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

PRINCIPAL INVESTIGATOR: M. Safwan Badr, M.D.

RECIPIENT: Wayne State University
Detroit, MI 48202

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6. AUTHOR(S)
M. Safwan Badr, M.D.

Ahmad Aldwaikat, M.D

E-Mail: mbadr@dmc.org; aldwaikat@wayne.edu

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14. ABSTRACT

We proposed to enroll a total of 100 chronic SCI patients. A sample of 20 completed individuals was the target to address Aim 1. A sample of 20 completed individuals was the target to address Aim 2. A sample of completed 11 individuals was the target to address Aim 3. Total of 287-night studies were performed. We consented 70 participants, some of them overlap between the 3 Aims. There were 30 participants who participated in more than one specific Aim. 46 participants withdrew/lost after being partially involved. We published 4 abstracts and presented 3 posters at ATS. Draft abstract is being prepared.

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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 O_2 will reduce central respiratory events and decrease respiratory variability during sleep. This aim will be accomplished by providing supplemental O_2 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 final report 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 was the target to address Aim 2. A sample of 11 individuals was the target to address Aim 3. We conducted 287 nocturnal sleep studies. We enrolled a total of 70 participants, many of them participated in more than one aim; specifically, 30 individuals participated in more than one specific Aim but were counte4d only once.

Table 1. Demographic data for the enrolled participants

N	70
Veteran	27
Gender	62 M, 8 F
Age	56.9 ± 12.5
Race *1 preferred not to answer	23 W 46 AA
BMI	27.8 ± 5.7
Ethnicity	5 Hispanic; 65 Non-Hispanic
Level of Injury (Cervical or Thoracic)	46 C, 19 T

Baseline Data: Sleep-disordered breathing and Periodic Legs Movements in individuals with chronic spinal cord injury.

We studied individuals with chronic SCI (level T12 and above) who were not dependent on a ventilator. Each participant underwent baseline polysomnography (PSG) and sleep related questionnaires [Epworth sleepiness scale (ESS), and Pittsburgh sleep quality index (PSQI). Sleep disordered breathing (SDB) was defined as apnea hypopnea index (AHI) >5 event/hour sleep. The presence of PLMs was defined by periodic legs movements' index (PLMI)> 15 PLM/hour sleep.

Results: A total of 78 participants completed the PSG and sleep related questionnaires (50 cervical and 28 thoracic). Their mean age was 51±14.7 years and body mass index were 27.2± 5.3 kg/m2. SDB was present in 90% of participants (mean AHI was 35.8±22.2 event/h). PLMs were present in 58 participants (74%), PLMI was 42.6±113.0, and majority of them were cervical SCI (62%). PLM index > 15 was found in 57.1% and 42.9% of cervical and thoracic SCI, respectively. No relationship was found between PLMI and SCI level, sleep related questionnaires or AHI (p=NS).

Table 2. Demographics and sleep parameters by SCI level

	All	Cervical	Thoracic
N	78	50	28
Veteran/Non-veteran	30/48	19/31	11/17
Age (yrs)	51±14.7	52.8±14.5	47.9±14.9
BMI (kg/m	27.2±5.3	26.9±5.4	27.8±5.3
Gender (M/F/%men)	67/11 86%	43/7 86%	24/4 86%
Race (White/AA)	21/57	14/36	7/21
ESS	9.5±4.8	9.8±5	9±4.5
PSQI	10.2±4	10.9±4.1	8.9±3.6
PLMI (event/h)	20.1±34.7	14.4±22.2	32.56±48.17
AHI (event/h)	32.6±23.5	34.3±21.5	28.7±26.5
AHI ≥5 event/h (%)	70 (90%) 35.8±22.2	47 (94%)	23 (82%)
AHI ≥15 event/h (%)	53 (70%) 44±19.3	36 (72%)	17 (60%)
CAI≥5	14 (18%)	11 (22%)	3 (11%)
CAI<5	64 (82%)	39 (78%)	25 (89%)
CAI=0	35	23	12
PLMI≥15	27	15	12
PLMI≥5	37	23	14
PLMI<5	41	27	14
PLMI=0	21	15	6

Conclusion: Sleep disordered breathing (SDB) and Periodic legs movements (PLMs) are common in chronic SCI. Periodic leg movements may be masked by the high prevalence of SDB in this population. Further studies are needed after SDB is treated to better determine the clinical effect of PLMs on sleep.

