Applied Psychophysiology and Biofeedback
https://doi.org/10.1007/s10484-020-09462-3

Symptom Management Among Cancer Survivors: Randomized Pilot Intervention Trial of Heart Rate Variability Biofeedback

James B. Burch[1,2,3,7] · J. P. Ginsberg[4] · Alexander C. McLain[1] · Regina Franco[5] · Sherry Stokes[6] · Kerri Susko[5] · William Hendry[5] · Elizabeth Crowley[5] · Alex Christ[5] · John Hanna[5] · Annie Anderson[5] · James R. Hébert[1,2] · Mark A. O'Rourke[5]

Abstract

Chronic cancer-related symptoms (stress, fatigue, pain, depression, insomnia) may be linked with sympathetic nervous system over-activation and autonomic imbalance. Decreased heart rate variability (HRV) is an indicator of autonomic dysregulation that is commonly observed among cancer survivors. HRV biofeedback (HRVB) training induces HRV coherence, which maximizes HRV and facilitates autonomic and cardiorespiratory homeostasis. This randomized, wait-list-controlled, pilot intervention trial tested the hypothesis that HRVB can improve HRV coherence and alleviate cancer-related symptoms. The intervention group (n = 17) received 4–6 weekly HRVB training sessions until participants demonstrated skill acquisition. Controls (n = 17) received usual care. Outcomes assessed at baseline and follow-up included 15-min HRV recordings (HRV Coherence Ratio), and symptoms of: stress, distress, post-traumatic stress disorder (PTSD), pain, depression, fatigue, and sleep disturbance. Linear mixed models for repeated measures were used to assess Group-by-Time interactions, pre- versus post-treatment differences in mean symptom scores, and group differences at follow-up. Mean HRV Coherence Ratios (± standard error) improved in the HRVB group at follow-up (baseline: 0.37 ± 0.05, post-intervention: 0.84 ± 0.18, p = 0.01), indicating intervention validity. Statistically significant Group-by-Time interactions indicated treatment-related improvements in HRV Coherence Ratios (p = 0.03, Pre-vs. post-treatment effect size [Cohen's d]: 0.98), sleep symptoms (p = 0.001, d = 1.19), and sleep-related daytime impairment (p = 0.005, d = 0.86). Relative to controls, the intervention group experienced trends toward improvements in stress, distress, fatigue, PTSD, and depression, although no other statistically significant Group-by-Time interactions were observed. This pilot intervention found that HRVB training reduced symptoms of sleep disturbance among cancer survivors. Larger-scale interventions are warranted to further evaluate the role of HRVB for managing symptoms in this population. Registration: NCT 03692624 www.clinicaltrials.gov

Keywords Autonomic · Cancer · Coherence · Fatigue · Sleep · Survivorship

Introduction

Advances in oncology have led to improvements in both cancer treatment and survival. By 2022, the number of cancer survivors living beyond five years is projected to increase to

This study was performed at the Greenville Health System Center for Integrative Oncology and Survivorship, and at the University of South Carolina, Columbia, SC.

✉ James B. Burch
burch@mailbox.sc.edu

[1] Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC, USA

[2] South Carolina Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC, USA

[3] WJB Dorn Department of Veterans Affairs Medical Center, Columbia, SC, USA

[4] Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

[5] Integrative Oncology, PRISMA Health Upstate Cancer Institute, Greenville, SC, USA

[6] Clemson University, Clemson, SC, USA

[7] Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, 915 Greene Street, Room 226, Columbia, SC 29208, USA

Published online: 01 May 2020

approximately 12 million, a 37% increase from 2012 estimates (de Moor et al. 2013). Cancer patients are typically burdened with a high prevalence of multiple chronic symptoms including pain, stress, fatigue, depression, and insomnia that may persist for years after treatment is completed (Bluethmann et al. 2016; Kwekkeboom 2016). Sympathetic nervous system over-activation and autonomic imbalance are key processes underlying the manifestation and perpetuation of these symptoms (De Couck et al. 2012; Kelly et al. 2016; Wood and Weymann 2013). Cancer-related fatigue is a particularly prevalent and persistent condition among cancer survivors that has been associated with low heart rate variability (HRV) (Arab et al. 2016; Crosswell et al. 2014; Wang and Woodruff 2015).

Cancer survival studies have documented a relationship between low HRV and increased mortality (Zhou et al. 2016). Furthermore, the potential benefits of improved autonomic function for reducing symptom burden and enhancing cancer survivorship have been acknowledged (De Couck et al. 2012; Gidron et al. 2014). There is a compelling need to improve quality of life among cancer survivors with interventions that reduce sympathetic over-activation and autonomic imbalance. HRV coherence is a normal physiological condition that occurs when the change in heart rate is rhythmic, with a sinusoidal waveform that is synchronized by breathing at a rate of approximately 6 breathes per minute (i.e., a 10 s period, or 0.1 Hz), which is known as the 'resonant frequency' of breathing. The HRV Coherence Ratio is a quantitative index of the amount of HRV power at the resonant frequency relative to the total amount of HRV power (Lehrer and Gevirtz 2014; McCraty and Zayas 2014; Shaffer et al.2014). HRV biofeedback (HRVB) is a technique that combines heart rate monitoring with paced breathing to teach subjects to achieve this rhythmic, diaphragmatic breathing pattern. Typically, visual feedback on a computer screen is provided so that the patient can recognize when they are breathing at the pace that produces HRV coherence. Elevated HRV coherence facilitates improved emotional regulation and attentional control, and patients who achieve this state self-report a range of positive emotions (e.g., serenity, compassion, joy, resilience, hope). Through consistent HRVB practice, subjects can learn to perform self-regulated resonant frequency breathing independently, without coaching or biofeedback (Lehrer and Gevirtz 2014; McCraty and Zayas 2014; Shaffer et al. 2014). HRVB has been used in multiple clinical settings to ameliorate stress, anxiety, post-traumatic stress disorder (PTSD), pain, depression, and sleep disturbances (Appelhans and Luecken 2008; Camm et al. 1996; Goessl et al. 2017; Lehrer and Gevirtz 2014; Nagpal et al. 2013; Sakakibara et al. 2013; van der Zwan et al. 2015), all conditions that are common among cancer survivors. However, studies examining the use of HRVB to treat cancer-related symptoms are limited (Greenberg et al. 2015; Groff et al. 2010; Ozier and Linden 2018). This pilot intervention trial tested the hypothesis that HRVB treatment among cancer survivors can increase HRV coherence and reduce symptoms of pain, stress, fatigue, depression, distress, PTSD, and insomnia relative to control patients.

