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ORIGINAL PAPER

A Pilot Study of the Efficacy of Heart Rate Variability (HRV) Biofeedback in Patients with Fibromyalgia

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Abstract Fibromyalgia (FM) is a non-inflammatory rheumatologic disorder characterized by musculoskeletal pain, fatigue, depression, cognitive dysfunction and sleep disturbance. Research suggests that autonomic dysfunction may account for some of the symptomatology of FM. An open label trial of biofeedback training was conducted to manipulate suboptimal heart rate variability (HRV), a key marker of autonomic dysfunction. *Methods:* Twelve women ages 18–60 with FM completed 10 weekly sessions of HRV biofeedback. They were taught to breathe at their resonant frequency (RF) and asked to practice twice daily. At sessions 1, 10 and 3-month follow-up, physiological and questionnaire data were collected. *Results:* There were clinically significant decreases in depression and pain and improvement in functioning from Session 1 to a 3-month follow-up. For depression, the improvement occurred by Session 10. HRV and blood pressure variability (BPV) increased during biofeedback tasks. HRV increased from Sessions 1–10, while BPV decreased from Session 1 to the 3 month follow-up. *Conclusions:* These data suggest that HRV biofeedback may be a useful treatment for FM, perhaps mediated by autonomic changes. While HRV effects were immediate, blood pressure, baroreflex, and therapeutic effects were delayed. This is consistent with data on the relationship among stress, HPA axis activity, and brain function.

Keywords Heart rate variability · Biofeedback · Fibromyalgia · Depression · Pain · Breathing

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Introduction

Fibromyalgia

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain and multiple tender points (Wolfe et al., 1990). It affects close to 2% of the population (Wolfe, Ross, Anderson, Russell, & Herbert, 1995), primarily women (Wolfe et al., 1990). Sufferers also complain of muscle stiffness, fatigue, sleep disturbance, and cognitive impairment (Wolfe et al., 1990). Co-morbid depression is extremely common with rates ranging from 22 to 80% (Epstein et al., 1999; Martinez, Ferraz, Fontana, & Atra, 1995). In addition, many FM patients have comorbid anxiety disorders (Thieme, Turk, & Flor, 2004) and other stress-related syndromes such as irritable bowel, chronic fatigue and multiple chemical sensitivity (Aaron, Burke, & Buchwald, 2000). Severe symptoms related to FM often result in significant disability (Henriksson & Liedberg, 2000). The etiology and pathophysiology of FM remain unclear although there is general agreement

that FM is a disorder of aberrant central pain processing (Goldenberg, Burckhardt & Crofford, 2004; Bennett, 2005). In light of the frequency of psychiatric co-morbidity, sleep disorder and depression have been identified as possible causal factors for the symptoms of FM. Alpha electroencephalogram (EEG) sleep patterns including phasic and tonic alpha EEG sleep appear to underlie the complaints of nonrestorative sleep in many FM patients (Moldofsky, 2001). Others have speculated that FM is one of a number of medical and psychiatric conditions referred to as affective spectrum disorders (Hudson et al., 2003). These disorders typically respond to antidepressant medications and are thought to be linked by heritable abnormalities (Hudson et al., 2003). This hypothesis is supported by a well-designed epidemiological study finding that the rates of major depressive disorder (MDD) in relatives of patients with FM but without a personal history of MDD are identical to rates of MDD in relatives of patients with a personal history of MDD without FM (Raphael, Janal, Nayak, Schwartz, & Gallagher, 2004).

Fibromyalgia and treatment considerations

Clinically, FM is generally treated with a combination of pharmacologic and nonpharmacologic modalities. However, there are no FDA indicated drugs for FM and no universally agreed upon treatment algorhythms (Goldenberg et al., 2004). The limited effectiveness of pharmacological agents (Leventhal, 1999) and the association of FM with psychological distress (Epstein et al., 1999) have led to the examination of more integrative treatments. A number of studies reporting good outcomes for FM include various forms of relaxation training including electromyography (EMG) biofeedback (Buckelew et al., 1998; Ferraccioli et al., 1987; Ferraccioli, Fontana, Scita, Chirelli, & Nolli, 1989; Mur, Drexler, Gruber, Hartig, & Gunther, 1999; Sarnoch, Adler & Scholz, 1997), meditation-based stress reduction (Kaplan, Goldenberg, & Galvin-Nadeau, 1993; Goldenberg et al., 1994; Creamer, Singh, Hochberg, & Berman, 2000) and qigong therapy (Creamer et al., 2000; Singh, Berman, Hadhazy, & Creamer, 1998). An important unifying factor of these interventions is slowing down the rate of breathing – the central focus of HRV biofeedback.

