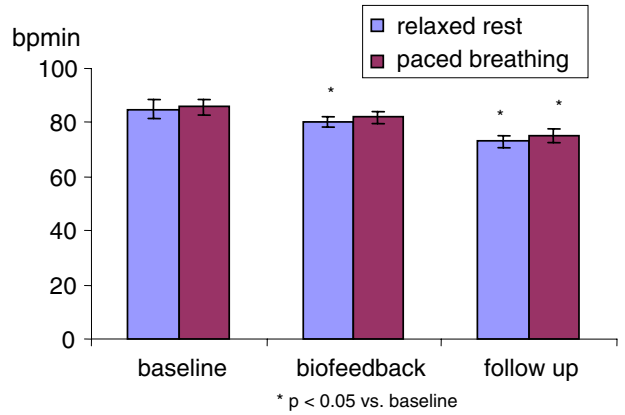

Fig. 1 Heart rate in depressed patients ($n = 14$) before, during and 2 weeks after termination of HRV biofeedback (bpmin; mean ± standard deviation)

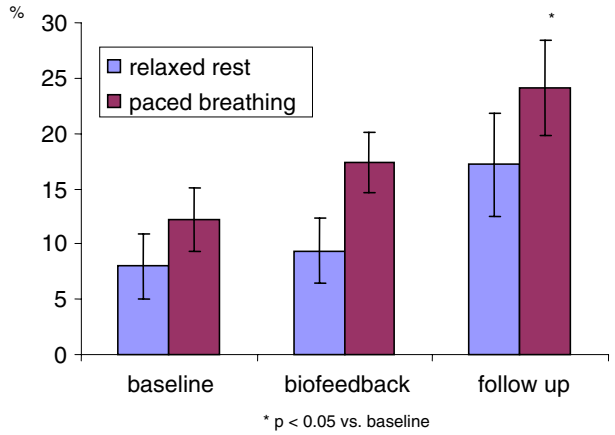

Fig. 2 pNN50 in depressed patients ($n = 14$) before, during and 2 weeks after termination of HRV biofeedback (per centage; mean ± standard deviation)

of paced breathing when being followed up ($F = 16.3$, $p < 0.0001$). As it is shown in Fig. 2 pNN50 was noted increased in depressed patients under conditions of paced breathing at follow up ($F = 7.1$, $p < 0.01$). Total power was noted increased in depressed patients under conditions of paced breathing at follow up (Chi-square = 6.1 with two degrees of freedom, $p < 0.05$), but power in the HF, LF and VLF bands and the LF/HF ratio did not differ significantly from baseline during biofeedback and at follow up (Table 3). No significant changes of heart rate and heart variability were observed in healthy subjects receiving biofeedback nor in those who were maintained under an active control condition (data not shown). Vasoconstrictory responses of cutaneous vessels were found unchanged in depressed patients (Fig. 3) as well as in healthy subjects receiving or not receiving biofeedback (data not shown). As it is shown in Table 4 scores of BDI and STAI were found reduced during biofeedback and at follow up as compared to baseline (Chi-square = 11.2 with two degrees of freedom, $p < 0.05$ and Chi-square = 8.7 with two degrees of freedom, $p < 0.05$, respectively). No mood changes were noted in healthy subjects receiving or not receiving biofeedback (data not shown).

Discussion

This pilot study evaluated whether a behavioural neurocardiac intervention could influence autonomic functions and subjective mood in patients with depression and in normals. Time and frequency domain parameters of HRV were found increased and subjective mood was noted improved in depressed patients when being followed up

Table 3 Absolute power in the VLF, LF and HF frequency bands (ms^2) and LF/HF ratio in depressed patients ($n = 14$) before, during and 2 weeks after termination of HRV biofeedback (median; 25% to 75% quartile)

Time	Parameter	Relaxed rest		Paced breathing	
		Median	25–75% quartile	Median	25–75% quartile
Baseline	TP (ms^2)	1449.4	396.6–3371.4	3375.8	1922.0–6059.8
	VLF (ms^2)	185.1	123.9–397.7	170.1	136.1–568.7
	LF (ms^2)	745.9	225.1–1709.5	2358.9	1387.9–5245.3
	HF (ms^2)	175.2	93.5–389.8	179.3	121.6–711.2
	LF/HF	3.04	1.57–4.90	13.66	3.92–18.0
Biofeedback	TP (ms^2)	2350.7	396.0–3549.8	4759.7	2685.6–7854.2
	VLF (ms^2)	349.2	141.7–645.5	182.6	101.3–287.0
	LF (ms^2)	1275.7	218.4–1593.2	3568.8	2102.6–6987.3
	HF (ms^2)	176.1	54.6–752.4	312.1	146.1–582.5
	LF/HF	4.05	1.27–8.10	6.47	5.36–17.4
Follow up	TP (ms^2)	3289.0	1367.9–5056.1	5528.7*	3202.6–11778.9
	VLF (ms^2)	475.0	101.1–805.7	521.3	256.1–1620.1
	LF (ms^2)	2250.2	244.6–3139.2	4984.5	2738.0–8409.6
	HF (ms^2)	236.7	97.8–910.3	359.5	133.2–997.6
	LF/HF	5.42	2.44–12.52	9.14	6.76–13.5

