Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Dr. J. Andrew Taylor, Ph.D.
Project Title:	Effect of Slow Breathing and Yogic-Derived Breathing on Respiration and Cardiovascular Variability in Spinal Cord Injury Patients
Version Date:	5/19/23
Version Name/Number:	Version 4

1. Background and Significance

Interest in mind-body medicine, which focuses on interventions such as meditation, yoga & tai chi, biofeedback, and cognitive behavioral therapy to promote health, has grown significantly in recent years with specific focus on the potential therapeutic effects of slow-breathing (<6 breaths /min *or* 0.1Hz), and traditional yogic (*pranayama)* breathing practices. Research shows that reduced respiratory rates may impact both blood pressure regulation (*1,2*) and cardiac autonomic tone (*2-4*). Moreover, cardiovascular variabilities (Heart Rate Variability (HRV) and Blood Pressure Variability (BPV)) are markedly impacted by breathing pattern and have even been exploited as indices of autonomic circulatory control (5). However, various pathophysiological processes can alter the relationships between breathing rate and depth and cardiovascular variabilities. Of note, Spinal Cord Injury (SCI) results in a variable pathophysiologic profile in which deficits vary with level and degree of injury but can markedly impact both autonomic and respiratory control (*6*). Therefore, the SCI population may be especially needful of therapeutic slow-breathing interventions to mitigate the impact of altered autonomic control of the heart and blood vessels and to improve the efficiency of respiration. Indeed, individuals with SCI > T6 experience persistent hypotension and bradycardia daily (20). SCI has repeatedly been linked to increased risk for cardiovascular disease (CVD) that may be related to increased BPV and decreased HRV (*21, 22*). Decreased HRV is associated with cardiac diseases and is prognostic for those with known CVD (*23, 24*). Moreover, HRV decreases with age, is lower in those with a sedentary lifestyle, and is inversely related to inflammatory markers in both healthy individuals and those with CVD (*25*). Specific to SCI, HRV is decreased within the first 24 months after injury, suggesting that this decline is mainly to a direct impact of autonomic injury itself rather than lifestyle effects of SCI (*26*).

It is known that slow breathing can result in a resonance phenomenon in heart rate and blood pressure. (*27, 28*) This results from low frequency respiratory sinus arrhythmia (RSA), the R-R interval shortening during inspiration and lengthening during expiration. Several studies have examined the effects of traditional slow breathing techniques on heart rate variability (*10-13*). One systematic review investigating slow breathing in healthy subjects showed that slow breathing rates generally results in greater HRV and greater synchronous BPV. Data from studies comparing three separate meditation techniques found that all practices create prominent low frequency oscillations coupled to the slow respiratory rate (*13*). In addition, previous studies investigating hemodynamic changes during yogic derived, slow breathing at 0.10 Hz have found decreased blood pressure during the slow breathing period in healthy subjects, subjects with hypertension, and subjects with congestive heart failure (*1,2,17-19*). Thus, while these findings suggest that slow breathing may induce acute changes in hemodynamics, there is limited insight to

the full effects that reduced respiratory rates may have on control of cardiovascular function, especially in individuals with a spinal cord injury.

c) Study Rationale

The relationship between respiratory patterns and cardiovascular variability in healthy persons has been previously studied. However, the impact of SCI on the interrelationships between the respiratory and cardiovascular systems remains relatively unstudied. The loss of autonomic control in SCI may mean that slow breathing has profound effects on cardiovascular variabilities. Hence, those with SCI may represent a population that could benefit from the potential physiologic effects of numerous yogic-based breathing patterns that can be applied anywhere any time. Hence, it is important to determine if slower breathing patterns can shift the cardiovascular control pattern towards important healthful effects. This physiological study will compare the effects of uncontrolled breathing and traditional yogic slow-breathing practices on cardiovascular variabilities in SCI patients.

2. Specific Aims and Objectives

Objective 1: To determine if those with spinal cord injury can successfully perform slow yogic breathing patterns and gain respiratory fitness with daily practice.

> *Hypothesis 1: Two weeks of at-home practice will result in better performance of respiratory control (maintenance of frequency and volume over time) in those who practice more, however, accurate performance of yogic breathing will be lesser in those with high thoracic injuries (T3-T6).*

Objective 2: To assess the respiratory and hemodynamic changes that accompany slow yogic breathing in spinal cord injury patients.