Subtask 1: Study Specific Aim 1

- For Specific Aim 1, we enrolled 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. Results of Aim 1 have been finalized in a peer-reviewed paper, which has been accepted for publication in *Physiological Reports*. The title of the paper is:" Tetraplegia is associated with increased hypoxic ventilatory response during NREM Sleep"

  Abstract of the paper:

People with cervical spinal cord injury (SCI) are likely to experience chronic intermittent hypoxia while sleeping. The physiological effects of intermittent hypoxia on the respiratory system during spontaneous sleep in individuals with chronic cervical SCI are unknown. We hypothesized that individuals with cervical SCI would demonstrate higher short-and long-term ventilatory responses to acute intermittent hypoxia (AIH) exposure than individuals with thoracic SCI during sleep. Methods: Twenty participants (10 with cervical SCI (9 male) and 10 with thoracic SCI (6 male)) underwent an AIH and sham protocol during sleep. During the AIH protocol, each participant experienced 15 episodes of isocapnic hypoxia using mixed gases of 100% nitrogen (N2) and 40% carbon dioxide (CO_2) to achieve oxygen saturation of less than 90%. This was followed by two breaths of 100% oxygen (O_2). Measurements were collected before, during, and 40 minutes after the AIH protocol to obtain ventilatory data. During the sham protocol, participants breathed room air for the same amount of time that elapsed during the AIH protocol and at approximately the same time of night. Results: Hypoxic ventilatory response (HVR) during AIH was significantly higher in participants with cervical SCI than those with thoracic SCI. There was no significant difference in minute ventilation (V.E.), tidal volume (V.T.), or respiratory frequency (f) during the recovery period after AIH in cervical SCI when compared to thoracic SCI groups.

Table 3. Participant Characteristics by Group

	All	Cervical	Thoracic
Number	20	10	10
Age (Years)	48.9 ± 14.5	51.8 ± 15.6	46.0 ± 13.3
BMI (Kg/m2)	27.8 ± 4.8	26.2 ± 5.4	29.4 ± 3.8
Gender (M/F)	15/5	9/1	6/4
AHI (events/hour)	25.1 ± 20.0	25.8 ± 17.4	24.4 ± 23.1
(<15 events/hour) N (%)	9 (45)	4 (40)	5 (50)
(≥15 events/hour) N (%)	11 (55)	6 (60)	5 (50)
ODI (events/hour) IQ Range	10.4 ± 15.2 0 – 58.7	9.5 ± 11.9 0.9 – 38.5	11.3 ± 18.6 0 – 58.7

Table 4. Effect of Acute Intermittent Hypoxia on Ventilation						
	Cervical			Thoracic		
	Pre-Hypoxia	During Hypoxia	Post-Hypoxia	Pre-Hypoxia	During Hypoxia	Post-Hypoxia
VE (L/min)	7.5 ± 2.6	11.5 ± 3.3*	6.9 ± 1.7	6.5 ± 2.6	10.5 ± 4.6*	6.4 ± 2.7
VT (L)	0.5 ± 0.2	0.7 ± 0.2*	0.5 ± 0.1	0.4 ± 0.1	0.6 ± 0.2*	0.4 ± 0.1
f (BPM)	14.0 ± 3.0	16.5 ± 4.2*	13.7 ± 3.0	15.9 ± 4.3	18.5 ± 4.5*	16.1 ± 5.4
SaO_2 (%)	96.1 ± 2.3	88.9 ± 2.5*	95.9 ± 1.8	95.6 ± 2.9	87.5 ± 2.7*	95.9 ± 1.4
$PETCO_2$	43.2 ± 5.0	43.9 ± 5.1	42.4 ± 5.5	41.2 ± 7.0	41.5 ± 6.4	40.8 ± 6.1

Summary of Findings: 1) Episodic hypoxia did NOT elicit LTF in individuals with SCI. 2) Peripheral chemoreflex sensitivity was increased in participants with chronic cervical SCI.