* $p < 0.05$ vs baseline

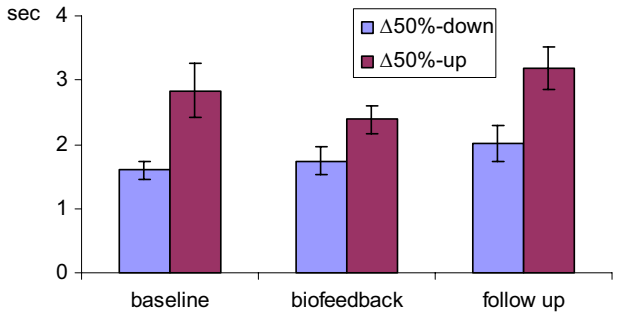

Fig. 3 Δt 50% down and Δt 50% up in depressed patients ($n = 14$) before, during and 2 weeks after termination of HRV biofeedback (sec; mean ± standard deviation)

Table 4 Scores of BDI and STAI in depressed patients ($n = 14$) before, during and 2 weeks after termination of HRV biofeedback (median; 25–75% quartile)

Time	Scale	Median	25–75% quartile
Baseline	BDI	21.5	15.0–29.0
	STAI	108.0	97.0–133.0
Biofeedback	BDI	11.5*	5.0–22.0
	STAI	88.0*	79.0–105.0
Follow up	BDI	5.50*	2.0–20.0
	STAI	85.5*	69.0–109.0

* $p < 0.05$ vs. baseline

after treatment with HRV biofeedback. These results are in line with case studies reported previously (Hassett et al. 2007; Karavidas et al. 2007). By contrast, no changes of mood nor HRV were be noted by us in healthy subjects receiving treatment with biofeedback nor in those who were maintained under an active control condition. HRV depends on autonomic parasympathetic and sympathetic balance. Cutaneous vasoconstriction is exerted by the sympathetic nervous system with norepinephrine binding on α1-receptors (Pergola et al. 1993). In the present study vasoconstrictory responses of cutaneous vessels following sympathetic stimulation were not found influenced by treatment with biofeedback in depressed patients nor in normals. Therefore, the decrease in heart rate and the increase in HRV observed by us may be due to enhanced parasympathetic activity. It is, however, not well understood how HRV biofeedback influences vagal control of heart rate. HRV biofeedback with paced breathing likely reinforces peripheral heart rate modulation by arterial baroreceptors as well as by chemoreceptors and cardiopulmonary mechanoreceptors (Bennaroch 1997; Lehrer et al. 2000). Lehrer et al. reported that enhanced HRV following biofeedback training was independent of respiration in a single session study, and in a controlled trial it was independent of both respiration and symptoms of relaxation (Lehrer et al. 2003). Biofeedback training may enhance vagal heart rate regulation by evoking focused concentration in combination with emotional self-control. This cognitive-emotional response is associated with a neural circuit in which the prefrontal and the anterior cingulate cortex play a prominent role, as the adaptive control of emotion and goal-directed behaviour is initiated and maintained (Thayer and Lane 2000). Interestingly, these structures are also functionally linked to neurocardiac regulation through reciprocal interconnections with the insula, amygdale, hypothalamus, and neural centres in the medulla involved in parasympathetic effector pathways to the heart (Bennaroch 1997).

Depressed patients—with or without concomitant cardiac disease—have an increased risk of cardiovascular mortality (Musselman et al. 1998; Nemeroff et al. 1998; Carney et al. 2002). Decreased vagal tone and/or excessive sympathetic nervous system activity, both of them due to neurohormonal dysregulation, have been proposed as major contributors to the increased risk of cardiovascular morbidity and mortality in depressed patients (Mück-Weymann 2002; Yeragani et al. 2002). Autonomic toxicity of treatment with antidepressant drugs, especially tricyclics and monoamine oxidase inhibitors, can aggravate the enhanced cardiovascular risk of patients suffering from depression (Cohen et al. 2000a, b). It has been demonstrated in patients with coronary artery disease that autonomic cardiac control can be improved by means of biofeedback training (Del Pozo et al. 2004). Therefore, HRV biofeedback training may be able to reduce the cardiovascular risk of depressed patients by increasing their parasympathetic input to the heart.

