Fiscal Year:	FY 2005	**Task Last Updated:**	FY 10/27/2005
PI Name:	Thomas, James David M.D.		
Project Title:	Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity		
Division Name:	Human Research		
Program/Discipline:	NSBRI Teams		
Program/Discipline--Element/Subdiscipline:	NSBRI Teams--Smart Medical Systems 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		
PI Email:	thomasj@ccf.org	**Fax:**	FY 216-445-7306
PI Organization Type:	NON-PROFIT	**Phone:**	216-445-6312
Organization Name:	The Cleveland Clinic Foundation		
PI Address 1:	Cardiovascular Medicine		
PI Address 2:	9500 Euclid Ave		
PI Web Page:			
City:	Cleveland	**State:**	OH
Zip Code:	44195-0001	**Congressional District:**	11
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2003 Biomedical Research & Countermeasures 03-OBPR-04
Start Date:	08/01/2004	**End Date:**	07/31/2008
No. of Post Docs:	2	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	2
No. of Master's Candidates:	2	**No. of Bachelor's Degrees:**	2
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Garcia, Mario (The Cleveland Clinic Foundation) Greenberg, Neil (The Cleveland Clinic Foundation) Deserranno, Dimitri (Case Western Reserve University) Kassemi, Mohammad (NASA GRC) Freed, Alan (NASA GRC) Notomi, Yuichi (The Cleveland Clinic Foundation) Popovic, Zoran (The Cleveland Clinic Foundation) Setser, Randolph (The Cleveland Clinic Foundation) Sallach, John (The Cleveland Clinic Foundation) Penn, Marc (The Cleveland Clinic Foundation) Rodriguez, Luis (The Cleveland Clinic Foundation)		
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Task Description:	Among the most serious of the risks identified by NASA in the area of cardiovascular alterations are serious dysrhythmias and the development of orthostatic intolerance. Prolonged exposure to microgravity may lead to a reduction in cardiac performance, particularly during times of stress and that undiagnosed cardiovascular disease may manifest during long missions. The PI and colleagues have worked closely with NASA and NSBRI over the last six years to optimize use of ultrasound in the space program as an investigative modality, addressing fundamental cardiovascular problems in need of countermeasures development. We propose the following specific aims: 1)Extension of work to calculate two-dimensional myocardial strain, improving sensitivity for detecting preclinical alterations in cardiac function. 2)Since early cardiac disease is usually manifest initially during exercise stress, we will develop and validate the tools to apply 2D strain in graded exercise to detect myocardial dysfunction in its earliest phases, allowing both diagnostic capabilities and a means of judging exercise as a countermeasure. 3)To continue our ongoing study of the magnitude and predictors of LV mass regression following acute volume and pressure unloading as a ground-based analog for manned spaceflight. This work will continue to focus on patients undergoing aortic valve surgery, but exploit recent knowledge of the roles of cytokines and integrins involved in cardiac hypertrophy and regression as well as emerging technologies such as gene chip analysis. 4)To develop, in collaboration with OBPR Fundamental Physics scientists from Glenn, a sophisticated fluid-structure model of the left ventricle constrained by the pericardium to investigate the impact that microgravity has on unloading the heart by a removal of pericardial constraint. This work will be closely focused on risks and critical questions identified by the Cardiovascular Alterations Team as described in the Bioastronautics Critical Path Road Map Baseline Document. If successful, this project will enhance assessment of cardiac function during long duration missions and potentially suggest cytokine promoters or signal transduction pathways that could be targeted for cardiac atrophy countermeasures. In addition, we will continue to provide the facilities of our Core laboratory for access by investigators throughout the NASA and NSBRI programs in need of assistance in acquiring or analyzing ultrasonic data.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	• Assessment of 2D strain and torsion will have an extensive application in earth-based clinical and research cardiology and might be expected to supplant Doppler methods. The 3D fluid-structure model of the left ventricle will also have an extensive application in earth-based research cardiology allowing investigators to alter fundamental inputs for myocardial function and assess the effects on ventricular performance. Wireless telemedicine systems for ultrasound enable transfer of ultrasound data within the hospital and remotely to workstations connected to our network. We have continued to investigate three-dimensional ultrasound capabilities. To date, we have performed over 3000 patient examinations with real-time 3D echocardiography. Building on our experience with the Volumetrics system, we have begun to use much improved acquisition devices (Philips Sonos 7500, and GE Medical Vivid 7) to obtain 3D examinations in a wide variety of cardiac pathologies. We have worked on the registration of CT and ultrasound data for improved understanding of both valvular and ventricular function. We are investigating prosthetic valve motion using both modalities to see if 3D ultrasound is able to noninvasively assess function. We are also working on the registration of 3D ultrasound data with nuclear medicine images for assessment of cardiac perfusion.
