Effects of Acute Intermittent Hypoxia (AIH) on Metabolism, Dysglycemia, and Substrate Partitioning during Exercise

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	HRP-503 Template Protocol (7)
1.	**Protocol Title**
	Effects of Acute Intermittent Hypoxia (AIH) on Metabolism, Dysglycemia, and Substrate Partitioning during Exercise
2.	**IRB Review History**
	NA
3.	**Objectives**
	Specific Aims ***Specific Aim 1:*** Assess whether 4 days of exposure to AIH at rest in overweight or obese individuals with and without SCI will result in improved glycemic control when compared to a normoxic (SHAM) condition. ***Specific Aim 1:*** Assess whether 4 days of exposure to AIH administered while at rest in overweight or obese individuals with and without SCI will result in a greater reliance on fat as a fuel source at rest and during exercise when compared to a normoxic (SHAM) condition.
4.	**Background**
	It is generally accepted that spending time in high altitude environments is associated with weight loss and enhanced insulin sensitivity (1, 6), suggesting that altitude exposure may be an effective therapeutic treatment for obesity and associated comorbidities. Intermittent hypoxia (IH) exposure is an effective way to benefit from hypoxic stimulus without undergoing potentially detrimental effects of prolonged exposure to altitude. Research has shown that IH (15%) in conjunction with 4-8 weeks of exercise training results in greater weight loss than exercise performed under normoxic conditions in obese individuals (-6.9 vs. -4.3 kg; n = 22 (4) and -1.14 vs. -0.03 kg; n = 20 (5)). Furthermore, improvements in body composition (3, 7), triglycerides, insulin resistance assessed by the proxy HOMA-IR, fasting insulin and area under the curve for insulin during an OGTT were greater when exercise was performed under hypoxic conditions (15%) compared to normoxia, even despite lower absolute work intensity (n > 20 in both studies) (3). Nonetheless, little research exists on passive exposure to IH independent of exercise training on weight loss or insulin sensitivity. Workman *et al (8)* examined post-metabolic responses to both acute (n = 11; 3 hours of exposure) and short-term passive hypoxia (n = 6; 3 hours of exposure for 7 days) in sedentary overweight males(8). Oxygen concentration was maintained at approximately 80% blood O_2 saturation during treatment. Both conditions demonstrated an increase in energy expenditure and basal metabolic rate as well as a shift in substrate partitioning to favor lipid oxidation. This may be especially relevant in individuals with SCI who have demonstrated a limited capacity for fat oxidation and lower maximal rates of whole body fat oxidation. A recent case study (2) examined the use of diet alone followed by IH in conjunction with diet in an obese female diagnosed with prediabetes. Weight loss during the 5-week IH plus diet treatment period (-7.3 kg from baseline) was more than twice the weight loss achieved during the diet only phase (-2.3 kg from baseline). Additionally, normal fasting blood glucose and remission from pre-diabetes was achieved after 9 weeks.

Optimal dosage and conditions, as well as possible mechanisms of action for IH remain unclear. Adequately powered randomized, controlled trials are required to confirm whether IH is viable as a longer-term treatment option for obesity and the associated comorbidities.

This proposed novel research addresses functional and medical concerns following SCI. The purpose of this proposal is to examine changes in glycemic control and metabolism while at rest and during exercise after 5 days of resting exposure to AIH when compared with a time-matched normoxia (SHAM) treatment.

5. Inclusion and Exclusion Criteria

Screening:
Subject candidates will be pre-screened by phone or personal contact to determine their eligibility based upon age and body habitus (i.e., height/weight). Subjects with SCI and non-injured control (CON) subjects will be recruited.

