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PI Name:	Thomas, James David M.D.		
Project Title:	Impact of Long Duration Space Flight on Cardiac Structure and Function		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Cardiovascular Alterations Team		
Joint Agency Name:	TechPort:	No	
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		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	44195-0001	Congressional District:	11
Comments:			
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Contact Monitor:	Contact Phone:		
Contact Email:			
Flight Program:			
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Key Personnel Changes/Previous PI:	NOTE: PI change to Zoran Popovic, M.D., Ph.D. in August 2014, per NSBRI (Ed., 1/8/15)		
COI Name (Institution):	Popovic, Zoran (The Cleveland Clinic Foundation) Bungo, Michael (The University of Texas Health Science Center at Houston) Martin, David (NASA Kennedy Space Center) Greenberg, Neil (The Cleveland Clinic Foundation) Borowski, Allen (The Cleveland Clinic Foundation) Levine, Benjamin (The University of Texas Southwestern Medical Center at Dallas) Kassemi, Mohammad (NASA Glenn Research Center)		
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Task Description:

As astronauts venture farther into space, the impact of long-term microgravity on cardiovascular function may become a critical limitation to mission safety and success. In order to better understand the impact of long-term spaceflight on the structure and function of the heart, the PI is already involved in echocardiographic analysis of the most detailed study of the heart in space ever undertaken. Unfortunately, the echocardiograph on the International Space Station is more than a decade old and does not provide contemporary information on cardiac function, such as strain (the best measure of regional and global contraction of the muscle) and torsion (the twisting motion of the heart that links the pumping and filling functions of the ventricle). Our first task in this proposal is to develop and validate methodology to extract strain and torsion from space station echoes and then combine it with the numerous pre- and post-flight studies that will be conducted over the next four years. From these data, we will have a comprehensive view of the heart in space, information which will be integrated into evolving mathematical models of the heart that the PI and collaborators have developed, and which will be made available to the general NASA community via integration into the Digital Astronaut project. Finally, the PI and colleagues are involved extensively in the development of the next generation of echo machines and have the unique opportunity to develop and validate advanced applications for space use. We will focus on massively parallelized echo machines capable of real-time 3D imaging with automated volume measurements and comprehensive 3D strain and torsion analysis. As these machines become smaller over time, they will provide the ideal diagnostic tool for future space missions, be they to low Earth orbit, a Lagrangian point, the moon, or even Mars. Exposure to microgravity induces short and long-term changes in the cardiovascular system, with cardiac atrophy, orthostatic hypotension, and impaired thermoregulation being the most recognizable. The most obvious issue, noted in the majority of astronauts after long-term space flight, is orthostatic hypotension. While its importance is clear, the etiology remains uncertain, with proposed mechanisms including hypovolemia, impaired baroreflexes, and left ventricular atrophy leading to systolic and/or diastolic dysfunction.

In order to better define these issues, NASA is currently conducting Flight Study E377, Cardiac Atrophy and Diastolic Dysfunction During and After Long Duration Spaceflight: Functional Consequences for Orthostatic Intolerance, Exercise Capacity, and Risk of Cardiac Arrhythmias (Ben Levine and Mike Bungo, Co-PIs, both of whom are Co-Is on this application). This program is also termed the Integrated Cardiovascular Study, or ICV. As part of this investigation, detailed imaging studies are conducted on astronauts before, during, and after space flight, including an extensive series of in-flight resting and exercise echocardiograms. The PI monitors all in-flight echoes remotely in real-time, and he and his colleagues at the Cleveland Clinic serve as the echocardiographic core lab for this study. We thus are in a unique position to guide on-flight acquisition as well as perform detailed examination of the ultrasound studies received. However, ICV was initially proposed in 1999 with echocardiographic techniques that are now over ten years old, focusing mainly on ventricular size, mass, and simple measures of systolic function, such as ejection fraction and stroke volume. Echocardiography has advanced considerably since then in the sophisticated ventricular mechanical data that can be extracted from ultrasound data.

