Fiscal Year:	FY 2021	**Task Last Updated:**	FY 10/14/2021
PI Name:	Ethier, Christopher Ph.D.		
Project Title:	Changes of the Optic Nerve Dura Mater in Astronauts and SANS (OPTIMA)		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
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Space Biology Special Category:	None		
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Comments:			
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No. of Post Docs:	1	**No. of PhD Degrees:**	
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No. of Bachelor's Candidates:	3	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/16/2021 per NSSC information (Ed., 7/7/20)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Laurie, Steven Ph.D. (KBR/NASA Johnson Space Center) Lee, Stuart Ph.D. (KBR/NASA Johnson Space Center) Loerch, Linda M.S. (NASA Johnson Space Center) Macias, Brandon Ph.D. (NASA Johnson Space Center) Martin, Bryn Ph.D. (University of Idaho, Moscow)		
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Task Description:	Astronauts experience multiple physiological changes during spaceflight. One such potential change is spaceflight associated neuro-ocular syndrome (SANS), a spectrum of ocular alterations that can affect sight. We do not understand why this occurs or how to prevent it. One hypothesis is that changes in the mechanical properties of the tissue sheath surrounding the optic nerve (the dura mater) can affect a sensitive region of the eye (the optic nerve head) where many alterations are observed in astronauts. Another hypothesis is that thickening of the choroid, a tissue within the eye that is known to swell during spaceflight, leads to abnormally large mechanical strains on the anterior part of the optic nerve head. Our central objective is to use existing, novel methods that we have developed to evaluate these hypotheses. First, we will compute the mechanical properties of the dura mater in astronauts, see whether these properties are different than in subjects who have not been in space, and see whether they correlate with the severity of SANS. To do so, we will use existing sets of magnetic resonance (MR) scans: one taken when the astronaut is lying supine, and the other taken when the astronaut is lying in 15 degree head-down tilt. By analyzing these images, and building a computational model of how the optic nerve sheath expands as fluid pressure changes within it due to head-down tilt, we can obtain a parameter of the dura mater known as the structural stiffness. Second, we will use an existing computational model to determine strains in the optic nerve head due to choroidal swelling, see if these strains are larger than those that occur on Earth, and see if they are related to the severity of SANS in astronauts. Choroidal swelling in space has already been measured using optical imaging technology, and thus we can immediately use our modeling approach with this data set. This work directly addresses the following stated goal of the Request for Applications (RFA): Quantification of the crew health and performance risks associated with human spaceflight for the various exploration missions. More specifically, it addresses two needs identified by NASA related to SANS. First, we do not know the etiological mechanisms and contributing risk factors for ocular structural and functional changes seen inflight and postflight, and this work could help determine such factors. Second, we need a set of validated and minimally obtrusive diagnostic tools to measure and monitor changes in intracranial pressure, ocular structure, and ocular function. The tools we propose to use will measure the function of a key ocular structure, namely the optic nerve sheath.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Spaceflight associated neuro-ocular syndrome (SANS) is similar in some respects to a terrestrial condition, idiopathic intracranial hypertension (IIH). Our understanding of IIH, and conditions in which choroidal swelling occurs, will benefit from this research.
Task Progress:	Overview: The objective of this grant was to quantify the strain induced in pre-laminar neural tissue due to in-flight choroidal swelling, using existing Optical Coherence Tomography (OCT) data and our existing finite element model. This is relevant to understanding how exposure to microgravity can cause physiological and pathophysiological changes in the human eye known as spaceflight associated neuro-ocular syndrome (SANS). Due to technology limitations and ethical reasons, numerical models are an attractive approach for determining biomechanical behavior that cannot be measured via existing imaging methods, and thus potentially provide insights into SANS. In order to create an accurate finite element method (FEM) model of the posterior eye, the model incorporated data obtained from OCT scans of astronauts in pre-flight and in-flight conditions. The OCT images provided data such as geometries of tissue components in the posterior eye and the amount of choroidal and retinal swelling during spaceflight. This data was used to generate the 3D geometry of the posterior eye and to apply suitable loading conditions for the FEM model. We then used the FEM model to determine strains in the optic nerve head due to choroidal swelling, with the goal of seeing if these strains are larger than those that occur on Earth. Accomplishments 1) Segmentation: The first step in the analysis of images is segmentation. We segmented tissues of the posterior eye from pre-flight OCT scans of astronauts in the seated position, focusing on a radial B-scan oriented 7.5 degrees inferiorly from the nasal-temporal line, which coincides with a line connecting the centers of the optic nerve head and fovea. After applying compensation to the radial B-scan, tissue boundaries were manually delineated in the custom software Multiview. The inner limiting membrane (ILM), retina, choroid, and sclera boundaries were delineated. Due to limitations of the OCT resolution, tissue boundaries of the lamina cribrosa (LC), optic nerve (ON), and dura mater were outlined as a generic model based on histologic images of the region. OCT scans of 4 astronauts were used. Segmentations from two individual observers were compared and the segmentation was finalized through a discussion between the observers to resolve any disagreements. The segmented tissue boundaries were used to establish a finite element model of the posterior eye. 2) Finite element model: 3-dimensional axisymmetric finite element models were established using the segmentations of OCT scans. The models contain retinal nerve fiber layer (RNFL), retina, choroid, sclera, LC, ON, and dura mater. Our preliminary results showed that whether Bruch's membrane (BM) is or is not included in the model did not result in significant differences in predicted displacement and strain in neighboring tissues (less than 5% difference). Since BM is very thin, which makes it challenging to mesh for finite element modeling, we did not include the tissue in the models. All tissue layers were extended circularly from the lateral margin of radial B-scans to make a globe with a typical eye globe radius of 12 mm. The boundaries of ON and dura mater at the posterior margin of the radial B-scan were extended posteriorly to 25 mm away from the posterior surface of the LC, where the tissues are constrained by the optic canal. A computational mesh was constructed using the commercial Ansys ICEM CFD software to conduct the finite element analysis. Tri-elements were used on the tissues within the radial B-scan for dealing with the complicated boundaries, and quad-elements were used on the extended area outside of the radial B-scan for reducing the number of elements. The 2-dimensional mesh elements were rotated around the anterior-posterior axis passing through the center of the optic nerve head (ONH) by 1 degree to build a 3-dimensional wedge domain and conduct an axisymmetric analysis. All tissues were modeled as incompressible isotropic hyperelastic neo-Hookean materials. 3) FEM results: Choroidal swelling causes strain concentration in the RNFL and posterior shift of Bruch's membrane opening (BMO): When choroidal swelling was applied without retinal swelling and intracranial pressure (ICP) change, strain concentrations in the RNFL, especially near the BMO, were observed in all subjects, while strain concentration in the post-lamina neural tissue depended on the detailed anatomy. BMO moved posteriorly due to choroidal swelling, as observed in comparison between pre- and post-flight astronauts in a previous study. The difference in stiffness between RNFL and sclera may explain the posterior movement of BMO, since the RNFL is softer and more easily stretched than the stiffer sclera, leading to posterior shift of the choroidal tip as the choroid swells. Retinal swelling causeS strain concentration in the RNFL: Retinal swelling caused strain concentration in the RNFL, especially near the BMO. Retinal swelling did not cause strain concentration in any other region. ICP elevation causes deformation of dura mater and moderate strain over all neural tissue regions, not concentrated on RNFL: ICP elevation

	from 0 to 10 mmHg caused displacement of the dura mater outward, representing inflation of the subarachnoid space. This caused a moderate amount of strain over all regions of neural tissues but the strain was not concentrated in the RNFL. Combination of effects of choroidal swelling, retinal swelling and ICP change: The effects on strain distribution due to choroidal swelling, retinal swelling, and increased ICP were additive. However, the dominant effect was due to choroidal swelling. There was a discrepancy between the measured displacement of Bruch's membrane opening (as observed by OCT) and that predicted by the models. We considered many possible causes for this discrepancy, and although we cannot definitively identify the cause, we suspect it may be related to OCT image alignment algorithms. Conclusions • Both retinal and choroidal swelling cause mechanical insult to be delivered to retinal ganglion cell (RGC) axons in the peripapillary region. These effects are dominated by choroidal swelling, are subject-specific, and are synergistic with changes in ICP. • Discrepancies between computed and measured values of Bruch’s membrane opening displacement (BMOd) should be resolved and may involve both measurement and modeling limitations. As a first step, a more thorough investigation of possible errors related to OCT alignment algorithms is recommended. • The magnitude of choroidal swelling observed by OCT in astronauts likely leads to pathological levels of mechanical insult being delivered to RGC axons, which may contribute to the observed papilledema seen in SANS and could negatively affect visual function if sustained chronically. Further investigation into such effects are strongly recommended, e.g., studying the relationship between predicted RGC axon strain and severity of SANS, quantified using Frisen grade.
Bibliography Type:	Description: (Last Updated: 11/26/2021)
Abstracts for Journals and Proceedings	Ethier CR, Lee C, Ferguson C, Pardon L, Laurie S, Macias B. "Impact of choroidal swelling on axonal biomechanical insult in astronauts." 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	Sater SH, Sass AM, Rohr JJ, Marshall-Goebel K, Ploutz-Snyder RJ, Ethier CR, Stenger MB, Kramer LA, Martin BA, Macias BR. "Automated MRI-based quantification of posterior ocular globe flattening and recovery after long-duration spaceflight." Eye (Lond). 2021 Jul;35(7):1869-78. https://doi.org/10.1038/s41433-021-01408-1 ; PMID: 33514895; PMCID: PMC8225832 , Jul-2021
Articles in Peer-reviewed Journals	Sater SH, Sass AM, Seiner A, Natividad GC, Shrestha D, Fu AQ, Oshinski JN, Ethier CR, Martin BA. "MRI-based quantification of ophthalmic changes in healthy volunteers during acute 15° head-down tilt as an analogue to microgravity." J R Soc Interface. 2021 Apr;18(177):20200920. https://doi.org/10.1098/rsif.2020.0920 ; PMID: 33906382; PMCID: PMC8086909 , Apr-2021