HEART RATE VARIABILITY AND PACED BREATHING: REVIEW: A PILOT STUDY

A Thesis

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by

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ABSTRACT

Background

Heart rate variability has been associated with better outcomes for multiple physical and mental health conditions. One method to increase heart rate variability has been proposed to be through modification of the autonomic nervous system though slow paced breathing periods during the day.

Objectives

The objectives of this study were to review the current literature for studies that attempted to institute slow paced breathing protocols and then to conduct a pilot trial to compare a slow paced breathing protocol to a normal rate but paced breathing protocol in health volunteers. The outcomes of the trial were within-subject change in heart rate variability and perceived psychological stress.

Methods

We performed a systematic, keyword driven database search including the following key phrases: paced breathing and treatment, paced breathing and intervention, controlled breathing and treatment, and deep breathing and treatment. Selected papers used slow paced breathing to treat different physical and mental health conditions. For the pilot trial, 22 volunteers were randomized to the slow paced breathing group of 5 breaths per minute (bpm) or to the normal but paced breathing group of 14 bpm. Participants were instructed to practice this breathing rate for 10 mins, twice/day (total of 20 mins). They were evaluated at the study site at enrollment

and at 2, 4, 6, 8, 10, 12, 14, 16, and 18 weeks during which they breathed at their assigned rate while wearing a Vivo Metric life-shirt, which automatically records heart and respiratory rate. Participants also completed the Perceived Stress Scale at enrollment and follow-ups.

Results

We reviewed 284 studies and included 23 studies that addressed slow paced breathing mostly for the treatment of hypertension, chronic heart failure, non-cardiac chest pain, neck pain, seizure disorder, space medicine, depression, hot flashes, COPD, induced inflammation, and stress. Of these, 7 were prospective cohort studies, 8 randomized control trials, and 3 case studies. Most studies reported some benefit from slow paced breathing and recommended a rate of ≤ 6 bpm. There were no reports of side effects from slow paced breathing, other than in a study of COPD patients where 3 bpm was associated with a drop in oxygen saturation. For the pilot trial, baseline characteristics of heart rate variability were similar for the treatment and control groups. Controlled paced breathing was sub-optimally applied in the treatment group. Paced breathing did not result in significant increases in heart rate variability in the treatment versus control group. Both groups had improvement in stress levels after sixteen weeks as measured by within-subject change on the Perceived Stress Scale.

Conclusions and Relevance

Preliminary evidence supports the use of slow paced breathing to affect heart rate variability by increasing it to high frequency variability. The pilot trial

demonstrated the challenges in applying and maintaining a paced breathing protocol. Suggestions for optimizing a protocol include strict monitoring of breathing tracings during each treatment session so that modifications to the protocol can be made in real time. Heart rate variability was obtained among participants who attained a breathing rate of 6 bpm. Future research should seek to optimize the methodology of slow paced breathing so it can more effectively impact existing physical and mental health and potentially also play a role in primary prevention.

BIOGRAPHICAL SKETCH

Skender Murtezani, MD is a clinical assistant professor at Weill Cornell, member of Endocrine Society and American Academy of neurology involved in neuendocrine research since 1991, interested in stress hormone Physiology. He has contributed extensively to teaching residents and medical students and promoting slow paced breathing as a treatment. His research career started with the study of estrogen metabolite related malignancies in 1991 to resume as chronic stress and hormone activity at hypothalamic level.

His interest has progressed to study the neuroendocrine aspect of slow paced breathing including safe non pharmacological treatment of inflammatory disease using Slow Paced Breathing.

Dr Murtezani likes sports. He was table tennis champion in all categories for a few years in Macedonia. Sports have enabled him to have a competitive edge and understanding personalities. His family encouraged him to explore research to investigate the unanswered questions in medicine.

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CHAPTER ONE

SLOW PACED BREATHING AS A PRIMARY OR SECONDARY TREATMENT OPTION IN DIFFERENT MEDICAL AND PSYCHIATRIC CONDITIONS: A REVIEW PAPER.

INTRODUCTION

Heart rate variability (HRV) has been a focus of investigation in cardiopulmonary and vascular physiology for more than 100 years. For the past 50 years, interest has expanded to other fields, including neurosciences, inflammation, psychiatry, occupational medicine, space medicine, and genetics.

The first report linking heart rate to respiration is credited to Karl Ludwig who, in 1847, observed that heart rate increased with inspiration and decreased with expiration. The exact change of heart rate during the respiratory cycle has been studied for the past century.

After extensively studying the relationship between slow paced breathing (SPB) and HRV in healthy volunteers, Hirsch and Bishop in 1981 uncovered very important information. Specifically, they concluded that SPB of only < 7 breaths per minute (bpm) was able to raise HRV to hf levels.[9] In 2004 DelPozo et al, using 6 bpm in patients post myocardial infarction was able to raise HRV from low frequency levels and maintain hfHRV for 6 months.[6]

In 2007, after a new theory was proposed that there is a strong relationship between the autonomic nervous system (ANS) and inflammation, Marsland et al in a randomized clinical trial had healthy volunteers age 30-54 in the experimental group (SPB) breathe 11 bpm, and then stimulated blood for inflammation before and after the intervention with lipopolysaccharide (LPS). The experimental group had less production of pro-inflammatory cytokines than the control group.[14] In another study in space medicine, HRV before and after flight improved unstable ANS 25 days after landing.[22]

In contrast, patients with diabetes and other chronic inflammatory diseases have low HRV and are very resistant to treatment with SPB.[12] It is hypothesized that patients with these conditions will require longer periods of treatment with a pace of less than 7 bpm.[9]

Thus SPB appears to be a promising stand-alone treatment for multiple conditions and as adjunct with other relaxation techniques.