Task Progress:	AIM 1: NEW TECHNIQUES TO ASSESS CARDIAC FUNCTION IN SPACE Strain is the best measure of regional ventricular contraction. We recently published normal age-corrected values for tissue velocity, displacement, strain, and strain rate and have begun work on a novel method to quantify 2D strain from B-mode ultrasound. We have previously validated measurement of intraventricular pressure gradients (IVPG) from color Doppler M-mode echos, and recently used them to document improvement in cardiac suction (1.5 ± 0.2 to 2.6 ± 0.3 mmHg, $p<0.001$) following septal ablation in hypertrophic cardiomyopathy. Torsion, the wringing motion of the heart, stores energy in systole and releases it in diastole to assist in the low-pressure filling of the heart. We have validated (against MRI) measurement of torsion by Doppler tissue imaging (r=0.95) [published in Circulation] and 2D speckle tracking (r=0.93) [published in JACC] and used it to document the complex maturation of ventricular contraction from $5.8\pm1{\cdot}3°$ in infancy to $13.8\pm3{\cdot}3°$ in mid-adulthood (Lancet, submitted). AIM 2: USE EXERCISE ECHO TO DETECT SUBCLINICAL CARDIAC DYSFUNCTION We have shown that the ability to augment IVPG is the best predictor of maximum exercise capacity (r=0.8, AJP, in press), and that the release of ventricular torsion during the isovolumic relaxation period is closely correlated (r=0.72) with IVPG, thereby linking systolic contraction to diastolic filling (AJP, submitted). AIM 3: ASSESS GENETIC PREDICTORS OF MASS REGRESSION FOLLOWING UNLOADING Cardiac atrophy may be a serious limitation in long-term space flight, and understanding its significance and genetic determinants is critical to designing appropriate countermeasures. We have shown by 3D echo that aortic valve replacement can result in up to 50% mass reduction in patients with aortic insufficiency of stenosis. We are continuing this study obtaining comprehensive echo studies pre and post-op (3, 7 days, 6, 12 months) with volumes, mass, ejection fraction, strain, torsion, and IVPG. In addition intraoperative myocardial biopsies will be obtained pre-pump and just before closing chest and analyzed with gene chips targeting apoptosis, inflammatory cytokines and receptors, NFKB signaling pathway, and modulators of the extracellular matrix, verified with real-time PCR. AIM 4: DEVELOP A 3D FLUID-STRUCTURE INTERACTION MODEL OF THE HEART Coding has been completed on a full 3D model of the left ventricle, using realistic myocardial fiber architecture and calcium-transient-based contraction and relaxation coupled with full Navier-Stokes description of blood flow. Although computationally intensive (~1 week on 8-CPU supercomputer), it will be unique in its ability to assess the impact on LV function and IVPG of 1) generalized atrophy; 2) localized infarction; 3) dyssynchrony; 4) hypertension. A less computationally intensive 2D model has demonstrated the relationship between IVPG,
Bibliography Type:	Description: (Last Updated: 04/09/2019)
Articles in Peer-reviewed Journals	401. Qin JX, Shiota T, Tsujino H, Saracino G, White RD, Greenberg NL, Kwan J, Popovic ZB, Agler DA, Stewart WJ, Thomas JD "Mitral annular motion as a surrogate for left ventricular ejection fraction: real-time three-dimensional echocardiography and magnetic resonance imaging studies" N/A , Jan-2004
Articles in Peer-reviewed Journals	Notomi Y, et al "Enhanced Ventricular Untwisting During Exercise: A Mechanistic Manifestation of Elastic Recoil Described by Doppler Tissue Imaging" N/A , Jan-2004
Articles in Peer-reviewed Journals	Notomi Y, et al "Ventricular Torsional Mechanics in Patients Receiving Cardiac Resynchronization Therapy" N/A , Jan-2004

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Articles in Peer-reviewed Journals	Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, Thomas JD "Measurement of Ventricular Torsion by Two-Dimensional Ultrasound Speckle Tracking Imaging" N/A , Jun-2005
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