PROTOCOL COVER PAGE

PROTOCOL NAME
Can brief exposure to hyperoxia improve function after chronic spinal cord injury?

PROTOCOL IDENTIFYING NUMBER
Pro00061817

PROTOCOL AMENDMENT VERSION
Version 13

PROTOCOL AMENDMENT DATE
October 1, 2021

GENERAL INFORMATION

Name and address of the sponsor and monitor of the study

University of Alberta, Edmonton, AB.

Name and address of the person authorized to sign the protocol and amendments

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Name, title and address of qualified physician who is responsible for trial-site related medical decisions

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Study Summary

Title	Can brief exposure to hyperoxia improve function after chronic spinal cord injury?
Short Title	N/A
Protocol Number	Pro00061817, Version 13
Phase	Proof-of-principle study
Methodology	Prospective, double-blind, randomized crossover design
Study Duration	Projected end date March 31, 2026
Study Center(s)	Single centre
Objectives	Determine if breathing an increased proportion of oxygen above the concentration in normal room air results in changes in the sensory and motor function in people with severe spinal cord injury (SCI).
Number of Subjects	35 (25 with spinal cord injury, 10 uninjured controls)
Diagnosis and Main Inclusion Criteria	Chronic and subacute, traumatic spinal cord injury; uninjured healthy controls for ensuring experimental protocol without using oxygen
Study Product, Dose, Route, Regimen	Study products are: 1) oxygen (DIN# 02014408), and 2) compressed air (DIN# 02014483), delivered during different experiments through a face mask with flow rate of 10 litres/min, once per experiment, over 2 experimental days, with experiments spaced by at least 2 weeks.
Duration of administration	2 minutes per experiment
Reference therapy	Placebo – compressed air (DIN# 02014483)
Statistical Methodology	Analysis will be guided by a statistician, Dr Ming Ye, consultant with the Faculty of Rehabilitation Medicine, Rehabilitation Research Centre.

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List of Abbreviations

ICH	International Conference on Harmonisation
CRF	Case Report Form
GCP	Good Clinical Practice
HREB	Health Research Ethics Board

1 Background

1.1 Investigational Agent

Pure oxygen (99%) from Praxair, Edmonton, DIN# 02014408, delivered through a face mask at a flow rate of 10 litres/min, for a period of 2 minutes. Reference (placebo) agent is compressed air from Praxair, DIN# 02014483, delivered in the same way.

1.2 Preclinical Data

An abstract from the preclinical trial in rodents is included below. This study details the mechanisms underlying chronic hypoxia in the spinal cord distal to a complete spinal cord transection in a rodent model, and how brief exposure to breathing high levels of oxygen modifies the motor behaviour of the rodent. Because there is no way to measure the oxygenation in the human spinal cord non-invasively, we wish to determine if brief exposure to pure oxygen in a human with severe spinal cord injury modifies the sensory and motor behaviour in a way similar to that in rodents. If so, it would suggest that the human spinal cord distal to a severe spinal cord injury is also chronically hypoxic, and interferes with sensory and motor function. Ways to restore oxygenation to the spinal cord could then be pursued in future studies.

Pericytes impair capillary blood flow and motor function after chronic spinal cord injury

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ABSTRACT

Blood vessels in the CNS are controlled by neuronal activity, including widespread vessel constrictions (tone) induced by brainstem neurons that release the monoamines serotonin and noradrenaline, and local vessel dilation mediated by glutamatergic neuron activity. We examine how vessel tone adapts to the loss of these monoamines after spinal cord injury (SCI) in rats. We find that, months after SCI, the cord below the injury is in a chronic state of hypoxia, produced by a paradoxical excess activity in monoamine receptors (5-HT1), despite the absence of monoamines. These receptors activate pericytes that locally constrict capillaries, reducing blood flow to ischemic levels. The paradoxical receptor activity results from trace amines (tryptamine) produced by pericytes that ectopically express the enzyme aromatic-L-amino-acid-decarboxylase (AADC),

which synthesizes trace amines directly from dietary amino acids (tryptophan). However, blocking monoamine receptors or AADC, or briefly inhaling increased oxygen, produces long-term relief from hypoxia and improves locomotor function.