Methods

Participants

The study population consisted of cancer patients ≥ 18 years old attending the Greenville Health System Cancer Institute's Center for Integrative Oncology and Survivorship (Greenville, SC; May, 2015 to November, 2016). Patients with a histopathologically confirmed cancer diagnosis (any stage, grade, or location) who had completed their initial treatment (e.g., radiation, surgery, chemotherapy), and reported at least one of the targeted symptoms (pain, stress, distress, fatigue, depression, insomnia) were eligible. Patients receiving concurrent cancer treatment were not eligible, except for those receiving hormonal and/or biologic therapy. Patients were not eligible if they had a cardiovascular condition that may affect HRV measures, including: paroxysmal supraventricular tachycardia, atrial fibrillation, myocardial infarction within 12 months, unstable angina, current medications that affect the cardiac rhythm (angiotensin converting enzyme, calcium channel blockers, or beta-adrenergic antagonists), a pacemaker or defibrillator, a heart transplant or by-pass surgery within 1 year, an active seizure disorder or use of anti-seizure or anti-convulsant medication prescribed specifically for seizure disorders. Patients also were excluded if they had: pre-existing dementia prior to cancer diagnosis; a moderate (i.e., without good recovery) or severe head injury or stroke within 6 months, evidence of active substance abuse or dependence, history of major psychiatric disorder or brain metastases, primary brain cancer, altered cognitive abilities, or use of long-acting opioids (short-acting opioid medications 'as needed' were allowed). Eligible patients meeting inclusion/exclusion criteria were randomly assigned to the intervention or wait-list control group prior to the baseline measurement session. Groups were assigned via blinded, random draw of numbered notecards (even number: experimental group; odd number: control). All participants provided informed consent and the study protocol was approved by the Institutional Review Boards of the participating institutions. The study was retrospectively registered at ClinicalTrials.gov (NCT 03692624).

Intervention Group

Individual HRVB training was conducted by a certified trainer following a previously established, standardized

protocol adopted by the Biofeedback Certification Institute of America. Participants in the intervention group (n = 17) completed a minimum of 4 and a maximum of 6 weekly training sessions until a criterion of HRV coherence was met. The criterion was defined as an ability to maintain, without coaching or biofeedback, an average of ≥ 80% HRV coherence for a minimum of 4 min out of a 5-min test session. HRVB training consisted of 25 min of individual biofeedback training/coaching using an emWave Pro system (HeartMath, Boulder Creek, CA) and earlobe or fingertip photoplethysmograph sensor, followed by a 15-min personal practice period. Feedback was provided using a dual-screen display of real-time HRV patterns and relaxing nature scenes as participants practiced focusing of attention, resonant frequency breathing, and positive imagery. Visual HRV feedback facilitated associations between the technique and elevated vagal parasympathetic output. The trainer informed participants about the connection between resonant frequency breathing and heart rate, and this was reinforced with coaching to find the resonant frequency of breathing using biofeedback. Participants also were provided with a portable plethysmograph (emWave2® hand-held personal stress reliever, HeartMath, Boulder Creek, CA) for home practice and use between weekly HRVB training sessions. Participants were encouraged to use this device for at least 15 min per day between each weekly training session.

Control Group

To control for the research environment or other potential placebo effects, control group participants (n = 17) received usual follow-up care for their cancer diagnosis without any HRVB training. Controls attended individual baseline and follow-up outcome assessment sessions with a similar time separation and duration as the intervention participants. During these clinic visits, control participants had their HRV and respiration recorded for 15 min, but no active training, coaching, or biofeedback was provided. During the passive 15-min HRV recording period, subjects viewed the same static, relaxing nature scenes (scrolling at 40-s intervals on the computer monitor), as was presented to the HRVB group. Controls who desired participation in the intervention were offered HRVB training, without data collection, after completion of their protocol.

Outcome Measures

Each outcome was measured at baseline and a week after their HRVB training or control period. Participants completed a 15-min HRV recording at each assessment (J&J I-330-C2 + 6 channel ECG encoder supported by Physiolab software, J&J Engineering, Poulsbo, WA). During the follow-up HRV recording, those in the HRVB group were instructed to 'do what you've been trained to do', whereas control group members completed a resting HRV recording. IBI files were exported and processed according to established guidelines (Camm et al. 1996). Kubios software (Kuopio, Finland) was used to de-artifact raw data and perform a fast Fourier transformation to obtain the HRV power spectrum on a 5-min segment of each data file. Time-domain (e.g., standard deviation of heart rate N–N intervals [SDNN], and RMSSD [the square root of the mean squared difference of successive N–N intervals]), and frequency-domain variables (e.g., high frequency [HF] and low frequency [LF] power) were calculated. The HRV Coherence Ratio was obtained by identifying the maximum peak in the 0.04–0.26 Hz HRV range, calculating the integral in a window 0.030 Hz wide centered on the highest peak in that region ('peak power', usually about 0.1 Hz), then calculating the total power of the entire spectrum. The HRV Coherence Ratio was then quantified as: peak power / (total power – peak power). The frequency range of 0.04–0.26 Hz was selected because it is the range within which HRV coherence (i.e., cardiorespiratory entrainment) occurs (Lehrer and Gevirtz 2014; McCraty & Zayas, 2014; Shaffer et al. 2014).