In the current proposal, we wish to validate extraction of these novel echocardiographic indices of ventricular mechanics (two-dimensional strain and torsion, among others) from the in-flight data acquired on the 10-year-old HDI-5000 ultrasound system aboard the International Space Station, which was never designed to provide such data. Once validated, we will be able to derive detailed regional ventricular mechanics from all of our in-flight studies, allowing direct comparison with the pre- and post-flight examinations to gain a much better understanding of the magnitude and time course of structural and functional changes in the cardiovascular system in microgravity. These enhanced data from ICV will provide the ideal input for mathematical modeling of the cardiovascular system in space. The PI and colleagues have long experience with mathematical modeling ranging from lumped parameter models to 2D structural models to full 3D finite element models. We will apply the structural and strain data from ICV to our evolving numerical models of the cardiovascular system. To model atrophy of the heart, we will use the actual astronaut geometry from pre- and post-flight examinations, to build realistic 3D finite element models. Chamber behavior will be extracted for use in our less computationally intense lumped parameter model. Such modeling will be made available to the NASA community to enhance the comprehensive Digital Astronaut model.

Finally, looking toward a future of long duration missions to the moon and on to Mars, we anticipate that even more sophisticated ultrasound data will be available through the expected commercial development of hand-held three-dimensional echocardiographs. Our group stands in a unique position to capitalize on these developments and to validate their eventual use in the manned space program. For all of these reasons, we believe this proposal is quite responsive to the charge to the Cardiovascular Alterations Team.

Rationale for HRP Directed Research:**Research Impact/Earth Benefits:**

Several aspects of this project are already generating significant real-world benefits with many more anticipated in the future. Our work attempting to harmonize strain measurements across platforms has pointed out intervendor variability that significantly limits penetration of strain echocardiography into clinical practice. To address this, I have (in my role of President of the American Society of Echocardiography) convened a task force in collaboration with the European Association of Echocardiography and technical representatives from multiple vendors (GE, Siemens, Philips, Toshiba, Esaote, Ziosoft, Zonare, among others). We have proposed a multipronged validation protocol, consisting of synthetic datasets, animal experiments, and clinical validation at upcoming international congresses. In addition, we have engaged the DICOM (Digital Imaging and Communications in Medicine) committee with 2 proposals: 1) development of a new standardized format for storing raw ultrasound data (ideal for strain measurements) and 2) development of standardized nomenclature for advanced mechanics parameters, so analysis packages of the various vendors can communicate their results with each other and between data and picture archives. Additionally, the modeling work being done in Cleveland and Auckland, while designed to allow simulation of the impact of physiological stressors in space flight on the cardiovascular system, will have widespread applicability in cardiology. For example, the user interface developed in Auckland allows any DICOM echocardiogram to be read into the program, segmentation and strain analysis to be performed, and then modeling of that heart using pre-existing fiber models of the ventricle. Once refined and validated, this should allow analysis of patients with regional and global dysfunction, as well as those with valvular heart disease. Work is also underway to allow 3D echoes to be read directly into the interface, including the full strain tensor as reported throughout the 3D space (Toshiba machine). Finally, we have leveraged our work in 3D echocardiographic strain to participate in an international consortium to establish normal values for global and regional 3D strain. 3D echocardiography is undergoing rapid development and this work will help to set normative standards against which clinical acquisitions can be compared.