While these non-pharmacological therapies seem promising, historically treatment in general has been limited by poor understanding of the pathophysiology of FM. However, current findings suggest that individuals with FM might be predisposed to having a dysfunctional response to physical and emotional stress due to central and peripheral nervous system and neuroendocrine abnormalities (Bennett, 2005). Clauw and Chrousos (1997) propose that various components of the central nervous system may be involved including pain processing pathways, the hypothalamic-pituitary-adrenal (HPA) axis, and the autonomic nervous system (ANS).

Fibromyalgia and autonomic dysfunction

Because autonomic dysfunction has been linked to many of the common features of FM including pain (Burr, Heitkemper, Jarrett, & Cain, 2000; Schurmann et al., 2000), chronic fatigue (Naschitz et al., 2000), sleep disturbances (Wiklund et al., 2000), depression (Agelink et al., 2001; Rechlin, 1994; Yeragani, Balon, Pohl, & Ramesh, 1995) generalized anxiety disorder (Thayer, Friedman, & Borkovec, 1996), and panic disorder (Cohen et al., 2000; Asmundson & Stein, 1994; Rechlin, Weis, Spitzer, & Kaschka, 1994), autonomic dysfunction has been the target of a number of investigations (Bou-Holaigah, Rowe, Kan, & Calkins, 1995; Clauw et al., 1996; Clauw, Radulovic, Heshmat, & Barbey, 1996; Cohen et al., 2000; Cohen et al., 2001; Elam, Johansson, Wallin, 1992; Kelemen, Lang, Balint, Trocsanyi, & Muller, 1998; Martinez-Lavin et al., 1997; Martinez-Lavin, Hermosillo, Rosas, & Soto, 1998; Qiao, Vaeroy, & Morkrid, 1991). Preliminary evidence supports the hypothesis that autonomic dysfunction, characterized by a high baseline state of sympathetic arousal and decreased parasympathetic activity resulting in a blunted sympathetic response to stressors, is a potential pathogenic mechanism in FM (Clauw & Chrousos, 1997; Martinez-Lavin, 2004). Tilt table testing has revealed that patients with FM may have neurally mediated hypotension, a form of autonomic dysfunction (Bou-Holaigah, Rowe, Kan, & Calkins, 1995; Raj, Brouillard, Simpson, Hopman, & Abdollah, 2000), suggesting poor modulation of parasympathetic reactivity. FM patients also have been found to have diminished total heart rate variability (HRV) over short (Cohen et al., 2000) and long (24-hr) periods (Martinez-Lavin, Hermosillo, Rosas, & Soto, 1998).

In two separate studies, Cohen et al., (2000, 2001) found increased sympathetic arousal and a decreased parasympathetic tone. The women in their samples exhibited more augmented sympathetic activity than the men, suggesting that women with FM may have more severe autonomic dysfunction. They speculated that decreased responsiveness of the baroreflex to blood pressure fluctuations might be involved in the abnormal sympathovagal response to postural change (Cohen et al., 2001). Without the benefit of prospective studies, it is difficult to determine whether autonomic nervous system dysfunction is the cause, effect or epiphenomenon of FM.

Heart rate variability biofeedback

HRV biofeedback is designed specifically to target autonomic reactivity. Clinical demonstrations of the effectiveness of this intervention have been published for the treatment of asthma (Chernigovskaya, Vaschillo, Petrash, & Rusanovsky, 1990; Lehrer et al., 1997; Lehrer, Smetankin, & Potapova, 2000; Lehrer et al., 2004), hypertension and various

anxiety disorders (Chernigovskaya, Vaschillo, Rusanovsky, & Kashkarova, 1990; McCraty, Atkinson, & Tomasino, 2003). Training involves slowing the breathing rate to the frequency at which, in each individual, amplitude of HRV is maximized. Vaschillo et al. have found evidence that breathing at this frequency stimulates the baroreflex, producing high amplitude heart rate and blood pressure oscillations due to resonance characteristics of the cardiovascular system (Vaschillo, Lehrer, Rishe, & Konstantinov, 2002). The resonant frequency in humans occurs between 0.075–0.12 Hz. Although every person has individual resonant frequency in this range, the average resonance frequency is 0.092 Hz, which corresponds to 5.5 breaths per minute (Vaschillo et al., 2002).