A structured, self-administered questionnaire was used to obtain sociodemographic (age, race, ethnicity, sex, body mass index, education, income, marital status), and lifestyle information (aspirin, alcohol, and caffeine consumption, tobacco use, health insurance status, circadian preference, employment status). Data from the patient's medical record included: cancer site and stage of diagnosis, type of cancer therapy initially received, time since cancer diagnosis, and time since the end of initial cancer treatment. Symptoms of: pain (Brief Pain Inventory [BPI], pain severity range: 0–10, pain interference range: 0–10 (Cleeland and Ryan 1994)), stress (Perceived Stress Scale [PSS], range 0–40 (Cohen et al. 1983)), distress (Suscro Distress Inventory [SDI], range 0–48 (Hudson et al. 2016)), fatigue (Multidimensional Fatigue Inventory [MFI], range 4–20 (Smets et al. 1995)), depression (Beck Depression Inventory II [BDI-II], range 0–63 (Beck et al. 1996)), PTSD (PTSD Check List—Civilian Version [PCL-C], range 17–85 (Blevins et al. 2015)), and Sleep (Insomnia Symptom Questionnaire [ISQ] (Okun et al. 2009)) were ascertained at baseline and follow-up following the 15-min HRV recording. Distress is a construct more broadly conceived than perceived stress, and includes: mood, anxiety, financial worry, fatigue, isolation, purpose and meaning, appearance, intimacy, sleep, support, diet and discomfort. Symptoms were scored according to documentation accompanying each instrument. For each outcome, higher scores correspond to increased symptom severity. Results with one or two missing items were pro-rated to the total score; if > 2 items were missing, the score was coded as missing. The ISQ is a self-report instrument designed to obtain information for a clinical case definition of insomnia

consistent with current diagnostic criteria (Okun et al. 2009). Scores obtained for questions from the two subscales targeting sleep symptoms (range 0–25) and sleep-related daytime impairment (range 0–32) were summed for each participant and time point, and analyzed as described below.

Data Analyses

All statistical analyses were performed in SAS® (v9.4, SAS Institute) or SPSS (v24.0, IBM Corp.). Group comparisons of sociodemographic and lifestyle characteristics at baseline were performed using Fisher's exact test. The proportion of participants in the HRVB group exceeding clinical cut-points at baseline and follow-up were computed for several outcomes (moderate to severe depression: BDI-II ≥ 20; distress: SDI ≥ 14; or moderate to severe PTSD, consistent with Diagnostic and Statistical Manual of Mental Disorders IV criteria ("Using the PTSD Checklist for DSM-IV (PCL),"2014)). Analyses were performed separately to evaluate the effect of HRVB on pre-specified primary (HRV Coherence Ratio, pain, stress, distress, fatigue, depression, insomnia) and secondary (PTSD) outcomes using linear mixed models for repeated measures (PROC MIXED in SAS) in order to assess Group, Time, and Group-by-Time effects. Unstructured and compound symmetric covariance matrices were tested, and final models specified the lowest Akaike information criterion. For the control group, two-sided tests of statistical significance were used for group comparisons of baseline and follow-up. Consistent with the a priori directional research hypotheses that HRVB would result in symptom improvement, one-sided hypothesis tests were used to compare differences between groups at follow-up, for pre-post comparisons within the intervention group, and for the Group-by-Time interaction (Cho and Abe 2013). All reported means and standard errors, and results of statistical hypothesis tests (F- and p-values) were based on least squares estimates from the mixed model analysis. A sensitivity analysis was conducted by analyzing the data among females only since all male participants were randomly assigned to the intervention group (n = 5). Effect sizes were estimated using Cohen's d statistic (Cohen 1969).

Results

Study Population Characteristics

Of the 179 patients who were screened, 62 were eligible to participate, and 38 were enrolled (61%). Among the patients who participated, 34 completed the protocol (89%). Reasons for declining participation were not provided. Participants were predominantly European American (79%), college-educated (62%) females (85%) with breast (59%) or hematologic malignancies (15%) (Table 1). The average age (± standard error of the mean) was 60 ± 3 and 59 ± 2 years among intervention and control groups, respectively. With the exception of sex, population characteristics at baseline did not differ by group (Table 1).

Relative to baseline, there were notable decreases in the proportion of HRVB group members who met clinical criteria for: moderate to severe depression (29% at baseline vs. 8% at follow-up, − 72% change); PTSD (41% vs. 12%, − 71%); and general distress (45% vs. 33%, − 27%). Less change in these outcomes was noted among controls (moderate to severe depression: 36% at baseline vs. 21% at follow-up (− 42%); PTSD: 53% vs. 41% (− 23%); distress: 71% vs. 64% (− 10%)).

HRV Coherence Ratio

The interaction term for Group (HRVB vs. Control) by Time (Pre- vs. Post-Treatment) of mean HRV Coherence Ratios was statistically significant ($p = 0.03$). Least squares means of the HRV Coherence Ratio in the treatment group at baseline (0.37 ± 0.05) increased following HRVB training (0.84 ± 0.18, $d = 0.98$), while control group values decreased slightly from baseline to follow-up (0.40 ± 0.05 to 0.33 ± 0.17, $d = 0.14$, Table 2). The simple effect of Time was statistically significant in the HRVB group ($p = 0.01$) but not in the control group ($p = 0.73$) as was the simple effect of Group (HRVB vs. Control) post-intervention ($p = 0.03$).

Sleep

The greatest effect of HRVB training was observed on the sleep indicators. The Group-by-Time interaction terms for ISQ sleep symptom and daytime impairment scores were both statistically significant ($p < 0.001$ and $p = 0.005$, respectively, Table 2). Mean sleep symptom scores in the HRVB group decreased from 14.5 ± 1.5 at baseline to 8.1 ± 1.3 at follow-up ($d = 1.19$), while control group scores increased slightly from 16.1 ± 1.4 to 17.9 ± 3.3 ($d = 0.33$, Table 2). Mean daytime impairment scores in the HRVB group decreased from baseline to follow-up (11.4 ± 1.8 to 5.4 ± 1.8, $d = 0.86$), and increased slightly among controls (13.3 ± 1.7 to 13.7 ± 1.8, $d = 0.06$). For both the sleep symptom and daytime impairment variables, the simple effect of Time was statistically significant in the HRVB group (both $p = 0.001$), but not in the control group (sleep symptoms: $p = 0.33$, daytime impairment: $p = 0.83$). In addition, statistically significant differences were observed between groups at follow-up (sleep symptoms: $p < 0.001$, daytime impairment: $p = 0.001$, Table 2).

