

<b>Fiscal Year:</b>	FY 2008	<b>Task Last Updated:</b>	FY 03/12/2009
<b>PI Name:</b>	Thomas, James David M.D.		
<b>Project Title:</b>	Echocardiographic Assessment of Cardiovascular Adaptation and Countermeasures in Microgravity		
<b>Division Name:</b>	Human Research		
<b>Program/Discipline:</b>	NSBRI		
<b>Program/Discipline--Element/Subdiscipline:</b>	NSBRI--Cardiovascular Alterations Team		
<b>Joint Agency Name:</b>	<b>TechPort:</b>	No	
<b>Human Research Program Elements:</b>	(1) <b>HHC:</b> Human Health Countermeasures		
<b>Human Research Program Risks:</b>	(1) <b>Cardiovascular:</b> Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
<b>Space Biology Element:</b>	None		
<b>Space Biology Cross-Element Discipline:</b>	None		
<b>Space Biology Special Category:</b>	None		
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<b>Organization Name:</b>	The Cleveland Clinic Foundation		
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<b>City:</b>	Cleveland	<b>State:</b>	OH
<b>Zip Code:</b>	44195-0001	<b>Congressional District:</b>	11
<b>Comments:</b>			
<b>Project Type:</b>	GROUND	<b>Solicitation / Funding Source:</b>	2003 Biomedical Research & Countermeasures 03-OBPR-04
<b>Start Date:</b>	08/01/2004	<b>End Date:</b>	07/31/2008
<b>No. of Post Docs:</b>	5	<b>No. of PhD Degrees:</b>	0
<b>No. of PhD Candidates:</b>	1	<b>No. of Master' Degrees:</b>	0
<b>No. of Master's Candidates:</b>	1	<b>No. of Bachelor's Degrees:</b>	0
<b>No. of Bachelor's Candidates:</b>	0	<b>Monitoring Center:</b>	NSBRI
<b>Contact Monitor:</b>	<b>Contact Phone:</b>		
<b>Contact Email:</b>			
<b>Flight Program:</b>			
<b>Flight Assignment:</b>	NOTE: Risk/Gap changes per HRP Master Task List information dtd 12/28/2012 (Ed., 3/13/13)		
<b>Key Personnel Changes/Previous PI:</b>			
<b>COI Name (Institution):</b>	Greenberg, Neil ( The Cleveland Clinic Foundation ) Kassemi, Mohammad ( NASA GRC ) Freed, Alan ( NASA GRC ) Popovic, Zoran ( The Cleveland Clinic Foundation ) Setser, Randolph ( The Cleveland Clinic Foundation ) Penn, Marc ( The Cleveland Clinic Foundation ) Rodriguez, Luis ( The Cleveland Clinic Foundation )		
<b>Grant/Contract No.:</b>	NCC 9-58-SMS00404		
<b>Performance Goal No.:</b>			
<b>Performance Goal Text:</b>			

<p><b>Task Description:</b></p>	<p>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:</p> <ol style="list-style-type: none"> <li>1) Extension of work to calculate two-dimensional myocardial strain, improving sensitivity for detecting preclinical alterations in cardiac function.</li> <li>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.</li> <li>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.</li> <li>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.</li> </ol> <p>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.</p>
<p><b>Rationale for HRP Directed Research:</b></p>	<p>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.</p> <p>Wireless telemedicine systems for ultrasound enable transfer of ultrasound data within the hospital and remotely to workstations connected to our network.</p> <p><b>Research Impact/Earth Benefits:</b></p> <p>We have continued to investigate three-dimensional ultrasound capabilities. Building on our experience with the Volumetrics system, we have begun to use much improved acquisition devices (Philips ie33 and GE Medical Vivid 7) to obtain 3D examinations in a wide variety of cardiac pathologies.</p> <p>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.</p>