1.3 Risk/Benefits

Oxygen therapy with up to 100% oxygen for much longer than we propose to use (which is 2 mins) is used in the management of pulmonary conditions and emergency medicine (Vogelsinger et al 2017; Branson 2018; Brugnliaux et al 2018), and is also used to enhance physical performance in athletics (Brugnliaux et al 2018). Symptoms of oxygen toxicity does not start to develop in humans breathing pure oxygen at normobaric (i.e., 1 atmospheric pressure, which is our proposed condition) until after 4 - 24 hours of exposure (Klein 1990). People with chronic, spinal cord injury have been exposed to much longer duration of oxygen (up to 4 hours) with no adverse effects reported (Gui et al 2014).

If there is any sign of discomfort during an experiment suggestive of early stage oxygen toxicity, such as tracheal irritation, abnormal rise in blood pressure or other symptoms (Klein 1990), oxygen will be discontinued. Dr Wong (co-investigator and medical expert on this trial) will be available by phone during all experiments with participants with spinal cord injury, and a licensed Physiotherapist (PT) will be present during these experiments.

If a participant has any signs of distress (related or unrelated to the study), the PT will evaluate the situation, and contact Dr Wong for consultation, or arrange for transportation to the emergency department if warranted. The laboratory where all the experiments will take place is located in the Clinical Sciences Building at the University of Alberta. This Building is physically connected with the University of Alberta Hospital.

1.4 Dose Rationale

Oxygen is delivered in the same way as has been tested in rodents. The percentage of oxygen is also similar to that used in the animal study (Li et al 2017). The period of exposure is chosen to be slightly longer than that used in rodents (1 min in rodents vs 2 min in humans) to allow delivery of oxygen in a much larger organism, but still well below the time frame when complications have been reported (≥4 hours) (Klein 1990).

1.5 Trial Conduct

This study will be conducted in compliance with the protocol approved by the University of Alberta Health Research Ethics Board (HREB), and according to Good Clinical Practice (GCP) standards. No deviation from the protocol will be implemented without the prior review and approval of the HREB, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the HREB as soon as possible.

1.6 Population

Subacute or chronic (≥3 months post-injury), traumatic spinal cord injury. See inclusion and exclusion criteria (Sections 4.1 and 4.2, respectively, below).

A small number of uninjured participants will be included to test the experimental set-up using compressed air only. These participants will not be included in the testing of the experimental agents, but rather are used to ensure that the protocol runs smoothly prior to testing participants with spinal cord injury.

1.7 Literature

Ways to promote recovery from severe spinal cord injury has been extremely limited in humans. Individuals with spinal cord injury, diagnosed with ASIA Impairment Scale A and B, have historically tended not to improve a great deal over time, or even progressively decrease in function (Steeves et al 2011; Zariffa et al 2011; Aimetti et al 2019). Recently, epidural stimulators implanted over the spinal cord have resulted in some return of function in such individuals (Harkema et al 2011; Angeli et al 2014; Angeli et al 2018), but it requires surgical implantation of a stimulator, which comes with all the potential complications of such a procedure.

Recent work in rats with complete and incomplete spinal cord injuries (Li et al 2017) suggests that the spinal cord distal to the lesion site suffers from chronic hypoxia, resulting from excessive activity of monoamine receptors in pericytes, which surround capillaries and constrict blood flow. Brief (1 min) inhalation of pure oxygen in these rats reduces the hypoxia for ~20 min, resulting in improved motor and sensory function. We will test this idea in humans with chronic, severe, spinal cord injury.

2 Trial Objectives

Determine if breathing an increased proportion of oxygen above the concentration in normal room air results in changes in the sensory and motor function in people with sub-acute and chronic, severe spinal cord injury (SCI).

3 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. The trial design is as follows (shown in schematic form in Figure 1).