METHODS

We based our search on the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA). We conducted a systematic review of published reports from 1980 to 2012 using the following PubMed search engine and Google scholar keywords: slow paced breathing AND inflammation, paced breathing AND inflammation, HRV AND inflammation, paced breathing AND treatment, paced breathing AND intervention, deep breathing AND treatment, and slow deep breathing AND treatment. We included review papers, RCTs and cohort studies; time limitations were not imposed on searches because there were few studies identified using these keywords.

Protocol and Registration

We included studies with subjects >18 years old, but not ≥75 years old.

Data Collection and Processing

Two study investigators (SM, MA) independently and in duplicate screened and retrieved abstracts and full text articles for initial consideration. Abstracts and full texts of each potential article were assessed by each reviewer and the ones not meeting inclusion criteria were excluded. Disagreements about any study inclusions were resolved by consensus. Data were collected and stored in EndNote software.

Data Extractions and Analysis

Details regarding study design, participant characteristics, study setting, assessments, and outcomes data were extracted from each of the included studies. Disagreements about extracted data were resolved by consensus. All studies were evaluated for potential confounding, measurement error and selection bias. The initial protocol also included results from meta-analysis.

RESULTS

We developed a comprehensive systematic review search strategy protocol in collaboration with the consulting librarian who was not a member of the research team, and the protocol was registered with PROSPERO. The protocol included searching PubMed, Web of Science, EBM and Google Scholar. Our search used the controlled vocabulary of each database and plain language, such as slow paced breathing AND inflammation, paced breathing AND inflammation, HRV AND inflammation, paced breathing AND treatment, paced breathing AND intervention, deep breathing AND treatment, and slow deep breathing AND treatment. Studies were included if they were

original studies that analyzed the use of SPB in acute and chronic diseases. We used frequency of SPB and duration of the study as primary criteria.

The initial search recognized 3,614 citations (Table 1), and after duplicates were removed and inclusion criteria were reviewed, 284 full text articles were retrieved. Of these 23 met inclusion criteria (most were excluded because they did not focus on SPB) and were reviewed in detail.

Table 1.1 SPB Review Paper

Search Criteria	PubMed	Web of Science	EBM	Google Scholar
Slow paced breathing AND inflammation	0	4	10	10
Paced breathing AND inflammation	4	4	8	162
Heart rate variability (HRV) AND inflammation	240	230	13	100

Table 1.1 Cont.

Paced breathing AND treatment	132	14	0	1,010
Paced breathing AND intervention	13	11	490	602
Deep breathing AND treatment	204	112	147	46
Slow deep breathing AND treatment	23	14	3	0

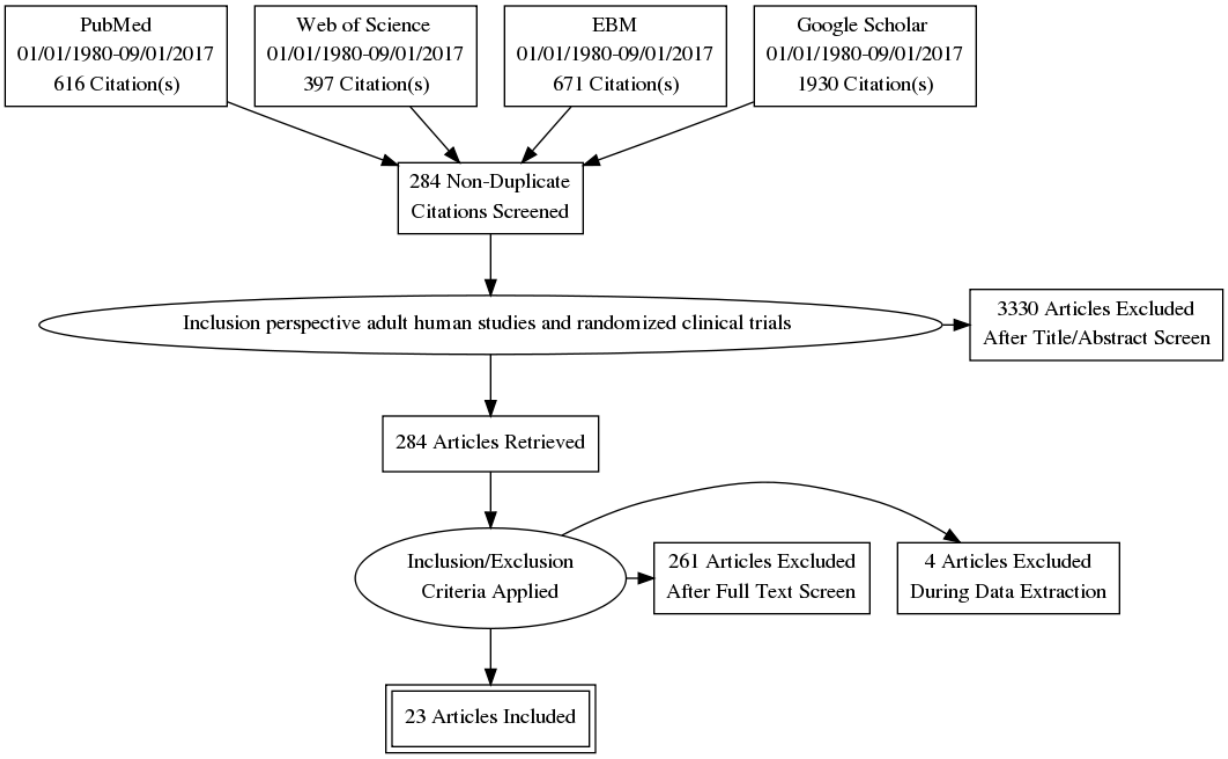

Fig 1.1 PRISMA for SPB and treatment

Description of studies

A systematic review of four major electronic databases of publications from 1980 to 2012 revealed a diverse collection of research in terms of methodology, subject characteristics, and outcome measures. Our review identified 23 studies (summarized in Table 2), of which 7 were prospective cohort studies, 8 were randomized control trials, and 2 were case studies. Our review included adults with wide age variation and some studies compared outcomes in different age groups. Although most studies were conducted in the United States, several were conducted at international sites and

thereby included a highly heterogeneous population. Studies used different frequency of SPB for different periods of time and did not distinguish among acute medical and psychiatric conditions.