> *Hypothesis 2: Respiratory rate will decrease, blood pressure will decrease, tidal volume will increase, and minute ventilation will remain unchanged during yogic slow breathing compared to spontaneous breathing.*

Objective 3: To discern the changes in the relationship between respiration, heart rate and blood pressure variabilities with yogic breathing.

> *Hypothesis 3: Slow yogic breathing will shift the relationship between heart rate and blood pressure variabilities toward more synchronized heart rate and systemic blood pressure fluctuations.*

3. General Description of Study Design

This study will be a small (N= 20) prospective cohort study with a one-time unblinded intervention of 4 differing breathing techniques compared to paced breathing. Participants will receive a log for at-home practice and instruction lasting 45 minutes around D1 and D7 with the option to have on coaching session via MGB's Zoom application. On D14 the participant will be asked to sequentially execute the randomized breathing techniques. The lab visit will last approximately 1.5 hours, during which beat-by-beat

cardiovascular variables and breath-by-breath respiratory variables will be recorded while slow breathing. The total in-person time commitment is about 4 hours **(Figure 2).**

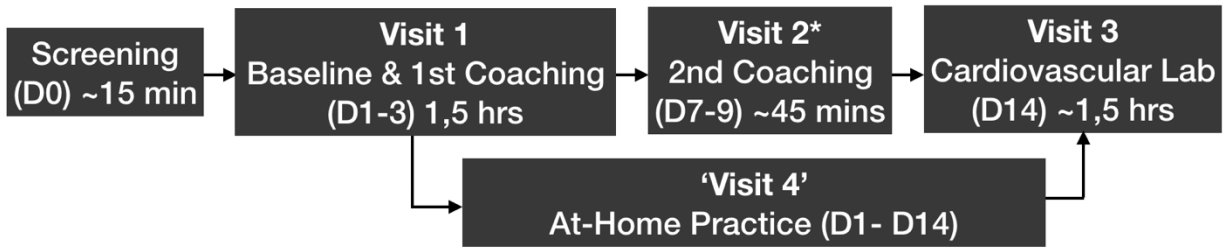

Figure 2: *Study schema with a timeline of participant contact hours and days. There will be two moments of coached practice during a period of two weeks with at-home practice encouraged throughout the period. At the conclusion of the two weeks the breathing practices will be repeated in the laboratory while obtaining respiratory and cardiovascular measurements. *It is possible for the participants to schedule the second visit via MGB's Zoom application.*

4. Subject Selection

a) Inclusion/Exclusion Criteria

We will complete studies on 20 individuals — men and women aged 18 to 60 years — with a spinal cord injury. A detailed medical history will be taken, and subjects will be selected based on the following:

Inclusion criteria:

1)	History of Spinal Cord Injury
2)	Age: 18-60 years old
3)	Wheelchair user
4)	Medically stable & able to follow directions
5)	Body mass index (18.5 - 35 kg/m2)

Exclusion criteria:

1) BP >140/90 mmHg
2) Current use of tobacco or cardioactive medications (except medication to support blood pressure)
3) Significant arrhythmia
4) Coronary artery disease
5) Diabetes
6) Renal Disease
7) Cancer
8) Epilepsy or other neurological diseases
9) Non-English Speakers

Source of subjects and recruitment methods

All volunteers will be considered regardless of race, ethnicity, or national origin. We plan to study both men and women. We will recruit individuals with a spinal cord injury from the Exercise for Persons with Disabilities (ExPD) program at Spaulding Hospital Cambridge.

Research Assistants will identify eligible individuals during scheduled ExPD workout sessions and from population of past ExPD participants. Where possible eligible individuals will be given a flyer. If the ExPD population is exhausted before reaching our desired number of participants, recruitment can be extended to the general SCI population of Boston via the use of flyers. If eligible and interested participants will be asked to complete a pre-screening phone survey.