Inclusion Criteria:

a. Males and females aged 18-60 years.
b. SCI only:
   1. Lower extremity weakness or paralysis at C5 or below resulting from spinal cord injury for at least one year.
   2. ASIA Classification A-D
c. Overweight or obese as classified by a Body Mass Index (BMI) (kg/m^2) of ≥ 25.0 (CON) and ≥ 22.0 (SCI).
d. Resting $SaO_2 \geq 95\%$

Exclusion Criteria SCI and CON:

a. Currently hospitalized
b. Resting heart rate ≥120 BPM
c. Resting systolic blood pressure >180 mm Hg
d. Resting diastolic Blood Pressure >100 mmHg
e. Self-reported history of unstable angina or myocardial infarction within the previous month
f. Previous cardiac surgery or condition that evidences ischemic heart disease
g. Cardiopulmonary complication such as COPD
h. Pregnancy determined by urine testing in sexually active females.

6. Number of Subjects

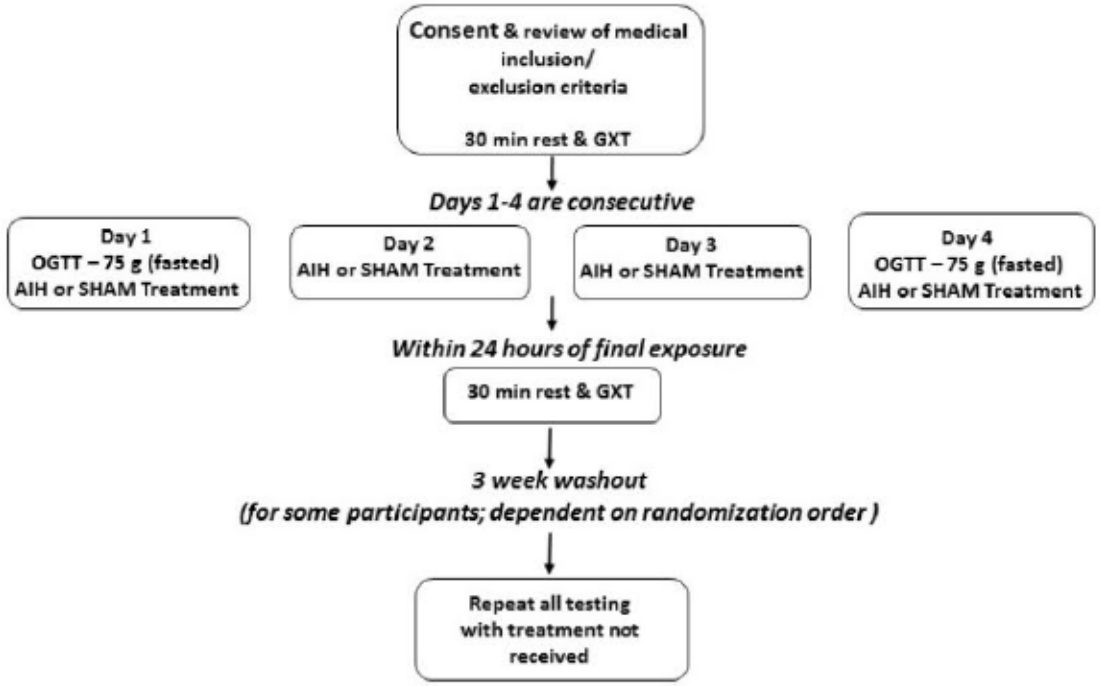
Total target accrual is N= 20; 10 SCI and 10 CON.

7. Study-Wide Recruitment Methods

Subject candidates will be recruited by word-of-mouth, casual contact, online advertisement on The Miami Project to Cure Paralysis website and phone calls.

The Miami Project maintains a database of persons who have volunteered their participation in research studies. This is a searchable database under the management of Kim Anderson-Erisman, Ph.D., Director of Education. The Miami Project also maintains a database of individuals who have participated in past studies and volunteered ongoing participation. These databases contain information such as age, date of injury and level of injury, and impairment scale score that will allow us to screen potential subjects. These individuals will be contacted via phone or email. As the target recruitment is 20 subjects, we are confident that this level of enrollment can be satisfied.

8. Study Timelines



9. Study Endpoints

The study will end after 20 participants have completed all testing. For each subject the study will end after AIH and SHAM exposures and post-testing (resting and exercise assessments) have been completed.

