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

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14. ABSTRACT

During this research period, 21 participants finished Aim 1, completing participant enrollment and participation for this aim. Initial data analysis has been completed. Recruitment for Specific Aim 2 began, and 18 participants have been enrolled. Thirteen participants have completed baseline studies, and 1 participant has completed the entire study. An abstract based on preliminary findings from Specific Aim 1 was submitted and accepted as a poster presentation for the Military Health Research Symposium (MHSRS).

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.

Subtask 1: Study Specific Aim 1

For Specific Aim 1, we consented a total of 32 participants. Ten participants with thoracic level injuries and 11 participants with cervical level injuries completed Aim 1, for a total of 21 completed. This completes participant enrollment and participation for Aim 1. Initial data analysis has been completed and data is being organized to send to the statistician for further analysis.

Subtask 2: Study Specific Aim 2

Recruitment began for Specific Aim 2. We have consented 18 participants for Aim 2, completing 2 study Milestones: (1) 1st participant consented, screened, and enrolled, and (2) Study 2 begins. Thirteen participants have completed baseline studies, and 1 participant has completed the entire study.

During the next reporting period, we will continue recruitment and studies for Specific Aim 2. 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.

3. IMPACT:

Nothing to Report

4. CHANGES/PROBLEMS:

Recruitment of participants has been more challenging than anticipated due to participants not showing up. In the last month, 7 potential participants that confirmed consent visits did not show up to the visit. Additionally, more participants than anticipated have not had central sleep apnea (CSA) or a narrow CO_2 reserve, disqualifying them from continuing in the study. Of the 18 participants currently enrolled, 5 did not have CSA or a narrow CO_2 reserve.

5. PRODUCTS:

An abstract based on preliminary findings from Specific Aim 1 was submitted and accepted as a poster presentation for the Military Health Research Symposium (MHSRS) August 20-23, 2018.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	M. Safwan Badr, M.D.
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	4
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:	4
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:	Lawrence Horn, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Dr. Horn performed work related to recruitment from DMC.
Funding Support:	

Name:	Harry Goshgarian, Ph.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
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:	1
Contribution to Project:	Dr. Yarandi performed work related to participant randomization and statistical oversight.
Funding Support:	

Name:	Sarah Vaughan, Ph.D.
Project Role:	Study Coordinator
Researcher Identifier:	
Nearest person month worked:	13
Contribution to Project:	Dr. Vaughan performed work related to the preparation of all regulatory documents and submissions to regulatory agencies. She also performed work related to research staff training, database set-up, participant recruitment, and data analysis.
Funding Support:	

Name:	Andria Caruso
Project Role:	Research Assistant

Researcher Identifier:	
Nearest person month worked:	12
Contribution to Project:	Ms. Caruso performed work related to participant recruitment, and performing PSG and overnight intervention studies.
Funding Support:	

Name:	Waleed Ayesh, M.D.
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	9
Contribution to Project:	Dr. Ayesh 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

Project Title: Treatment of sleep apnea in patients with cervical spinal cord injury

PI: M. Safwan Badr, M.D., M.B.A **Log Number:** SC150201 **Award Number:** W81XWH-16-1-0436

Q1. Project Description:

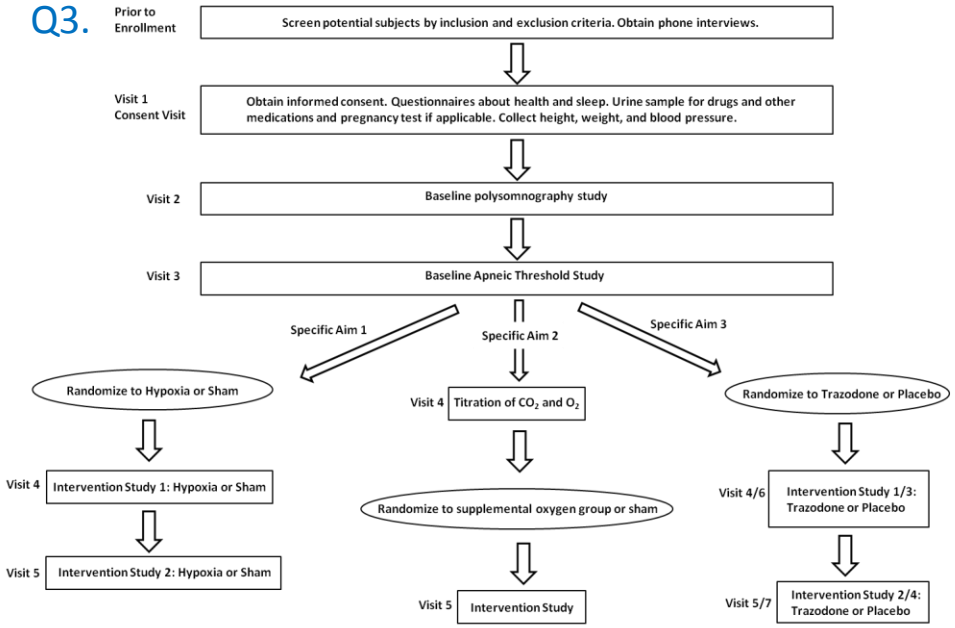
Total Award Amount Requested $: 2,851,225.00

Start Date – End Date : *(08/01/2016) - (07/31/2020)*

Describe Key Research Aims:

- Aim 1: To test the hypothesis that patients with cervical SCI will demonstrate greater magnitude of long-term facilitation (LTF) following episodic hypoxia during sleep, compared to patients with thoracic Spinal cord injury. The primary endpoints will be the change in V_T and V_E in the recovery period.
- Aim 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. The primary endpoints will be the change in CO_2 reserve compared to baseline.
- Aim 3: To test the hypotheses that: a)Acute administration of trazodone in patients with cervical SCI and central SDB will decrease respiratory-related arousals and central apnea index compared to placebo, and b) Chronic (1 week) administration of trazodone will result in decreased propensity to central apnea, evidenced by widening of the CO_2 reserve. The primary endpoints will be the change in respiratory related arousals.

Q3.



Q2. Scientific Innovations:

The development of central SDB in patients with cervical SCI may seem predictable until we ask *why* these patients develop this condition. While one would expect SDB among SCI patients with diurnal hypoventilation, we have noted this phenomenon in patients with normal daytime ventilation and oxygenation who are not using opiates for pain and have no evidence of impaired phrenic or hypoglossal nerve activity. However, the most innovative aspect of our proposal is that we will gain an understanding of the mechanistic underpinnings of central SDB in cervical SCI patients, leading to identification of novel therapeutic targets or a more individualized use of existing therapies that can be tested among other SDB patients as well. Another innovation is the use of in-lab enhanced polysomnography with quantitative measurements of air pressure and airflow. Our methods will allow us to quantify ventilation, measure the severity of inspiratory flow limitation, characterize upper airway mechanics, and evaluate chemical stimuli. Our goal is to:

1. Identify therapeutic strategies that could be tested in large clinical trials.
2. Improve quality of life among patients with cervical SCI who also experience central SDB.

Q4. Timelines:

Tasks	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Complete all regulatory reviews and finalize study components					
Aim 1: Subject Recruitment					
Aim 1: 20 Participants Complete Aim 1					
Aim 2: Subject Recruitment					
Aim 2: 20 Participants Complete Aim 2					
Aim 3: Subject Recruitment					
Aim 3: 20 Participants Complete Aim 3					
Complete Data Analysis and Report Results					