Task Progress:	<p>Specific Aim 1: Validate strain and torsion data from HDI-5000 data: Due to difference of in-flight and pre/post flight testing systems, test use Velocity Vector Imaging (VVI) to extract strain and torsion from the HDI-5000 data that will agree with data from the same subjects analyzed on an IE-33 system. We have completed a study of 100 subjects at Cleveland Clinic, demonstrating strong correlation ($r=0.9$) between strain measurements on different platforms.</p> <p>Specific Aim 2: Quantitative analysis of echo data: compare the temporal evolution of LV volume, mass, and function with echo, MRI, and hemodynamic data. All pre-, post-, and in-flight echocardiographic data obtained for the Integrated Cardiovascular Study (E377) has been measured. Analysis of this data continues, but presentations of interim results have been made on the impact of microgravity on cardiac shape and strain.</p> <p>Specific Aim 3: Integration of the pre-, in-, and post-flight data into evolving numerical models of the cardiovascular system. (A) In collaboration with the Auckland Bioengineering Institute, an approach for integrated cardiac function modeling and analysis has been developed. A comprehensive computer model of the cardiovascular system was developed specifically for NASA and NSBRI. This model transforms anatomic images of the heart into representations of the myocardial architecture, converting strain in the longitudinal, circumferential, and radial directions into actual myofibril shortening. This framework has been installed at the Cleveland Clinic for cardiac consultant trials.</p> <p>(B) In collaboration with the National Center for Space Exploration Research (NCSER) at the NASA Glenn Research Center an Orthotropic 3D Finite Element Heart Model is being utilized for the Prediction of Cardiac Gravitational Deformation and Stress Distribution. A finite element model of the heart is developed to investigate the impact of different gravitational loadings of Earth, Mars, Moon, and Microgravity on the cardiac shape and strain/stress distributions in the left ventricle.</p> <p>Specific Aim 4: Derivation of ventricular mechanics from three-dimensional echocardiography: propose to work closely with emerging three-dimensional echocardiographic units to develop and validate speckle tracking algorithms utilizing three-dimensional data. Investigation on the definition of normal values for 3D strain data is ongoing with an International Consortium with Toshiba Medical. Utilization of Philips 3D native data for post-processing is currently being explored in collaboration with Ivan Salgo (Philips).</p>
Bibliography Type:	Description: (Last Updated: 04/09/2019)
Abstracts for Journals and Proceedings	<p>Negishi K, Popovic ZB, Greenberg N, Borowaski A, Martin DS, Bungo MG, Levine BD, Thomas JD. "Impact of Spaceflight on intra-ventricular pressure gradient: An interim analysis from the integrated cardiovascular study." 2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013.</p> <p>2013 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-14, 2013. , Feb-2013</p>
Articles in Peer-reviewed Journals	<p>Iskovitz I, Kassemi M, Thomas JD. "Impact of weightlessness on cardiac shape and left ventricular stress/strain distributions." J Biomech Eng. 2013 Dec;135(12):121008. http://dx.doi.org/10.1115/1.4025464 ; PubMed PMID: 24048335 , Dec-2013</p>
Articles in Peer-reviewed Journals	<p>Gladding PA, Cave A, Zareian M, Smith K, Hussan J, Hunter P, Erogbogbo F, Aguilar Z, Martin DS, Chan E, Homer ML, Shevade AV, Kassemi M, Thomas JD, Schlegel TT. "Open access integrated therapeutic and diagnostic platforms for personalized cardiovascular medicine." J Pers Med. 2013 Aug 21;3(3):203-37. http://dx.doi.org/10.3390/jpm3030203 ; PubMed PMID: 25562653 ; PubMed Central PMCID: PMC4251391 , Aug-2013</p>
Articles in Peer-reviewed Journals	<p>Negishi K, Borowski AG, Popovic ZB, Greenberg NL, Martin DS, Bungo MW, Levine BD, Thomas JD. "Effect of gravitational gradients on cardiac filling and performance." J Am Soc Echocardiogr. 2017 Dec;30(12):1180-8. https://doi.org/10.1016/j.echo.2017.08.005 ; PubMed PMID: 29056408 , Dec-2017</p>
Awards	<p>Iskovitz I, Kassemi M, Thomas JD. "Recipient of the best paper award. 2nd International Conference on Mechanical Engineering and Mechatronics (ICMEM'13), Toronto, Canada, August 9-9, 2013." Aug-2013</p>
Papers from Meeting Proceedings	<p>Iskovitz I, Kassemi M, Thomas JD. "Impact of Gravitational and Pressure Loading on Cardiac Shape and Stress/Strain Distributions Using the Finite Element Method." 7th MIT Conference on Computational Fluid and Solid Mechanics: Multiphysics and Multiscale, Cambridge, MA, June 12-14, 2013.</p> <p>7th MIT Conference on Computational Fluid and Solid Mechanics: Multiphysics and Multiscale, Cambridge, MA, June 12-14, 2013. , Jun-2013</p>
Papers from Meeting Proceedings	<p>Iskovitz I, Kassemi M, Thomas JD. "Gravitational Effects on Cardiac Shape and Stress." 2nd International Conference on Mechanical Engineering and Mechatronics (ICMEM'13), Toronto, Canada, August 8-9, 2013.</p> <p>2nd International Conference on Mechanical Engineering and Mechatronics (ICMEM'13), Toronto, Canada, August 8-9, 2013. Paper 197. , Aug-2013</p>