Findings from studies

Hypertension is presently the condition most successfully treated with slow pace breathing at the rate of <10 times a minute using the Respirate, an FDA-approved device for this purpose. As described by Jones et al in 2010, thirty patients using the device 30 min twice daily for 8 weeks had clinically valuable reductions in moderate hypertension.[9] Another study using the same device in hypertensive patients with obstructive sleep apnea (OSA) had the same outcome of lowered systolic blood pressure.[3]

SPB as an intervention was tried in several studies with patients with congestive heart failure (CHF). In 1998 Bernardi et al used a six times a minute breathing pattern compared to a spontaneous breathing pattern in a control group. The intervention had an excellent outcome, as the slow respiratory rate reduced dyspnea and improved both resting and pulmonary gas exchange.[1] In 2002 Bernardi conducted another study that had the same outcomes, this time using a treatment group of 50 patients and 11 controls. In this study investigators added another parameter to the outcome, which was increase in baro-reflex sensitivity. This study revealed that if breathing frequency is lower to 3 or less per minute, the O_2 saturation drops close to 90%.[2] Another study in CHF patients using the same device (Respirate) in a home setting for 10 weeks at 18 minutes twice a day found similar results.[15]

Some studies addressing physiological outcomes and showed promising results. For example, Raupach et al found that at baseline sympathetic nerve activity was significantly elevated in COPD patients and baro-reflex sensitivity was decreased (5.0 versus 8.9 mmHg). [17] Breathing at a rate of 6 bpm caused sympathetic activity to drop significantly in COPD patients (from 61.3 to 53.0, bursts per 100 heartbeats) but not in control subjects (39.2 versus 37.5 bursts per 100 heartbeats). In both groups, slowed breathing significantly enhanced baro-reflex sensitivity. A review paper by Yuen in 2010 found that breathing at 6 bpm twice a day reduced seizure activity in patients that had at least one seizure a week.[23] Hypothesized mechanisms include an increase in the seizure threshold induced by SPB.

Regarding the outcome of pain, Pearce et al in 1990 conducted a 12 week study with 56 patients who had non-cardiac chest pain using 11 bpm once a day and found a reduction in pain in the treatment group[16]. Hollman et al in 2011 used SPB in 33 patients with neck pain; after 10 weeks there were improvements in perceived overall health.[8]

Regarding psychological outcomes, Chung et al in 2010 used home-based breathing training three times a day for 10 minutes at breathing 3 bpm in 28 patients post myocardial infarction. [5] Thirty four control patients received only supportive telephone calls. Outcomes focused on depressive symptoms measured by two questionnaires, the Beck Depression Inventory-II and the Patient Health Questionnaire-9. Patients were assessed at week 0 and after treatment at week 4. Intervention patients had a reduction in depressive symptoms compared to controls. In another study

addressing psychological well-being, Sood et al in 2011 evaluated stress levels, anxiety and resilience in physicians.[21] In this study 20 physicians were enrolled in the treatment arm breathing 5 bpm for 15 minutes twice daily; 20 physicians were enrolled as controls. Treatment participants had better outcomes as measured by before and after responses to the Connor Davidson Resilience Scale, the Perceived Stress Scale, the Smith Anxiety Scale, and the Linear Analog Self-Assessment Scale.

Another successful use of SPB has been for treatment of hot flashes in post-menopausal women. Most reports have concluded that 6 bpm twice a day for 15 minutes results in a decrease in event rate or a complete cure.[13] The mechanism for this potential effect is debated and will require further study.

TABLE 1.2

Slow Paced Breathing (SPB) Evaluation Studies

Study	Duration of SPB cycle only	Treatment Group (n)	Control Group (n)	Outcome Measures	Findings
Bernardi (1998) Prospecti	slow breathing rate (6 breaths/min) compared with spontaneous	81	21	Arterial baro-reflex sensitivity was measured by spectral analysis	Slowing respiratory rate reduces dyspnea and improves both resting pulmonary gas exchange and exercise

Table 1.2 Cont.

ve Cohort Study	breathing, could modify the baro-reflex sensitivity in CHF patients (age 58 years)			using the "-angle" method.	performance in patients with CHF.
Bernardi (2002) Prospecti ve Cohort Study	Patients with stable CHF and healthy volunteers as controls 15 bpm, 6 bpm, and 3 bpm. Only 15 and 6 where with positive effect on 02	50	11	Slowing respiratory rate reduces dyspnea and improves both resting pulmonary gas exchange and exercise performance in patients with CHF.	In patients with CHF, slow breathing, in addition to improving oxygen saturation and exercise tolerance as has been previously shown, may be beneficial by increasing baro-reflex sensitivity.
Bertisch (2011) Prospecti ve Cohort Study	Subjects were asked to perform device-guided paced respiration <10 BPM 30 min a	25	0	Primary outcome measures blood pressure, additional data collection	Device-guided paced respiration may lower systolic blood pressure in patients with hypertension and OSA.

Table 1.2 Cont.

	day for 8 weeks.			Statistical analysis	
Busch (2012) Prospecti ve Cohort Study	healthy volunteers	16	0	DSB affects RSA and influences pain intensity	Results suggest that deep breathing decisively influences autonomic and pain processing, thereby identifying DSB in concert with relaxation as the essential feature in the modulation of sympathetic arousal and pain perception.
Chung (2010) Randomiz ed Controlle d Trial	3 x 10min, daily 6 bpm/4 week period	28	34	Both the BDI-II and the PHQ-9 were assessed at baseline (week 0) and after the treatment period	Home-based deep-breathing training was effective in reducing depressive symptoms as compared with telephone support in patients with CHD.