5. Subject Enrollment

The principal or co-investigators will obtain volunteer consent in accordance with guidelines established by the Institutional Review Board during the first study visit to the Cardiovascular Laboratory. Participants are encouraged to ask questions and are reminded that participation is strictly voluntary and will not affect their current or future care at Spaulding Rehabilitation Hospital or any of its affiliates. Each subject will be told that he/she will be free to discontinue participation in the experiment at any time and that the investigators reserve the right to discontinue the research protocol at any time. A copy of the signed informed consent form will be given to the subject. All study subjects will participate in the same study protocol, differing only by the randomization of the order of the yogic breathing techniques.

6. Study Procedures

a) Study Components

YOGIC BREATHING INTERVENTION

The subject will receive one-on-one coaching on breathing techniques with the co-investigator two times. The subject may opt to complete the second coaching session via MGB's Zoom application.

The breathing techniques will be varied in:

1. breath frequency (between 0.25 and 0.08 Hz)
2. Inspiratory – Expiratory ratio (I:E) or 'Duty Cycle'
3. with and without ujjayi (yogic throat constriction)
4. with and without inspiratory/expiratory breath holding

AT-HOME PRACTICE

At the end of the first visit the subject will be given a log to record their at-home practice of the breathing techniques they were coached on. Participants will also receive an information pamphlet and audio track with information about the exercises covered during the first coaching session.

b) Study Visits

Pre-Screening

All study subjects from the ExPD program at Spaulding Hospital will be preliminarily screened over the telephone to ensure that they meet preliminary eligibility requirements. Eligible members will be approached after their workouts by the co-investigator to ask permission to call for screening.

Screening

Subjects who meet preliminary eligibility criteria and are interested in participating will be called by the co-investigator to screen inclusion and exclusion criteria and to discuss additional information about the study. Participants will be sent the informed consent letter at least one week before the first visit. Informed consent will be obtained at Spaulding Rehabilitation Hospital, Cambridge.

Visit 1 — History, Baseline, 1st Coaching

During participants first visit the study procedures will be reviewed in detail with study staff, the subject will give a detailed health history and their written informed consent to the principal or co-investigator. The participant will then proceed to complete a baseline pulmonary function test (PFT) lasting about 30 minutes. Leaving about 45 minutes to cover relevant breathing techniques and exercises.

Visit 2 — 2nd Coaching

The second coaching visit can optionally be completed via MGB's Zoom application and will be shorter and more focused on questions, concerns, or struggles of the participant.

Visit 3 — Breathing & Measurement

Two weeks after inclusion, the subjects will return to the cardiovascular laboratory for assessments. All subjects will be instructed to abstain from vigorous exercise for 1 day prior to each study to avoid autonomic and neuroendocrine effects of exercise. In addition, subjects will refrain from caffeine and alcohol for the previous 24 hours and be studied at least 2 hours after a meal. All breathing patterns and techniques will be practiced with the participant before the day of measurement and the participant will also be coached by a pre-recorded audio track during measurement.

Measurements

1) *Pulmonary function test*

All subjects will perform standard spirometry for spinal cord injury, as describe in (44). The same technician will test all subjects. Subjects will be seated with belts or pant waists loosened and with a nose clip. The maneuver will be demonstrated, and instructions will be given to inhale completely and "blast" the air out. The subject will be encouraged to exhale maximally and sustain the effort at least 6 sec or longer, if possible, depending on the ability and willingness of the subject to continue. The volume-time curve will be recorded on a kymograph, and the flow-volume loop will be electronically displayed for review. An acceptable effort will be a minimum exhalation time of 6 sec with a rapid start and a well-defined early peak in flow that is smooth and continuous. Three acceptable efforts will be obtained.

2) *CV Lab Measurement*

Throughout the protocol, subjects will lie 30° supine and will be instrumented with a 5-lead EKG, pulse oximeter, finapress with sphygmomanometer, doppler, chest and abdominal belts, a microphone and a face mask with a two-way respiratory valve; for measurements of QRS-complex, SpO2,

beat-by-beat arterial pressure, brachial blood flow, respiratory excursions, ujjayi sound mixed expired CO2, ventilation and end-tidal CO2.
After instrumentation and calibration, the subject will undergo a period acclimation with a resting breathing pattern for ~7 minutes. We will then record the breathing techniques for ~7 minutes each. Other than the acclimation period with resting breathing frequency the order of the other 5 breathing patterns will be randomized. Upon completion subjects will be asked to turn-in their two-week breathing logs. Participants will proceed to perform an exit-PFT and will then be finished with their contribution to the study.

