Fiscal Year:	FY 2017	**Task Last Updated:**	FY 04/13/2017
PI Name:	Bershad, Eric M. M.D.		
Project Title:	SPACE-COT: Studying the Physiological and Anatomical Cerebral Effects of Carbon Dioxide and Tilt		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Smart Medical Systems and Technology Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **VIIP**:Risk of Spaceflight-Induced Intracranial Hypertension/Vision Alterations (IRP Rev E)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	Houston	**State:**	TX
Zip Code:	77030-3411	**Congressional District:**	9
Comments:			
Project Type:	GROUND	**Solicitation:**	Directed Research
Start Date:	05/01/2015	**End Date:**	12/31/2016
No. of Post Docs:	0	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	1	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: Extended to 12/31/2016 per NSBRI (Ed., 4/11/16)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Strangman, Gary Ph.D. (Massachusetts General Hospital) Kramer, Larry M.D. (The University of Texas Health Science Center at Houston)		
Grant/Contract No.:	NCC 9-58-SMST00008		
Performance Goal No.:			
Performance Goal Text:			

1. Original project aims/objectives
We studied the effects of carbon dioxide (CO2) and head down tilt (HDT) on brain physiology in a ground-based analog of spaceflight. Our major goal was to develop a quantitative approach to measuring brain physiological response to CO2 and fluid shifting, using modern technologies. These results will allow for monitoring of an individual astronaut's response to CO2 and microgravity related fluid shifts.

2. Key findings

Environmental conditions: Atmospheric CO2 levels were maintained at target levels during the experiment. Environmental parameters were recorded every minute. On days with ambient atmosphere the mean CO2 level was 0.04

± 0.01% whereas on days with increased ambient CO_2 the mean CO_2 level was 0.48 ± 0.02%.

General Health Indicators: 24 h pooled urine volume significantly increased from 2,533.8 ml during the baseline period to 3,038.5 ml during 12 HDT with ambient air ($p=0.04$) and from 2,671.8 ml during the baseline period to 3,185.2 ml during 12 HDT + 0.5% CO_2 ($p=0.03$); there was no significant main effect of atmosphere ($p=0.4$). No significant main effects of time or atmosphere were found for mean arterial pressure ($p=0.97$, $p=0.6$), systolic blood pressure ($p=0.5$, $p=0.6$), diastolic blood pressure ($p=0.5$, $p=0.8$), or heart rate ($p=0.2$, $p=0.4$).

Blood Parameters: WBC (white blood cell) count increased from baseline and was further aggravated by the short duration exposure to 3% CO_2. The observed increase in polymorphonuclear cells in our study is consistent with an acute stress response.

Vital signs: Blood pressure and heart rate did not significantly change from baseline to the late HDT time point in either the HDT alone or HDT with 0.5% CO_2 condition.

MRI brain: There was a 6-8% significant increase in internal carotid artery resistive index from baseline to HDT + ambient air and HDT + 3% CO_2. There was a 17-20% decrease in cerebral blood flow (CBF) from baseline to HDT + ambient air ($p=0.002$) or HDT + 0.5% CO_2 ($p=0.01$), which was partially reversed by brief 3% CO_2 exposure ($P=0.13$). There was a significant 21% increase in cerebrospinal fluid (CSF) velocity amplitude from baseline to HDT + 3% CO_2 following HDT + ambient air. There was a 2-3% increase in lateral ventricular CSF volume from baseline as compared to HDT + ambient air ($p=0.03$), and trend for HDT + 0.5% CO_2.

Non-invasive Intracranial pressure (ICP): No significant difference in ICP was detected between the HDT + 0.5% vs HDT + ambient air conditions.

Task Description:

Intraocular pressure (IOP): IOP increased significantly from baseline to initial HDT, $p < 0.001$ (both conditions combined), but did not increase further overtime; No significant difference between atmospheres.

Optical coherence tomography: No significant increases in retinal nerve fiber layer thickness was detected from baseline to end of HDT period in either atmosphere.

Transcranial Doppler: Mean cerebral blood flow velocities (MCBFVs) increased significantly ($p=0.01$) from baseline in the HDT + 0.5% CO_2 group. MCBFVs were significantly higher in the HDT + 0.5% CO_2 group compared to HDT + ambient air. MCBFVs were further increased with a brief 3% CO_2 exposure (2 hours) after both HDT + 0.5% CO_2 or HDT + ambient air.

Near infrared spectroscopy measurement of cerebral blood volume pulsatility: Cerebral blood volume pulsatility significantly increased over time both at cardiac frequencies and Mayer wave frequencies The Mayer-related pulsatility increase was significantly greater in 0.5% CO_2 than in ambient air (p Cognition: In contrast to expectations cognitive performance improved in several subtasks of cognition testing in the HDT + 0.5% CO_2 group as compared to HDT + ambient air, including motor praxis accuracy, visual object learning task, fractal 2-back (F2B) working memory, and psychomotor vigilance accuracy. This may be due to facilitation of cerebral blood flow in the 0.5% CO_2 condition as compared to the HDT alone condition.