The major limitations of this study were its small size, and the absence of an active control condition in depressed patients. It is unclear whether patient improvement of mood and HRV was due to an interventional effect i.e. administration of antidepressant medication or some other factor or series of factors rather than HRV biofeedback. Clinical observations and pilot trials have suggested that selective serotonin reuptake inhibitors (SSRIs) could increase HRV (Rissanen et al. 1998; Cohen et al. 2000a, b). However, it was previously demonstrated in well controlled studies that antidepressant treatment does not improve an impaired HRV in depressed patients nor do SSRIs increase HRV in healthy humans (Sattler et al. 2000; Siepmann et al. 2003; Glassman et al. 2007). HRV biofeedback may exert benefitial effects on cardiovagal regulation and thereby reduce the cardiovascular risk of depressed patients. In future studies, the effects of HRV biofeedback should be compared with those of sham or another form of biofeedback in depressed patients. Additionally, patients should be followed for a longer time period in order to assess the duration of treatment effects. We also note that we tested a Caucasian sample and the

majority of our depressed patients were females. In summary, despite the limitations inherent in this small open label trial HRV biofeedback demonstrates promise for the adjunctive treatment of depression. Further evaluation of this promising intervention is warranted in randomized-controlled trials.

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References

Agelink, M. W., Boz, C., Ullrich, H., & Andrich, J. (2002). Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. *Psychological Research, 113*(1–2), 139–149. doi:10.1016/S0165-1781(02)00225-1.

Beck, A. T., Ward, C., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561–571.

Bennaroch, E. E. (Ed.). (1997). *Central autonomic network: functional organization and clinical correlations*. Armonck, NY: Futura Publishing Company, Inc.

Carney, R. M., Freedland, K. E., Miller, G. E., & Jaffe, A. S. (2002). Depression as a risk factor for cardiac mortality and morbidity. A review of potential mechanisms. *Journal of Psychosomatic Research, 53*, 897–902. doi:10.1016/S0022-3999(02)00311-2.

Catipovic-Veselica, K., Galic, A., Jelik, K., et al. (2007). Relation between major and minor depression and heart rate, heart-rate variability, and clinical characteristics of patients with acute coronary syndrome. *Psychological Reports, 100*(3 Pt2), 1245–1254. doi:10.2466/PR0.100.3.1245-1254.

Cohen, H., Gibson, G., & Alderman, M. H. (2000a). Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *The American Journal of Medicine, 108*(1), 2–8. doi:10.1016/S0002-9343(99)00301-0.

Cohen, H., Kotler, M., Matar, M., & Kaplan, Z. (2000b). Normalization of heart rate variability in post-traumatic stress disorder patients following fluoxetine treatment: preliminary results. *The Israel Medical Association Journal, 2*(4), 296–301.

Del Pozo, J. M., Gevirtz, R. N., Scher, B., & Guarneri, E. (2004). Biofeedback treatment increases heart rate variability in patients with coronary artery disease. *American Heart Journal, 147*(3), E11. doi:10.1016/j.ahj.2003.08.013.

Glassman, A. H., Bigger, J. T., Gaffney, M., & Van Zyl, L. T. (2007). Heart rate variability in acute coronary syndrome patients with major depression: influence of sertraline and mood improvement. *Archives of General Psychiatry, 64*(9), 1025–1031. doi:10.1001/archpsyc.64.9.1025.

Hassett, A. L., Radvanski, D. C., Vaschillo, E. G., et al. (2007). A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. *Applied Psychophysiology and Biofeedback, 32*, 1–10. doi:10.1007/s10484-006-9028-0.

Karavidas, M. K., Leherer, P. M., Vaschillo, E., et al. (2007). Preliminary results of an open lable study of heart rate variability biofeedback for the treatment of major depression. *Applied Psychophysiology and Biofeedback, 32*, 19–30. doi:10.1007/s10484-006-9029-z.

Krittayaphong, R., Cascio, W., Light, K., et al. (1997). Heart rate variability in patients with coronary artery disease: Differences in patients with higher and lower depression scores. *Psychosomatic Medicine, 59*, 231–235.

Lehrer, P. M., Vaschillo, E., & Vaschillo, B. (2000). Resonant breathing biofeedback training to increase cardiac variability: Rationale and manual for training. *Applied Psychophysiology and Biofeedback, 25*(3), 177–191. doi:10.1023/A:1009554825745.

Lehrer, P. M., Vaschillo, E., Vaschillo, B., et al. (2003). Heart rate variability biofeedback increases baroreflex gain and peak expiratory flow. *Psychosomatic Medicine, 65*(5), 796–805. doi:10.1097/01.PSY.0000089200.81962.19.