10. Procedures Involved

General

Participant Burden:

a. The informed consent process and screening will require approximately 30 minutes.
b. The oral glucose tolerance test will take 2 hours plus 15 minutes of preparation time and 15 minutes to achieve post-treatment homeostasis.
c. Graded exercise testing will require approximately 60 minutes.
d. AIH and SHAM exposures will be administered on 4 consecutive days for approximately 60 minutes each day.

Research Design: A mixed models repeated measures (time) design examining metabolism and dysglycemia for subjects undergoing 2 treatment conditions (AIH and SHAM).

Protocol:

1. Study personnel will screen all subjects for study eligibility based upon inclusion/ exclusion criteria listed in section 5 of this protocol.

2. Subjects clearing all screening evaluations will undergo a graded exercise test on an arm ergometer (SCI subjects) or an electronically braked cycle ergometer (CON) to provide cardiac clearance and establish peak exercise capacity. Participants will refrain from activity/alcohol/caffeine 12h prior to testing and perform a continuous GXT (LodeAngio isokinetic arm ergometer or Monark 829e cycle ergometer) at a constant 60 rpm propulsion rate. After 30 minutes of rest, subjects with paraplegia will begin cycling with an initial workload of 0 W and will be increased by 15 W every 3 min until the subject can no longer maintain the target propulsion rate or requests to stop. Subjects with tetraplegia will be challenged by transitional workloads of 5 W. Control subjects will begin cycling at 50 W and the workload will be increased by 35 W increments every 3 minutes until 150 W and then by 10-15 W increments every 3 minutes until exhaustion. Expired gases will be continuously collected in a Hans-Rudolph Softmask worn by the subject and analyzed by an open-circuit indirect calorimetry system (Vmax229, Viasys, Inc.) with 12-lead EKG (Cardiosoft) rhythm detection. The ECG detection will use a standard 12-lead electrode array following washing of the electrode sites on the skin with an alcohol swab. Exercise termination will be consistent with the ACSM Guidelines for Exercise Testing and Training [9th Edition]. Indications for stopping the testing protocols in this research study include the following:

    a. the onset of chest pain, or
    b. any drop in systolic blood pressure of 20 mm Hg, or
    c. an absence of increased systolic blood pressure with increased intensity of exercise, or
    d. a rise in blood pressure greater than 260 mm Hg for systolic pressure and greater than 115 mm Hg for diastolic pressure, or
    e. if the participants experiences any combination of these signs and symptoms: lightheadedness, confusion, nausea, cold skin, clammy skin, pale skin, blue skin, lack of muscle coordination, or
    f. an absence of increased heart rate with increased intensity of exercise, or
    g. noticeable abnormal changes in heart rhythm, or
    h. participant requests to stop the testing protocol, or
    i. signs and symptoms of severe fatigue, or

j. any failure of the testing or recording equipment.

Without need for additional data collection we will calculate resting and whole body fat oxidation from ventilator data. Total energy expenditure (TEE), and whole body carbohydrate (CH_2O), and fat oxidation rates will be calculated using the following stoichiometric equations assuming negligible urinary nitrogen excretion rates:

$$\textbf{TEE (kcal/min)} = 3.9\ VCO_2/RER + 1.11\ VCO_2$$
$$\textbf{CH}_2\textbf{O oxidation (g/min)} = 4.55\ VCO_2 - 3.219\ VO_2$$
$$\textbf{Fat oxidation (g/min)} = 1.67\ VO_2 - 1.67\ VCO_2$$

where VCO_2 is the rate of carbon dioxide produced in L/min, RER is the respiratory exchange ratio (VCO_2/VO_2), and VO_2 is the rate of oxygen consumed in L/min. Rates of whole body CH_2O and fat oxidation will be converted to weight relative units (μmol/kg·min) using the molecular weights of glucose (180 g/mol) and a representative TG (860 g/mol). Fat oxidation will be converted to fatty acid oxidation by multiplying by 3 (3 mol fatty acids/mol TG).

Ratings of perceived exertion (RPE) will be assessed using the Categorical-Ratio (1-10) scale of Borg. Subjects will be shown a laminated sheet containing descriptors of their perceived effort ranging from 'nothing at all' (0) to very, very hard (Maximal=10). Subjects will state the number that corresponds to their perception of the difficulty of their task with specific respect to: a) their arms and b) their effort of respiration.