Vaschillo has noted that, at resonant frequency, the amplitude of heart rate oscillations elicited by breathing is greater than at any other frequency (Vaschillo, Vaschillo & Lehrer, 2004). It also has been noted that producing voluntary increases in HRV amplitude causes a subject to breathe at his or her resonant frequency (Lehrer et al., 1997; Cooke et al., 1998). Vaschillo and colleagues have provided evidence that breathing at the resonant frequency stimulates the baroreflexes that underlie the low frequency waves, and that such stimulation "exercises" them, and thereby promotes their efficiency (Vaschillo, Lehrer, Rishe, & Konstantinov, 2002; Lehrer et al., 2003). This, in turn, should directly produce more effective blood pressure modulation and indirectly, through anatomical projections from the baroreceptors to the hypothalamus and limbic system (Mini, Rau, Montoya, Palomba, & Birbaumer, 1995; Lacey & Lacey, 1978), it should increase modulation of autonomically- and emotionally-mediated reflexes throughout the body. Recent research supports Vaschillo's theories, as it was demonstrated that HRV biofeedback greatly increases baroreflex gain during performance of biofeedback exercises, and that regular daily practice of the technique increases baroreflex gain *at rest* (Lehrer et al., 2003).

HRV biofeedback is based on the premise that breathing at this resonant frequency will strengthen baroreflexes and thus improve the functioning of the autonomic nervous system. Evidence that patients with FM tend to have decreased heart rate variability, orthostatic hypotension, and impaired baroreflex function suggests that autonomic dysfunction may play a very important role in the manifestation and mediation of FM. Thus, because HRV biofeedback might offer benefits to patients with FM beyond improved relaxation/stress management, a pilot study examining its efficacy is warranted. Herein we gather preliminary data related to the effectiveness of HRV biofeedback on various aspects of FM, including overall functioning, depression, pain, and sleep quality.

Participants and methods

Participants and study design

Twelve female patients between the ages of 18 and 60 were recruited from the rheumatology clinic at the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School (UMDNJ-RWJMS). Qualified participants were those who had a diagnosis of FM made by a board certified rheumatologist using the diagnostic criteria established by the American College of Rheumatology (Wolfe et al., 1990). Because women account for over 85% of FM patients (Wolfe et al., 1995) only women were recruited as subjects. Patients were required not to change their regimen during the study period (approximately three months). The protocol was approved by the Institutional Review Board of the UMDNJ-RWJMS.

All patients received 10 weekly sessions of biofeedback training at the direction of a Biofeedback Certification Institute of America certified biofeedback technician and participated in a 3-month follow-up session. Patients were instructed to practice at home for two 20-minute periods per day and to refrain from taking any caffeine or alcohol for at least twelve hours prior to all sessions where physiological measures were to be collected. At the beginning of the study, participants were introduced to the setting, equipment, and basic procedures of biofeedback. Assessments were taken at Sessions 1 and 10, and at the 3-month follow-up session. These sessions included questionnaire completion and recording physiological data. Physiological data were recorded during four 5-minute tasks: 1) Task A – baseline before biofeedback training; 2) Task B – the first five minutes of biofeedback training; 3) Task C – the last 5 minutes of the biofeedback training; and 4) Task D – baseline after biofeedback training.

All data collection sessions for each participant were conducted at approximately the same time of day in the Psychophysiology Laboratory in the Department of Medicine at UMDNJ-RWJMS. Psychophysiological data collection and HRV biofeedback training were performed with the participant seated in a reclining chair, situated in a comfortable therapy room, with ambient temperature between 70-75 degrees Fahrenheit.

Questionnaires

Fibromyalgia Impact Questionnaire (FIQ)

The FIQ is a 19-item self-report questionnaire designed to assess physical impairment, physical functioning, pain, fatigue, sleep quality, muscle stiffness, anxiety, and depression

(Burckhardt, Clark, & Bennett, 1991). Functioning was measured by using the overall score.

