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TITLE: Acute Intermittent Hypoxia and Respiratory Strength Training to Improve Breathing Function after SCI

PRINCIPAL INVESTIGATOR: Emily Fox

CONTRACTING ORGANIZATION: University of Florida
GAINESVILLE, FL 32611

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Emily Fox

E-Mail: ejfox@phhp.ufl.edu

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University of Florida
Division of Sponsored Research

AND ADDRESS(ES)
1523 Union Rd. Rm 2017
Gainesville, FL 32611-1941

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Spinal cord injury (SCI) disrupts neural pathways to respiratory motor neurons, causing muscle paralysis and decreased breathing capacity. Since respiratory impairment is the major cause of illness and death with SCI, it is critical to devise new strategies to restore breathing function. One promising strategy to restore breathing capacity following SCI is to strengthen spared neural pathways by inducing spinal neuroplasticity. Our research group has developed novel methods to induce spinal respiratory plasticity in rats via repetitive exposure to brief episodes of low oxygen (acute intermittent hypoxia or AIH). In rats with incomplete SCI, repeated AIH restores lost breathing ability. These preclinical findings translate to humans with SCI; a single day of AIH, or daily AIH for 5 days (dAIH; 1-2 min of 9% oxygen, 1 min intervals), induces recovery of respiratory and non-respiratory motor function (such as walking or hand function). We demonstrated that AIH increases respiratory function in humans with chronic SCI. However, additional pre-clinical studies demonstrate that AIH-induced functional benefits are enhanced by combining AIH with task-specific training. Unfortunately combined dAIH and task-specific respiratory training has not been studied despite the promise of this novel therapeutic approach. It is essential to fill this knowledge gap as we work to translate this simple, safe and effective treatment modality to restore breathing function in Veterans with breathing impairment due to SCI. Central Hypothesis: Combined dAIH and respiratory strength training will elicit greater and more sustained gains in respiratory function than either treatment alone in people with chronic SCI.

Aim 1: Test the hypothesis that combined dAIH and respiratory strength training improves respiratory function more than dAIH or respiratory strength training alone. In adults with chronic, incomplete SCI and demonstrated breathing impairment, the effects of combined dAIH (5 days; 15, 1.5-min episodes of 9% oxygen; 1-min room air intervals) and respiratory strength training (inspiratory and expiratory training; 4 sets of 6-10 breaths per day; pressure-threshold device set to 80% of each individual's maximum) will be compared to the effects of each treatment alone and sham protocols.

Aim 2: Test the hypothesis that functional improvement from combined dAIH and respiratory strength training elicits more sustained effects than either treatment alone. Functional respiratory gains 3 days and 1week (primary outcome) after 5-day interventions will be assessed as an absolute change from pre-intervention, and as a fraction of the gains observed 1 day post-intervention.

Study Design: A double-blind, placebo-controlled, randomized, cross-over design is proposed. Participants will include 53 adults with chronic, incomplete SCI with >20% respiratory impairment based on maximal inspiratory or expiratory pressure generation (average annual enrollment is 14).

Clinical Impact: Innovative strategies are needed to reduce the impact of respiratory dysfunction in Veterans and civilians with SCI, particularly since the incidence of SCI has increased in the recent military conflicts, and recovery rates for battle-induced SCIs are lower than for non-combat SCIs.

15. SUBJECT TERMS:
NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

RESPONSE: The object of this research project is to test the hypothesis that combined acute intermittent hypoxia (AIH) and respiratory strength training will elicit great and more sustained gains in respiratory function than either treatment alone in people with chronic spinal cord injury (SCI). Aim 1 will specifically test the hypothesis that combined AIH and respiratory strength training improves respiratory function more than AIH or respiratory strength training alone. Aim 2 will test the hypothesis that functional improvements from combined AIH and respiratory strength training elicits more sustained effects than either treatment along. Functional respiratory gains 3 days and 1week (primary outcome) after 5-day interventions will be assessed. To achieve these aims, a double-blind, placebo-controlled, randomized, cross-over design will be used. Participants will include 53 adults with chronic, incomplete SCI with >20% respiratory impairment based on maximal inspiratory or expiratory pressure generation. Innovative strategies are needed to reduce the impact of respiratory dysfunction in Veterans and civilians with SCI, particularly since the incidence of SCI has increased in the recent military conflicts and respiratory impairment is the major cause of illness and death after SCI.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