Table 1 Baseline population characteristics by group, Greenville Health System Cancer Institute, Center for Integrative Oncology and Survivorship

Characteristic n (%)	HRVB Intervention (n = 17)	Control (n = 17)	p-value[a]
Body mass index (kg/m^2)			0.91
Normal	8 (47.1)	6 (35.3)	
Overweight	5 (29.4)	7 (41.2)	
Obese	4 (23.5)	4 (23.5)	
Sex			0.05
Male	5 (29.4)	0 (0)	
Female	12 (70.6)	17 (100)	
Ethnicity			0.60
Hispanic or Latino	1 (5.9)	0 (0)	
Not Hispanic or Latino	15 (88.2)	14 (82.3)	
Missing	1 (5.9)	3 (17.7)	
Race			0.35
European American	14 (82.3)	13 (76.4)	
African American	1 (5.9)	2 (11.8)	
Native American/Alaskan Native	2 (11.8)	0 (0)	
Missing	0 (0)	2 (11.8)	
Education			0.93
High school	4 (23.5)	4 (23.5)	
College	7 (41.1)	6 (35.3)	
Graduate school	3 (17.7)	5 (29.4)	
Missing	3 (17.7)	2 (11.8)	
Income			0.77
Under $50,000	6 (35.3)	5 (29.4)	
$50,000–$100,000	4 (23.5)	5 (29.4)	
$100,000 or more	6 (35.3)	4 (23.5)	
Missing	1 (5.9)	3 (17.7)	
Smoking status			0.48
Current smoker	0 (0)	1 (5.9)	
Former smoker	8 (47.1)	5 (29.4)	
Never smoker	9 (52.9)	11 (64.7)	
Marital status			0.86
Married/living with a partner	12 (70.6)	11 (64.7)	
Separated/divorced	3 (17.6)	2 (11.8)	
Widowed	1 (5.9)	3 (17.6)	
Single	1 (5.9)	1 (5.9)	
Primary cancer site			0.83
Breast	9 (52.9)	11 (64.7)	
Hematologic	2 (11.8)	3 (17.6)	
Gastric/urogenital	1 (5.9)	1 (5.9)	
Prostate	2 (11.8)	0 (0)	
Head/neck	1 (5.9)	1 (5.9)	
Colon/rectum	1 (5.9)	0 (0)	
Gynecological	0 (0)	1 (5.9)	
Lung	1 (5.9)	0 (0)	
Cancer stage			0.78
I	6 (35.3)	6 (35.3)	
II	3 (17.6)	2 (11.8)	
III	1 (5.9)	3 (17.6)	
IV	0 (0)	1 (5.9)	
Missing/other	7 (41.2)	5 (29.4)	

[a]Fisher's exact test (2-sided)

Other Outcomes

No other Group-by-Time interaction terms were statistically significant. However, fatigue and stress had a statistically significant or nearly significant simple effect of Time within the HRVB group, but not the control group (Table 2). This provides some evidence that the HRVB intervention reduced these symptoms even though the two groups were not statistically different at follow-up. The results for distress indicated a marginal Group-by-Time interaction ($p = 0.09$), as well as a simple effect of Time within the HRVB group ($p = 0.003$, $d = 0.77$), but not in the control group at follow-up ($p = 0.19$, $d = 0.29$, Table 2). There also was a statistically significant difference in distress scores between groups at follow-up ($p = 0.007$). PTSD results were similar to those for distress except there also was a simple effect of Time within the control group at follow-up (Table 2). Results for depression showed a statistically significant effect of Time in the HRVB group ($p = 0.03$, $d = 0.48$), but there also was a simple within-group effect for the control group ($p = 0.02$, $d = 0.65$), indicating that both groups improved from baseline to follow-up (Table 2).

Sensitivity Analysis

After removing males from the analysis, the pre-post differences in fatigue scores were no longer statistically significant in the HRVB group (Difference: -1.2 ± 0.9, $p = 0.10$). For PTSD scores, group differences at follow-up were no longer statistically different (HRVB: 29.7 ± 3.1 vs. control: 35.3 ± 2.6, $p = 0.09$). No other notable differences were observed.

Discussion

Cancer patients suffer from multiple symptoms (e.g., fatigue, pain, stress, depression, insomnia) that diminish quality of life and shorten survival; and many of these symptoms persist long after treatment is completed (Bluethmann et al. 2016; de Moor et al. 2013; Kwekkeboom 2016). The current study is one of only a few to examine the role of HRVB in ameliorating symptoms among cancer survivors. The completion rate among participants (89%), and increases in HRV coherence at follow-up indicate that the protocol was successfully implemented and had a measurable physiologic effect on those undergoing HRVB training. Robust improvements in scores for sleep symptoms and sleep-related daytime impairment were observed following HRVB training, with some favorable but less definitive improvements in fatigue, stress, distress, PTSD, and depression. Among previous studies that used HRVB among cancer patients, one performed among non-small cell lung cancer patients ($n = 8$) was terminated prematurely primarily because the intervention was delivered during chemotherapy and patient dropout became an issue (Greenberg et al. 2015). However, the investigators reported some positive trends, with patients receiving HRVB showing increases in HRV, and reporting reductions in stress and better coping (Greenberg et al. 2015). Another pilot study ($n = 9$) that tested the feasibility of HRVB among distressed primary brain tumor survivors included eight weekly trainings coupled with daily, 20-min home practice sessions (Ozier and Linden 2018). Increases in HRV coherence were reported in response to HRVB along with relatively encouraging effect sizes for depression (0.75) and anxiety (0.87) (Ozier and Linden 2018). A feasibility study using HRVB among breast cancer survivors six months post-therapy ($n = 6$) provided 17–23 training sessions (approximately 30-min each) over a six week period (Groff et al. 2010). Results from this case series also supported the feasibility of achieving increases in HRV coherence as well as self-reported well-being among participants (Groff et al. 2010). Interpretation of results from these pilot investigations is limited by the small samples sizes and lack of control conditions, although they are consistent with other studies that suggest improvements in sleep, and reductions in stress, anxiety, PTSD, and depression in response to HRVB training (Appelhans and Luecken 2008; Goessl et al. 2017; Lehrer and Gevirtz 2014; Nagpal et al. 2013; Sakakibara et al. 2013; van der Zwan et al. 2015). Results from the present study provide evidence for a reduction in these symptoms as well as fatigue, a common, persistent condition among cancer survivors (Arab et al. 2016; Crosswell et al. 2014; Wang and Woodruff 2015). It has been suggested that decreased HRV may play an etiologic role in cancer-related fatigue and serve as an objective physiological marker of fatigue among cancer survivors (Arab et al. 2016; Crosswell et al. 2014; De Couck et al. 2012; Gidron et al. 2014; Greenberg et al. 2015; Wang and Woodruff 2015). Another HRVB trial reported improvements in fatigue among patients with chronic fatigue syndrome (Windthorst et al. 2017). Results from the current and previous investigations suggest that appropriately timed HRVB training is feasible and potentially effective for symptom reduction among cancer survivors.