<p><b>Task Progress:</b></p>	<p><b>AIM 1: NEW TECHNIQUES TO ASSESS CARDIAC FUNCTION IN SPACE</b></p> <p>We found that early diastolic IVPGs are associated with LV contractility. These findings may explain the proposed mechanism in which potential energy stored during systole is released during diastole to provide for adequate ventricular filling, even under low filling pressures. Left ventricular(LV) untwisting starts early during the isovolumic relaxation phase and proceeds throughout the early filling phase, releasing elastic energy stored by the preceding systolic deformation. Studies in our animal model demonstrated moderately strong correlation of peak LV twisting with peak LV untwisting rate. In a multivariate analysis, peak LV untwisting rate was an independent predictor of tau and IVPG. The start of LV untwisting coincided with the beginning of relaxation and preceded suction-aided filling resulting from elastic recoil.</p> <p><b>AIM 2: USE EXERCISE ECHO TO DETECT CARDIAC DYSFUNCTION</b></p> <p>We have shown that the ability to augment IVPG is the best predictor of maximum exercise capacity, and that the release of ventricular torsion during the isovolumic relaxation period is closely correlated with IVPG, thereby linking systolic contraction to diastolic filling. We have also shown that the loss of IVPG during exercise is strongly linked to the loss of untwisting velocity to and to the loss of torsion. We have studied the effects of exercise on left ventricular diastolic function using strain techniques from AIM 1 and found that the longitudinal strain rate in healthy volunteers was the best predictor of the increase of untwisting velocity and IVPG.</p> <p><b>AIM 3: ASSESS PREDICTORS OF MASS REGRESSION FOLLOWING UNLOADING</b></p> <p>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.</p> <p><b>AIM 4: DEVELOP A 3D FLUID-STRUCTURE INTERACTION MODEL OF THE HEART</b></p> <p>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 calcium transients (instead of</p>

	previous model based on fixed systolic elastance). This novel model has been published in the Ann of Bio Eng, shows more realistic hemodynamics than the previous one, and is used to as an input to the 3D fluid-structure interaction model. A second manuscript was also submitted to Biomechanics and Modeling in Mechanobiology.
<b>Bibliography Type:</b>	Description: (Last Updated: 04/09/2019)
<b>Articles in Peer-reviewed Journals</b>	Firstenberg MS, Greenberg NL, Garcia MJ, Thomas JD. "Relationship between ventricular contractility and early diastolic intraventricular pressure gradients: a diastolic link to systolic function." J Am Soc Echocardiogr. 2008 May;21(5):501-6. <a href="#">PMID: 17928198</a> , May-2008
<b>Articles in Peer-reviewed Journals</b>	Lim P, Buakhamsri A, Popovic ZB, Greenberg NL, Patel D, Thomas JD, Grimm RA. "Longitudinal strain delay index by speckle tracking imaging: a new marker of response to cardiac resynchronization therapy." Circulation. 2008 Sep 9;118(11):1130-7. <a href="#">PMID: 18725491</a> , Sep-2008
<b>Articles in Peer-reviewed Journals</b>	Matsumura Y, Fukuda S, Tran H, Greenberg NL, Agler DA, Wada N, Toyono M, Thomas JD, Shiota T. "Geometry of the proximal isovelocity surface area in mitral regurgitation by 3-dimensional color Doppler echocardiography: difference between functional mitral regurgitation and prolapse regurgitation." Am Heart J. 2008 Feb;155(2):231-8. <a href="#">PMID: 18215591</a> , Feb-2008
