Improving Ventilatory Capacity in Those with Chronic High Level SCI

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I. BACKGROUND AND SIGNIFICANCE

Chemoreceptive regulatory feedback is crucial for precise ventilatory control, especially during exercise [1]. However, individuals with high-level SCI have a reduced chemoreceptive drive to breathe. Studies have shown lesser increases in minute ventilation and mouth pressure during hypercapnia in those with tetraplegia [2,3]. Peripheral factors rather than central factors appear to cause the reduction of the ventilatory response to hypercapnia [2]. This reduced ventilatory drive may have functional impact on exercise ventilation in patients with high level SCI [3] and enhancing ventilatory drive may improve exercise ventilation in high-level SCI.

Currently, there are no treatments to overcome these functional deficits that affect daily activity and exercise-based rehabilitation recovery. However, previous work in an animal model of SCI has found that that a serotonin agonist markedly increases respiratory responses to carbon dioxide. Treatment with a serotonin 5HT1A agonist effectively improved the ventilatory drive after both acute [4] and chronic [5] spinal cord injuries in rats. One potential mechanism is increased excitability of the ventral motoneurons that have survived the spinal cord injury. 5-HT1A receptors do exist on these neurons [6], and when activated, amplify the excitatory output [7]. Another mechanism resides at the intercostal and abdominal muscle afferents which influence supraspinal respiratory group neurons in the brainstem and motor output to the muscles of breathing [8,9]. Hence, serotonin agonists may act on neural pathways in the spinal cord responsible for transferring afferent information from intercostal muscles to supraspinal centers. Lastly, 5-HT1A receptors may also be involved in functional plasticity of neural respiratory pathways, in particular ipsilateral phrenic nerve activity [10] [11]. Up regulation of 5-HT1A receptors due to denervation supersensitivity could result in postsynaptic hyperresponsivity due to loss of descending input.

BuSpar/Buspirone is a serotonin 5HT1A agonist and used as an anxiolytic in humans. It does not cause sedation, has minimal effects on psychomotor performance or cognition, and has low threshold for abuse potential or dependence liability [12]. Prior studies have found Buspirone to be well tolerated [13,14]. It has been used safely in spinal cord injury, but not for respiratory purposes [15]. (Though there is one clinical trial in process: Role of Enhancing Serotonin Receptors Activity for Sleep Apnea Treatment in Patients With SCI.) However, Buspirone up to 60 mg daily has been used to treat disturbed respiratory rhythms in multiple sclerosis [16], brain cancer [17], and brainstem infarction [18]. Interestingly, in patients with COPD, a 14-day oral administration of buspirone (20 mg) found improved anxiety and depression as well as increased exercise tolerance with lesser sensations of dyspnea [19]. Hence, buspirone may offer a treatment to improve hypercapnic ventilatory drive. Given that oral administration of 30 mg results in peak plasma levels at one hour and that the average elimination half-life is about 2 to 3 hours, buspirone is an attractive and safe approach to exploring the ability to both acutely and chronically improve respiratory responses to exercise and/or hypercapnia exposure in those with high level spinal cord injury that limits breathing capacity.

HYPOTHESIS

We hypothesize that oral buspirone increases ventilatory drive (chemosensitivity) in response to progressive hypercapnia and in response to exercise in individuals with SCI,.

II. SPECIFIC AIMS

1) To determine if two weeks of administration of the serotonin agonist buspirone augments the ventilatory responses to hypercapnia in individuals with a spinal cord injury at T4 and above
2) To determine if two weeks of administration of the serotonin agonist buspirone augments the ventilatory responses to exercise in individuals with a spinal cord injury at T4 and above

III. SUBJECT SELECTION

Inclusion criteria
Individuals with chronic high-level SCI
Aged 18 to 50 years
Medically stable with SCI at neurological level ≥T4 with American Spinal Injury Association grade A or B or C.
Subjects must be able to perform arm crank exercise

Exclusion criteria

Cardiomyopathy; significant arrythmias; blood pressure >140/90 mmHg; coronary disease; diabetes; other neurological disease; renal disease; cancer; recent weight change ≥15 pounds; regular use of tobacco; intrathecal baclofen pump; grade 2 or greater pressure ulcers at erlevant contact site; peripheral nerve compressions or rotator cuff tears that limit the ability to exercise; history of bleeding disorder; current use of cardioactive, tricyclic antidepressants (amitriptyline, timipramine), other sedating agents; suicidal ideation; pregnant and/or breastfeeding women.