Subtask 2: Study Specific Aim 2

A total of 65 participants were enrolled since the beginning of recruitment for Aim 2, A total of 16 participants were randomized and 13 participants completed the study.

Protocol: Research staff screened potential subjects for inclusion and exclusion criteria and obtained basic information through a phone interview. At the first study visit, informed consent was obtained, and the participants completed questionnaires about health and sleep. Baseline sleep studies included a polysomnography (PSG) and apneic threshold (AT) study with and without oxygen, and a study of critical closing pressure (PCrit). A Pap titration study was performed if central apnea was present. Subsequently, the participants were randomized to receive either oxygen or room air for 6 weeks. Following the 6-week treatment period, the participants returned for a follow-up PSG/AT study.

Table 5. Demographic data for the effect of acute O_2 therapy	
N	21
Gender	3F, 18M
Veteran	9 Yes, 12 No
Race	15AA, 5W, 1 unknown
Ethnicity	21 non-Hispanic
Level of Injury	13C, 8T
BMI	24.6±4.7
Age	58±13

Table 6. Sleep indexes for the O_2 therapy		
	Baseline	O2
AHI	40.3±23.5	22.6±15.0**
CAHI	10.0±12.4	2.1±3.8**
CAI	5.5±9.7	1.2±2.8**
OAI	10.1±15.8	9.4±13.0
ODI	21.3±19.5	1.0±1.4**

Key Finding: Administration of supplemental oxygen decreased the frequency of central respiratory events.

Table 7. Effect of supplemental O_2 on the Apneic Threshold			
Baseline	CO_2 Reserve	PG (avg)	CG (avg)
N	19		
Mean	-3.0±1.5	7.2±3.2	1.8±0.8
O_2	CO_2 Reserve	PG (avg)	CG (avg)
N	15		
Mean	-3.1±1.2	8.0±3.8	2.9±3.3

Preliminary analysis does not demonstrate a change in the propensity for induced central apnea. Analysis of these experiments is ongoing, and we plan to complete the analysis for a scientific meeting and then to submit as an original peer-review manuscript.

Table 8. Demographic data for home O_2 therapy		
	Room air	O_2
N	6	6
Age	52.5±17	56.66±11.7
Sex M/F	5/1	5/1
BMI	27.3±3.6	24.8±3
NC, cm	38.58±7.2	37.28±4.5
Level of Injury	4C, 2T	4C, 2T

Table 9. Sleep indexes after chronic oxygen therapy				
	Room Air		Oxygen therapy	
	Baseline	6-week therapy	Baseline	6-week therapy
AHI	42.87±26.7	36.67±25.8	41.15±29.7	46.17±18.3
CAHI	9.5±5.2	2.17±3.1	10.5±11.2	7.83±12.1
CAI	4.17±3.8	1.67±2.9	4.17±4.3	10.5±10.7
OAI	14±15.7	10±15.3	13.17±24.1	10.5±10.6
ODI	24.1±20	25.25±24.2	14.7±19.5	15.32±10

Key Findings: Chronic O2 therapy was not associated with improvement in indices of obstructive or central SDB.

Table 10. Apneic Threshold for the 6 weeks treatment				
	Room Air (N=6)		Oxygen therapy (N=6)	
	Baseline	6-week therapy	Baseline	6-week therapy
CO_2 reserve	-2.77±0.93	-3.00±0.77	-2.40±0.83	-2.29±0.96
Plant Gain	7.41±0.97	7.60±1.78	8.41±4.83	8.01±5.50
Controller Gain	1.87±1.04	1.60±0.73	1.61±1.19	2.52±1.52

Subtask 3: Study Specific Aim 3

A total of 21 participants have been enrolled since the beginning of recruitment for Aim 3. Ten participants completed Aim 3.