Table 1.2 Cont.

				(week 4) in both groups.	
Del Pozo (2004) Randomized Controlled Trial	1 and 8 weeks 16 weeks f/u	31	32	To determine if cardiorespiratory bio- feedback increases HRV in patients with documented coronary artery disease (CAD).	Biofeedback increases HRV in patients with CAD and therefore may be an integral tool for improving cardiac morbidity and mortality rates.
Dixhoorn (1998) Prospective Cohort Study	The relaxation intervention induced a slower breathing pattern which was associated with beneficial effects on resting HR and RSA.				
Hallman (2011) Single Blind	52 weeks study	33	0	Erythrocyte sedimentation rate or CRP, function score, pain score,	This pilot study indicates improvement in perceived health over a 10 week intervention with HRV-biofeedback

Table 1.2 Cont.

Randomized Study				clinician and patient global scores were assessed for PS/SY, total power and tension index measures of autonomic reactivity	in subjects with chronic neck pain, suggest that this intervention protocol is suitable for a larger controlled trial.
Hirsch (1981) Case Study	Low-frequency intercept, corner frequency, and roll-off characterize an individual's RSA-frequency relationship during both voluntarily controlled and spontaneous breathing.				
Hjelland (2007) Randomized Controlled Trial	6 BPM, 5 min/d, 4 weeks, and vagal bio-feedback.	20	20	Gastric emptying, drinking capacity, intragastric volumes, quality of life	Breathing exercises with vagal Bio-feedback increased drinking capacity and improved quality of life in FD patients, but did not improve baseline vagal tone.

Table 1.2 Cont.

Jones (2010) RCT and partially blinding	30 mins, twice daily for 8 weeks	30	0	Laboratory-based blood pressure measurement; blood pressure was measured between 9.00 and 12.00 am with an automatic digital bedside monitor after at least 15 minutes of rest while sitting.	Home-based training with a simple device is well tolerated by patients and produces clinically valuable reductions in blood pressure. Adding an inspiratory load of 20 cmH2O enhanced the decrease in systolic blood pressure.
Logtenberg (2007) Randomized Single Blind Control Trial	10 BPM for 8 weeks using the Respirate device thirty min/day	30		The primary outcome measures were change in office and home BP. The secondary outcome measure was change in QOL.	The effects of Respirate on BP and QOL were not significantly different from those found in the control group. Furthermore, 40% of patients did not reach the target breathing frequency, making this device less

Table 1.2 Cont.

					suitable for clinical practice in patients with DM2.
Mann (2011) Randomized Control Trial	Ninety-six (96) women who have completed their main treatment for breast cancer and who have been experiencing problematic hot flushes and night sweats for over two months	50	46	First randomized controlled trial of relaxation and paced respiration, stress management, cognitive therapy for unhelpful thoughts and beliefs, managing sleep and night sweats and maintaining changes.	First trial of cognitive behavioral therapy for hot flushes and night sweats that measures both self-reported and physiologically indexed symptoms.
Marsland (2007) Case Study	community volunteers age 30-54; 11 BPM, 5 min periods	175		LPS induction of inflammatory markers; blood stimulation	This study provides novel evidence for an association between individual differences

Table 1.2 Cont.

				before and after treatment with LPS	in cardiac PS (vagal) activity, as measured by indicators of HRV assessed during paced respiration, and LPS-stimulated production of pro inflammatory cytokines by peripheral immune cells among relatively healthy midlife adults.
Parati (2008) Randomized Control Trial	Patients with CHF randomized to control or intervention group, 10 week study, 18 min 2x/day; >10 BPM	12	12	Pulmonary stress test; cardiopulmonary stress test; quality of life	This pilot investigation demonstrates that device-guided paced breathing at home is feasible and results in an improvement in clinically relevant parameters for patients with heart failure and systolic dysfunction.
Pearce (1990)	3-12 weeks of treatment and	56	Pts are pre	Non-cardiac chest pain that had	Subjects in the treatment group had a

Table 1.2 Cont.

Prospecti ve Cohort Study Multicaus al Model	follow up; paced breathing 11 sessions of treatment		and post	persisted for more than three months following negative investigation and reassurance	significantly better outcome than the control assessment-only group on measures of chest pain, limitation of daily activity and use of medication
Raupach (2008) Prospecti ve Cohort Study	Subjects were instructed to breathe 15 BPM 1- 4 min, followed by 4 min at 6 bpm (3 s insp,7 s ex)	15	15	Investigate whether there is sympathetic activation in COPD patients in the absence of hypoxia and whether slow breathing has an impact on sympatho-excitation and baro-reflex sensitivity.	Sympatho-vagal imbalance is present in normoxic chronic obstructive pulmonary disease patients. The possibility of modifying these changes by slow breathing may help to better understand and influence this systemic disease.

Table 1.2 Cont.

Ritz (2009)	four 3-min paced breathing trials at 8, 10.5, 13, and 18 BPM	26		Resistance of the airways while breathing in a different pace	A small reduction in resistance was only observed under conditions of variable volume at 18 breaths; there were minimal effects on resistance of the airway passages.
Salkovski (1986) Case Study	9 patients clear from other illnesses, 7 of them on psych medications PCO2 measured	9	9	Diary for recording panic attacks; Training in paced breathing; Total of 9 sessions, 4 during pure respiratory treatment and 5 during exposure.	Respiratory control treatment was associated with significant reductions in panic attack frequency and self-ratings of anxiety. Patients' initial resting pCO2 levels were significantly lower than a group of age- and sex-matched controls,

Table 1.2 Cont.

					and increased to normal levels during the course of treatment.
Shields (2009) Review Paper	Research into heart rate variability (HRV) and respiration over the past 150 years has led to the insight that HRV with deep breathing (HRVdb) is a highly sensitive measure of cardio-vagal or parasympatheti c cardiac function.	RP	RP		The two most widely used methods are the mean heart rate range (MHRR) and the expiratory -to-inspiratory ratio (E:I). The MHRR method is typically measured from a series of successive deep breaths, usually 6 breaths at a rate of 5 or 6 breaths per min.
Sood (2011)	40 physicians	20	20	Primary outcome measures assessed at	A brief training to enhance resilience and decrease stress among

Table 1.2 Cont.