In addition, subjects must have no known hypersensitivity to buspirone hydrochloride and must not be taking a monoamine oxidase inhibitor. Subjects taking midodrine to treat hypotension will be allowed to participate in this study.

IV. SUBJECT ENROLLMENT

The Principal Investigator who is a Doctoral level physiologist with over 20 years of experience in performing these types of physiologic studies in humans will obtain consent during the first visit to the laboratory. Participants will be sent the consent form at least a week in advance so they have ample time to read and ask questions. 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.

V. STUDY PROCEDURES

Study design
A double-blind placebo controlled cross-over study in 20 individuals with high-level SCI will be performed to compare ventilatory responses after administration of placebo or 30 mg buspar. Ventilatory responses to a CO_2 rebreathing test and a bout of moderate to high intensity exercise will be assessed. In addition, an evaluation of sleep quality will be performed prior to, and following each drug phase.

Specifically, after two weeks of daily administration of buspar (dosing: starting at 15 mg 1 time a day for 2 days and increasing to 30 mg (15 mg in the morning and 15 mg at night) or placebo.

Subjects will also taper off the full dose of buspar by taking Buspar (15mg) 1 time a day for 2 days at the end of the two weeks. Ventilatory responses to a CO_2 rebreathing test, a bout of moderate to high intensity exercise, and sleep will be assessed again at the end of each two weeks phase.

Detailed procedures

Once recruited for the study, the volunteers will visit the laboratory for a health screening session to further determine eligibility, obtaining informed consent, detailed health history, and set-up for an at home sleep over night evaluation. The following da a three-hour session (Visit 1) includes resting pulmonary function test, resting heart rate and blood pressure, height and weight, as well as a baseline CO_2 rebreathing test and a maximal incremental arm crank exercise test to determine maximal workload and aerobic capacity.

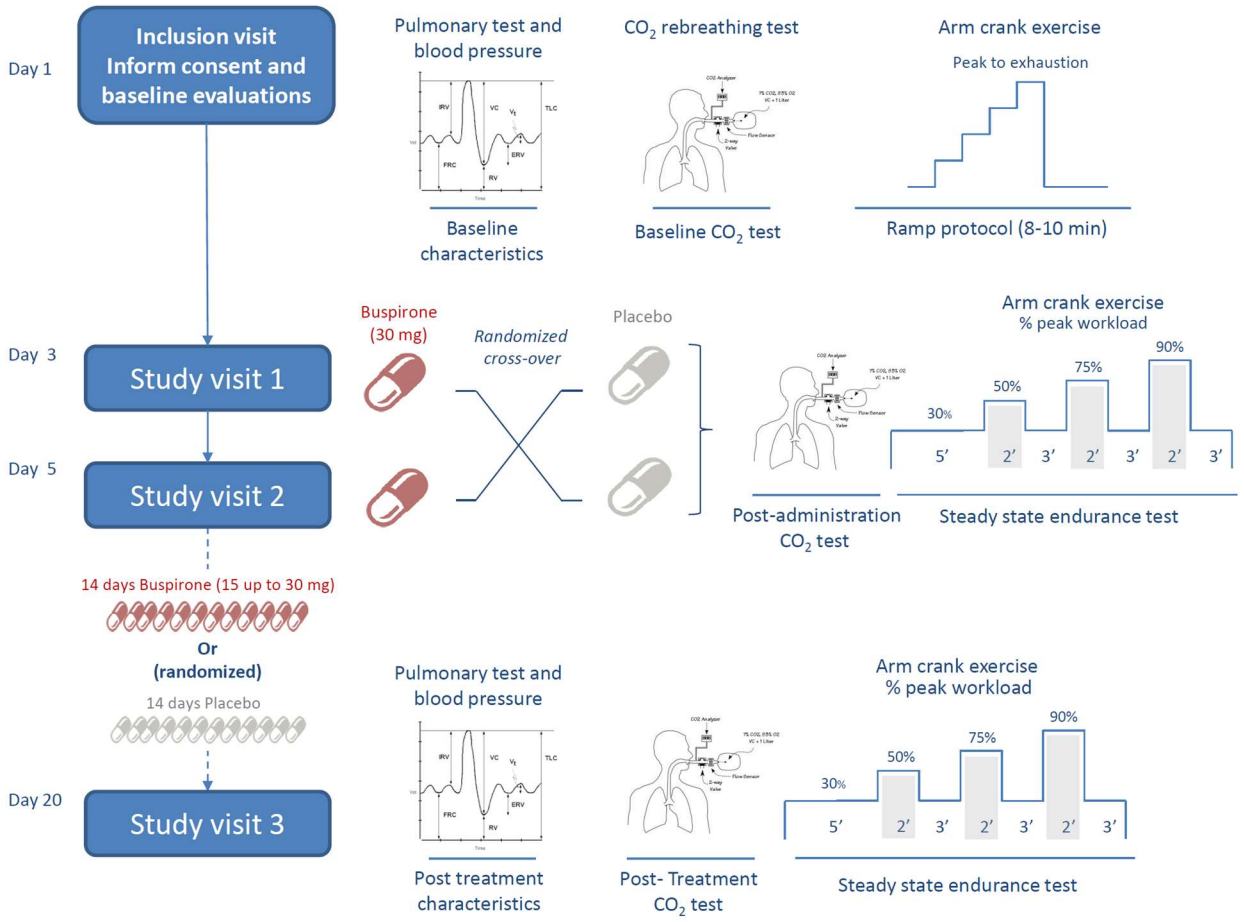
After volunteers complete the screening process, they will return for two visits to investigate the effect of buspirone or placebo on ventilatory responses (cross-over design, please see Figure 1).