<b>Articles in Peer-reviewed Journals</b>	Matsumura Y, Saracino G, Sugioka K, Tran H, Greenberg NL, Wada N, Toyono M, Fukuda S, Hozumi T, Thomas JD, Yoshikawa J, Yoshiyama M, Shiota T. "Determination of regurgitant orifice area with the use of a new three-dimensional flow convergence geometric assumption in functional mitral regurgitation." J Am Soc Echocardiogr. 2008 Nov;21(11):1251-6. <a href="#">PMID: 18992676</a> , Nov-2008
<b>Articles in Peer-reviewed Journals</b>	Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. "Ventricular untwisting: a temporal link between left ventricular relaxation and suction." Am J Physiol Heart Circ Physiol. 2008 Jan;294(1):H505-13. <a href="#">PMID: 18032523</a> , Jan-2008
<b>Articles in Peer-reviewed Journals</b>	Lim P, Mitchell-Heggs L, Buakhamsri A, Thomas JD, Grimm RA. "Impact of left ventricular size on tissue Doppler and longitudinal strain by speckle tracking for assessing wall motion and mechanical dyssynchrony in candidates for cardiac resynchronization therapy." J Am Soc Echocardiogr. 2009 Jun;22(6):695-701. <a href="http://dx.doi.org/10.1016/j.echo.2009.04.015">http://dx.doi.org/10.1016/j.echo.2009.04.015</a> ; PubMed <a href="#">PMID: 19501329</a> , Jun-2009
<b>Articles in Peer-reviewed Journals</b>	Buakhamsri A, Popovic ZB, Lin J, Lim P, Greenberg NL, Borowski AG, Tang WH, Klein AL, Lever HM, Desai MY, Thomas JD. "Impact of left ventricular volume/mass ratio on diastolic function." Eur Heart J. 2009 May;30(10):1213-21. Epub 2009 Mar 20. <a href="http://dx.doi.org/10.1093/eurheartj/ehp084">http://dx.doi.org/10.1093/eurheartj/ehp084</a> ; PubMed <a href="#">PMID: 1930474</a> , May-2009
<b>Articles in Peer-reviewed Journals</b>	Asada-Kamiguchi J, Tabata T, Popovic ZB, Greenberg NL, Kim YJ, Garcia MJ, Wallick DW, Mowrey KA, Zhuang S, Zhang Y, Mazgalev TN, Thomas JD, Grimm RA. "Non-invasive assessment of left ventricular relaxation during atrial fibrillation using mitral flow propagation velocity." Eur J Echocardiogr. 2009 Oct;10(7):826-32. <a href="#">PMID: 19692424</a> , Oct-2009
<b>Articles in Peer-reviewed Journals</b>	Phillips KP, Popovic ZB, Lim P, Meulet JE, Barrett CD, Di Biase L, Agler D, Thomas JD, Grimm RA. "Opposing wall mechanics are significantly influenced by longitudinal cardiac rotation in the assessment of ventricular dyssynchrony." JACC Cardiovasc Imaging. 2009 Apr;2(4):379-86. <a href="#">PMID: 19580717</a> , Apr-2009
<b>Articles in Peer-reviewed Journals</b>	Puwanant S, Park M, Popovic ZB, Tang WH, Farha S, George D, Sharp J, Puntawangkoon J, Loyd JE, Erzurum SC, Thomas JD. "Ventricular geometry, strain, and rotational mechanics in pulmonary hypertension." Circulation. 2010 Jan 19;121(2):259-66. <a href="#">PMID: 20048214</a> , Jan-2010
<b>Articles in Peer-reviewed Journals</b>	Saraiva RM, Matsumura Y, Yamano T, Greenberg N, Thomas JD, Shiota T. "Relation of left atrial dysfunction to pulmonary artery hypertension in patients with aortic stenosis and left ventricular systolic dysfunction." Am J Cardiol. 2010 Aug 1;106(3):409-16. <a href="#">PMID: 20643255</a> , Aug-2010
<b>Articles in Peer-reviewed Journals</b>	Beach JM, Mihaljevic T, Rajeswaran J, Marwick T, Edwards ST, Nowicki ER, Thomas J, Svensson LG, Griffin B, Gillinov AM, Blackstone EH. "Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis." J Thorac Cardiovasc Surg. 2014 Jan;147(1):362-369.e8. Epub 2013 Jan 11. <a href="https://doi.org/10.1016/j.jtcvs.2012.12.016">https://doi.org/10.1016/j.jtcvs.2012.12.016</a> ; PubMed <a href="#">PMID: 23312984</a> , Jan-2014