RESPONSE: Respiratory function, breathing impairment, human SCI, chronic SCI, acute intermittent hypoxia, respiratory strength training, spinal plasticity

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

RESPONSE:
The Major Tasks for the entire study period, as stated on the approved SOW are:
Major Task 1: Coordinate and establish study operations which includes
- Subtask 1-Prepare regulatory documents and study protocols
  - Milestone: IRB approval
  - Milestone: HRPO approval
- Subtask 2-Complete training of personnel
- Subtasks 3-Establish study operations and assess adherence
  - Milestone: Site and personnel operations established

Major Task 2: Conduct a randomized, double-blind, repeated measures crossover study
- Subtask 1-Initiate and continue recruitment
  - Milestone: Subject enrollment and testing underway
- Subtask 2-Conduct testing and intervention protocols
  - Milestone: Complete data collection on 42 of 53 enrolled subjects

Major Task 3: Draft manuscript on the effect of combined dAIH and respiratory muscle strength training in humans with chronic incomplete SCI
- Subtask 1-Analyze study results
  - Milestone: Submit manuscript

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

RESPONSE:

Within this first annual reporting timeframe the following activities and objectives were addressed:

Major Task 1: Coordinate and establish study operations which includes

Subtask 1-Prepare regulatory documents and study protocols:

Regulatory documents were completed and study protocols established. Approval from the University of Florida IRB was achieved on Mar 20, 2019. Documentation for the HRPO review was prepared and submitted on May 7, 2019. The HRPO replied with a review of the project July 2019. The HRPO review required a revision to the IRB protocol. This revision, which involved addressing the role of our independent research monitor and adjusted our adverse event reporting, was approved by the University of Florida IRB 9/13/2019.

Also during this time, a second minor revision was submitted to the IRB and approved Aug 2019. This revision included minor adjustments to the clinical respiratory tests and added recording of surface respiratory muscle electromyograms as a component of the respiratory function tests. The respiratory strength training protocol also was adjusted to include a warm-up set of exercise and three (versus four) sets of respiratory strength training. All changes were minor to refine our protocol.

Subsequent to the IRB revisions, a response to the HRPO questions is underway. At the time of this report, we have not fully satisfied the HRPO questions. Communication is ongoing to resolve and address the HRPO questions regarding this project.

-Milestone achieved: IRB approval

-Milestone: HRPO approval is in progress

Subtask 2-Complete training of personnel

Study personnel have been established and trained in all aspects of this research protocol. Training has been completed for all aspects such as equipment set up, equipment operations and cleaning, completion of respiratory tests, trouble shooting of tests and equipment, implementation of respiratory strength training, recording of surface electromyograms for respiratory function tests, administration of spinal cord injury (SCI) assessments, administration of SCI questionnaires, data storage, file organization, data security, communication and scheduling. Personnel have been involved in the development of study procedures manual and refinement of procedures. Regular meetings are ongoing with study personnel and study leadership, PIs Fox and Mitchell. During this year, postdoctoral associate, Alicia Vose, SLP, PhD was recruited and hired for this clinical trial. Dr. Vose is a clinician with expertise in neurologic populations and also an emerging scientist. Using another funding source, we also recruited and hired postdoc Joseph Welch, PhD, a respiratory physiologist. As part of his training (though paid through other, non DoD sources), he will assist with this clinical trial and contribute to the study team expertise. Aligned with the training and elevation of personnel knowledge, PIs Fox and Mitchell worked with post-doctoral research associates, Dr. Alicia Vose and Dr. Joe Welch, on a review paper directed at the potential mechanisms of combined intermittent hypoxia and task specific training (i.e. respiratory strength training and directly aligned with this project; Welch et al., Hypothetical Model: Synergy between Acute Intermittent Hypoxia and Task Specific Training. *Exercise and Sport Sciences Reviews*. In revision.)

Subtasks 3-Establish study operations and assess adherence

Study operations are established. The study team has established operations as stated above in training of personnel. Established operations have been documented in a study procedures manual. Regular review and training sessions have been scheduled and attended to reinforce study operations, continue troubleshooting and to ensure adherence.