Blood pressure will be measured by a calibrated ambulatory pressure monitor (A&D Engineering, Inc.) placed on the dominant arm.

For determination of lactate concentration, capillary blood will be sampled from the earlobe in the last 15 seconds of each 3 minute stage as well as 1, 3, 5 and 10 minutes after cessation of exercise. The earlobe will be prepared using alcohol swabs and will then be punctured with a lancet. Samples will be analyzed immediately using a precalibrated analyzer (Lactate Plus, Nova Biomedical, Waltham, MA)

3. Participants will be randomly assigned (by the flip of a coin) to receive both AIH or SHAM intervention and then the alternate intervention no less than 3 weeks later. The order of treatment will be randomly assigned and counterbalanced. Participants will be blinded to the intervention they are receiving. Intervention order will be stored in a password protected document.

   Participants will receive intermittent exposure to moderate hypoxia (AIH) (HYP-123; Hypoxico Inc, New York, NY) under resting conditions. IH treatment will take place over a period of 4 consecutive days involving daily (Monday-Friday,) hour long sessions of alternating 6-minute hypoxic intervals (FIO2 = 0.09-0.12) with 3-minute normoxic intervals (FIO2 = 0.21). During hypoxic intervals, oxygen concentration may be adjusted to maintain participants SpO2 levels between 75-90% (as previously described in IRB approved protocol #20150117). SHAM protocol will be the same as described above with FIO2 = 0.21 at all times.

   Blood oxygen concentration (SpO2) will be continuously monitored with a pulse oximeter to ensure that participants do not fall below 75%. The following will also be monitored during and after hypoxia treatments: headaches, pain, lightheadedness, dizziness, altered vision, respiratory distress, cyanosis, spasms, autonomic dysreflexia or change in function.

4. On day 1 and day 4 of each treatment series, subjects will undergo a fasted OGTT (as described below #5.). On day 1, the OGTT will be performed before the treatment and on day 4 it will be performed after the treatment. Each treatment series will be followed by a repeat of the graded exercise tests within 24 hours of the final exposure session as described in Section 10.3 of this document.

5. Subjects will undergo a 2-hour oral glucose tolerance test using a 75-g oral glucose load (Trutol) ingested over a 5 minute period. Subjects will fast overnight (8 hours) and will be prepared under antiseptic conditions with an indwelling 21g antecubital venous catheter (Jelco) having a multi-sample Luer connector cap, which will be kept patent with sterile physiological (0.9%) saline. Blood samples obtained in vacutainer tubes containing NaF and clot lysis activator will be centrifuged and assayed for glucose and insulin (via Roche auto-analyzer) which we have reported. We will plot glucose concentrations at 0, 30, 60, 90, and 120 minutes and measure area under the curve (AUC) using Graphpad PrismTM software. An additional assessment of whole-body insulin sensitivity will encompass both hepatic and peripheral tissues, which is derived by combining the insulin sensitivity index (ISI) during the oral glucose tolerance test (OGTT) with that obtained during the basal state, the latter of which primarily reflects hepatic insulin sensitivity. This composite 'whole-body ISI' during the OGTT [ISI(composite)] will be calculated as: 1002/[(FPG x FPI)x (GMEAN x IMEAN)]0.5, where 1002 represents a constant that generates values ranging from 0 to 12, FPG = fasting plasma glucose, FPI = fasting plasma insulin, and GMEAN and IMEAN reflect the 2-hour (75g) OGTT averages for glucose and insulin, respectively. The ISI (composite) has been comprehensively compared against other standardized methods used to determine insulin sensitivity, and is strongly correlated ($r = 0.73$, $p < 0.0001$) with the direct measure of insulin sensitivity derived from the euglycemic insulin clamp.

Data And Specimen Banking

Data Banking

Specimens – General – Whole blood will be taken for the OGTT. Centrifuged plasma will be discarded after assays for insulin and glucose are completed.