The current study indicated that HRVB may be particularly useful for improving sleep among cancer survivors. The findings are consistent with other reports suggesting that HRVB may ameliorate various sleep disturbances. A randomized controlled trial in Amsterdam that compared HRVB with other stress relief strategies reported modest improvements in sleep following a 5-week HRVB home practice protocol, with better responses reported among poor sleepers and those with greater protocol compliance (van der Zwan et al. 2015). Others have reported that HRVB may improve sleep in diverse populations including: postpartum mothers (Kudo et al. 2014), subjects attending a

Table 2 Symptoms among cancer survivors receiving HRV biofeedback or control treatment, Greenville Health System Cancer Institute, SC, USA

Outcome	A = Intervention B = Control	Baseline (T1) μ ± SE	n	Follow-up (T2) μ ± SE	n	Mean difference T2 − T1 ± SE (F, p)	Group (F, p) Time (F, p) Group × Time (F, p)
HRV coherence ratio	A	0.37 ± 0.05	16	0.84 ± 0.18	13	0.47 ± 0.19 (6.0, 0.01)	(3.4, 0.04)
	B	0.40 ± 0.05	15	0.33 ± 0.17	16	− 0.06 ± 0.17 (0.13, 0.73)	(2.5, 0.07)
	A-B ± SE (F, p)	− 0.03 ± 0.07 (0.14, 0.71)	31	0.50 ± 0.25 (4.1, 0.03)	29		(4.2, 0.03)
Stress (PSS)	A	22.8 ± 1.1	17	20.9 ± 0.87	14	− 1.9 ± 1.3 (2.1, 0.07)	(0.2, 0.33)
	B	22.1 ± 1.1	16	20.8 ± 0.59	15	− 1.3 ± 1.3 (1.0, 0.32)	(3.0, 0.05)
	A-B ± SE (F, p)	0.7 ± 1.5 (0.20, 0.66)	33	0.1 ± 1.0 (0.01, 0.45)	29		(0.1, 0.38)
Distress (SDI)	A	16.1 ± 2.4	11	10.1 ± 2.2	12	− 6.0 ± 2.0 (8.8, 0.003)	(4.6, 0.02)
	B	20.4 ± 2.2	14	18.1 ± 2.1	14	− 2.3 ± 1.7 (1.9, 0.19)	(10.0, 0.002)
	A-B ± SE (F, p)	− 4.3 ± 3.2 (1.7, 0.20)	25	− 8.0 ± 3.0 (6.9, 0.007)	26		(2.0, 0.09)
PTSD (PCL-C)	A	32.1 ± 3.0	16	28.0 ± 2.6	14	− 4.1 ± 1.5 (7.2, 0.006)	(4.0, 0.03)
	B	40.2 ± 3.1	16	35.3 ± 2.6	16	− 4.9 ± 1.5 (11.4, 0.002)	(18.2, < 0.001)
	A-B ± SE (F, p)	− 8.1 ± 4.3 (3.6, 0.07)	32	− 7.7 ± 3.6 (3.9, 0.03)	30		(0.16, 0.69)
Pain severity (BPI)	A	1.9 ± 0.5	17	2.0 ± 0.6	17	0.1 ± 0.6 (0.03, 0.97)	(3.0, 0.04)
	B	3.5 ± 0.5	17	2.5 ± 0.6	17	− 0.9 ± 0.6 (2.5, 0.12)	(1.0, 0.16)
	A-B ± SE (F, p)	− 1.6 ± 0.8 (4.5, 0.04)	34	− 0.6 ± 0.8 (− 0.6, 0.23)	34		(1.5, 0.12)
Pain interference (BPI)	A	2.7 ± 0.7	15	2.6 ± 0.7	12	− 0.1 ± 0.5 (0.05, 0.41)	(0.1, 0.35)
	B	3.4 ± 0.7	16	2.6 ± 0.6	16	− 0.8 ± 0.4 (3.3, 0.08)	(1.9, 0.09)
	A-B ± SE (F, p)	− 0.7 ± 1.0 (0.5, 0.50)	31	0 ± 0.9 (0, 0.50)	28		(1.1, 0.15)
Depression (BDI)	A	12.4 ± 2.1	16	8.3 ± 2.5	12	− 4.2 ± 2.1 (3.8, 0.03)	(2.0, 0.09)
	B	17.1 ± 2.3	12	11.7 ± 2.3	14	− 5.4 ± 2.3 (5.8, 0.02)	(9.5, 0.003)
	A-B ± SE (F, p)	− 4.7 ± 3.2 (2.2, 0.15)	28	− 3.4 ± 3.4 (1.0, 0.16)	26		(0.2, 0.35)
General fatigue (MFI)	A	12.8 ± 1.1	16	11.2 ± 1.1	14	− 1.4 ± 0.08 (3.1, 0.04)	(1.9, 0.09)
	B	14.4 ± 0.7	16	13.1 ± 0.9	15	− 1.2 ± 0.7 (2.4, 0.13)	(5.5, 0.01)
	A-B ± SE (F, p)	− 1.6 ± 1.3 (1.5, 0.22)	32	− 1.7 ± 1.4 (1.6, 0.11)	29		(0.03, 0.43)

