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TITLE: Treatment of Sleep Apnea in Patients With Cervical Spinal Cord Injury

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this research period, manuscript for Aim 1 was submitted for publication. Recruitment for Specific Aim 2 is still active, and 4 participants have been enrolled. 31 baseline studies were completed for both new and old enrollees, and 5 participants completed the entire study.
Recruitment for Specific Aim 3 is active. We have enrolled 5 participants and 3 of them have not started yet. A total of 7 participants completed both arms and 1 participant completed arm 1.

15. SUBJECT TERMS

NONE LISTED

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INTRODUCTION:

This proposal aims to investigate potential therapeutic approaches for sleep-disordered breathing (SDB) in patients with chronic cervical spine injury (>6 months post-injury). Our central hypothesis is that cervical SCI is associated with frequent episodes of hypoxia, resulting in chronic intermittent hypoxia (CIH), recurrent arousals from sleep, and increased peripheral chemoreceptor activity. To test our central mechanistic hypothesis, we propose a series of experiments to investigate the following Specific Aims: (1): To test the hypothesis that patients with cervical SCI will demonstrate greater magnitude of LTF following EH during sleep, compared to patients with thoracic SCI. This aim will be accomplished by measuring the effect of acute episodic hypoxia on post-hypoxic ventilation and upper airway mechanics in both groups. (2): To test the hypothesis that dampening peripheral chemoreceptor activity in patients with cervical SCI and central SDB with supplemental O2 will reduce central respiratory events and decrease respiratory variability during sleep. This aim will be accomplished by providing supplemental O2 to patients with cervical SCI and central SDB. (3): To test the hypothesis that administration of trazodone, in patients with cervical spinal cord injury and central SDB will decrease respiratory-related arousals and the central apneas index, compared to placebo. To accomplish this aim, trazodone, a sedating serotonergic agent will be administered to cervical SCI patients with central SDB. The proposed experiments will identify therapeutic approaches for the treatment of central SDB in patients with cervical spinal cord injury, which can potentially be generalized to patients with other neuromuscular disease and across the continuum of SDB in the general population.

1. KEYWORDS:

Sleep disordered breathing, spinal cord injury, chronic intermittent hypoxia, long term facilitation, episodic hypoxia, trazodone, central sleep disordered breathing

2. ACCOMPLISHMENTS:

The progress during this annual reporting period includes completion of Milestones under Major Task 2: Participant Recruitment, Informed Consent, Screening Visit, and Performance of Studies. **We proposed to enroll a total of 100 chronic SCI patients**. A sample of 20 individuals was the target to address Aim 1. A sample of 20 individuals will be studied to address Aim 2. A sample of 11 individuals will be studied to address Aim 3. So far we have consented 68 participates, some of them overlap between the 3 Aims. There are 30 participants who participated in more than one Specific Aim.

Subtask 1: Study Specific Aim 1

For Specific Aim 1, a total of 37 participants were enrolled, and a total of 21 participants completed the study (10 participants with thoracic-level injuries and 11 participants with cervical-level injuries). This completed participant enrollment and participation for Aim 1. A manuscript has been submitted for publication and is currently under review; we received comments from the reviewers that we are currently working on.

Subtask 2: Study Specific Aim 2

A total of 63 participants were enrolled since the beginning of recruitment for Aim 2. A total of 12 participants have completed the study and currently there are 15 active participants.

Since the last annual report (09/01/2019), we have enrolled additional four participants for Aim 2. Between 09/01/2019 and 08/31/2020, 31 baseline studies were completed on both new and old enrollees. In addition, 5 participants were randomized, and 5 participants completed Aim 2. Unfortunately, the COVID-19 pandemic has resulted in an administrative suspension of human research at our institution (both WSU and all VA facilities) starting in March 2020. Therefore, we have not been able to enroll additional subjects for the past 6 months.

During the next reporting period, we will continue screening with phone interviews. Due to Covid-19, there is a hold on in-person visits and studies for all human investigation. We are in constant discussion with the institutional IRB regarding resumption of in person research activity. At this point, our IRB is limiting human research to activities that are of direct clinical benefit such as cancer clinical trials. In the meantime, we are exploring options for potential assessments that could be performed remotely.

To prepare for resumption of in person research, our research staff will screen available data complete Aim 2, research staff screen potential subjects for inclusion and exclusion criteria and obtain basic information through a phone interview. At the first study visit, informed consent is obtained and the participants complete questionnaires about health and sleep. Baseline sleep studies include a polysomnography (PSG) and apneic threshold (AT) study with and without oxygen, and a study of critical closing pressure (PCrit). If participants are found to have central sleep apnea based on the PSG/AT they will do a titration study and will then be randomized to receive oxygen or room air for 6 weeks at home. Following the 6-week treatment period, the participants will return for a follow-up PSG/AT study.