McCraty, R., Atkinson, M., & Tomasino, D. (2003). Impact of a work-place stress reduction program on blood pressure and emotional health in hypertensive employees. *The Journal of Complementary and Alternative Medicine, 9*(3), 355–369. doi:10.1089/107555303765551589.

Mück-Weymann, M. (2002). Die Variabilität der Herzschlagfolge - Ein globaler Indikator für Adaptivität in bio-psycho-sozialen Funktionskreisen. *Praxis Klinische Verhaltensmedizin und Rehabilitation, 60*, 324–330.

Mück-Weymann, M., & Beise, R. (2005). Herzkohärenztraining – eine moderne Form der Stressbewältigung. *Forum Stressmedizin, I*, 1–5.

Mück-Weymann, M., Loew, T., & Hager, D. (1996). Multiparametrisches Bio-Monitoring mit einem computerunterstützten System für psychophysiologische Diagnostik, psychophysiologisch gesteuerte Therapie und Biofeedback. *Psycho, 5*, 378–384.

Mück-Weymann, M., Moesler, T., Joraschky, P., Rebensburg, M., & Agelink, M. W. (2002). Depression modulates autonomic cardiac control: A psyhopsychophysiological pathway linking depression and mortality? *German Journal of Psychiatry, 5*, 67–69.

Mück-Weymann, M., & Rechlin, T. (1996). Reflexes of cutaneous microcirculation in amitriptyline and in fluoxetine treated patients. *Psychopharmacology, 124*(3), 241–244. doi:10.1007/BF02246663.

Musselman, D. L., Evans, D. L., & Nemeroff, C. B. (1998). The relationship of depression to cardiovasucular disease. Epidemiology, biology and treatment. *Archives of General Psychiatry, 55*(7), 580–592. doi:10.1001/archpsyc.55.7.580.

Nahshoni, E., Aravot, D., Aizenberg, D., et al. (2004). Heart rate variability in patients with major depression. *Psychosomatics, 45*(2), 129–134. doi:10.1176/appi.psy.45.2.129.

Nemeroff, C. B., Musselman, D. L., & Evans, D. L. (1998). Depression and cardiac disease. *Depression and Anxiety, 8*(Suppl 1), 71–79. doi:10.1002/(SICI)1520-6394(1998)8:1+<71::AID-DA11>3.0.CO;2-X.

Nolan, R. P., Kamath, M. V., Floras, J. S., & Stanley, J. (2005). Heart rate variability biofeedback as a behavioral neurocardiac intervention to enhance vagal heart control. *American Heart Journal, 149*(6), 1137. doi:10.1016/j.ahj.2005.03.015.

Pergola, P. E., Kellogg, D. L., Jr., Johnson, J. M., et al. (1993). Role of sympathetic nerves in the vascular effects of local temperatue in human forearm skin. *The American Journal of Physiology, 265*(3 Pt 2), H785–H792.

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*(4), 271–275. doi:10.1016/0165-0327(94)90091-4.

Rissanen, A., Naukkarinen, H., Virkunnen, M., Rawlings, R. R., & Linnoila, M. (1998). Fluoxetine normalizes increased cardiac vagal tone in bulimia nervosa. *Journal of Clinical Psychopharmacology, 18*(1), 26–32. doi:10.1097/00004714-199802000-00005.

Sattler, H. D., Richter, P., Fritzsche, M., von Turner, A., & Barnett, W. (2000). Neurophysiologic tests during antidepressive

treatment—an exploratory study. *Pharmacopsychiatry, 33*(6), 229–233. doi:10.1055/s-2000-8354.

Siepmann, M., Grossmann, J., Mück-Weymann, M., & Kirch, W. (2003). Effects of sertraline on autnomic and cognitive functions in healthy volunteers. *Psychopharmacology, 168*(3), 293–298. doi:10.1007/s00213-003-1448-4.

Siepmann, M., Joraschky, P., Rebensburg, M., et al. (2005). Is autonomic cardiac control disturbed in patients with depression and coronary artery disease? *Zeitschrift für Klinische Psychologie und Psychotherapie, 34*(4), 277–281. doi:10.1026/1616-3443.34.4.277.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (Eds.). (1970). *State-trait anxiety inventory, manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologist Press.

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders, 61*(3), 201–216. doi:10.1016/S0165-0327(00)00338-4.

Yeragani, V. K., Rao, K. A., Smitha, M. R., Pohl, R. B., Balon, R., & Srinivasan, K. (2002). Diminished chaos of heart rate time series in patients with major depression. *Biological Psychiatry, 51*(9), 733–744. doi:10.1016/S0006-3223(01)01347-6.