Electronic Data – All electronic files are stored on password-protected computers in rooms 1-48 and 1-50 of the Lois Pope Life Center. Computer security is provided by data encryption, firewall protection, and backup on the Miami Project Server.

Data – storage location - Data are stored in a locked room (LPLC 1-50), in a locked cabinet which is only accessible to study personnel in the Lois Pope Life Center, 1095 NW 14th Terrace, Miami, FL 33136. A security badge is needed to open the office door where the data is stored. A security guard is located in the front lobby and the hallway to the storage site secured by proximity card entry.

12. Data Management

Data Analysis

We will use a mixed-model ANOVA and a repeated measures design to examine main effects of ***test condition*** (AIH versus SHAM) and time. Post hoc analyses will use the Least Significant Difference test. Significance for all tests will be set *a priori* at $\alpha \leq 0.05$.

The outcomes being addressed have never been studied for this population and there are no data on which to empirically base study power. We will be using this study to obtain data necessary to compute effect sizes for future work.

Data will be analyzed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) version 22.0 software.

Security, Confidentiality, Privacy

Security & Confidentiality

Please see section 26. Confidentiality – local procedures.

Privacy
Please see section *27. **Provisions to Protect the Privacy Interests of Subjects.***

13. Provisions to Monitor the Data to Ensure the Safety of Subjects

a) Participants will be screened and approved for study participation by a physician boarded in physical medicine and rehabilitation.
b) Blood oxygen concentration (SpO2) will be continuously monitored during the study treatments with a pulse oximeter to ensure that participants do not fall below 75%.
c) We will monitor for the following both during and for 15 minutes (or until cardiovascular responses return to baseline) after treatments: headaches, pain, lightheadedness, dizziness, altered vision, respiratory distress, cyanosis, spasms, autonomic dysreflexia or change in function. We will also monitor cardiovascular responses to treatment to ensure that participants do not exceed heart rate < 40 bpm or > 180 bpm, systolic blood pressure levels < 85 mm Hg or > 160 mm.
d) Testing is being performed at a medical center that is located near an emergency room.
e) Security personnel who staff the LPLC are "first responders", and we have standing policies and procedures for emergencies in the Center (outlined in supporting documents). All lab staff hold current CPR certificates.

g) All adverse events – 'serious' or 'not serious'- will be reported to the IRB within the mandated time period.
For any adverse event the PI will immediately notify and consult with the Study Physician, and come to an opinion as the relatedness of the event and the study procedures as described in the protocol.

Adverse events will be evaluated by the Study Physician using the following criteria:
Grade 1, Mild: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or daily activities
Grade 2, Moderate: May be ameliorated by simple therapeutic measures; may interfere with, but not keep the participant from performing usual daily care or participating in daily activities.
Grade 3: Incapacitating event, inability to perform usual activities
Grade 4, Life-threatening/Disabling: Patient is at risk for death, or worsening disability or impairment as existed at the time of the event

For the first two grades the Investigators will observe the participant and as necessary institute standard medical or therapeutic care. **Repeated occurrence** of Grade 1 and 2 events may be cause for notification of the IRB by the Investigators that stoppage is appropriate. The Investigators may take this action and the IRB will be so notified.
Grade 3 and 4 events will be individually evaluated. **Any occurrence** of Grade 3 and 4 events may be cause for notification of the IRB by the Investigators that stoppage is appropriate. The investigators may take this action and the IRB will be so notified. Otherwise, upon on an IRB determination that the (S)AE was related to the protocol, the study will stop and undergo evaluation for continuation.

14. Withdrawal of Subjects

Subjects may withdraw from the study without prejudice to medical treatment at the center or involvement in future studies. The ICF advises students and employees of the rights with respect to study withdrawal.

We may end a subject's participation in the study if s/he experiences any of the following adverse effects as a result of assessment and/or treatment: headaches, pain, lightheadedness, dizziness, altered vision, respiratory distress, cyanosis, muscle spasms, autonomic dysreflexia or change in function. We will also monitor cardiovascular responses, and discharge any subject whose responses are not in accordance with Guidelines for Graded Exercise and Testing of the American College of Sports Medicine (9th Edition).