Aim 3 protocol: Research staff screened potential participants for inclusion and exclusion criteria and obtain basic information through a phone interview. At the first study visit, informed consent was obtained, and the participants completed questionnaires about health and sleep. Baseline sleep studies included a polysomnography (PSG) and apneic threshold (AT). If participants are found to have central sleep apnea based on the PSG/AT they were randomized to receive Trazodone or Placebo for one week.

Table 11. Demographic data for Aim 3	
N	20
Gender	1 F, 19 M
Veteran	8 Yes,12 No
Race	13 AA,7W
Ethnicity	20 Not Hispanic/Latino
Injury level	15 Cervical, 5 Thoracic
BMI	27.4±5.8
Age	56.5±12.4

Table 12. Apneic Threshold for Aim 3						
Placebo	CO_2 Reserve	AT	Hyperoxia	CG	PG	LG
N	7	6	7	6	6	6
Mean	-1.63+0.40	37.69+3.70	70.15+12.2	4.00+1.61	7.48+2.17	28.05+9.1
Trazodone	CO_2 Reserve	AT	Hyperoxia	CG	PG	LG
N	7	6	6	6	6	6
Mean	-2.8+1.08**	36.7+1.41	80.6+10.38**	2.2+1.06**	7.6+2.21	15.4+5.07**

Key findings: Administration of trazodone resulted in decreased propensity to central apnea, evidenced by widening of the CO_2 reserve, due to decreased controller gain. Trazodone did not affect peripheral chemoreflex sensitivity, evidence by the lack of change in the hyperoxic response.

Table 13. Arousal Threshold for Aim 3				
Arousal Threshold - Placebo vs Trazodone				
N=8	Placebo Day 1	Placebo Day 7	Trazodone Day 1	Trazodone Day 7
Mean	-16.4±7.1	-10.2±13.3	-17.3±5.0	-18.0±6.5

Key Findings: Trazodone administration did NOT alter the arousal threshold.

Table 14. Sleep indexes for Aim 3								
N=8	Placebo							
	AHI		CAHI		ODI		RAI	
	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8
Mean	52.4±29.6	47.9±24.3	10.8±20.2	7.1±13.5	38.1±33.3	25.0±28.4	23.3±15.8	34.3±18.3
N=8	Trazadone							
	AHI		CAHI		ODI		RAI	
	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8
Mean	45.8±22.5	35.4±32.7	4.2±4.4	13.6±28.1	30.3±24.9	21.2±31.5	16.2±13.3	15.3±12.8

Table 15. Sleep stages percentages for Aim 3								
N=8	**Placebo**							
	N1 percent Sleep		N2 Percent Sleep		N3 Percent Sleep		REM Percent Sleep	
	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8
Mean	31.3±15.6	38.3±28.9	61.5±14.8	48.5±20.5	2.8±8.0	9.6±25.3	4.5±5.2	3.6±6.3
N=8	Trazadone							
	N1 percent Sleep		N2 Percent Sleep		N3 Percent Sleep		REM Percent Sleep	
	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8
Mean	32.6±17.7	35.1±26.0	61.0±15.6	50.6±15.6	1.5±4.2	5.9±12.7	5.0±11.1	8.5±11.1

Table 16. Sleep Parameters for Aim 3								
N=8	Placebo							
	Total Sleep Time		Sleep Efficiency		Sleep Latency		Wake After Onset	
	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8	Day 1	Day 7/8
Mean	162.3±88.0	121.9±19.2	77.4±12.9	82.4±14.1	5.8±4.7	2.2±2.8	38.3±36.1	27.6±31.6
N=8	Trazadone							
	Total Sleep Time		Sleep Efficiency		Sleep Latency		Wake After Onset	
	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8	Day 1	Day 6/7/8
Mean	134.4±26.5	117.6±26.7	89.3±8.7	78.9±16.1	5.4±8.9	6.9±9.6	15.3±14.6	27.4±21.6

