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

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14. ABSTRACT Since the 2020 annual report (08/31/2020), unfortunately, the COVID-19 pandemic has continued to be hindered due to an administrative hold 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. We filed for and have received IRB approval to amend the study as a direct benefit study and resume study activity on 6/3/2021. For Aim 2, we have contacted the current participants, and have scheduled 6 to resume study activity, have had 3 state COVID continues to be a concern, have had 1 withdraw, and have been unable to reach 4. For Aim 3, We have contacted the current participants, and have scheduled 2 to resume study activity, have had 1 state COVID continues to be a concern, have had 1 turned to be ineligible.					
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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 participants, 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. - A manuscript for AIM 1 is currently under review.

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 14 active participants. One participant deceased during the pandemic while the study was on an administrative hold.

Since the 2020 annual report (08/31/2020), unfortunately, the COVID-19 pandemic has continued to be hindered due to an administrative hold 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. We filed for and have received IRB approval to amend the study as a direct benefit study and resume study activity on 6/3/2021. We have contacted the current participants, and have scheduled 6 to resume study activity, have had 3 state COVID continues to be a concern, have had 1 withdraw, and have been unable to reach 4 .

In order to 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 we have received IRB approval to amend the study as a direct benefit study, we have contacted the current participants, and have scheduled 2 to resume study activity, have had 1 state COVID continues to be a concern, have had 1 turned to be ineligible.

During the next reporting period, we will continue recruitment and studies for Specific Aim 3. In order to complete Aim 3, research staff will 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.

During the next reporting period, we will be working on to finish the study by completing current participants and recruiting new participants. We project we need 12 additional participants (8 for Aim 2 and 4 for Aim 3) to complete the study and have scheduled 8 to resume in total so far.

3. IMPACT:

In September 2019, VA had implemented a new policy in which we were no longer able to recruit non-veterans. For this reason, our recruitment process 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. We received a full board IRB amendment approval to resume the study as a direct benefit study on 06/03/2021.

4. CHANGES/PROBLEMS:

Recruitment of participants has been more challenging than anticipated for many reasons. COVID-19 continues to be a significant challenge and has resulted in the facility implementing restrictions on space and study protocols. Subjects have had significant concerns about possible exposure to COVID-19, especially with the rise in variant cases. 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. Subjects at virtual consent appointments have opted to delay consenting and participation until the COVID-19 pandemic improves. 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.

5. PRODUCTS:

- 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:	28
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:	28
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:	25
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:	25
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:	25
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:	26
Contribution to Project:	Dr. Aldwaikat 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:	27
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