Beck Depression Inventory-II (BDI-II)

The BDI-II is a well-validated 21-item self-report measure that assesses the cognitive, affective, and neurovegetative symptoms of depression (Beck, Steer, & Brown, 1996; Steer & Clark, 1997). To make the BDI-II more consistent with DSM-IV criteria for depression, items dealing with weight loss, changes in body image and somatic preoccupation have been replaced. These modifications make the BDI-II less sensitive to medical factors, resulting in a more appropriate measure for a chronic pain population.

McGill Pain Questionnaire (MPQ)

The MPQ is a self-report measure consisting of 78 single-word pain descriptors each chosen for its ability to describe various aspects of pain. Pain was measured using the number of words chosen method (Melzack, 1975).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI consists of 19 self-rated questions assessing a wide array of factors related to sleep quality including sleep: quality, latency, duration, habitual efficiency, and disturbances and use of sleep medication (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Acceptable measures of reliability and validity have been established (Buysse et al., 1989; Carpenter & Andrykowski, 1998).

Equipment and technical procedures

Electrocardiogram (ECG) and respiration recording, HRV biofeedback, and breathing pacer presentation were provided using a J&J Engineering (Poulsbo, WA) I-330 DSP-12 physiograph unit. A noninvasive blood pressure monitor Finapres (Ohmeda) provided recording beat-to-beat (BP). ECG electrodes were placed on the participant's right arm and left leg (active electrodes) and left arm (ground electrode). Digital ECG and BP recording was conducted using a sample rate of 512 Hz. Respiration was recorded by strain gauges placed around the chest and on the abdomen, and digitized at the rate of 32 samples per second. The J&J unit measured RR intervals of ECG on-line and calculated current heart rate and its Fourier spectrum within the band of .005–.4 Hz on-line. The spectrum was updated on the screen approximately every second, and reflects the frequency of heart rate fluctuations within the past 30 s. The J&J unit presented to the patients a respiration curve, current heart rate and on-line Fourier spectrum of the heart rate as biofeedback information on a computer screen. Physiology data analysis was performed using WinCPRS software (Absolute Aliens AY: Turku, Finland) (Badra et al., 2001). Spectral and cross-spectral analyses were performed for RRI (time between successive normal R spike to R spike intervals in the EKG wave) and beat-to-beat BP data. Indices of RRI and blood pressure variability (BPV) and low frequency alpha baroreflex gain (BRSAlphaLF) were calculated for each (A, B, C, D) 5-minute task. We estimated baroreflex gain over coherent LF (0.04–0.15 Hz) segments from the transfer function between systolic pressure and RR intervals. The modulus of the transfer function was used to estimate baroreflex gain (Badra et al., 2001). The following HRV and BPV indices were calculated: total RRI variability within the range of .005–.05 hertz (HRTot) and total blood pressure (BPTot) as total power of RRI and BP spectra; low frequency RRI variability (HRLF) and low frequency blood pressure variability (BPLF) as spectral power in range of 0.04–0.15 Hz; and high frequency heart rate variability (HRHF) and low frequency blood pressure variability (BPLF) as spectral power in range of 0.15–0.5 Hz.

HRV biofeedback

Each of 10 weekly sessions included 20 minutes of biofeedback training using the J&J I-330 unit. The first three sessions contained the following additional procedures. Adhering to the protocol described by Lehrer, Vaschillo and Vaschillo (2000), in the first session the participant was asked to breath for about 2 minutes at each of 5 specific frequencies (6.5, 6.0, 5.5, 5.0, and 4.5 breaths per minute respectively) in order to determine personal resonant frequency. A "pacing stimulus" was provided for this purpose: a light display that moves up and down on the computer screen at the target respiratory rate. The participant was instructed to breathe at the rate indicated by stimulus. Heart rate oscillation amplitudes were measured. The frequency yielding the highest low frequency HRV on the moving Fourier analysis data collected and displayed by the I-330 physiograph was considered to be the resonant frequency. Then the participant was taught to breathe at her personal resonant frequency, as a first step to training the individual how to produce maximal increases in amplitude of HRV. In subsequent sessions, the individual was given biofeedback for 20 min broken up into four five-minute "tasks." The participant was instructed to practice breathing at her own resonant frequency at home for a 20-min period twice daily using a clock with a second hand. Throughout training the individual was cautioned to breathe shallowly and naturally, in order to avoid hyperventilation.