A major aspect of operations is establishment of subject recruitment procedures. We have worked closely with our study coordinators and Brooks Rehabilitation Research Recruitment specialists to establish recruitment plans. Recruitment plans include both active and passive strategies with Brooks Rehabilitation and in the community. Recruitment has not been initiated. Recruitment will be underway and emphasized once HRPO approval is obtained.

-Milestone: Site and personnel operations are established but not underway; working with HRPO to achieve their approval.

Major Task 2: Conduct a randomized, double-blind, repeated measures crossover study

Subtask 1-Initiate and continue recruitment

Subtask 2-Conduct testing and intervention protocols

Major Task 2 and Sub-tasks 1 and 2 have not been initiated since we do not yet have HRPO approval for the conduct of human subject research.

Efforts have been focused on Major Task 1 to ensure that we are fully ready to initiate Major Task 2 as soon as HRPO approval is obtained.

What opportunities for training and professional development has the project provided?

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

RESPONSE: This project was not specifically intended to provide training and professional development opportunities. However, the team members have been engaged in several training opportunities. Training and professional development aspects in this first year included:

a. Engagement of the postdoctoral research associates in monthly scientific seminars, many seminars given by international experts in topics focused on control of breathing, effects of neurologic injury, central nervous system regulation of motor functions, and rehabilitation.
b. Engagement of study personnel, including postdoctoral research associates in weekly journal club discussions focused on rehabilitation, control of breathing, intermittent hypoxia, neurologic injuries such as SCI, rehabilitation and nervous system plasticity.
c. Establishment of study procedures and personnel training involved extensive opportunities for team member engagement with study leadership, one on one mentorship, specific training in aspects such as equipment use, SCI participant safety monitoring, test procedures, respiratory training procedures, as well as research regulations and data security.

d. All team members and personnel participated in the UF Department of Physical Therapy NIH T32 Neuromuscular Plasticity Research Symposium (March 2019) which featured international experts in brain and spinal cord function.
e. Drs. Vose and Welch worked closely with PIs Fox and Mitchell on a scientific review paper directed at the potential mechanisms of combined intermittent hypoxia and task specific training (i.e. respiratory strength training; Welch et al., Hypothetical Model: Synergy between Acute Intermittent Hypoxia and Task Specific Training. *Exercise and Sport Sciences Reviews*. In revision.)

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

RESPONSE: Results from this study were not disseminated, as the study is not yet underway or approved for human subject research. However, there have been many outreach activities undertaken to reach members of the community and increase interest. These activities included

a. Brooks Rehabilitation Research Spotlight Event, Jacksonville, FL, August 2019. Information about this clinical trial and related pilot studies (not funded by this award) were presented at a community meeting of multidiscipline clinicians, physicians and community leaders.
b. Brooks Rehabilitation, '*Brooks Beyond'* publication featured a story of PIs Dr. Fox and Mitchell and their collaborative work including plans for this DoD funded clinical trial. *Brooks Beyond* is disseminated locally, nationally via mailings and online.
c. UF Health Science Center '*Post'* featured a story on research of intermittent hypoxia, Dr. Mitchell's historical career in science and Dr. Fox and Dr. Mitchell's collaborative work, including discussion of this clinical trial. The *Post* is disseminated locally and online.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."
Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

RESPONSE:

A primary, immediate goal is to achieve approval from the HRPO for the conduct of human subject research. PI Fox is, and will continue, to communicate with the HRPO officer to resolve the issues and concerns from the HRPO review. PI Fox also will continue to communicate and work closely with the University of Florida IRB in resolving these matters of human subject research.

Once HRPO approval is achieved, the immediate priority is to recruit and enroll subjects so that Major Task 2 is immediately underway. Thus, during this current, extended period without approval for human subject research, our team has worked continuously to ensure procedures are established and maintained, personnel remain engaged, and an aggressive recruitment plan is ready to initiate, once the study receives HRPO approval. The study team is working collaboratively with other ongoing SCI research trials at Brooks to ensure recruitment databases are updated and individuals (Brooks' patients) who wish to be contacted for research may be reached and informed of this DoD clinical trial.