3. IMPACT:

Our study findings have greatly enhanced our understanding of the physiological underpinnings that will inform future clinical trials:

- Most individuals with SCI have sleep-disordered breathing (SDB) and co-morbid periodic-leg movements (PLMs). These two conditions conspire to produce major sleep fragmentation and may contribute to poor daytime function. Whether PLMs are etiologically linked to SDB cannot eb determined from our cross-sectional data.
- Our findings also suggest that central apnea is common in individuals with cervical SCI as one out of every five individuals will have central sleep apnea.
- Cervical SCI is associated with significant increase in peripheral chemoreceptor activity, which is a major destabilizer of respiration. Therefore, treatment options that could dampen peripheral chemoreflex activity are likely to exert a major salutary effect of sleep-disorder3ed breathing.
- Supplemental oxygen is the most physiologic intervention to dampen peripheral chemoreceptor activity. Our studies suggest that even a modest level of supplemental O_2 is adequate to stabilize respiration and reduce the severity of central apnea/hypopnea.
- Trazodone is associated with decreased severity of central apnea. Interestingly, this effect does not seem to be mediated via decreased arousal threshold.
- While our findings were derived from individuals with SCI, they are potentially applicable to all conditions where increased peripheral chemoreflex sensitivity is expected such as heart failure, neuromuscular disease, and long-standing obstructive sleep apnea.

4. CHANGES/PROBLEMS:

- The VA has promulgated a new policy that required a change in how non-veterans are enrolled in studies conducted on VA premises. This change slowed down enrollment until a new arrangement was negotiated with the affiliated university to assume medical legal responsibility.
- Individuals with SCI experience a multitude of co-morbid conditions that affect their ability to participate in research studies, including unanticipated acute health problems. Therefore, we have experienced a markedly higher not-show or cancellation that our non-SCI participants, especially in the winter months.
- Transportation remains a major barrier, as transportation companies frequently change their rates, routes, and rules. This issue added a substantial administrative burden to the study staff as they tried to search for suitable companies.
- The COVID-19 pandemic has hindered enrollment owing to the administrative hold of human research at our institution (both WSU and all VA facilities) 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 w-19 surges and the emergence of variants further affected enrollment as many potential participants were either concerned about the risk of exposure or were found to have COVID-19 on screening.
- Overall, recruitment of participants was more challenging than anticipated for many reasons. COVID-19 continued to be a significant challenge and resulted in the facility implementing restrictions on space and study protocols. Potential participants also expressed significant concerns about COVID-19 exposure risk, especially with the rise in variant cases. In fact, we noted that some participants at virtual consent appointments opted to delay consenting and participation until the COVID-19 pandemic improved. Other reasons were that many participants had difficulty coordinating their transportation and/or caregiver services, and hence were “no show” despite repeated confirmation of appointments. Finally, acute health issues are more common in this population, further impeding participation.

Opportunities for improvement for participants with SCI:

- Enhancing collaboration with the VA to allow for non-veteran enrollment in VA based studies. SCI is a challenging condition that is a critical area of focus for the DOD and the VA. Joining forces will ensure that critical research is completed without delay. The potential benefit to the community is immense.
- Investment in virtual platforms to allow for screening, consent, review, or even some study interventions to be completed virtually. This would allow for conducting virtual study visits to obtain informed consent, with electronic signature as well as virtual educational sessions.
- One potential approach is to explore central IRB for SCI studies, which will require negotiation with individual universities/VAs to ensure that such studies are conducted successfully.
- Establishing registries to pool data from multiple investigative teams in a standardized fashion. For example, it is conceivable that critical data could be acquired and combined in a number of Spinal Cord Injury Research Program (SCIRP) studies.
- New higher resolution at-home sleep diagnostic devices are now available, an evaluation and implementation of these devices may reduce burden but preserve quality data collection.
- Many SCI participants struggle with adherence to therapy due to co-morbidities and frequent hospital visits, more flexible therapies or therapies that are more portable may increase compliance. Investigating barriers and solutions to adherence would be a major advance in the science and practice.
- Socioeconomic factors are rarely considered as a contributing factor to development and natural history of disease. Our preliminary analysis revealed that most of our participants have a high Social-Vulnerability Index. Investigating social determinants of health is a critical opportunity for individuals living with SCI.