At the second session, the participant was directly given biofeedback for cardiac variability, and instructed to increase the amplitude of heart rate fluctuations that occur in conjunction with respiration. The feedback was given in several

forms. One was using a beat-to-beat heart rate display, superimposed on a measure of respiratory activity taken from a strain gauge. The participant was instructed to breathe in phase with heart rate changes, with the goal of maximally increasing amplitude of HRV. In another display, the participant was shown a moving frequency analysis of heart rate, within the band of .005–.4 Hz. The display was updated approximately every second, and reflected the frequency of heart rate fluctuations within the past 30 seconds. Next, the participant was taught the "pursed lips abdominal" breathing technique then instructed to increase the spectral power peak that occurred at approximately resonant frequency.

In the third session, a stand-alone device was provided for home practice (Cardiosignalizer CS-03 by Biosvyaz, St. Petersburg, Russia). This system analyzes heart rhythms and provides a display sensitive to changes. The participant was instructed to use the Cardiosignalizer for daily practice and to the log whether or not she practiced each day, the length of each practice session, and any questions or observations.

Statistical analysis

Questionnaires data results were compared from session 1 to session 10 as well as from session 1 to 3 months follow-up session using a linear mixed effects model with subject as a random effect. Physiological data results on Task A were compared across sessions using a linear mixed effects model controlling for respiration rate because respiration can affect HRV independently of sympathetic or parasympathetic nerve traffic. Physiological results across tasks were analyzed using a linear mixed effects model controlling for session. The contrast comparing Task D to Task A was performed in order to assess short-term carry-over effects of HRV biofeedback. This contrast was also controlled for respiration rate. Comparisons between biofeedback periods (tasks B and C) and rest periods (Tasks A and D) were made in order to assess the immediate effects of biofeedback. They were not controlled for respiration, because the primary mode of action of HRV biofeedback is through respiration. Therefore, although these results can assess the output of various reflexes comprising the complex of HRV oscillation frequencies, they do not reflect autonomic balance. Instrumentation malfunction limited our ability to measure beat-to-beat blood pressure. For only six of the twelve patients in this trial were beat-to-beat blood pressure data available at session 10 and data were available for only two patients at the 3 month follow-up. Thus the physiological data contained missing observations; the mixed effects model allows for missing observations under a missing at random assumption. To correct for multiple comparisons, nominal p-values were adjusted using Hochberg's method, a less conservative variant of the well-known Bonferroni correction that still controls the experiment-wise error rate (Hochberg, 1988).

Results for questionnaires, for physiological responses across sessions, and for physiological responses within sessions were all adjusted separately. Both unadjusted and adjusted p-values are given in the results section. The R statistical environment was used for statistical analysis (R Development Core Team, 2005). There were no missing observations in the questionnaire data.

Results

Overall functioning

The session 1 baseline mean score on the FIQ in this patient sample ($M = 55.5$, $SD = 18.4$) was slightly above the expected mean ($M = 50.00$). Although there was not a significant improvement in FIQ scores from session 1 to session 10, improvement in functioning scores from session 1 to 3 months follow-up session was significant (unadjusted $p = 0.0022$, adjusted $p = 0.0175$). A summary of descriptive statistics for all outcome measures and demographic variables appears in Table 1 and is depicted graphically in Figure 1.

Depression

The BDI-II measures depression on a continuous scale with established norms for mild, moderate and severe depression.

Table 1 Summary of questionnaire responses and demographic variables

Variable	Session 1	Session 10	P-value for Session 10 v Session 1	3 Month Follow Up	P-value for 3 Month v Session 1
FIQ	55.5 (18.4)	48.0 (17.7)	0.0686	41.9 (19.5)	0.0022*
BDI-II	21.7 (12.3)	15.9 (10.5)	0.0089*	15.5 (12.1)	0.0055*
MPQ	25.1 (8.9)	23.4 (9.2)	0.4551	21.1 (16.2)	0.0060*
PSQI	11.5 (3.9)	9.5 (4.0)	0.0148	10.2 (4.8)	0.1126
Age	38.5 (12.5)				
Education	15.2 (2.3)				

Note. Session values are Mean (SD). P-values are unadjusted. P-values marked with an "*" remain significant after adjusting with Hochberg's Method. MPQ was log-transformed for significance testing.

