Fiscal Year:	FY 2021	**Task Last Updated:**	FY 07/01/2021
PI Name:	Diaz Artiles, Ana Ph.D.		
Project Title:	Predicting Acute Cardiovascular and Ocular Changes due to Changes in the Gravitational Vector and Effects of Countermeasures		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	Yes
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes (2) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	adartiles@tamu.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	617-909-0644
Organization Name:	Texas A&M University		
PI Address 1:	Aerospace Engineering Department		
PI Address 2:	701 Ross Street		
PI Web Page:			
City:	College Station	**State:**	TX
Zip Code:	77843-0001	**Congressional District:**	17
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2019 HERO 80JSC019N0001-FLAGSHIP & OMNIBUS: Human Research Program Crew Health. Appendix A&B
Start Date:	09/01/2020	**End Date:**	08/31/2022
No. of Post Docs:	0	**No. of PhD Degrees:**	
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:	5	**Monitoring Center:**	NASA JSC
Contact Monitor:	Stenger, Michael	**Contact Phone:**	281-483-1311
Contact Email:	michael.b.stenger@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 8/31/2022 per NSSC information (Ed., 8/13/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Dunbar, Bonnie Ph.D. (Texas A&M University)		
Grant/Contract No.:	80NSSC20K1521		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

Exposure to weightlessness results in the removal of hydrostatic pressure gradients and a permanent headward fluid shift, causing a redistribution of blood. Additionally, in space postural changes don't occur and thus, astronauts are not exposed to daily fluid shifts (between supine and upright postures) as we are on Earth. This has currently unknown consequences, but it might be related to a series of neuro-ocular and functional changes developed in some astronauts during both short and long-duration spaceflight, collectively known as Spaceflight Associated Neuro-Ocular Syndrome (SANS). While the exact etiology of SANS is currently unknown, chronic fluid redistribution affecting intravascular, interstitial, and cerebrospinal fluids and pressures is widely hypothesized to be a contributing factor. Additionally, recently demonstrated stagnant and retrograde blood flow and venous thrombosis in the left internal jugular vein during spaceflight could also be associated with sustained headward blood and tissue fluid shift.
Based on the current knowledge and hypotheses, countermeasures focused on producing hydrostatic gradients or reducing the microgravity-induced fluid shift, such as lower body negative pressure (LBNP) or centrifugation, become particularly interesting. LBNP shifts fluids from the head to the lower body is expected to reduce the translaminar pressure across the eye and thus, might prevent some of the ocular changes and remodeling associated with SANS. LBNP is also a promising countermeasure to enhance venous flow in the upper body. Similarly, head-to-foot (Gz) centrifugation also produces a fluid shift and induces hydrostatic gradients within the vessels in the body, which may also reduce intraocular pressure (IOP), reduce the translaminar pressure, and enhance venous flow. However, at present, it is not possible to estimate the overall physiological response (neither acute nor long term) of a particular "dose" of artificial gravity (AG) or LBNP, and more specifically and relevant to our purposes, the response in the upper body and around the eye. As a first step and in the context of this short project, we propose to focus on acute responses. Our objective is to generate acute gravitational dose-response curves of cardiovascular (CV) and ocular variables due to changes in the gravitational vector, with and without countermeasures. We propose to conduct a series of experimental studies (using tilt table, LBNP, and centrifugation), and combine the results with numerical modeling to leverage the advantages of both experimental and computational methodologies. Then, we propose to exert the full flexibility of the numerical framework to investigate CV and ocular responses in additional configurations where data collection is difficult, expensive, or infeasible.

A short-description of the experiments is shown below:

- Experiment 1: Tilt table. Subjects will be exposed to multiple tilt angles, from 45° HUT (head up tilt) to 45° HDT (head down tilt), in both prone and supine configurations. CV and ocular measures will be collected and used to generate gravitational dose-response curves as a function of tilt angle.

- Experiment 2: LBNP. Subjects will be exposed to multiple levels of negative pressure (from 0 to -50 mmHg), in both supine and 15° HDT. Similarly, CV and ocular measures will be collected and used to generate gravitational dose-response curves as a function of external pressure.

- Experiment 3: Centrifugation. Subjects will be exposed to multiple levels of artificial gravity on the human short-radius NASA centrifuge that is being relocated and installed at Texas A&M University (TAMU). CV and ocular measures will be collected and used to generate gravitational dose-response curves as a function of g-level.