15.	**Risks to Subjects**
	Cardiovascular Morbidity and Mortality: Morbidity risks occur in 1/10,000 cases of intense cardiac exercise, and mortality occurs in 1/30,000 cases. Participants may find the exercise test exhausting, and may remain tired for the rest of the day. There is a risk of injuring the shoulders during intense arm cranking, which may make daily activities more difficult to perform. The mask placed over the mouth and nose for metabolic analysis may feel confining to some subjects, although it is flow-rated to 120 L/min and thus does not restrict breathing during exercise. Risks of exposure to prolonged or chronic intermittent hypoxia include hypertension, heart attack and stroke. Adhesive Allergy: Some individuals may experience brief, minor skin irritation or redness where the Cardiosoft ECG electrodes are placed. When occurring this is transient and typically goes away within several hours. The risks of blood drawing include: fainting, the occurrence of temporary discomfort and/or bruise at the site of puncture; rarely, infection or the formation of a small clot or swelling to the vein and surrounding area may occur. There may be slight discomfort in the arm or hand during the inserting of the catheter into the vein. Occasionally, a small accumulation of blood (hematoma) may form at the point of insertion of the catheter. This may result in a small lump that will disappear. Occasionally, a small amount of bleeding may occur around the catheter site. On rare occasions, a local infection may occur around the catheter site.
16.	**Potential Direct Benefit to Subjects**
	Direct benefits are not anticipated.
17.	**Vulnerable Populations**
	We are not enrolling pregnant women, prisoners, persons under age 18, or cognitively impaired adults.
18.	**Multi-Site Research**
	NA
19.	**Community-Based Participatory Research**
	This project does not involve community based participatory research.
20.	**Sharing of Results with Subjects**
	Study outcomes for individual and group results will be shared with study participants upon completion of the study.
21.	**Setting**
	Procedures described in section ***5. Procedures Involved*** will be completed in the Lois Pope Life Center on the Miller School of Medicine Medical Campus. Blood samples will be analyzed in the Clinical Biochemistry Lab or the DRI (3rd. Floor),
22.	**Resources Available**
	=Study Personnel =

	Mark S. Nash, PhD is a Professor in the in the Department of Neurological Surgery and Rehabilitation Medicine, and a Principal Investigator (Applied Physiology Research) for the Miami Project. He will serve as a Principal Investigator on the protocol and assessments, and will assist with data interpretation and dissemination. **Robert W. Irwin, MD,** is an Associate Professor in the Department of Rehabilitation Medicine, who is boarded in Rehabilitation Medicine. He will conduct physician evaluations of study subjects and be notified of any (S)AEs. He will be responsible for all medical aspects of the study, injuries, and participant care. **Jennifer Maher, PhD** is a Post-doctoral Associate at the Miami Project to Cure paralysis. She will be responsible for recruiting and consenting participants. She will schedule participants for visits, and oversee all assessments. **Armando Mendez, PhD,** is a Research Associate Professor of Medicine and Director of the Clinical Biochemistry Lab of the DRI. He will assay all bloods for glucose and insulin and provide source data for the study on these analytes. **Other Resources:** As the target recruitment 6 per group, we are confident that this level of enrollment can be satisfied with our planned recruitment methods. The Miami Project maintains a database of persons who have volunteered their participation in research studies. This is a searchable database under the management of Kim Anderson-Erisman, Ph.D., Director of Education. The Miami Project also maintains a database of individuals who have participated in past studies and volunteered additional participation. Research will be conducted in the Lois Pope Life Center Applied Physiology Laboratory (1-45), a medical center that is located near an emergency room. Security personnel who staff the building are all "first responders", and have standing policies and procedures for emergencies in the Center. All lab staff hold current CPR certificates. All necessary study supplies and equipment are located in this facility.
23.	**Prior Approvals**
	NA
24.	**Recruitment Methods**
	Subject candidates will be recruited by word-of-mouth and casual contact. The Miami Project maintains a database of persons who have volunteered their participation in research studies. This is a searchable database under the management of Kim Anderson-Erisman, Ph.D., Director of Education. The Miami Project also maintains a database of individuals who have participated in past studies and volunteered additional participation. As the target recruitment is twenty subjects, we are confident that this level of enrollment can be satisfied. **Remuneration** Participants will be paid for their participation in this study. Participants will be paid $50 after the first treatment and $50 at the end of all testing. Total value of remuneration for subjects is $100.
25.	**Local Number of Subjects**
	We will recruit 20 subjects; 10 SCI and 10 CON. All subjects will live locally.
26.	**Confidentiality – local procedures**
	Data – Identification of Research Participants Please see section *27. **Provisions to Protect the Privacy Interests of Subjects*** **Data Storage**