Randomized Controlled Clinical Trial	8 weeks, 5 BPM 5-15 minutes 2x/day			baseline and week 8 included the Connor Davidson Resilience Scale (CDRS), Perceived Stress Scale (PSS), Smith Anxiety Scale (SAS) and Linear Analog Self-Assessment Scale (LASA).	physicians using the SMART program was feasible. Further, the intervention provided statistically significant improvement in resilience, stress, anxiety, and overall quality of life.
Yuen (2010) Review Paper		RP	RP		Slow breathing exercises affected cortical activity and hence seizure thresholds. It is also possible that slow breathing exercises might reduce seizure frequency by reducing anxiety.

Table 1.2 Cont.

Verheyden (2007) Case Study	Two paced-breathing protocols at 6 and 12 BPM were performed in the standing and supine positions before spaceflight, and after 1 and 25 days upon return.	5	0	Sympathetic implications on vagal-cardiac assessments after spaceflight	Results indicate that short-duration spaceflight reduces respiratory modulation of HR and decreases cardiac baro-reflex gain without affecting post-flight arterial blood pressure dynamics. Altered respiratory modulation of human autonomic rhythms does not persist until 25 days upon return to earth.

DISCUSSION AND SUMMARY

This review focused on the effect of SPB on treatment outcomes for various medical and psychological conditions. Overall, there is preliminary evidence supporting the use of SPB to affect heart rate variability (HRV), specifically by increasing it to high frequency variability (hf)HRV. This level of HRV is controlled by the parasympathetic nervous system. There also is evidence that for most acute diseases, such as seizure disorders, depression, inflammation, and acute and chronic stress, measured HRV is of low frequency

(lf) or ultra-low frequency (ulf). Mortality and morbidity are known to be high at these low levels. Thus, attempts to increase hfHRV are being sought as hypothesized methods to improve outcomes in these and other conditions.

Changes in heart rate with respiration have given scientists excellent opportunities to investigate the function of the autonomic nervous system. Respiration is an autonomic function which can be voluntarily controlled. Heart rate variability is calculated from heart rate changes while breathing. Based on the knowledge gleaned from this clinical review paper and knowledge of the basic pathophysiology, we support future investigations for paced breathing as an intervention for patients and healthy subjects.

This is the first review paper to summarize the use of slow paced breathing in a different medical and psychiatric conditions. Our findings suggest that this technique can be added to the armamentarium of behavioral interventions aimed at improving outcomes for hypertension, inflammatory diseases, chronic and acute pain, seizure disorders, panic attacks, anxiety and depression. Additional research is needed to determine the optimal treatment protocol to maximize results.

Of note, all studies we reviewed focusing on SPB in adults with moderate hypertensive led to the conclusion that the device called the Respirate was effective. Also, the concomitant use of music as a relaxation technique was contributory as was a breathing rate of < 10 bpm. In COPD patients, a breathing rate of 6 bpm was more successful in increasing oxygen saturation and enhancing baro-reflex sensitivity. Also, 6 bpm was very successful in decreasing seizure event rates and 5-6 bpm for 15 minutes twice a day was effective in lowering anxiety levels and panic attacks. Finally, given that the function of the

autonomic nervous system among astronauts is impaired up to 25 days after returning from a mission, SPB may have an important role in pre-launch preparations.

In summary, despite limited information to date, SPB has multiple potential benefits for increasing heart rate variability that are supported by known physiological mechanisms. Additional research is needed to ascertain which breathing protocols are most effective, feasible, and acceptable to patients. In addition, standard outcomes measures need to be agreed upon so that comparisons across studies can be made. Finally, in addition to the therapeutic role of SPB, additional research is needed to ascertain its potential role in primary prevention.

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Chapter Two

A PILOT STUDY OF PACED BREATHING:

FOCUS ON METHODOLOGY

ABSTRACT

Objectives

The primary objectives of this study were to determine if slow paced breathing (SPB) could increase and maintain heart rate variability (HRV) and reduce stress in healthy volunteers in a pilot study. The secondary objective was to compare our methodology to that reported by others investigators.

Background

Diminished autonomic nervous system (ANS) function is observed in hypertension, cardiovascular diseases, inflammation, depression, pain, hot flashes, seizure disorders and other acute and chronic diseases. One method to measure ANS is to measure HRV. In cardiovascular disorders (i.e. post myocardial infarction and post coronary bypass graft surgery), in neurovascular disorders (i.e. stroke and cognitive impairment), infectious diseases (i.e. sepsis), and connective tissue disorders, HRV has been shown to be a predictor of increased morbidity and mortality. Evidence suggests that various lifestyle changes can improve HRV. The objectives of this study were to determine if paced breathing could increase and maintain HRV, and simultaneously decrease stress as measured at the beginning, during, and at the end of a pilot study of slow paced breathing.

Methods

A total of 22 volunteers were randomized to the SPB group of 5 bpm or the normal (but paced) group of 14 bpm. Participants were instructed to practice this

breathing rate for 10 mins, twice/day (total of 20 mins). They were evaluated at the study site at enrollment and at 2, 4, 6, 8, 10, 12, 14, 16, and 18 weeks during which they breathed at their assigned rate while wearing a Vivo Metric life-shirt, which automatically records heart and respiratory rate. Participants also completed the Perceived Stress Scale at enrollment and follow-ups.