In addition to the experiments, we will develop a numerical model from two different but complementary lumped-parameter models that have been previously validated and published in the literature: 1) A full-body model that provides an accurate simulation of short-term CV regulatory changes during changes in the gravitational vector (i.e., different tilt angles, centrifugation) and countermeasures (i.e., LBNP, exercise). This model features a more accurate body representation, including a cardiac pacemaker (i.e., pulsatile waveform), baroreceptor and cardiopulmonary feedback control of heart and arterial parameters, and a large number of compartments, particularly in the Gz direction, allowing for an improved representation of hydrostatic gradients in this direction and overall body hemodynamics. 2) An eye model that simulates volume/pressure alterations in the eye during gravitational changes. We will combine both approaches leveraging the advantages of each one of them into a unique more powerful and versatile model to study SANS, the cranial venous system, and other fluid shifts mechanisms and the effects of potential countermeasures. The model will be validated with the experimental data generated during the experiments.

Results from this investigation will inform current and future countermeasure development and in-flight prescriptions.

Rationale for HRP Directed Research:

Research Impact/Earth Benefits:

This project investigates the influence of gravity (or more generally fluid shifts) on cardiovascular and ocular responses using a variety of interventions, including tilt paradigms, Lower Body Negative Pressure (LBNP), and centrifugation. Results will provide critical information for current and future cardiovascular and ocular related countermeasures and in-flight prescriptions. In addition, this research effort has direct application to cardiovascular and ocular pathologies on Earth, for example, orthostatic hypotension and conditions related to cardiovascular regulation.

The objective of this ground-based research effort is to generate acute gravitational dose-response curves of cardiovascular and ocular variables when exposed to different types of orthostatic stress. We propose to use both experimental and computational approaches to leverage the advantages of each one of these research methodologies. Our study consists of three different ground experiments where the same 12 male subjects are exposed to different levels of tilt (from 45° HUT to 45° HDT, experiment 1), different levels of lower body negative pressure or LBNP (from 0 mmHg to -50 mmHg, in both supine and -15° HDT, experiment 2), and centrifugation (from 0g to 2g, measured at the center of mass, experiment 3). In all experiments we are collecting objective measures related to human performance and cardiovascular regulation, including continuous CV variables (Finapres NOVA), non-invasive cardiac output (Innocor, Innovision), ECG (electrocardiogram) and autonomic responses (Finapres NOVA), intraocular pressure (IOP) (I-care tonometer), brachial blood pressure for calibration (Omron), metabolic data (Innocor), blood volume (Blood Tec), Internal Jugular Vein (IJV) pressure (Vein Press), and cross-sectional areas of the IJV (left and right side) and the Common Carotid Arteries (CCA, left and right side) (Ultra sound VScan Extend). We will derive other metrics such as Ocular Perfusion Pressure. When possible, measurements are continuously monitored during the pre- (baseline), during-, and post-experimental testing (e.g., Finapres); otherwise, measurements are collected after an appropriate time of exposure to the intervention to ensure steady state (typically 5 min). During baseline, all data are also collected in upright seated position.
To date, we have successfully completed the first two experiments (i.e., tilt and LBNP), and data analysis is underway. For experiment 3, we are planning to use the Aerospace Human Centrifuge at TAMU, which is a NASA-funded facility