These two study visits will take approximately 3 hours to complete and will be 14 days apart.

The sessions will be similar to the initial sessions but with a resting pulmonary function test and blood pressure preceding the CO_2 rebreathing and arm-crank tests. Following each of these segments an over night sleep assesment will also be performed.

The study sessions will take place at Spaulding Hospital Cambridge under the direct supervision of Cardiovascular Research Laboratory with a responsible physician on site, aware that the exercise session is taking place and readily available via pager or telephone if complications arise. This medical coverage falls into the “Physician Coverage” category as per the approved Spaulding Rehabilitation Hospital Policy and Procedure “General Safety Precautions and Procedures for the Conduct of Human Research.”

Figure 1: Study schema



Pre-screening procedures
All study subjects will be preliminarily screened over the telephone to ensure that they meet preliminary eligibility requirements. Subjects who meet preliminary eligibility criteria and are interested in participating will be sent the informed consent letter at least one week before the first visit.

Screening & at home sleep evaluation
Informed consent will be obtained at Spaulding Rehabilitation Hospital, Cambridge. Subjects will be screened to ensure they meet preliminary eligibility criteria. All subjects will undergo a clinical interview to determine the presence of any medical disorders.

The following study assessments will be completed:
- Sleep Evaluation

Visit 1: Baseline Evaluation Visit

The following study assessments will be completed:
- Height and Weight

- Resting blood pressure and heart rate
- Pulmonary function test
- CO_2 rebreathing test
- Maximal arm-crank exercise test

Visit 2 & 3: Laboratory Testing Visit
The second and third laboratory visits will be separated by fourteen days. All subjects will be instructed to abstain from vigorous exercise for 2 days prior to avoid muscle fatigue as well as autonomic and neuroendocrine effects of exercise, and instructed to refrain from caffeine and alcohol for the previous 24 hrs.

Distribution of Study Medication at the end of visit 1 and 2
After initial screening testing measures are complete, study medication (Buspar/Placebo) will be distributed to all volunteers by a study physician. Participants will be instructed as to how to take the medication dose. The initial dose of buspirone will be 15 mg daily (for two days) and will be increased by 15 mg to a dose of 30mg/day (15 mg in the morning and 15 mg iat night) with a 2-day 15 mg daily taper at the end of the two weeks.

Follow-up between visit ~~3~~ 1-2 and 4 2-3: Adverse Event Monitoring (Telephone) day
Study staff will check in with study participants over the telephone at one week intervals to monitor any side effects or adverse events of the medication. If subjects are experiencing intolerable side effects, they will be taken off of the medication while completing the remaining study procedures. Participants will be informed that they may call study staff directly to report any side effects or adverse events at any time during the study.