Preliminary Results

Baseline characteristics of heart rate variability were similar for the treatment and control groups. Controlled paced breathing was sub-optimally applied in the treatment group. Paced breathing did not result in significant increases in HRV in treatment versus control groups. Both groups had improvement in stress levels after sixteen weeks as measured by within-subject change on the Perceived Stress Scale.

Relevance

This study demonstrates the challenges in applying and maintaining a paced breathing protocol. Suggestions for optimizing a protocol include strict monitoring of breathing tracings during each treatment session so that modifications to the protocol can be made in real time. Heart rate variability was obtained among participants who attained a breathing rate of 6 breaths per minute.

INTRODUCTION

Heart rate variability (HRV) is defined as fluctuations in heart rate (HR) from beat-to-beat as measured in milliseconds (ms). The standard deviation of normal-to-normal beats (SDNN) is significantly related to autonomic nervous system function. Measuring heart rate variability (HRV) is a valuable noninvasive method to assess autonomic nervous system (ANS) function.

Since 1987, interest in the use of HRV and slow paced breathing (SPB) to learn about ANS function and the ability of SPB to stabilize a dysfunctional ANS has expanded. Applicable fields include cardiovascular, neuroscience, inflammation, psychiatry, occupational medicine, and space medicine.

Previous investigators experimented with various rates of breathing and duration of paced breathing episodes. For example, many used 6 breaths per minute (bpm), for 10 min/twice a day, for 16 weeks. For example, Angelone reported he found very strong evidence of maximal increase in frequency of HRV (RSA) at about 5-6 bpm. [1] Hirsch and Bishop set up a model to investigate the correlation between different breathing patterns and HRV (Figure 1, with permission). They showed that a respiratory rate of less than or equal to 6 cycles/min can raise and maintain high frequency heart rate variability (hfHRV). [3]

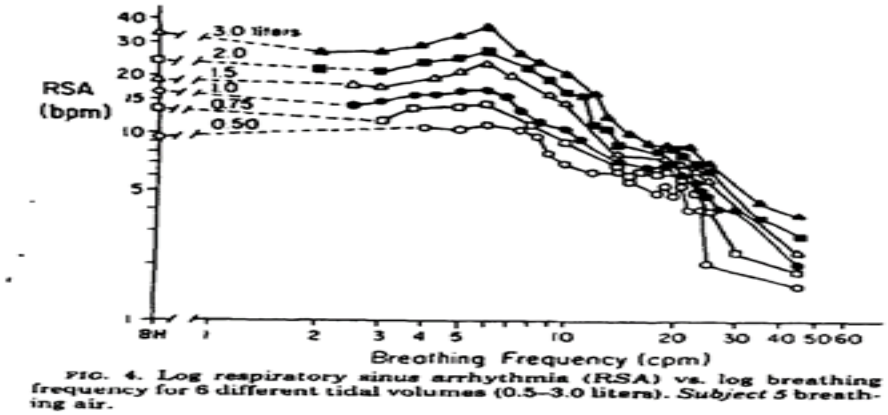

FIG. 4. Log respiratory sinus arrhythmia (RSA) vs. log breathing frequency for 6 different tidal volumes (0.5–3.0 liters). *Subject 5* breathing air.

Figure 2.1

In a study of in healthy volunteers, Mehlsen also demonstrated that maximum changes in heart rate happen at the range of 5.5 to 7 bpm. [4] Del Paso demonstrated that low rates of paced breathing had a strong effect on increasing the frequency of HRV with paced breathing at 6 bpm. [6]

Wilhelm helped improve the calculation of HRV by considering behavioral effects. He was successful in maintaining hf-HRV in healthy volunteers breathing at 9 bpm. [7] Larsen stated that paced breathing presently is the only method to measure autonomic system function. His work opened a new chapter in the concept of HRV concept by demonstrating cardio-respiratory coupling, i.e. respiration and heart rate affect each other in a positive way. In addition, Lehrer demonstrated that training subjects to maximize peak HR differences with visual and auditory feedback can increase homeostatic reflexes, lower blood pressure, and improve lung function. He postulated that this reflects improved homeostatic function within the sympathetic and parasympathetic nervous systems. [8, 9]

Some studies, however, were not successful in raising HRV using similar paced breathing patterns. For example, Hiromitsu and Kobayashi in a study of 55 healthy subjects did not report increases in HRV during slow paced breathing. In this study, only the rhythm and not the tidal volume of breathing was controlled during SPB. Full control of breathing is more efficient for improving the reproducibility of HRV measurements. Thus, future studies are warranted to improve the extent of the reproducibility of HRV measurements by fully controlling breathing. [10] Stark also had similar findings when he compared a spontaneous breathing condition with a frequency-matched paced condition. He found paced breathing provoked a reduction in heart period, but this decrease was not accompanied by changes in HRV; thus he also questioned the validity of autonomic function measures. [11] Ritz addressed the issue of safety during pace breathing and found no significant changes in inspiratory or expiratory resistance while breathing 8, 10.5, 13 and 18 bpm. [12]

There is evidence that short-term power spectral measures of HRV also are powerful predictors of all-cause death, cardiac-related deaths, and arrhythmic deaths. For example, Kleiger calculated that the relative risk of mortality was 5.3 times higher in a group with HRV of less than 50 ms compared to a group with HR variability more than 100 ms. [16] In a follow-up at 31 months, Bigger showed that the same low frequency HRV was an indicator of increased mortality in cardiac patients. [16] In another study, Dekker calculated that a HRV of 2 min was enough to conclude that lf-HRV is a “marker of less favorable health.” In another study, Wolf reported on the relationship of sinus arrhythmia to extended hospital stay in post myocardial infarction patients. This study was one of the first to explore the clinical relevance of sinus

arrhythmia and HRV. [13] Similarly, Dekker attributed increases in mortality post myocardial infarction to autonomic dysfunction [14], and Kleiger et al. reported that reduced HRV was related to increased mortality after myocardial infarction (MI) [19]. Cowen reported that patients who survived cardiac arrest regained high RSA using paced breathing first at 12 then 6 bpm over five weeks. [15] Finally, Wilhelm attempted to learn about the parasympathetic effect by eliminating confounders while measuring HRV in another study with healthy volunteers. His findings suggest that some behavior elements may affect the calculation of RSA, such as anxiety and hyperventilation. He demonstrated that SPB starting at 9 bpm gave higher RSA results that 13.5 and 18 times per minute.