Additionally, PIs Fox and Mitchell will continue to work closely with team members to provide training, communication and mentorship to advance the team and create learning opportunities that will benefit this clinical trial and our long term SCI research objectives.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

RESPONSE: Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

RESPONSE: Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

RESPONSE: Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

RESPONSE: Nothing to Report.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

RESPONSE: Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

RESPONSE: A delay in our project has occurred due to a delay in achieving HRPO approval. PI Fox is working with the HRPO officer to understand the issues and steps necessary to resolve the issues and satisfy HRPO requirements. PI Fox also is working closely with the University of Florida IRB to ensure the steps to resolve HRPO concerns/questions are congruent with UF IRB policies and regulations. PI Fox also is consulting with PIs of other intermittent hypoxia studies to gain insights into similar situations. Co PIs Fox and Mitchell are working diligently to take all necessary steps to resolve issues and get the clinical trial approved and under way.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

RESPONSE: Expenditures are less than anticipated during this first annual reporting period since human subjects research has not been initiated. For instance, there have been no expenses related to human subject payments or payments for participant travel. Personnel costs are less than anticipated since study procedures with enrolled participants is not yet underway.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects
RESPONSE: Nothing to Report.

Significant changes in use or care of vertebrate animals
RESPONSE: Not applicable to this human subject clinical trial.

Significant changes in use of biohazards and/or select agents
RESPONSE: Nothing to Report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

RESPONSE: Nothing to Report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

RESPONSE: Nothing to Report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  RESPONSE: Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  RESPONSE: Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  RESPONSE: Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*

- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

RESPONSE: Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

RESPONSE:

Name: Emily Fox, DPT, PhD, NCS
Project Role: Principal Investigator
Researcher Identifier: ORCID ID - 0000-0003-0142-3497
Nearest person month worked: 4
Contribution to project: Dr. Fox provided oversight of all activities including establishment of procedures, personnel training, refinement of study protocol, compliance with regulations and documentation, leadership of investigative team, establishment of regular communications, data storage and secure data sharing, as well as oversight of recruitment planning.

Name: Gordon Mitchell, PhD
Project Role: Co-Principal Investigator
Researcher Identifier: ORCID ID- 0000-0002-8489-1861
Nearest person month worked: 1
Contribution to project: Dr. Mitchell provided oversight of study activities including refinement of procedures, compliance with regulations, leadership of investigative team and communication strategies.

Name: Joseph Welch, PhD
Project Role: Post-doctoral scientist
Researcher Identifier: NA
Nearest person month worked: 2
Contribution to project: Dr. Welch has trained in study procedures, contributed to the refinement of respiratory testing and completion of the study manual of procedures. He also led development of the intervention procedures for respiratory training, participated in study communications.
Funding Support: University of Florida McKnight Brain Institute Research Training Fellowship

Name: Alicia Vose, PhD, CCC-SLP
Project Role: Post-doctoral scientist
Researcher Identifier: NA
Nearest person month worked: 6
Contribution to project: Dr. Vose has trained in study procedures, contributed to the refinement of respiratory testing and completion of the study manual of procedures. She assisted in the development of intervention procedures for respiratory training, participated in study communications and data management as well as development of the procedures manual.

Name: Lou DeMark, DPT, NCS
Project Role: Study Coordinator
Researcher Identifier: NA
Nearest person month worked: 3
Contribution to project: Lou DeMark provided assistance with development of procedures, assisting Drs. Fox and Mitchell with set up of operations. A particular focus is on recruitment planning and ensuring communication, data storage and sharing.

Name: Kathryn Cavka (Doughty), DPT, NCS
Project Role: Research Physical therapist
Researcher Identifier: NA
Nearest person month worked: 2
Contribution to project: Kathryn Cavka (Doughty) provided assistance with development of procedures, assisting Drs. Fox and Mitchell with set up of operations. A particular focus has been on development of the procedures manual.