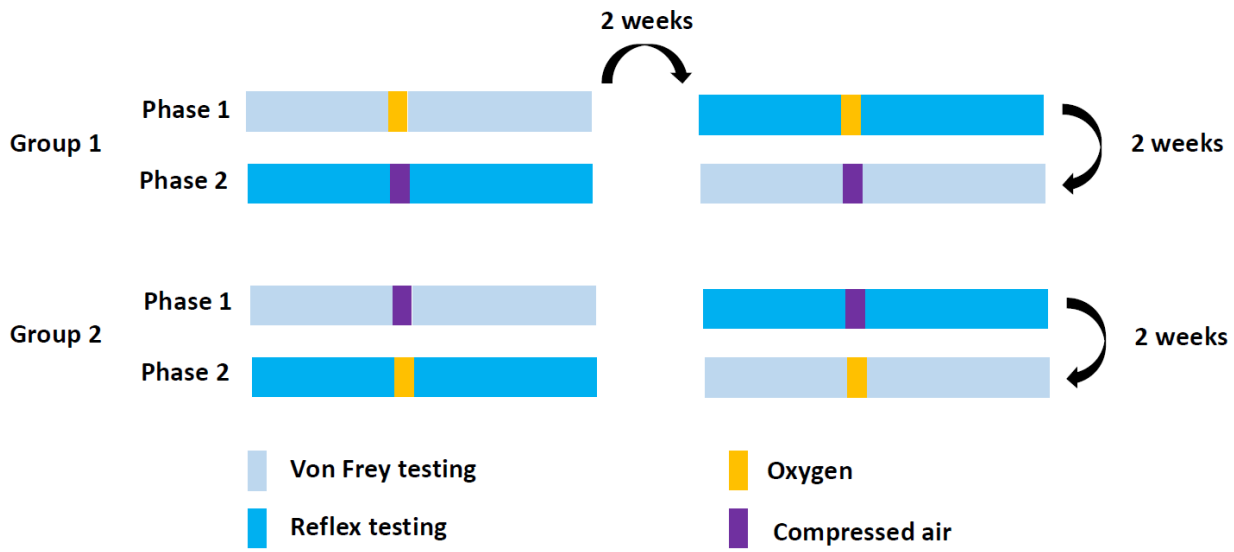

Figure 1. Crossover experimental design for participants with spinal cord injury. Participants will be randomized into Group 1 or Group 2. Group 1 will receive oxygen during Phase 1, and compressed air in Phase 2. Group 2 will receive the same agents in opposite order. Measures will be taken before and after the exposure. Experiments will be spaced at least 1 week apart.

- This is a prospective, double-blind, interventional, placebo controlled trial. Participants will be randomly allocated to Group 1 or Group 2. Group 1 will receive oxygen (99%) in Phase 1, and room air (placebo) in Phase 2. Group 2 will receive the agents in opposite order to Group 1. Measures of sensory function will be taken before and after each exposure. Two experimental days are planned for each phase, so that von Frey hairs and reflexes are tested on separate occasions to avoid cross-contamination. Both high oxygen and room air will be delivered through a loose fitting face mask approved by Health Canada (license #81363, supplied by Glenwood Labs, Canada, part # 1041). The flow rate will be 10 litre/min for a 2-min period.
- The participants with SCI will be blinded. The experiments will be spaced by at least 2 weeks.
- Primary outcome measure: skin sensation will be collected at regular intervals using calibrated Von Frey Hairs. Reflex and skin sensation will be recorded throughout the 30 min prior to and 30 min after exposure to high oxygen or room air at regular intervals. Secondary outcome measure: leg reflexes will be elicited by electrical stimulation of the skin, and responses measured by surface electromyography.
- The experimenter collecting the sensory data and the experimenter analyzing the reflex data will be blinded to the oxygen/air exposure, to avoid bias. The blinding ends for both the participant and the experimenter once the both experiments are completed for that participant.
- Stopping rules/discontinuation criteria: if any symptoms of early oxygen toxicity emerge, including acute tracheobronchitis, which could be a mild tickling sensation, later followed by inspirational pain, cough, or a constant retrosternal burning sensation (Klein 1990), the experiment will be stopped immediately. Normally, these types of symptoms are not

experienced until after 3 or more hours of exposure to high oxygen. If such an incident occurs with any participant, the study team will consider terminating the study.

Uninjured participants (n=10) will be included to test the study protocol for reflexes and von Frey hairs, but using compressed air only. This is to ensure the smooth running of experiments for the participants with spinal cord injury, and to provide reliability information on our testing procedures. Four experiments will be included to test the von Frey hairs and the reflexes in separate experiments, each repeated once to examine reliability of the testing (see Figure 2).