Thus, based on current research, paced breathing appears to be a promising technique to increase HRV. We performed a prospective pilot study to further explore if paced breathing can improve HRV in healthy volunteers.

METHODS

This study was conducted at the Weill Cornell Graduate School of Medical Sciences - Center for Integrative Medicine and an ambulatory clinic in Flushing NY between September 2010 and April 2011. The study was approved by the Institutional Review Board at the Weill Cornell Medical College and all participants provided written informed consent and HIPPA authorization. Participants were eligible if they were 18-60 years old and had no chronic medical conditions. Exclusion criteria were presence of a pacemaker, being pregnant or lactating, taking medications acting on the

SA or AV node, current use of daily psychotropic medications, active substance abuse, and psychiatric illness requiring immediate treatment. Participants were screened by telephone or in-person with the Perceived Stress Scale (described below) and were excluded if they scored ≥ 20. Participants were asked to refrain from taking over the counter medications and to report if they were newly prescribed any medications for any reason.

22 individuals met inclusion criteria and were randomly assigned to the treatment or control group. Participants randomized to the treatment group were asked to breathe 5/bpm (paced) and participants randomized to the control group were asked to breathe 14/bpm (paced). While the latter group was breathing at a normal rate, their breathing was paced for purposes of this study. The Table summarizes demographic and clinical characteristics for the two groups.

For both groups, HRV (plus other physiological measurements, described below) were measured in a standardized fashion using life-shirt Vivo Metric equipment during periodic study visits (outlined below). The life-shirt is a garment (not necessarily a shirt) developed by Vivo Metrics, which monitors vital signs. In addition to heart rate, it also measures respiration by noting chest wall and abdominal expansion while breathing. (It also has the capacity to measure sweat production.) The life-shirt continuously records and transmits the wearer's encrypted physiologic data to a remote command center. Data are also stored on the recorder's compact flash memory card and are updated once a second.

Participants were encouraged to practice paced breathing at home at their assigned rate at least twice a day, for ten minutes using a compact disc to provide a

standardized stimulus to minimize deviation from the assigned rate. They also received instructional material to help facilitate home practice.

HRV measurements and PSS answers were collected at the initial visit, and at week 2, 4, 6, 8, 10, 12, 14, 16 and 18 during study visits while breathing at the assigned rate. Each participant also was given a bi-weekly chart to log daily breathing practice, and any discomfort or other observations they experienced.

The PSS is a valid and reliable scale with total scores ranging from 10-40 with higher scores indicating greater stress. Questions are phrased both as positive and negative statements with response options on a 5-point Likert scale ranging from "never" to "not often." Sample questions are "in the last month, how often have you felt confident in your ability to handle your personal problem" and "in the last month, how often have you felt that things were going your way?" [19, 20, 21]

When examining heartbeats, we split a beat if the recording was approximately twice the expected value, we added 2 heart beats if the recording was approximately half the expected value, and we averaged 2 beats if the recording had ne elongated beat followed by an unusually short beat.

Data were analyzed using Cardio Edit and Cardio Batch software.

Table. Demographic and clinical results. Group 14 indicates controls (breathing at 14 bmp); group 5 indicates the SPB group (breathing at 5 bpm).

Table 2.1

GROUP - ID	AGE	M/F	MARRIED S/D/W	CHOL PRE	CHOL POST	HR PRE	HR POST	HRV PRE	HRV POST	PSSQ PRE	PSSQ POST
14-11	54	F	M	200	250	53	59	0	0	23	13
14-10	55	M	M	140		66	62	4		17	11
14-20	34	F	S	262	166	75	72	6	6	19	6
14-06	38	F	M							14	6
14-13	42	F	M	201	233					19	
14-09	50	F	S			67	87	6	7	24	5
14-08	55	F	M	104		73	74	6	2	24	16
14-07	58	M	M			69	66	5	6	16	2
14-21	34	M	S								
14-02	27	M	S							10	
14-17	57	M	M	109		50	66	3	4	20	6
5-03	55	F	M	188	175	67	68	4	4	17	6
5-04	64	M	M		185	87	86	7	5	16	6
5-05	56	F	D			70		6		18	11
5-12	50	M	S			54	70	5	6	19	1
5-14	42	F	M	177							
5-15	22	M	S		102						

Table 2.1 Cont.

5-18	35	F	S			67	69	7	6	27	5
5-01	39	M	M								
5-22	25	F	S	150	144	89	85	6	6	20	19
5-19	37	F	S			88	71	5	5	24	10
5-16	54	F	M	297	257	79	82			19	0

PRELIMINARY FINDINGS

In total, 35 individuals volunteered to participate; few were screened by telephone and most presented in person for consideration; 22 met inclusion criteria and were randomly assigned. Six participants did not complete the study. There were no significant demographic differences between those who discontinued the study and those who completed the study.

Assigned breathing was to practice at home for 10 minutes/day, twice/day (i.e. 20 minutes total). Compliance of 100% was considered 2520 minutes over the course of the 18-week treatment. There was a broad range of reported compliance with the recommended treatment program: 10 participants claimed they fulfilled 90% or more of the required practice, 8 participants fulfilled between 50% to 89% of the required practice, and 4 participants fulfilled between 16% and 49% of the required practice. The mean practice time was 72%. This translates to an average of approximately 13 min/day.