Table 2 (continued)

Outcome	A = Intervention B = Control	Baseline (T1) μ ± SE	n	Follow-up (T2) μ ± SE	n	Mean difference T2 − T1 ± SE (F, p)	Group (F, p) Time (F, p) Group × Time (F, p)
Sleep symptoms (ISQ)	A	14.5 ± 1.5	15	8.1 ± 1.3	14	− 6.9 ± 2.0 (11.5, 0.001)	(17.2, < 0.001)
	B	16.1 ± 1.4	17	17.9 ± 1.3	16	1.9 ± 1.9 (1.0, 0.33)	(3.2, 0.04)
	A-B ± SE (F, p)	− 1.4 ± 2.1 (0.44, 0.51)	32	− 10.1 ± 1.8 (30.2, < 0.001)	30		(9.9, 0.001)
Daytime impairment (ISQ)	A	11.4 ± 1.8	16	5.4 ± 1.8	14	− 6.0 ± 1.7 (13.0, 0.001)	(5.2, 0.01)
	B	13.3 ± 1.7	17	13.7 ± 1.8	16	0.33 ± 1.5 (0.05, 0.83)	(6.3, 0.01)
	A-B ± SE (F, p)	− 1.94 ± 2.5 (0.62, 0.44)	33	− 8.29 ± 2.6 (10.5, 0.001)	30		(7.9, 0.005)

Note Least square means and standard errors presented by group and time point. All tests of significance are based on estimated means within the mixed model. Two-tailed p-values were used for baseline comparisons and pre-post comparisons in Group B. One-tailed p-values were used for a priori directional research hypotheses for pre-post comparisons within the intervention group and for group differences at follow-up. Intercept was included in all models, and covariance matrices (diagonal or unstructured) were selected based on minimum AIC value. *HRV* heart rate variability. *PSS* perceived stress scale. *SDI* Suscro distress inventory. *PTSD* post-traumatic stress disorder. *PCL-C* PTSD checklist–civilian. *BPI* brief pain inventory. *BDI* Beck depression inventory-II. *MFI* multidimensional fatigue inventory. *ISQ* insomnia sleep questionnaire

sleep laboratory (i.e., to address the 'first night effect' on sleep) (Ebben et al. 2009), or soldiers in a combat setting (McLay and Spira 2009). The restorative properties of deep sleep are related to the resonance frequency breathing, cardiorespiratory coupling, and parasympathetic dominance that typically occur during non-rapid eye movement (NREM) and slow-wave sleep (Garcia et al. 2013; Jerath et al. 2014). A study that quantified high frequency HRV amplitudes (a marker of parasympathetic activity) during sleep reported that HRVB training immediately prior to bed-time increased the 'cardiorespiratory resting function of sleep' relative to active or no-treatment controls (Sakakibara et al. 2013). In a study among insomniacs (n = 14 insomniacs vs. 14 normal sleepers), 20 min of paced breathing at the resonant frequency prior to bedtime over five consecutive days led to improvements in polysomnographic measures of: sleep onset latency, the time needed to enter slow wave sleep, total wake time after sleep onset, and sleep efficiency relative to controls (spontaneous breathing, or paced breathing at a control frequency of 0.2 Hz) (Tsai et al. 2015). Another study among healthy young adults (N = 64) using a smartphone application (Breath Pacer) found that 30 days of resonant frequency breathing 15 min before the sleep period was associated in improvements in subjective sleep quality relative to a control condition (Laborde et al. 2019). Results from the present study support previous results, and suggest that increased HRV coherence may facilitate homeostasis between the ANS and cardiopulmonary systems, thereby promoting cardiorespiratory coupling and more restorative sleep mediated by parasympathetic activity (Garcia et al. 2013; Jerath et al. 2014).

Pain is common among cancer survivors and HRVB training in other populations has shown improvements in pain symptoms (Appelhans and Luecken 2008; Lehrer and Gevirtz 2014). In the current study, pain severity ratings at baseline were lower than expected, which may have impeded the ability to detect a treatment-related effect. The inability to detect a treatment-related reduction in pain severity may have been affected by the sample size. The final sample (17 per group) resulted from screening of 179 patients and was the maximum number of subjects that could be recruited within the accrual period. Compliance to completion was 89%. Nonetheless, the sample size may have resulted in insufficient power to detect a difference in pain severity between groups, and the results are vulnerable to type II (false negative) error. It also is possible that decreases in pain severity may take longer to manifest following HRVB than the follow-up period that was used in this study. For these reasons, further research on HRVB and pain may be warranted.

Several limitations of this study are noteworthy. The sample size was small and did not include an active, attentionally equivalent, control group. At baseline, pain severity and PTSD scores were greater in controls than the intervention group, indicating that controls began the study with a higher symptom burden than those in the treatment group. Differences in these or other symptoms at baseline may have contributed to an inability to detect some treatment-related

effects, and to inconsistencies between this study and some previous investigations. Differences in the methods used for this and other studies regarding HRVB coaching, data collection, amount of home practice, or the HRV variables included in the analysis, also may have contributed to some of the observed inconsistencies.

There also were several study strengths. A previously developed, standardized protocol was used that included random assignment and a wait-list control group. The protocol required demonstration of skill acquisition that facilitated documentation of whether the intervention criterion was attained. The HRV Coherence Ratio was used to quantify receipt of intervention, and the results provided quantifiable evidence of intervention validity. This study also achieved favorable compliance, with a completion rate of 89%.