Parameters to be measured
- Resting blood pressure and heart rate
- Pulmonary function test
- CO_2 rebreathing test
- Arm-crank Maximal exercise test
- Sleep Evaluation

Measurements

1) *Pulmonary function test and resting blood pressure*
Standard measurement of resting brachial arterial blood pressure and heart rate (electrocardiogram) will be performed.

All subjects will performed standard spirometry for spinal cord injury, as previously described [20]. 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) *CO_2 rebreathing test*

We will use the Duffin's Modifiication of the Read-rebreathing method from a bag containing ~~93~~ 95% O_2 [to suppress peripheral chemoreceptor activity] and 5% CO_2, as previously described in the literature [21]. Subjects will be on a mouthpiece and wearing nose clips. Subjects will be coached to hyperventilate in room air for ~5 min. Then, they will be asked to exhale below functional residual capacity and then switched to the rebreathing bag for rebreathing ~~-~~95% O_2 and 5% CO_2. The PCO_2 measured at the mouth will approximate the PCO_2 at the level of the chemoreceptors. Rebreathing will continue until end-tidal PCO_2 ($PETCO_2$) reaches 55 mmHg (or 7.5% at a barometric pressure of 755 mmHg) and will be termintaed if the subject feels that he or she cannot continue. Minute ventilation, $PETCO_2$, tidal volume, inspiratory time, expiratory time and respiratory frequency will be measured.

3) Maximal incremental arm crank exercise

Subjects will perform arms crank exercise with increasing increasing power output every 1 to 2 minutes until volitional exhaustion. Online computer-assisted open circuit spirometry will be used to determine O_2 consumption, CO_2 production, and respiratory exchange ratio. Expired O_2 and CO_2 gas fractions will be measured with a paramagnetic O_2 and infrared CO_2 analyzers. Ventilation will be measured via a Hans Rudolph 3813 pneumotachograph. To ensure attainment of maximal exercise capacity, at least 3 of the following criteria will be met: 1) O_2 consumption plateaus despite increasing workload, 2) respiratory exchange ratio equals or exceeds 1.10 at end exercise, 3) peak lactate greater than 7.5 mmol/L, 4) perceived exertion is rated at least 17 on the Borg scale of 6-20. Immediately after exercise, subjects will have a finger tip pricked with a safety lancet to obtain a drop of blood to measure peak lactate levels.

4) *Sleep Evaluation*

An in-home Single night Polysomnography (PSG) using the type 2 level NOX A1 (NoxMedical) device will provide quantitative assessments of levels of overnight hypoxemia, apneas and hypopneas, sleep stage distributions, and will provide quantitative data on snoring. The recording montage will include five, self-applied frontal electroencephalogram electrodes, thoracic and abdominal respiratory inductance plethysmography, airflow via nasal cannula, ECG (4 electrodes on torso), leg movement sensors, finger pulse oximetry, and snoring microphone. Participants will be instructed on self-application of all sensors before bedtime, using simple pictorial aides and will be provided a phone number of a staff member to contact should any problems in set-up be encountered. Instructions will be given on how to move about with the recording unit, and how to self-remove the electrodes and sensors. The NOX A1 PSG units will be returned by to the study personnel on the following day or at the participant's earliest convenience.

PSG studies will be downloaded from collection equipment to the SRC computer using commercial software. Scoring of the PSGs will be made by a trained member of the study group through visualizing each epoch on a high resolution computer monitor using specialized software. Respiratory events, sleep stages and EEG (cortical) arousals will be scored according to standard guidelines.

VI. STATISTICAL ANALYSIS

Sample Size

Sample size is based on previous data from our laboratory. We used mean and standard deviation of peak ventialtion during arm crank exercise in individuals with low and high level SCI (Battikha

et al. 2014). We assume that Buspirone would increase peak ventialtion by 35% in humans, though to our knowledge, there is no reference available on the ventilatory effect of Buspirone in individuals with SCI. Thus, with a highest SD of 8.3 L/min, we expect that peak ventilation during arm crank ergometer exercise in high level individuals with SCI will be increased from 31.3 L/min at baseline to 42.1 L/min with buspirone, as compared with no change in the placebo-controlled group. With an a p level of 0.05 and a power of 80%, the sample size calculation indicates that we need at least 9 participants per group. Anticipating 10% drop out, we will need 10 participants per group, for a total of 20 participants.