3. Impact of key findings:

We demonstrated a significant decrease in CBF with HDT from the supine baseline to 12 degree HDT, regardless of atmosphere. This suggests that the effect of HDT on cerebral blood flow is more potent than the counteracting effects of sustained 0.5% CO_2. The short exposure to higher levels of CO_2 at 3% counteracted decreases in CBF. If the effects of microgravity on CBF are similar to the effects of HDT, then this may indicate the astronauts have decreased CBF on the International Space Station (ISS) as compared to Earth. Further work is needed to determine whether the decrease in CBF also correlates with cognitive effects. The results of cognitive testing from our study suggest that moderate increases in CO_2 are not harmful on cognition, which may be related to increased CBF.

We also determined that the :envihab facility was a suitable ground based analog to allow for precise adjustment of atmospheric conditions, and other environmental conditions similar to those on ISS, and with the infrastructure that allowed for integration of multiple technologies for physiological monitoring. This will allow for successful implementation of longer duration bed rest studies at :envihab with various experimental conditions, and help to shed light on several important spaceflight related conditions including the microgravity ocular syndrome (i.e., VIIP), and cognitive function, and others.

4. Proposed research plan for the coming year: Main data analysis is completed, two manuscripts are now accepted for publication in Journal of Applied Physiology, and further integrative analyses between body systems measured in SPACE-COT is ongoing.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

This study evaluated the effects of elevated carbon dioxide and head down tilt on the human body physiology, with a focus on the brain and cognitive effects. We observed that head down tilt resulted in a decrease in cerebral blood flow. This may have implications for body posture in patients in various setting where cerebral blood flow may be impaired including in the intensive care unit setting, emergency rooms, and in patients with ischemic stroke, subarachnoid hemorrhage, or traumatic brain injury. We determined that moderate levels of carbon dioxide were not associated with adverse cognitive effects, which is reassuring that breathing moderate elevated levels of carbon dioxide did not result in any observable cognitive effects. This may be relevant for Earth based atmospheres with ventilation that allows for accumulation of moderate CO_2 in the atmosphere. We evaluated various non-invasive technologies that may be useful for monitoring of neurological patients in various remote and austere environments. These may be useful for brain monitoring in conditions where expertise is not available on site for more invasive monitoring, or in patient populations where the risks of an invasive monitor are not warranted.

Task Progress:	Study enrollment successfully completed by July 2015. Data presented at various meetings including 66th Annual International Astronautical Congress, 2015; NASA Human Research Program (HRP) 2016 and NASA HRP 2017 meetings; ASMA (Aerospace Medical Association) meetings 2016. Several manuscripts were submitted for publication in Journal of Applied Physiology; three are now in press and available online (April 2017). Meeting with the NASA Human Systems Risk Board to discuss relevant findings from study in April 2016. SPACE-COT investigators meeting 2016 was completed, and formulation of strategy for further data analysis and publication of data completed.
Bibliography Type:	Description: (Last Updated: 10/30/2019)
Articles in Peer-reviewed Journals	Strangman GE, Zhang Q, Marshall-Goebel K, Mulder E, Stevens B, Clark JB, Bershad EM. "Increased cerebral blood volume pulsatility during head-down tilt with elevated carbon dioxide: The SPACE-COT Study." J Appl Physiol (1985). 2017 Jul 1;123(1):62-70. Epub 2017 Mar 30. http://dx.doi.org/ ; PubMed PMID: 28360122 , Jul-2017
Articles in Peer-reviewed Journals	Marshall-Goebel K, Mulder E, Donoviel D, Strangman G, Suarez JI, Venkatasubba Rao C, Frings-Meuthen P, Limper U, Rittweger J, Bershad EM. (the SPACECOT Investigators Group) "An international collaboration studying the physiological and anatomical cerebral effects of carbon dioxide during head-down tilt bed rest: The SPACECOT study." J Appl Physiol (1985). 2017 Jun 1;122(6):1398-405. Epub 2017 Feb 23. http://dx.doi.org/ ; PubMed PMID: 28235859 , Jun-2017
Articles in Peer-reviewed Journals	Kramer LA, Hasan KM, Sargsyan AE, Marshall-Goebel K, Rittweger J, Donoviel D, Higashi S, Mwangi B, Gerlach DA, Bershad EM. "Quantitative MRI volumetry, diffusivity, cerebrovascular flow and cranial hydrodynamics during head down tilt and hypercapnia: The SPACECOT study." J Appl Physiol (1985). 2017 May 1;122(5):1155-66. Epub 2017 Feb 16. http://dx.doi.org/ ; PubMed PMID: 28209740 , May-2017
Articles in Peer-reviewed Journals	Marshall-Goebel K, Stevens B, Rao CV, Suarez JI, Calvillo E, Arbeille P, Sangi-Haghpeykar H, Donoviel DB, Mulder E, Bershad EM. "Internal jugular vein volume during head-down tilt and carbon dioxide exposure in the SPACECOT study." Aerosp Med Hum Perform. 2018 Apr;89(4):351-6. https:// ; PubMed PMID: 29562964 , Apr-2018
Articles in Peer-reviewed Journals	Basner M, Nasrini J, Hermosillo E, McGuire S, Dinges DF, Moore TM, Gur RC, Rittweger J, Mulder E, Wittkowski M, Donoviel D, Stevens B, Bershad EM. "Effects of -12° head-down tilt with and without elevated levels of CO2 on cognitive performance: The SPACECOT study." J Appl Physiol (1985). 2018 Mar 1;124(3):750-60. Epub 2017 Dec 14. https:// ; PubMed PMID: 29357516 , Mar-2018