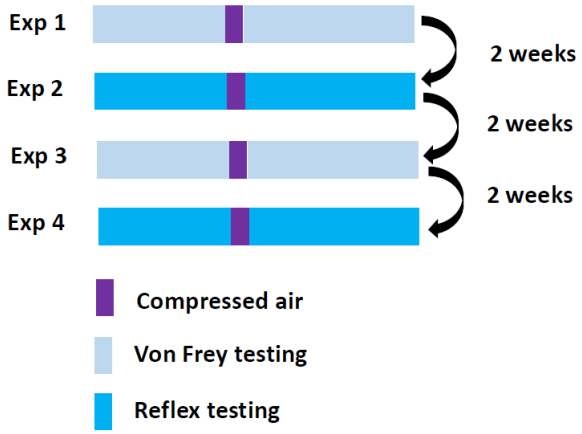

Figure 2. Experimental design for uninjured participants. Four experiments are planned for each participant. Only compressed air will be used in these experiments. Von Frey Hairs will be used to test sensation on 2 separate occasions, and reflexes will be used in the other 2 occasions.

3.1 Primary Study Endpoints/Secondary Endpoints

The primary endpoint is the skin sensation as quantified by von Frey Hairs at specific skin locations above and below the level of injury. The exact skin location will vary, since different participants will have different levels of injury. The secondary endpoint is the reflex excitability as measured by surface electromyography (EMG) in the leg muscles, and induced by electrical stimulation of the surface of the skin on the foot arch.

3.2 Study Design/Type

Prospective, double-blind, placebo controlled cross-over trial, with randomized order of presentation of high concentration of oxygen (99%) vs room air (placebo). All participants will be exposed twice to both conditions over the course of the 4 experiments, and measures will be taken before and after each exposure. See Figure 1 and Point 3 Study Design for details.

3.3 Randomization

The allocation of participants into Group 1 or Group 2 will be block randomized (block size 2-4) for each participant using a random sequence generator. Only one researcher present in the experiment will know the order of presentation for ease of administration and for safety, but all other experimenters doing the measurements and analyzing the data will be blinded.

Maintenance: the order of presentation can be disclosed to the participant and experimenters after all data has been collected on a participant.

3.4 Trial Treatment

The trial is an exposure to high oxygen (99%), delivered to the participant through a Health Canada approved (lic. #81363) face mask (supplied by Glenwood Labs Canada, Part #1041). The oxygen and room air are stored in high-pressure cylinders, which will be labelled with the investigational product name, study title, lot number and expiry date. The pressure is stepped down with Health Canada approved regulators, supplied by Western/Scott Fetzer Enterprise: WES M1-346-15FM for room air, and WES M1-540-15FM for high oxygen. The exposure to high oxygen and room air will both be for 2 min, and will occur on different experimental days.

3.5 Duration

The participant will be involved in four sessions of testing at a minimum of 2-week intervals between every testing session, each of which will take approximately 1.5 to 2 hours. A total duration of involvement in the study is a minimum of 7 weeks, with some possibly longer to fit in the 4 experiments according to participant and experimenter availability.

3.6 Discontinuation

Early signs of oxygen toxicity include acute tracheobronchitis, including a mild tickling sensation, later followed by inspirational pain, cough, and if more severe, a constant retrosternal burning sensation. If any of these symptoms are reported, we will immediately stop the delivery of high concentration of oxygen. Normally, these types of symptoms are not experienced until after 3 or more hours of exposure to high oxygen (Klein 1990).

3.7 Product Accountability

We will test oxygen exposure against room air (placebo).

3.8 Data Identification

The data will be recorded on RedCap with the assistance of the office of Quality Management for Clinical Research at the University of Alberta. RedCap data will include all relevant Case Report Forms, Informed Consent Forms, data from the von Frey hairs, and analyzed data from the reflexes.

4 Selection and Withdrawal of Subjects

4.1 Inclusion Criteria

SCI participants:

i) traumatic SCI with onset ≥3 months prior,
ii) between 18 - 65 yr old,
iii) ASIA Impairment Scale at discharge classified as A, B or C,
iv) injury level between C5 and T10,
v) able to give informed, written consent.

Uninjured controls:

i) no previous spinal cord injury or health condition that would confound the experiment or make it unsafe for the participant (see exclusion criteria),
ii) between 18-65 yr old,
iii) able to give informed, written consent.