Besides the standard deviation of normal-to-normal beats (SDNN), two other measures of HRV were considered: the SDANN (standard deviation of the average of NN intervals) and the RMSSD (square root of the mean squared differences of successive (NN intervals). A mixed analysis of variance and 2 one-way analyses of

variance were carried out to examine SDANN and RMSSD. The within-group subject factor was time; the between-group subject factor was treatment. A p value < .05 was regarded as significant. [17] Results are depicted in the figures.

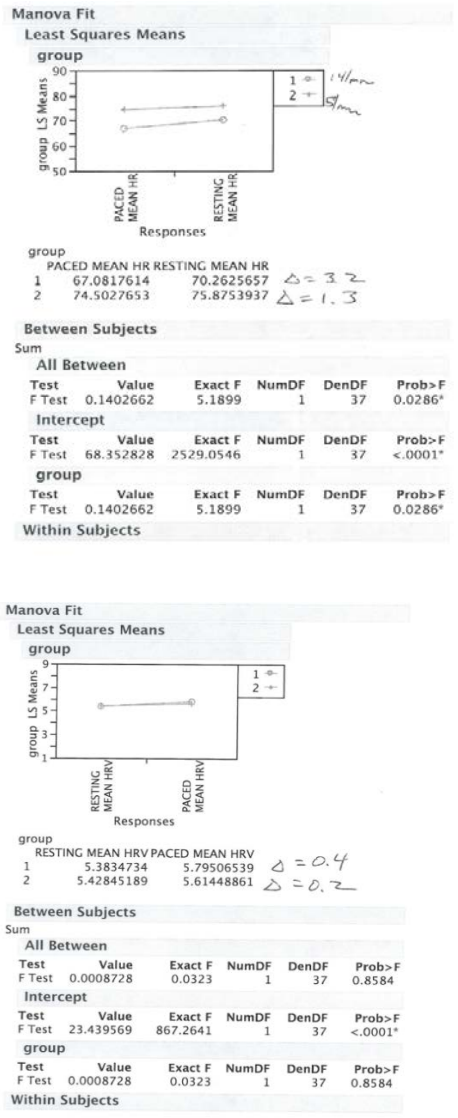

Figure 2.2

There was a significant time by treatment interaction, such that the treatment group and the control group had a minimal improvement over time. Both groups had a

small insignificant increase of HR between week 1 and week 18, with a slight decrease in HR in the slower paced breathing group. HRV did not change much or vary between subjects.

With respect to stress, the PSS scores decreased in both group (figures).

Present Data: Perceived stress scale questionnaire

5 Sreaths per min

	Visit 1	visit 2	visit 3	visit 4	visit 5	visit 6	visit 7	visit 8	Diff Week 1-8
SS-1	---	---	---	---	---	---	---	---	
SS-3		17	18	13	11	9	9	9	11	6
SS-4		16	16	14	7	7	4	11	15	1
SS-5		18	20---		16		18	19		-1
SS-12		19	17	15	15	13	13	12	14	5
SS-14		22---	---	---	---	---	---	---		
SS-15		24---	---	---	---	---	--	---		
SS-16		19---	---		12	15	16	16	19	0
SS-18		27	24	22---	---	---				5
SS-19		24	18	17---	---		14			10
SS-22		20	19	19						

14 Breaths per min

S14-2		10---	---	---	---	---	---	---	
S14-6		14	6---	---	---	---	---	---	
S14-7		16		14	18---	---		14	14	2
S14-8		24---		23	21---	---		12	8	16
S14-9		24	20	20	20	20---		20	19	5
S14-10		17	5	5	6	4	11	4	6	11
S14-11		23	14	13	12	15	10	11	10	13
S14-13		19---	---	---	---	---	---	---		
S14-17		20---	---		11	14	13	15	14	6
S14-20		19		12---	---		9		13	6
S14-21		18---		18			18			

Figure 2.3

Thus, the effects of paced breathing on the reproducibility of HRV measurements were not significant and were not consistent. A possible reason for this outcome was the inability of subjects to completely control their respiration during periodic study measurements. However, it is notable that among participants who did breathe 5 bpm there was an increase in HRV. No adverse events occurred in either group.

This study has several limitations. First, we did not have a placebo control. However, we did include a control group, which is an improvement over prior

published studies. It is difficult to hypothesize how a placebo could affect HRV, but we cannot rule these effects out in the absence of a placebo. Second, our sample was ethnically and socioeconomically homogenous; therefore, the results may not be directly applicable to other populations. Third, although we provided a several week follow-up, we did not measure clinical outcomes. Finally, we did not closely observe participants during bi-weekly office slow paced breathing sessions. Instead, we reviewed recordings at the end of the study. Reviews at each visit would have offered the opportunity to optimize the methodology in real time.

FUTURE RESEARCH

Future studies are warranted to improve the reproducibility of HRV measurements by fully controlling breathing rate. During this pilot study and based on our review of similar studies, we learned more about the technical and practical details involved in this type of quantitative research. In particular, close observation of participants while breathing at the assigned rate will ensure the desired measurements. Most of the prior paced breathing studies point to the possibility that this intervention can be a powerful tool in the treatment of many chronic diseases that currently require medications with serious side effects. Even if SPB succeeds in decreasing the dose of medications, it has the potential to offer clinical benefits. This is particularly promising since we know SPB is a harmless intervention.

Our results support continued research in this area with the goal to establish a reproducible methodology to administer and measure the effects of SPB. Given it is well-known that many chronic diseases (i.e. cardiovascular, depression, seizure

disorder, space medicine) may benefit from SPM, it behooves researchers to optimize the methodology of SPB to increase the rate of HRV. Currently the recommended rate is less than 6 bpm. However, some studies have shown that "a personal best bpm rate" should be determine to raise HRV. In addition, ascertaining what is the best time of day and how many times/day of practice and whether an accompanying relaxation device should be included are additional questions. Thus, more research is needed with cohort and RCT studies to establish which methodology is best as a SPB intervention.

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