Effective symptom management strategies are needed for cancer survivors, yet there are currently few, if any, mechanism-driven interventions for alleviating their symptoms (Arab et al. 2016; Crosswell et al. 2014; Wang and Woodruff 2015). Inflammation and the stress response are considered primary biological processes driving the development and perpetuation of cancer-related symptoms (Kelly et al. 2016; Wood and Weymann 2013). Fortuitously, there is a well-described neural pathway mediated by the vagus nerve that has the potential to normalize stress-related sympathetic dominance and activate anti-inflammatory processes (Olshansky 2016). The potential benefits of improved autonomic function for ameliorating cancer symptoms or for prolonging cancer survival have been acknowledged (De Couck et al. 2012; Gidron et al. 2014; Greenberg et al. 2015). HRVB is a noninvasive, nonpharmacological, easily implemented therapy, and interventions to improve HRV suggest that it can reduce symptoms commonly observed among cancer survivors, including: stress, anxiety, PTSD, pain, depression, and sleep disturbances (Appelhans and Luecken 2008; Camm et al. 1996; Goessl et al. 2017; Lehrer and Gevirtz 2014; Nagpal et al. 2013; Sakakibara et al. 2013; van der Zwan et al. 2015). Results from the current pilot study suggest that HRVB may be useful for improving sleep and potentially for managing stress, fatigue, distress, depression and PTSD among cancer survivors. Larger more rigorous studies are suggested to fully evaluate the efficacy and optimize the effectiveness of HRVB in this population.

Acknowledgements This study was partially supported by the Greenville Health System Office of Philanthropy and Partnership. Ms. Courtney Petersen and Mr. Jameson Sofge provided technical assistance with data collection and processing. J.B.B. was supported by grants from the Department of Veterans Affairs Office of Research and Development (Merit Award: I01BX007080), and Health Services Research and Development Office (PPO 09–246). J.P.G. was supported by a Merit Award from the Department of Veterans Affairs Office of Research and Development (I01BX007080). J.R.H. was supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Compliance with Ethical Standards

Conflict of interest The authors have no competing interests to report.

References

Appelhans, B. M., & Luecken, L. J. (2008). Heart rate variability and pain: associations of two interrelated homeostatic processes. *Biological psychology, 77*(2), 174–182. https://doi.org/10.1016/j.biopsycho.2007.10.004.

Arab, C., Dias, D. P., Barbosa, R. T., Carvalho, T. D., Valenti, V. E., Crocetta, T. B., ... Ferreira, C. (2016). Heart rate variability measure in breast cancer patients and survivors: A systematic review. *Psychoneuroendocrinology, 68*, 57–68. https://doi.org/10.1016/j.psyneuen.2016.02.018

Beck, A. T., Steer, R. A., & Brown, G. G. (1996). *Manual for Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The posttraumatic stress disorder checklist for dsm-5 (pcl-5): development and initial psychometric evaluation. *Journal of traumatic stress, 28*(6), 489–498. https://doi.org/10.1002/jts.22059.

Bluethmann, S. M., Mariotto, A. B., & Rowland, J. H. (2016). Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiology Biomarkers and Prevention, 25*(7), 1029–1036. https://doi.org/10.1158/1055-9965.EPI-16-0133.

Camm, A. J., Malik, M., Bigger, J. T., Breithardt, G., Cerutti, S., Cohen, R. J., ... Singer, D. (1996). Heart rate variability - Standards of measurement, physiological interpretation, and clinical use. *Circulation, 93*(5), 1043–1065.…

Cho, H. C., & Abe, S. (2013). Is two-tailed testing for directional research hypotheses tests legitimate? *Journal of Business Research, 66*(9), 1261–1266.

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the brief pain inventory. *Annals of the Academy of Medicine, Singapore, 23*(2), 129–138.

Cohen, J. (1969). *Statistical Power Analysis for the Behavioral Sciences*. NY: Academic Press.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24*(4), 385–396.

Crosswell, A. D., Lockwood, K. G., Ganz, P. A., & Bower, J. E. (2014). Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology, 45*, 58–66. https://doi.org/10.1016/j.psyneuen.2014.03.011.

De Couck, M., Mravec, B., & Gidron, Y. (2012). You may need the vagus nerve to understand pathophysiology and to treat diseases. *Clinical science, 122*(7), 323–328. https://doi.org/10.1042/CS20110299.

de Moor, J. S., Mariotto, A. B., Parry, C., Alfano, C. M., Padgett, L., Kent, E. E.,... Rowland, J. H. (2013). Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiology Biomarkers and Prevention, 22*(4), 561–570. https://doi.org/10.1158/1055-9965.EPI-12-1356

Ebben, M. R., Kurbatov, V., & Pollak, C. P. (2009). Moderating laboratory adaptation with the use of a heart-rate variability biofeedback device (StressEraser). *Applied Psychophysiology and Biofeedback, 34*(4), 245–249. https://doi.org/10.1007/s10484-009-9086-1.

Garcia, A. J., 3rd, Koschnitzky, J. E., Dashevskiy, T., & Ramirez, J. M. (2013). Cardiorespiratory coupling in health and disease. *Autonomic Neuroscience: Basic & Clinical, 175*(1–2), 26–37.

Gidron, Y., De Couck, M., & De Greve, J. (2014). If you have an active vagus nerve, cancer stage may no longer be important. *Journal of Biological Regulators and Homeostatic Agents, 28*(2), 195–201.

Goessl, V. C., Curtiss, J. E., & Hofmann, S. G. (2017). The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychological Medicine, 47*(15), 2578–2586. https://doi.org/10.1017/S0033291717001003.

Greenberg, B. R., Grossman, E. F., Bolwell, G., Reynard, A. K., Pennell, N. A., Moravec, C. S., et al. (2015). Biofeedback assisted stress management in patients with lung cancer: a feasibility study. *Applied Psychophysiology and Biofeedback, 40*(3), 201–208. https://doi.org/10.1007/s10484-015-9277-x.

Groff, D., Battaglini, C., Sipe, C., Peppercorn, J., Anderson, M., & Hackney, A. C. (2010). Finding a new normal: Using recreation therapy to improve the well-being of women with breast cancer. *Annual in Therapeutic Recreation, 18*, 40–52.