4.2 Exclusion Criteria

SCI participants:

i) frequent uncontrolled autonomic dysreflexia,
ii) uncontrolled high blood pressure,
iii) cardiac or cardiovascular disease,
iv) cancer,
v) active urinary tract infection,
vi) active pressure sores,
vii) signs of deep vein thrombosis in the legs,
viii) severe swelling of the feet and/or legs,
ix) severe cognitive impairment,
x) pulmonary dysfunction such as chronic obstructive pulmonary disease or acute respiratory infection,
xi) any condition which would be exacerbated by sitting or lying in one position for 2 hours, such as low back pain,
xii) pregnancy.

Uninjured controls:

i) any active medical or neurological disorders,
ii) cardiac or cardiovascular disease,
iii) cancer,
iv) signs of deep vein thrombosis in the legs,
v) severe swelling of the feet and/or legs,
vi) severe cognitive impairment,
vii) pulmonary dysfunction such as chronic obstructive pulmonary disease or acute respiratory infection,
viii) any condition which would make it difficult to remain sitting or lying in one position for over 2 hours, such as low back pain,
ix) pregnancy.

4.3 Subject Withdrawal

Participants can withdraw at any time without consequence to them. They simply have to tell us they do not wish to continue. There will be no follow-up, and no consequence to the participants. There will be no need to replace participants, as this is not a clinical trial. We have factored in 10%-15% attrition.

4.4 Treatment of Subjects

During an experiment, participants will transfer to a wide, physical therapy plinth, and positioned in sitting, with the torso about 45 degrees from the vertical. The agent, high oxygen or room air, will be administered just once for a short duration. No other treatment is involved. On each testing day, participants will be exposed to one condition, either high oxygen or room air, and outcome measures will be taken before and after each exposure. On 2 of the testing days, the participants will be exposed to high oxygen, and on the other 2 days they will be exposed to room air. Testing sessions are spaced at least 2 weeks apart from each other.

4.5 Medication

As we have excluded all people with respiratory dysfunction, none of the participants will be on respiratory medications. We will document all other medications the participants are taking.

4.6 Monitoring for subject compliance

Not applicable. Participants will be in our lab the entire time.

5 Assessment of Efficacy

This is a one-time exposure to high oxygen during two experimental sessions. It is not meant to be efficacious as a treatment at this time. The experiment is a scientific study to determine how high oxygen, delivered for a short period, affects people with and without spinal cord injury. If exposure to high oxygen has a similar effect as it does in other animals with spinal cord injury, then new studies will be designed in the future to explore ways to improve oxygenation in people with spinal cord injury.

5.1 Efficacy Parameters

Not applicable. The study is a proof-of-principle study that the high oxygen results in motor and sensory changes below the level the spinal cord injury in the short term. It is not meant to be a therapeutic agent.

5.2 Method and Timing

N/A

6 Assessment of Safety

6.1 Safety Parameters

Screening: Participants will be screened in person by a study team member and will be required to sign a release to allow the study team to examine their medical record, to ensure there are no contraindications for the study. An approval form will be signed by their family physician, or Dr.

Ho (co-investigator) in the case where a potential participant does not have a family physician. The approval indicates they see no medical reason why the individual should not participate.

COVID-19 precautions: During the Covid-19 pandemic, additional measures have been taken to protect both the participants and the experimenters. These measures are as follows:

- All participants and experimenters must be fully vaccinated with a Health Canada Approved vaccine at least 2 weeks prior to the initial visit. This is in keeping with the University of Alberta regulations for all individuals attending campus.
- A screening questionnaire will be administered prior to admission to the lab at every visit to ensure an absence of symptoms and close contact with Covid-19 positive individuals.
- All participants and experimenters must wear medical grade masks provided by the laboratory.
- During administration of the agent, a medical grade mask will be placed over the oxygen mask to protect both the experimenters and participants.
- Documentation of people in and out of the lab with dates and times will be enforced.
- Reporting of a Covid-19 positive test subsequent to a visit is required of all people attending the experiment. Should such an incident occur, all people in the lab who could have been exposed to the virus will be notified by phone.

6.2 Method and Timing

Participants will be instrumented with a non-invasive heart rate (HR) and tissue oxygen saturation monitor, clipped to the finger (Pulsox-300). HR will be constantly monitored through the experiment, including 30 min after the termination of the exposure. We expect HR could decrease slightly (~10 beats/min) (Waring et al 2003) during exposure. If these changes exceed 10 bpm during the intervention exposure, the intervention will be stopped. The participants will be monitored for 30 min after the exposure only, because there are no known subsequent effects from the short, 2-min exposure to oxygen. To ensure that there are no lingering effects, they will be contacted by phone by a physical therapist the following day to check for any issues. The phone check will be done for exposure to both oxygen and compressed air to ensure blinding.