	Physical/paper records will be stored in a locked room (LPLC 1-50), in a lockable file cabinet only accessible to study personnel in the Lois Pope Life Center, 1095 NW 14th Terrace, Miami, FL 33139. A security badge is needed to open the office door where data are stored. Access to LPLC 1-50 is via a university-issued hallway proximity card or a security guard located in the front lobby. There are two types of electronic records, 1) source data and 2) pdf versions of all paper and electronic data. 1) Source electronic data will be stored in the original collection location. In addition, a copy of the electronic file may be stored on the Miami Project Server in a working group with restricted access. The Miami Project server is behind UM firewalls and is backed up electronically daily, with tapes of older copies archived off site in a fire/hurricane secure facility. 2) All electronic and paper source data will also be stored electronically as pdf's in an electronic version of the participant's folder. Paper source data will be scanned and electronic source data will be saved as a pdf. **Data Storage – Duration** Physical records will be kept for a minimum of 3 years after enrollment is closed and destroyed by shredding services provided to our center. Electronic records will be kept indefinitely. **Data – Access** During execution of the study access to identifiable information or links to identifiable information will be restricted to study personnel. However, coded information will be accessible to study personnel and may be provided to non-study personnel on a limited basis to gain assistance with data entry, management, analyses, and interpretation.
27.	**Provisions to Protect the Privacy Interests of Subjects**
	To protect subject privacy, participant consent forms will be stored in a file that is separate from their source data. Records/source data (physical and electronic) will be identified by a numeric ID. Numerical codes will be linked to participant names and contact info in a password protected electronic file accessible only by the PI and authorized study personnel. Linkage codes will be maintained until data analyses are completed. Once the data have been analyzed and published, the linkage codes will be destroyed.
28.	**Compensation for Research-Related Injury**
	There is no money available for research-related injury.
29.	**Economic Burden to Subjects**
	Subjects will be responsible for costs associated with travel to the research facility, parking at the research facility (if applicable), and for any food or drinks purchased while at the research facility (if applicable).
30.	**Consent Process**
	Consent will take place in the Lois Pope Life Center on the University of Miami Miller School of Medicine Medical Campus. We will abide all regulatory mandates and suggestions of the FDA '**A Guide to Informed Consent - Information Sheet'** www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm Before signing the ICF study subject candidates will be encouraged to share the ICF with family, a trusted family friend, their physician, or a member of the clergy. Candidates invited to the center will be required to read the approved consent form, and sign in the presence of a witness. The person obtaining consent will ask several questions to assure they understand the study procedures and risks. A statement on the consent form will advise university employees that their participation (or failure to participate) will not affect their employment or academic status. The statement in the consent will advise individuals with spinal cord injury that their participation (or decision to not participate) will not influence their treatment or candidacy for other studies in any way. Individuals will be given the right to stop the exercise test and may withdraw at any time without prejudice.

	Subjects will be presented with and asked to review the consent form. They will be queried whether they have any questions and if so, these questions will be addressed by the principal investigator. Once the consent form is signed, witnessed and signed by the principal investigator (or other person obtaining consent) a copy of the consent will be provided so that the subject can review their rights.
31.	**Process to Document Consent in Writing**
	See consent process in section ***30. Consent Process***
32.	**Drugs and Devices**
	This project does not involve drugs. The device used in protocol # 20160818 (HYP 123 Hypoxic Generator) has been used for the same purpose in previously approved protocols #20150117 and 20160337.