Fiscal Year:	FY 2011	**Task Last Updated:**	FY 10/12/2011
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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:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2009 Crew Health NNJ09ZSA002N
Start Date:	05/01/2010	**End Date:**	09/30/2014
No. of Post Docs:	5	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**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:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Popovic, Zoran (The Cleveland Clinic Foundation) Bungo, Michael (University Of Texas, Houston) Martin, David (Wyle Laboratories, Inc.) 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)		
Grant/Contract No.:	NCC 9-58-CA02203		
Performance Goal No.:			
Performance Goal Text:			

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:	Task 1: Strain validation is ongoing but comparisons of Polar (EchoPAC) vs DICOM (Velocity Vector Imaging, VVI) data have been performed and shown at ACC 2011 (American College of Cardiology; featured abstract with press release) and ASE 2011 (American Society of Echocardiography; featured oral presentation). Work on regional strain validation has been accepted for presentation at the AHA2011 Conference. Validation project extension has been approved by IRB to exam pediatric population as well. Goal: Analyze > 100 studies, with manuscript submission by year's end. Customized software has been created to run validation statistics in a semi-automated fashion. Interplatform analysis of strain data is ongoing comparing these ultrasound modalities: GE Vivid 7, Philips HDI5000, and Philips iE33. Task 2: All 2D and Doppler parameters have been measured for pre-, in-, and post-flight studies for all enrolled subjects (>10,000 measurements). There are insufficient subjects enrolled at this time to perform hypothesis testing, but interim analysis for safety has shown no areas of concern (e.g., ejection fraction varied from 65.2+/-5.6% preflight to 64.0+/-6.7% inflight to 67.7+/-4.4% postflight). 3D and advanced mechanics measurements are on-going. Task 3: Completed software to segment ultrasound images and fit a finite-element mesh to the left ventricle. From an ApLAx view, the software segments and fits a mesh, subject to user verification, in a vendor independent manner from DICOM images. Strain analysis is based on mesh deformation. Embedding muscle-fibre structure allows fiber strain to be calculated. Presented Poster and Oral Abstract at American Society of Echocardiography 2011 Annual Conference. For the actual modeling, a rigorous orthotropic material model was developed to capture the nearly incompressible cardiac tissue together with the nonlinear elastic characteristics of the muscle fibers and laminae. To simulate the structural response of the heart at end-diastole in 1g and microgravity, this orthotropic model was incorporated into a comprehensive 3D finite element structural model of the heart, based on fiber and laminae sheet architecture of the left and right ventricles provided by P. Hunter's group at University of Auckland. The model was implemented into the finite element code, ADINA, validated on a global level against intact whole heart in-vitro pressure-volume inflation data, and then used to predict and assess the impact of the gravitational field on the shape of the heart at end-diastole. The effect of gravity on the sphericity of the heart (ratio of LV long to short axis) has been shown for the different gravitational levels of Earth, Moon, Mars, and orbiting spacecraft (see uploaded file). Task 4: To begin assessment of 3D strain acquisitions, we have implemented a protocol using the GE Vivid E9 to acquire both 2D and 3D strain in a variety of clinical patients. Early analysis suggests slight underestimation of longitudinal strain by 3D, likely related to lower frame rate.
Bibliography Type:	Description: (Last Updated: 04/09/2019)
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