6.3 Adverse Event Reporting

We will comply with HREB requirements to report any adverse events. The event will be reported in writing to the HREB, using the approved Local Serious Adverse Event Report form. Further, all serious unexpected adverse drug reactions (SUSARs) will be reported in writing to Health Canada.

6.4 Definitions

Unanticipated events are any events during the exposure or through the 30 min following the exposure that exceed the HR changes described above or other health issues.

Serious events are any events during the same period of time (i.e., exposure to oxygen and 30 min period following exposure) that led to the need to seek immediate medical attention at a hospital emergency and requires inpatient hospitalization.

Related events will be defined as events that occurred during or after exposure (within 30 min) to the agent (99% oxygen) which were not present prior to exposure.

6.5 Adverse Event Follow-up

We will follow-up with the participant daily, either through phone, email or in-person until the condition has been resolved. The HREB will be notified.

7 Statistical Plan

7.1 Statistical Methods

The data will be analyzed promptly, typically within a week of data collection. Statistical analysis will be done later after all data is collected and a statistician will be consulted to assist with analyses. The staff analyzing the reflex data off-line will be blinded.

7.2 Subject Population(s) for Analysis

This is a pilot study. Participant numbers are very small, as there is no prior data to allow a calculation of sample size. Data on leg reflexes, skin sensation and oxygen saturation levels over time will be analyzed pre- and post-exposure and compared with the control condition (i.e., , room air).

7.3 Significance

$P<0.05$

7.4 Termination Criteria

If serious adverse events (defined in 6.4) related to the exposure to high oxygen occurs in a participant, the study will be re-evaluated, and termination of the study considered.

7.5 Accountability Procedure

Missing data could occur if a participant drops out of the study prior to completion of all measurements. In that case, we will use whatever data is collected, as it will still be useful to understand any changes that were attributable to the intervention/placebo.

7.6 Deviation Reporting

Any deviation(s) from the original statistical plan will be described and justified in the protocol and/or in the final report.

8 Direct Access to Source Data/Documentation

We will provide direct access to trial-related monitoring, audits, IHREB review and regulatory inspection(s), in full compliance with the HREB regulations. All source data will be retained for a minimum period of 25 years, in accordance with regulations for clinical trials.

9 Quality Control and Quality Assurance

The study will be in compliance with the Good Clinical Practice (GCP) guidelines, as documented in the ICH Harmonised Tripartite Guideline. The investigators welcome audits and allow access to source data from the Institutional Health Research Ethics Board and the Office of Quality Management in Clinical Research at the University of Alberta.

10 Ethical Considerations

This study will be conducted according to Canadian and international standards of GCP. Applicable government regulations and University of Alberta research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Alberta HREB for formal approval to conduct the study. The decision of the HREB concerning the conduct of the study will be made in writing to the investigator.

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the HREB. The formal consent of a participant, using the HREB-approved consent form, will be obtained before that participant is submitted to any study procedure. This consent form must be signed by the participant, and the investigator-designated research professional obtaining the consent.

11 Data Handling and Record Keeping

Only the researchers and their trainees and laboratory staff will handle the data. The majority of data collected will be in electronic form. All electronic data will be coded by a participant number, so there will be no identifiable information stored with the data. The data will be stored on the computer servers in Corbett Hall, and in RedCap. Identifiable information in hardcopy will be stored in a locked room within a locked cabinet. If there is any electronic data that contains identifiable information, such as a master copy of the participants and their codes, this will be encrypted on the servers. Hardcopy, identifiable information will include the participants' full name, contact information (email and/or phone number), AHS number, physician's name and number, and medical information extracted from the AHS files. We need contact information to schedule the experiment, and medical information to confirm suitability for the experiment.

12 Finance and Insurance

There will be no cost to the participant. Parking or public transit costs will be covered by the researchers. Insurance is covered by the University, as this is a research project carried out on the University campus, by University employees.

13 Publication Plan

The results of this study will be published in a scientific journal. The results may also be presented at national and international conferences.

14 Supplements

- Safety Data Sheet for compressed air
- Safety Data Sheet for pure oxygen

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