Name: Clayton Wauneka, PhD
Project Role: Clinical Research Engineer
Researcher Identifier: NA
Nearest person month worked: 1
Contribution to project: Clay Wauneka has provided oversight of lab operations, set up of equipment, equipment maintenance, computer support, signal processing, oversight of data acquisition, data storage and security.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

RESPONSE:

This is the first annual report for this project. Since the start of this project the following changes in active other support have occurred:

a. PI Fox is now a co-investigator on the following VA RR&D funded project

VA SPiRE 11/2018-10/2020
VA RR&D Service .36 calendar months
Spinal excitation to enhance mobility in elderly adults
The objective of this study is to assess the use of textured shoe insoles and/or transcutaneous spinal direct current stimulation to enhance walking function in older adults.
Role: Co-I (PI: D Clark)

b. PI Fox is now PI on the following NIH REACT Center Pilot project:

Pilot Grant 9/2018-8/2020
NIH Center for Rehabilitation Research to Enhance Clinical Trials .48 calendar
Transcutaneous spinal direct current stimulation to enhance locomotion after spinal cord injury
This pilot study will examine the use of transcutaneous spinal direct current stimulation to enhance walking rehabilitation for individuals with chronic spinal cord injury.
Role: PI (Co-PI Clark)

c. PI Fox is now a co-I and leading an NIH SPARC-funded sub project:

NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) OT2OD0023854
8/2019-7/2020
Functional mapping of peripheral and central circuits for airway protection and breathing
.96 calendar
The project goal is to understand fundamental principles of modulation and plasticity in afferent pathways, brain networks and efferent systems controlling breathing and airway defense. Dr. Fox will study the effects of intramuscular diaphragm stimulation in humans after cervical spinal cord injury.
Role: Co-Investigator (PI Bolser)

d. PI Fox is now a co-I on the following PVA funded study:

Paralyzed Veterans of America 6/2019-5/2020 .60 calendar
Perceptions of Individuals living with spinal cord injury regarding autonomous vehicles
The project goal is to elucidate the perceptions of people with SCI before and after riding in an autonomous vehicle to understand their values and beliefs regarding autonomous vehicles.
Role: Co-I (PI: S Classen)

e. Co-PI Mitchell is now PI on the following NIH funded study:

R01 HL147554-A0 (PI Mitchell) 4/1/2019 – 3/31/2024 3.0 calendar
NIH/NHLBI
Optimizing Respiratory Plasticity with Chronic Cervical Spinal Cord Injury
This application focuses on optimization of acute intermittent hypoxia protocols and mitigation of factors undermining its therapeutic efficacy to enhance functional recovery of breathing after chronic spinal cord injury.

f. Co-PI Mitchell is now PI on the following NIH funded study:

R01 HL148030-A0 (PI Mitchell) 7/1/2019 – 6/30/2024 3.0 calendar
NIH/NHLBI
Regulation of intermittent hypoxia-induced respiratory motor plasticity
This application focuses on fundamental intra-cellular mechanisms of acute intermittent hypoxia induced phrenic motor plasticity, including mechanisms of enhanced phrenic long-term facilitation after repetitive AIH preconditioning, and the impact of age and sex on these mechanisms.

g. Co-PI Mitchell is now PI on the following NIH funded study:

R01 HL149800-A0 (PI Mitchell) 9/1/2019 – 8/31/2024 2.4 calendar
NIH/NHLBI $443,661 direct per year
Microglial regulation of intermittent hypoxia induced phrenic motor plasticity
This application concerns inter-cellular mechanism whereby microglia regulate serotonin- and adenosine-dependent forms of phrenic motor plasticity induced by acute intermittent hypoxia.

h. Co-PI Mitchell is now PI on the following state (FL) funded study:

Ed & Ethel Moore Alzheimer's Research (PI Mitchell) 2/1/2019- 1/31/2021 0.36 calendar
Florida Department of Health
Two Faces of Hypoxia in Alzheimer's Disease
This application concerns the impact of low and high dose intermittent hypoxia on Tau phosphorylation, tangle formation and neurodegeneration in a murine model of Tau pathology.

i. Co-I Danny Martin retired from his faculty position and no longer key personnel on this study.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

RESPONSE:
As detailed in the Statement of Work, Brooks Rehabilitation is a partner organization on this funded project.

