Fiscal Year:	FY 2006	**Task Last Updated:**	FY 08/21/2007
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--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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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:	1	**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) Rodriguez, Luis (The Cleveland Clinic Foundation) 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)		
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Performance Goal No.:			
Performance Goal Text:			

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 We pursue work on linear and shear strains, regional measures of ventricular mechanics, and torsion, the wringing motion of the heart that reflects shear strain. We have validated (against MRI) measurement of torsion by Doppler tissue imaging (r=0.95) [Circulation] and 2D speckle tracking (r=0.93) [JACC]. We used these techniques to document the maturation of ventricular contraction from 5.8±1·3° in infancy to 13.8±3·3° in mid-adulthood (Circulation), and to document the link between the torsion and left ventricular filling during exercise. We also started the experimental work on the assessment of factors that affect strain, most important of which is myocardial ischemia. We are currently validating the response of subendocardial vs. subepicardial strains on the effects of ischemia. We developed a model that uses sonomicrometric crystals as a gold standard of strain measurements and are currently developing, with the collaboration of industry, the software that would separately analyze subendocardial strains. 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, published), 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). We have also shown that the loss of IVPG during exercise is strongly linked to the loss of untwisting velocity to (r=0.75) and to the loss of torsion (Circulation). 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. 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. We also constructed a novel lumped-parameter model of the cardiovascular system, based on the calcium transients (instead of our previous model that was based on fixed systolic elastance). This novel model currently in press in Ann Biomed Eng, shows more realistic hemodynamics than the previous one, and is used to as an input to the 3D fluid-structure interaction model.
Bibliography Type:	Description: (Last Updated: 04/09/2019)
Articles in Peer-reviewed Journals	Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, Thomas JD. "Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging." Circulation. 2006 May 30;113(21):2524-33. PMID: 16717149 , May-2006
Articles in Peer-reviewed Journals	Notomi Y, Srinath G, Shiota T, Martin-Miklovic MG, Beachler L, Howell K, Oryszak SJ, Deserranno DG, Freed AD, Greenberg NL, Younoszai A, Thomas JD. "Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood." Circulation. 2006 May 30;113(21):2534-41. PMID: 16717154 , May-2006
Articles in Peer-reviewed Journals	Popovic ZB, Richards KE, Greenberg NL, Rovner A, Drinko J, Cheng Y, Penn MS, Fukamachi K, Mal N, Levine BD, Garcia MJ, Thomas JD. "Scaling of diastolic intraventricular pressure gradients is related to filling time duration." Am J Physiol Heart Circ Physiol. 2006 Aug;291(2):H762-9. PMID: 16679403 , Aug-2006
Articles in Peer-reviewed Journals	Popovic ZB, Sun JP, Yamada H, Drinko J, Mauer K, Greenberg NL, Cheng Y, Moravec CS, Penn MS, Mazgalev TN, Thomas JD. "Differences in left ventricular long-axis function from mice to humans follow allometric scaling to ventricular size." J Physiol. 2005 Oct 1;568(Pt 1):255-65. PMID: 16002448 , Oct-2005
Articles in Peer-reviewed Journals	Qin JX, Jones M, Travaglini A, Song JM, Li J, White RD, Tsujino H, Greenberg NL, Zetts AD, Panza JA, Thomas JD, Shiota T. "The accuracy of left ventricular mass determined by real-time three-dimensional echocardiography in chronic animal and clinical studies: a comparison with postmortem examination and magnetic resonance imaging." J Am Soc Echocardiogr. 2005 Oct;18(10):1037-43. PMID: 16198880 , Oct-2005
Articles in Peer-reviewed Journals	Rovner A, Greenberg NL, Thomas JD, Garcia MJ. "Relationship of diastolic intraventricular pressure gradients and aerobic capacity in patients with diastolic heart failure." Am J Physiol Heart Circ Physiol. 2005 Nov;289(5):H2081-8. PMID: 15937093 , Nov-2005
Articles in Peer-reviewed Journals	Thomas JD, Popovic ZB. "Assessment of left ventricular function by cardiac ultrasound." J Am Coll Cardiol. 2006 Nov 21;48(10):2012-25. PMID: 17112991 , Nov-2006