5. PRODUCTS:

ATS:

- **ATS2019:** Long-Term Facilitation Following Acute Intermittent Hypoxia is Present in People with Cervical Spinal Cord Injury during Non-REM Sleep.
- **ATS 2020:** Effect of Trazodone on Ventilatory Control Instability in Individuals with Chronic Spinal Cord Injury.
- **ATS2021:** Effect of Trazodone on Airway Mechanics and Ventilatory Control Instability in Individuals with Chronic Spinal Cord Injury.
-

Abstract/Publication:

- Vaughan, S, Sankari AG, Carrol S, Eshraghi M, Obiakor H, Yarandi H, Chowdhuri S, Salloum S, and Badr MS. Tetraplegia is associated with increased hypoxic ventilatory response during NREM sleep. Physiological Reports (In Press)
- Ventilatory response following acute intermittent hypoxia during sleep in individuals with spinal cord injury. Sarah Vaughan, Ph.D., Abdulghani Sankari, MD, Ph.D., Sean Carroll, MS Mehdi Eshraghi, MS, Harold Obiakor, MD, Ph.D., Hossein Yarandi, Ph.D. Susmita Chowdhuri, MD, MS, Anan Salloum, MD1 M. Safwan Badr, MD, MBA
- The Effect of Supplemental Oxygen on Central Sleep Apnea in Individuals with Spinal Cord Injuries and Sleep-Disordered Breathing. A. Caruso1, A. Sankari1, M. Eshraghi1, B. Ahmad1, H. Pereira1, J.

Adepoju1, A. Aldwaikat1, K. L.Arvai1, N. Pandya1, H. T. Obiakor1, S. W. Carroll1, M. Husainat1, A. Altairi1, S. Zeineddine2, A.Salloum2, M. Badr1

- Effect of Trazodone on Ventilatory Control Instability in Individuals with Chronic Spinal Cord Injury. H. Obiakor1, A. Sankari1, S. Carroll1, M. Eshraghi1, J. Adepoju1, A. Aldwaikat1, B. Ahmad1, N. Pandya1, K. Arvai1, A. Caruso1, S. Zeineddine1, A. Salloum1, S. Chowdhuri1, M. Badr2
- Tetraplegia is associated with increased hypoxic ventilatory response during NREM sleep. Vaughan, Sarah; Sankari, Abdulghani; Carroll, Sean; Eshraghi, Mehdi; Obiakor, Harold; Yarandi, Hossein; Chowdhuri, Susmita; Salloum, Anan; Badr, Safwan
- DRAFT Abstract "Periodic Legs Movements In Patients With Chronic Spinal Cord Injury" A. Sankari, A. Aldwaikat, S. Carroll, M. S. Badr

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	M. Safwan Badr, M.D.
Project Role:	PI
Researcher Identifier:	
Nearest person month worked:	40
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:	40
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:	37
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:	37
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:	37
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:	38
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:	Sean Carroll
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	39
Contribution to Project:	Mrs. Carroll 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 analysis.
Funding Support:	

Name:	Nishtha Pandya
Project Role:	Research Assistant
Researcher Identifier:	
Nearest person month worked:	39
Contribution to Project:	Ms. Pandya performed work related preparation of regulatory documents, participant recruitment, and scoring sleep studies.
Funding Support:	

7. SPECIAL REPORTING REQUIREMENTS:

Supporting documents.

8. APPENDICES:

None