-Organization Name: Brooks Rehabilitation, Brooks Clinical Research Center
-Location of Organization: Jacksonville, FL (main offices/facilities) and surrounding areas (associated clinical centers)
-Partner's contribution to the project: As detailed in our study description, protocol and regulatory documentation, Brooks Rehabilitation is involved in providing facilities for research activities and collaborating personnel. The University of Florida College of Public Health & Health Professions has a research collaboration with Brooks Rehabilitation (the Brooks-PHHP Research Collaboration) and PI Fox is a leading faculty member

in this collaboration. She and her projects are supported by the resources, facilities and personnel of both organizations.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

RESPONSE: Not applicable

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

RESPONSE: See attached

9. APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

RESPONSE: Nothing to report

Acute intermittent hypoxia and respiratory strength training to improve breathing function after spinal cord injury

Log SC170276
Award W81XWH-18-1-0718

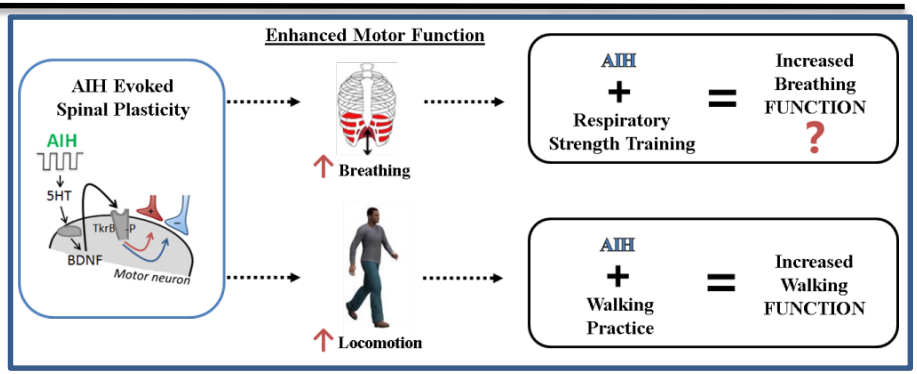
PI: Emily J. Fox, DPT, PhD **Co-PI: Gordon S. Mitchell, PhD** **Org: University of Florida** **Total Budget: $2,364,552**

Study Aims

- **Aim 1:** Test the hypothesis that combined daily acute intermittent hypoxia (dAIH) and respiratory strength training improves respiratory function more than dAIH or respiratory strength training alone in adults with chronic incomplete spinal cord injuries (SCI).
- **Aim 2:** Test the hypothesis that functional improvement from combined dAIH and respiratory strength training elicits more sustained effects than dAIH or respiratory strength training alone.

Approach

A double blind, placebo-controlled, randomized order, cross-over design is proposed. Participants will include 53 adults with chronic incomplete SCI and >20% respiratory impairment based on maximal inspiratory or expiratory pressure generation. The effect of combined training will be compared to each intervention alone and to sham dAIH. A 3-week washout period will separate 5-day protocols. Primary outcomes will be maximal inspiratory and expiratory pressure generation 1 day (Aim 1) and 1 week post-intervention (Aim 2).



Our group developed methods to induce spinal plasticity via exposure to acute intermittent hypoxia (AIH). We now have an IRB-approved protocol and established methods to test effects of AIH and respiratory strength training in humans with SCI. We are completing our response to the HRPO review.

Timeline and Cost

Activities / CY	18-19	19-20	20-21	21-22
Regulatory approval, site set-up				
Recruitment, enrollment				
Testing and data collection				
Manuscript preparation and submission				
Estimated Budget ($K)	**$534**	**$599**	**$615**	**$616**

Updated: 10/14/2019

Goals/Milestones

CY18-19 Goals–Regulatory approval and initiation of study
❑ IRB and HRPO approval [*IRB approved; awaiting HRPO]
☑ Site and personnel operations established
CY19-20 Goals–Subject enrollment and testing
❑ Subject enrollment and testing initiated
CY20-21 Goals–Subject enrollment and testing
❑ Subject enrollment and testing throughout year
CY21-22 Goals–Complete data collection and disseminate findings
❑ Complete data processing and statistical analysis
❑ Submit manuscript

Comments/Challenges/Issues/Concerns: Awaiting HRPO approval. Extended the timeline for approval and adjusted enrollment and data collection timelines.

Budget Expenditure to Date:
Projected Expenditure: ~$500K
Actual Expenditure: $39,000.00 due to initial institution holding funds and awaiting HRPO approval. Funds recently released. Expenses less due to delay in approvals/operations.