Subtask 3: Study Specific Aim 3

A total of 20 participants have been enrolled since the beginning of recruitment for Aim 3. A total of 7 participants completed Aim 3, and 4 participants are currently active. Since the last annual report (09/01/2019), we have enrolled 5 participants and 3 of them have not started yet. Three participants who had completed both arms were brought back for repeat data sets to collect additional data points. A total of 7 participants have completed both arms and 1 participant has completed 1 arm.

During the next reporting period, we will continue recruitment with phone interviews. Due to Covid-19, there is hold on in-person visits and studies for Specific Aim 3. In order to complete Aim 3, research staff screen potential subjects for inclusion and exclusion criteria and obtain basic information through a phone interview. At the first study visit, informed consent is obtained and the participants complete questionnaires about health and sleep. Baseline sleep studies include a polysomnography (PSG) and apneic threshold (AT). If participants are found to have central sleep apnea based on the PSG/AT they will randomized to receive Trazodone or Placebo for one week.

3. IMPACT:

As of September 2019, VA has implemented a new policy in which we are no longer able to recruit non-veterans. For this reason, our recruitment process has significantly slowed down. In addition, we had a high rate of cancellations during the winter season. The VA and the university worked out a new arrangement to allow for enrollment of non-Veterans in research. We have obtained IRB and RRD approval to resume enrollment of non-Veterans in July 2020.

As of March 2020, due to Covid-19, our institution issued an administrative hold for all in-person recruitment/enrollment; including screening visits, in-person interaction or intervention with human subjects and in-person follow-up visits. This applies to all sites where human research is conducted. We have notified the IRB of this administrative hold.

4. CHANGES/PROBLEMS:

Recruitment of participants has been more challenging than anticipated for many reasons. The main reason is the administrative hold due to Covid-1, which affected our enrollment during the spring and summer, when many of our participants are able to enroll in studies. Other reasons are that many participants have difficulty coordinating their transportation and/or caregiver services, many confirm appointments and then no show and potential participants often have health care issues that prevent them from consenting. Additionally, more participants than anticipated have not had central sleep apnea (CSA) or a narrow CO2 reserve which disqualifies them from continuing in the study.
For Aim 2: Of the 4 participants enrolled, 1participant did not qualify.
For Aim 3: Of the 5 participants enrolled, 2participants did not qualify.

Furthermore, we have found that medical conditions commonly seen in spinal cord injury participants have complicated the continuation and scheduling of many participants. The most common of these conditions are bradycardia, hypertension, and bed sores.

Patients need medical transportation to get to site, our medical transportation companies are small and unable to accommodate our patient schedule.

5. PRODUCTS:

- Manuscript for Aim 1 was submitted for publication to the Journal of Applied Physiology (JAPPL). The manuscript is under review and we are currently in the process of revising the manuscript.
- An abstract has been submitted to the Thoracic Society conference (ATS) scientific meeting.
- Aim 3 abstract was also submitted to the American Thoracic Society meeting.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	M. Safwan Badr, M.D.
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	16
Contribution to Project:	Dr. Badr performed work related to the preparation, conduct, and administration of all aspects of the project.
Funding Support:	
Name:	Abdulghani Sankari, M.D., Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	16
Contribution to Project:	Dr. Sankari performed work related to the oversight of regulatory document preparation and gaining approval from all required regulatory agencies.
Funding Support:	

Name:	Summar Raslan, PhD
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	13
Contribution to Project:	Dr. Raslan performed work related to recruitment from DMC.
Funding Support:	

Name:	Harry Goshgarian, Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	13
Contribution to Project:	Dr. Goshgarian performed work related to project oversight
Funding Support:	

Name:	Hossein Yarandi, Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	13
Contribution to Project:	Dr. Yarandi performed work related to participant randomization and statistical oversight.
Funding Support:	

Name:	Ahmad Aldwaikat M.D
Project Role:	Study Coordinator
Researcher Identifier:	
Nearest person month worked:	14
Contribution to Project:	Dr.Aldwaiakt performed work related to the preparation of all regulatory documents and submissions to regulatory agencies. He also performed work related to research staff training, database set-up, participant recruitment, and data scoring.
Funding Support:	

Name:	Nishtha Pandya
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	15
Contribution to Project:	Ms. Pandya performed work related preparation of regulatory documents, participant recruitment, and scoring sleep studies.
Funding Support:	

7. SPECIAL REPORTING REQUIREMENTS:

A study Quad Chart is attached.

8. APPENDICES:

None