Task Progress:	that was formerly at the University of Texas Medical Branch (UTMB) in Galveston (TX). The final installation and check-out of the centrifuge are currently underway. This process has experienced important delays due to COVID, but we expect to have the centrifuge operational later this year. We are also investigating gravitational dose responses using modeling approaches. We are developing a comprehensive numerical framework capable of predicting the expected acute cardiovascular responses and ocular changes when exposed to different types of orthostatic stress. We will use our own experimental data to validate the model. To date, we modified an existing numerical model of the eye (Nelson et al., 2017) to model Intraocular Pressure (IOP) during a full range of tilt positions (360°, which covers both prone and supine positions). Experimental data collected in 13 subjects supported the hypothesis that IOP is statistically significantly higher in prone position than in supine position due to the extra hydrostatic column between the eye globe and the coronal plane, and this is true at most of the tilt angles investigated. Our modified version of the model successfully reproduced these results and a manuscript is currently in preparation. Additionally, we have conducted a comprehensive sensitive analysis in a “full body” numerical model (Diaz Artiles et al. 2019) to investigate individual differences in cardiovascular responses to orthostatic stress (Whittle and Diaz-Artiles 2021). Conditions simulated include constant gravity conditions (from 0g to 1g, in increments of 0.25g), and gravitation stress generated by a short-radius centrifuge, which induce a strong gravity gradient in the head-to-toe direction (from 0g to 1g, in increments of 0.25g, measured at the center of mass). Results from the constant gravity conditions show that model parameters related to the length, resistance, and compliance of the large veins and parameters related to right ventricular function have the most influence on model outcomes. For most outcome measures considered, parameters related to the heart are dominant. Results highlight which model parameters to accurately value in simulations of individual subjects’ CV response to gravitational stress, improving the accuracy of predictions. Influential parameters remain largely similar across gravity levels, highlighting that accurate model fitting in 1 g can increase the accuracy of predictive responses in reduced gravity. These research efforts have been captured in the following peer-reviewed publication: - Whittle R.S. and Diaz-Artiles A. “Modeling individual differences in cardiovascular response to gravitational stress using a sensitivity analysis.” Journal of Applied Physiology 2021, 130: 1983-2001 Similar analysis is currently being conducted in the centrifugation conditions and a manuscript is in preparation. Future modeling efforts include the integration of the “full body model” and “the eye model” to leverage the advantages of each one of them into a unique more powerful and versatile model to study SANS, the cranial venous system, and other fluid shifts mechanisms and the effects of potential countermeasures. References Nelson ES, Mulugeta L, Feola A, Raykin J, Myers JG, Samuels BC, Ethier CR. The impact of ocular hemodynamics and intracranial pressure on intraocular pressure during acute gravitational changes. J Appl Physiol 123: 352–363, 2017. Diaz-Artiles A, Heldt T, Young LR. Computational Model of Cardiovascular Response to Centrifugation and Lower-body Cycling Exercise. J Appl Physiol 127: 1453–1468, 2019. Whittle R.S. and Diaz-Artiles A. Modeling individual differences in cardiovascular response to gravitational stress using a sensitivity analysis. Journal of Applied Physiology 130: 1983-2001, 2021.
Bibliography Type:	Description: (Last Updated: 07/28/2023)
Abstracts for Journals and Proceedings	Whittle RS, Lee J, Sieker J, Petersen JCG, Petersen LG, Diaz-Artiles A. "Modeling changes in intraocular pressure associated with the physiological response to changes in the gravitational vector." 2021 AsMA 91st Annual Scientific Meeting, Denver, CO, August 29-September 2, 2021. AsMA 2021 Proceedings, in press as of July 2021. , Jul-2021
Abstracts for Journals and Proceedings	Whittle R, Keller N, Stapleton LM, Hall EA, Dunbar BJ, Diaz-Artiles A. "Acute gravitational dose-response curves in hemodynamic and ocular variables induced by tilt." International Society for Gravitational Physiology (ISGP) 2021 Meeting, Virtual, May 24-27, 2021. ISGP 2021 Proceedings. International Society for Gravitational Physiology (ISGP) 2021 Meeting, Virtual, May 24-27, 2021. , May-2021
Abstracts for Journals and Proceedings	Vellore H, Davis L, Karri A, Diaz-Artiles A. "Cardiovascular effects during parabolic flight: Literature review." International Society for Gravitational Physiology (ISGP) 2021 Meeting, Virtual, May 24-27, 2021. ISGP 2021 Proceedings. International Society for Gravitational Physiology (ISGP) 2021 Meeting, Virtual, May 24-27, 2021. , May-2021
Abstracts for Journals and Proceedings	Diaz-Artiles A, Whittle RS, Stapleton L, Dunbar BJ. "Predicting Acute Cardiovascular and Ocular Changes due to Changes in the Gravitational Vector." 2021 NASA Human Research Program Investigators’ Workshop, Virtual, February 1-4, 2021. Abstracts. 2021 NASA Human Research Program Investigators’ Workshop, Virtual, February 1-4, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Whittle RS, Diaz-Artiles A. "Modeling individual differences in cardiovascular response to gravitational stress using a sensitivity analysis." J Appl Physiol (1985). 2021 Jun;130(6):1983-2001. https://doi.org/10.1152/japplphysiol.00727.2020 ; PMID: 33914657 , Jun-2021
Papers from Meeting Proceedings	Whittle RS, Diaz Artiles A. "Metabolic Modeling in Altered-Gravity." 2020 IEEE Aerospace Conference, Big Sky, MT, March 7-14, 2020. IEEE Conference on Aerospace, March 2020. https://doi.org/10.1109/AERO47225.2020.9172582 , Mar-2020
Significant Media Coverage	Revels M. "The Human Research Program is funding two research proposals to study the effect of altered gravity on bimanual coordination and cardiovascular and ocular health." Texas A&M Today, January 15, 2021. https://today.tamu.edu/2021/01/15/nasa-funds-texas-am-research-on-effects-of-altered-gravity/ , Jan-2021