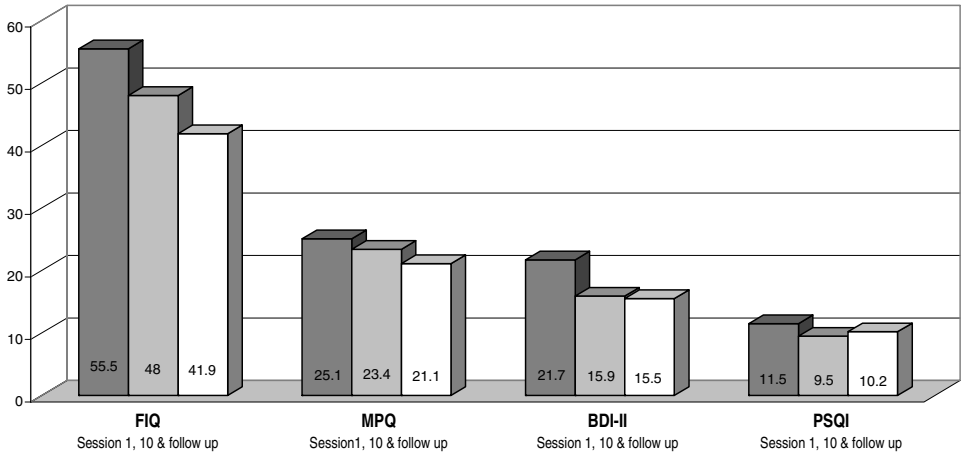

Fig. 1 Questionnaire Scores Across Sessions. Scores for the overall functioning (FIQ), pain (MPQ), depression (BDI-II) and sleep quality (PSQI) at baseline session 1, post-treatment session 10 and at the three month follow up

At baseline, 8 of the 12 patients met criteria for at least mild depression with three earning scores in the severe range. There were significant decreases on the total BDI-II scores between Sessions 1 and Session 10 (unadjusted $p = 0.0089$, adjusted $p = 0.0444$), that persisted at 3 months, (unadjusted $p = 0.0055$, adjusted $p = 0.0362$).

Pain

Improvement in overall pain scores was not statistically significant at Session 10; however, at the 3 month follow-up session clinically significant improvement in pain scores was observed in most patients (unadjusted $p = 0.0060$, adjusted $p = 0.0362$). Eight of the 12 patients were considered responders reporting at least a 25% improvement in pain with 6 of the 12 reporting at least a 50% improvement in pain. Moreover, pain improvement was not contingent upon improvement in sleep or depression. For hypothesis testing, pain scores were log-transformed to better approximate normality.

Sleep quality

There also were suggestive reductions in PSQI global sleep scores from baseline compared to 10 weeks (unadjusted $p = 0.0148$, adjusted $p = 0.0592$), but this improvement was not apparent at 3 months.

Physiology within sessions

Summary information is given in Table 2. Because of their right-skewed distributions, blood pressure and baroreflex gain measures were log-transformed for testing. We compared the mean of biofeedback tasks (Tasks B and C) to rest (non-biofeedback) periods (the mean of tasks A and D) in order to examine the immediate effects of HRV biofeedback while subjects were practicing the technique. We found significant biofeedback-induced increases in total HRV (HRTot, unadjusted $p = .0002$, adjusted $p = .0022$), HRLF ($< .0001$, .0005), and BPLF ($< .0001$, .0002), controlling for session effects. We also examined the changes in these measures

Table 2 Summary of physiological variables across tasks

Variable	Task D–Tast A		p-value	Tasks B & C–Tasks A & D		p-value
RRITot[ms^2/Hz]	957.77	(719.59)	0.1862	3812.65	(981.41)	0.0002∗
RRILF[ms^2/Hz]	671.94	(601.38)	0.2664	3631.65	(842.38)	< 0.0001∗
RRIHF[ms^2/Hz]	129.98	(105.11)	0.2194	−214.55	(147.70)	0.1497
BPTot[mmHg^2/Hz]	0.23	(0.28)	0.4179	0.46	(0.43)	0.2902
BPLF[mmHg^2/Hz]	0.54	(0.25)	0.0336	1.94	(0.42)	< 0.0001∗
BPHF[mmHg^2/Hz]	0.02	(0.21)	0.9166	0.42	(0.30)	0.1696
BRSAlphaLF[ms/mmHg]	3.60	(1.37)	0.0112	0.96	(1.89)	0.6142

Note. Spectral and cross-spectral analyses were performed for RRI (time between successive normal R spike to R spike intervals in the EKG wave) and beat-to-beat BP data. Indices of RRI (total [Tot], low frequency [LF] and high frequency [HF]) and blood pressure variability (BPV) and low frequency alpha baroreflex gain (BRSAlphaLF) were calculated for each (A, B, C, D) 5-minute task. Contrasts controlled for session effects. Contrast values are Mean (SD). P-values are unadjusted. The D – A contrasts control for respiration rate; the other contrasts do not. P-values marked with an "∗" remain significant after adjusting with Hochberg's Method. BPTot, BPLF, BPHF, and BRSAlphaLF were log-transformed for significance testing.