Hudson, M. F., Franco, R. A., Susko, K., Crowley, E., Sprouse, C., Douglas, M., . . . O'Rourke, M. A. (2016). Characteristics of the Suscro Distress Inventory (SDI) for cancer survivors. *Journal of Clinical Oncology, 34*(15_suppl), e21541-e21541. doi:10.1200/JCO.2016.34.15_suppl.e21541

Jerath, R., Harden, K., Crawford, M., Barnes, V. A., & Jensen, M. (2014). Role of cardiorespiratory synchronization and sleep physiology: effects on membrane potential in the restorative functions of sleep. *Sleep Medicine, 15*(3), 279–288. https://doi.org/10.1016/j.sleep.2013.10.017.

Kelly, D. L., Dickinson, K., Hsiao, C. P., Lukkahatai, N., Gonzalez-Marrero, V., McCabe, M., et al. (2016). Biological basis for the clustering of symptoms. *Seminars in Oncology Nursing, 32*(4), 351–360. https://doi.org/10.1016/j.soncn.2016.08.002.

Kudo, N., Shinohara, H., & Kodama, H. (2014). Heart rate variability biofeedback intervention for reduction of psychological stress during the early postpartum period. *Applied Psychophysiology and Biofeedback, 39*(3–4), 203–211. https://doi.org/10.1007/s10484-014-9259-4.

Kwekkeboom, K. L. (2016). Cancer symptom cluster management. *Seminars in Oncology Nursing, 32*(4), 373–382. https://doi.org/10.1016/j.soncn.2016.08.004.

Laborde, S., Hosang, T., Mosley, E., & Dosseville, F. (2019). Influence of a 30-Day slow-paced breathing intervention compared to social media use on subjective sleep quality and cardiac vagal activity. *Journal of Clinical Medicine, 8*(2), 193. https://doi.org/10.3390/jcm8020193.

Lehrer, P. M., & Gevirtz, R. (2014). Heart rate variability biofeedback: How and why does it work? *Frontiers in Psychology, 5*, 756. https://doi.org/10.3389/fpsyg.2014.00756.

McCraty, R., & Zayas, M. A. (2014). Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. *Frontiers in Psychology, 5*, 1090. https://doi.org/10.3389/fpsyg.2014.01090.

McLay, R. N., & Spira, J. L. (2009). Use of a portable biofeedback device to improve insomnia in a combat zone, a case report. *Applied Psychophysiology and Biofeedback, 34*(4), 319–321. https://doi.org/10.1007/s10484-009-9104-3.

Nagpal, M. L., Gleichauf, K., & Ginsberg, J. P. (2013). Meta-analysis of heart rate variability as a psychophysiological indicator of posttraumatic stress disorder. *Journal of Trauma and Treatment, 3*(182), 1–8. https://doi.org/10.4172/2167-1222.1000182.

Okun, M. L., Kravitz, H. M., Sowers, M. F., Moul, D. E., Buysse, D. J., & Hall, M. (2009). Psychometric evaluation of the Insomnia Symptom Questionnaire: a self-report measure to identify chronic insomnia. *Journal of Clinical Sleep Medicine, 5*(1), 41–51.

Olshansky, B. (2016). Vagus nerve modulation of inflammation: Cardiovascular implications. *Trends in Cardiovascular Medicine, 26*(1), 1–11. https://doi.org/10.1016/j.tcm.2015.03.016.

Ozier, D., & Linden, W. (2018). Heart variability biofeedback as supplementary care for brain cancer: A feasibility study. *Journal of Alternative And Complementary Medicine*. https://doi.org/10.1089/acm.2017.0393.

Sakakibara, M., Hayano, J., Oikawa, L. O., Katsamanis, M., & Lehrer, P. (2013). Heart rate variability biofeedback improves cardiorespiratory resting function during sleep. *Applied Psychophysiology and Biofeedback, 38*(4), 265–271. https://doi.org/10.1007/s10484-013-9232-7.

Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology, 5*, 1–19. https://doi.org/10.3389/fpsyg.2014.01040.

Smets, E. M. A., Garssen, B., Bonke, B., & De Haes, J. C. J. M. (1995). The Multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research, 39*(5), 315–325.

Tsai, H. J., Kuo, T. B., Lee, G. S., & Yang, C. C. (2015). Efficacy of paced breathing for insomnia: enhances vagal activity and improves sleep quality. *Psychophysiology, 52*(3), 388–396. https://doi.org/10.1111/psyp.12333.

Using the PTSD checklist for DSM-IV (PCL). (2014). Retrieved from www.ptsd.va.gov

van der Zwan, J. E., de Vente, W., Huizink, A. C., Bogels, S. M., & de Bruin, E. I. (2015). Physical activity, mindfulness meditation, or heart rate variability biofeedback for stress reduction: a randomized controlled trial. *Applied Psychophysiology and Biofeedback, 40*(4), 257–268. https://doi.org/10.1007/s10484-015-9293-x.

Wang, X. S., & Woodruff, J. F. (2015). Cancer-related and treatment-related fatigue. *Gynecologic Oncology, 136*(3), 446–452. https://doi.org/10.1016/j.ygyno.2014.10.013.

Windthorst, P., Mazurak, N., Kuske, M., Hipp, A., Giel, K. E., Enck, P., ... Teufel, M. (2017). Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study. *Journal of Psychosomatic Research, 93*, 6–13. https://doi.org/10.1016/j.jpsychores.2016.11.014.…

Wood, L. J., & Weymann, K. (2013). Inflammation and neural signaling: etiologic mechanisms of the cancer treatment-related symptom cluster. *Current Opinion in Supportive and Palliative Care, 7*(1), 54–59. https://doi.org/10.1097/SPC.0b013e32835dabe3.

Zhou, X., Ma, Z., Zhang, L., Zhou, S., Wang, J., Wang, B., et al. (2016). Heart rate variability in the prediction of survival in patients with cancer: A systematic review and meta-analysis. *Journal of Psychosomatic Research, 89*, 20–25. https://doi.org/10.1016/j.jpsychores.2016.08.004.