Statistics

These projects will employ typical/appropriate statistical approaches to compare changes within and between groups. Statistical significance will be set at 0.05, and power at 80%. Statistical tests, conformity of the data to required statistical assumptions (e.g., normal distribution) will be verified using standard methods (e.g., Kolmogorov-Smirnov statistics and Q-Q plots). If assumptions for parametric tests do not hold, non-parametric alternatives will be employed. Correlations between variables will be assessed when necessary by Pearson's or Spearman's coefficient depending on the normality of the variables. If significant relations are found, appropriate regression analyses will be employed.

VII. RISKS AND DISCOMFORTS

Moderate risks are associated with exercise (arm-crank) testing. Some discomfort and feeling of fatigue will be experienced during these tests. There are other risks associated with these tests including abnormal blood pressure responses, fainting, irregular, fast or slow heart rhythm, and in rare instances, heart attack, stroke, or death. Wearing the mouthpiece during the arm-crank exercise testing may cause feelings of claustrophobia. Exercise testing may also induce some muscle or joint discomfort when and could result in tendonitis and/or musculoskeletal injuries. There is some discomfort with the lancet used on the finger for lactate measurement.

There are no known risks associated with the EKG or blood pressure measurement. A subject must remove or lift up his or her shirt and have sticky patches applied to the chest for the electrocardiogram (EKG). In some cases, chest hair may have to be shaved where the EKG patches are placed. If an abnormality is identified on an EKG, the subject would be given this information and referred to his or her own doctor for further evaluation. Subjects may feel lightheaded or short of breath during the pulmonary function tests, there is also a slight chance that individuals become dizzy. The CO_2 re-breathing may cause slight lightheadedness in some people; however, this can be reversed almost immediately by switching them back to room air.

Buspar: BuSpar(r) (Buspirone HCl, USP) is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedatives/anxiolytics drugs. The mechanism of action of Buspirone is unknown but it does not exert anticonvulsant or muscle relaxant effect and it has no prominent sedative effect. Common side effects include: drowsiness, fatigue, dry mouth, or an increase in nightmares or dreams. Rare, but serious side effects include: an allergic reaction (difficulty breathing; hives; swelling of lips, tongue or face); chest pain or an irregular heartbeat; headache, dizziness, lightheadedness, slurred speech, confusion or blurred vision; numbness or tingling in hands, feet, arms or legs; depression; or uncontrolled movements of arms, legs tongue or lips.

Polysomnography: Sleep may be disturbed during the polysomnography study causing next day sleepiness. Skin irritation or discoloring may occur under adhesives used to attach the study sensors.

VIII. POTENTIAL BENEFITS

This research may help physicians and scientists to better understand how the interaction between a serotonin agonist pharmacological agent (buspar) and minute ventilation during hypercapnia and exercise. Although it is possible volunteers may better tolerate CO_2- rebreathing and exercise with buspar, this is a pilot study and further work may be necessary to establish the benefical effects of buspar for those with high level spinal cord injury.

IX. MONITORING AND QUALITY ASSURANCE

The research coordinator will be responsible for monitoring the completeness of all data and source documents. The Principal Investigator will monitor the informed consent procedures in accordance with the Informed Consent Compliance Checklist of Partners HealthCare Systems HRQIP. The subjects data/protocol adherence will be monitored by the research coordinator at each step in the study including. Checklists and note pages are used to note any deviations or omissions from the protocols. All spinal cord injured participants will be asked the “Pre-Study Screening” questions before every visit. The Cardiovascular Research Laboratory Medical Emergency Safety Plan will be followed in the case of an adverse medical event. Any clinical/health related issues would be immediately presented to the subject (i.e. abnormal EKG, blood chemistries, etc) to determine appropriate notification (ie. current physician or appropriate specialist) Based on the seriousness of the situation a physician may be contacted to provide clinical guidance on the appropriate course of action.

Serious adverse events will be reported to the IRB via phone, email, or fax. The principal investigator will follow this with a full written report using the PHRC Adverse Event Form within 10 working days. If a mild or moderate adverse event occurs that is definitely, probably, or possibly related to the study, a written report will be sent to the IRB within 20 working days. All other events will be summarized in a progress report at continuing review.

X. REFERENCES

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