Table 3 Summary of physiological variables for task A

Variable	Session 1	N	Session 10	N	p-value for Session 10 v Session 1	3 Months	N	p-value for 3 Months v Session 1
RRITot[ms^2/Hz]	1839.4 (2006.5)	11	2190.3 (1258.8)	9	0.0286	997.8 (1006.6)	8	0.6912
RRILF[ms^2/Hz]	706.6 (992.2)	12	755.9 (738.4)	9	0.4089	1378.2 (2806.8)	9	0.1500
RRIHF[ms^2/Hz]	296.6 (182.7)	10	613.4 (479.5)	9	0.0156	209.8 (221.6)	8	0.5727
BPTot[mmHg^2/Hz]	46.6 (50.2)	10	35.0 (36.3)	8	0.1954	17.1 (3.2)	2	0.1893
BPLF[mmHg^2/Hz]	8.2 (6.3)	10	6.4 (3.5)	8	0.6980	5.2 (2.1)	2	0.3966
BPHF[mmHg^2/Hz]	7.0 (6.1)	10	2.8 (1.8)	8	0.0735	1.5 (0.5)	2	0.1281
BRSAlphaLF[ms/mmHg]	6.6 (4.8)	6	8.5 (4.0)	6	0.2516	5.6 (1.4)	2	0.7747

Note. Session values are Mean (SD) N. P-values are unadjusted; mixed effects model included a term for respiration rate. No tests remained significant after adjusting with Hochberg's Method for multiple testing. BPTot, BPLF, BPHF, and BRSAlphaLF were log-transformed for significance testing.

from Task A to Task D, controlling for session and respiration rate, in order to examine the within-session "carry-over" effects of biofeedback to resting conditions. We found no significant increases in baroreflex gain, after controlling for respiration rate.

Physiology across sessions

Summary information is given in Table 3. Blood pressure and baroreflex gain measures were log-transformed for testing. In order to examine changes in resting levels of HRV across sessions, we examined differences across sessions in physiological variables for Task A, but found no significant effects.

Discussion

These data suggest that HRV biofeedback may be helpful as a treatment for FM. The major findings of this study indicate that a ten session trial of HRV biofeedback significantly improved overall functioning and depression in patients with FM. Also, some experienced clinically significant improvements in pain and there was a trend suggestive of improvements in sleep. We found that the technique was acceptable to patients with FM, was easily learned, and had no known adverse side effects. Further, most participants reported that they benefited from treatment and would recommend that a friend with FM try the intervention.

These findings are consistent with those from others examining the potential benefits of biofeedback for FM although most previous studies assessed the value of EMG biofeedback. Other researchers also found it useful to classify patients as responders and non-responders and examine potential explanatory factors. Drexler and colleagues (2002) classified patient participants with FM as either "psychologically normal or abnormal" and found that those with psychopathology derived the most benefit from the biofeedback treatment. In contrast, Ferraccioli et al. (1987) found that more than half of their subjects experienced clinically significant improvement; however, those with clinical depression formed a subgroup of poor responders. In contrast, results from this study of HRV biofeedback in FM suggest that those with depression may derive the greatest benefit from this treatment.

Investigators from this laboratory (Lehrer at al., 2003; Lehrer at al., 2004) have theorized that the therapeutic effects of HRV biofeedback are due to the production of high amplitude oscillations in autonomic functions at specific frequencies. The oscillations represent various modulatory reflexes that control the ANS. Increasing these oscillations trains these reflexes and thereby helps to restore sympathetic-vagal balance and to improve autonomic regulation.