Note: Subjects that completed Lab Visit 3 before 5/19/23 will be invited back to repeat Lab Visit 3 with the addition of dead space ventilation measurements that has been added to this protocol.

7. Risks and Discomforts

The proposed study will utilize non-invasive cardiovascular and respiratory monitoring techniques with minimal risks. The attachment and removal of ECG electrodes and inflation of the blood pressure cuff may cause mild discomfort. Slow breathing may cause hypercapnia and lightheadedness, which quickly resolves when normal breathing resumes.

8. Benefits

a. Benefits to Participating Individuals

There are no direct benefits other than increased knowledge of different traditional breathing practices and their mental and physical effects.

Financial Compensation

Participants in this study will be compensated financially up to $100USD relative to their time. As completion of all study visits is necessary for analysis participants will be paid $20 for each study visit they complete. Payments will be made via check and participants SSN will be collected.

Note: Subjects that have already completed the protocol and repeat the LabVisit 3 protocol will be paid $20 for this additional visit.

b. Benefits to Society

This research may help physicians and scientists to better understand how slow breathing patterns influence the cardiovascular system in persons with SCI, potentially informing future interventional studies in this population.

9. Statistical Analysis

Specific data variables being collected: We will collect data on RR interval, heart rate, blood oxygenation, beat-to-beat blood pressure, brachial blood flow, breathing frequency/depth, ventilation volumes and end-tidal carbon dioxide levels.

b) Data analysis

Data analysis will begin with summary of important variables**.** Continuous data will be summarized using means and standard deviations, and categorical data will be summarized using frequencies and proportions. Spectral analysis will be used when appropriate. Mean values for these variables will be compared within subjects using t-tests or Wilcoxon Rank Sum tests. Effects of the important covariates including age, BMI, time since injury, and level of injury will be adjusted for via regression analysis. Co-variates will be compared using a t-test or Wilcoxon Rank Sum test in case of continuous variables and they will be compared using chi-squared test and Fisher's Exact test. Significant co-variates will be used in the above regression analysis.

10.Monitoring and Quality Assurance

As these studies represent physiologic investigation and not clinical trials, no formal quality assurance programs will be implemented but will be overseen by the principal and co-investigators.

Safety

All volunteers will be thoroughly screened prior to study. Studies are conducted in a well-supervised hospital facility and subjects are under constant observation by skilled professionals. Appropriately trained laboratory personnel are present during the procedures and continuous cardiovascular monitoring is performed. Procedures are stopped if the volunteer exhibits potentially serious side effects. In the event of adverse reactions or emergency, resuscitation equipment and medical care are immediately available at Spaulding Rehabilitation Hospital. All volunteers are provided a contact number should there be any complications following study.

Adverse Events

Any adverse events will be promptly reported to the Human Research Committee for review according to HRC guidelines. Serious adverse events either expected or unexpected will be reported immediately (within 24 hours of event) by telephone, fax or email followed by a full written report using the PHRC Adverse Event Form within 10 working days/14 calendar days. Mild to moderate unexpected or expected adverse events will be reported in writing using the PHRC Adverse Event Form within 20 working days/30 calendar days.

Confidentiality

Maintaining study participants privacy and keeping personal identifiers confidential is important to the study staff. All research activity including subject screening and data collection will be performed and stored at Spaulding Cambridge. Subject names, contact information, health history, and other information that can be traced back to the subject will be kept separately from data collected for the study. Personal information will be kept in a locked office or on a password-protected computer and away from data. Collected data will have the subject's identification code and some computer software used to collect data will have the date and time marked on the file. Protocol sheets used during data collection will only have the subject's ID. Spaulding Hospital certifies key personnel have completed education on the use of human subjects in compliance with NIH regulations.

11. Privacy and Confidentiality

- ☑ Study procedures will be conducted in a private setting
- ☑ Only data and/or specimens necessary for the conduct of the study will be collected
- ☑ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☑ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☑ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☑ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☑ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☑ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☑ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☐ The DMC/DSMB is independent from the study team and study sponsor.

☐ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☐ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☐ Describe number and types of (i.e., qualifications of) members:
Click or tap here to enter text.

☐ Describe planned frequency of meetings:
Click or tap here to enter text.

☐ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☐ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.