Physiological data within sessions show that HRV biofeedback produced high amplitude oscillations in both HR and BP oscillations at the subject's resonant frequency, which invariably occurred in the low-frequency range. In contrast to the findings of Lehrer et al., among healthy people (2003) and asthma patients (2004), and the known effect of HRV biofeedback to stimulate the baroreflex (Vaschillo et al., 2002), there were no concomitant increases in baroreflex gain. However, for only six of the subjects were there pre and post-test data available for the assessment of baroreflex gain, thus no firm conclusions should be drawn about the potential this intervention might have for baroreflex gain in FM. Yet, based on the limited data, it is possible that the blood pressure changes induced by slowed respiration during this technique were not modulated by baroreflex effects, and showed no attenuation with respect to heart rate oscillation amplitudes. If replicated in a larger sample, this finding would be consistent with the possibility of impaired baroreflex function among patients with FM.

Nevertheless, the baroreflex was affected in this study. Resting baroreflex gain, assessed during rest periods, when HR and BP oscillations were not being directly stimulated by respiration, was greater after training sessions than before them, thus showing a "carry-over" effect of treatment. This effect apparently was not strong enough to affect pre-session baroreflex gain across training sessions. Unlike in

healthy people (Lehrer et al., 2003), neuroplastic increases in baroreflex function do not occur among FM patients in this 10-week protocol. It is nevertheless possible that daily home practice of the technique over several months produces the same kind of delayed neuronal changes as those that occur from biochemical interventions such as antidepressant therapy (McEwen & Olie, 2005). Central plasticity is affected by various agents leading to structural and functional changes that reduce sympathetic arousal and HPA axis activity, while simultaneously reducing symptoms of depression (McEwen & Olie, 2005).

The mechanisms by which FM is affected by HRV biofeedback was not adequately investigated in this study. We did study autonomic mechanisms, but failed to find persistent changes. This is potentially due to our small number of subjects and some instrumentation problems. Assessing the role of the ANS could reveal much about FM and the related effects of HRV biofeedback. Thayer and Brosschot (2005) have noted that the ANS includes not only the afferent interoceptive arm and the efferent visceral motor arms of the sympathetic and parasympathetic nervous systems, but also includes higher level integrative and regulatory neural networks found at various levels in the brain. It is possible that dysfunction in these integrative and regulatory neural circuits may in part be the source of the dysautonomia that characterizes FM. Indeed, there is a growing consensus that FM is due to central sensitization (Goldenberg et al., 2004; Bennett, 2005), which may be generated in part by dysfunction in these ANS integrative and regulatory neural networks. The common comorbidity of FM and MDD (Epstein et al., 1999; Martinez, Ferraz, Fontana, & Atra, 1995) and evidence of shared heritable abnormalities (Raphael et al., 2004) further suggest a potential role for dysfunction in theses neural networks. Mayberg (2003) has delineated the nature and function of the neural networks in which dysfunction generates the symptoms and signs of MDD. One of our most dramatic findings was the significant improvement in depression. This further supports the hypothesis that the effects of HRV biofeedback on these higher-level brain functions may be involved in symptom amelioration in FM.

It is also possible that the effects occurred by psychosocial processes other than those measured in this study. For example, patients practicing HRV biofeedback often report experiences of relaxation. Learning to relax and practicing relaxation on a regular basis has already been found to be helpful for FM sufferers. Thus the effects could derive from the general consequences of stress reduction and lowered sympathetic arousal. Second, becoming an active participant in treatment returns some level of control to the patient thus enhancing self-esteem. This is particularly important because patients with FM tend to catastrophize and feel helpless in their ability to control pain (Hassett, Cone, Patella, & Sigal, 2000). And third, sublimating the energy associated with somatic hypervigilance into activities leading to demystifying bodily processes and taking action can be empowering. Finally, this study provided direct evidence to suggest that HRV biofeedback directly targets the elevated sypathetic arousal and greater autonomic reactivity found among many FM sufferers (Kelemen, Lang, Balint, Trocsanyi, & Muller, 1998).

The major limitations of this study were its small size, particularly for examining blood pressure and, hence, baroreflex effects, and the absence of a control group. It is unclear whether patient improvement was due to placebo effect or some other factor or series of factors rather than the intervention. In futures studies, HRV biofeedback should be compared to sham or another form of biofeedback. Additionally, our sample was one of convenience and was not guided by power analyses. Future studies should consist of an adequate number of subjects to detect true differences between groups. In summary, despite the limitations inherent in this small open label trial, HRV biofeedback shows promise for the adjunctive treatment of FM. Most participants derived significant improvement in functioning, depression and pain without experiencing adverse effects. Further evaluation of this promising intervention is warranted in larger, controlled trials.

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