Fiscal Year:	FY 2007	**Task Last Updated:**	FY 02/01/2008
PI Name:	Levine, Benjamin D M.D.		
Project Title:	The Multisystem Effect of Exercise Training/Nutritional Support During Prolonged Bed Rest Deconditioning: An Integrative Approach to Countermeasure Development for the Heart, Lungs, Muscles and Bones		
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 (2) **Renal Stone**:Risk of Renal Stone Formation		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	benjaminlevine@texashealth.org	**Fax:**	FY 214 345-4618
PI Organization Type:	UNIVERSITY	**Phone:**	214-345-4619
Organization Name:	The University of Texas Southwestern Medical Center at Dallas		
PI Address 1:	Institute for Exercise and Environmental Medicine (IEEM)		
PI Address 2:	7232 Greenville Ave, Suite 435		
PI Web Page:			
City:	Dallas	**State:**	TX
Zip Code:	75231-5129	**Congressional District:**	5
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2004 NSBRI NNH04ZUU003N Human Health in Space
Start Date:	09/01/2005	**End Date:**	04/30/2010
No. of Post Docs:	2	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: New end date is 4/30/2010, per N. Gibbins/NSBRI; previous end date was 8/31/2009 (8/09)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	NCC 9-58-CA00701		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	1). Original Aims: Sustained exposure to microgravity leads to adaptive changes in the cardiovascular and musculoskeletal systems that results in substantial morbidity. For example cardiovascular deconditioning may lead to orthostatic hypotension and syncope. Atrophy of skeletal muscle will diminish work capacity and may lead to muscle injury. Bone demineralization increases the risk of kidney stone formation and may reduce bone strength increasing the risk of fracture. Bone resorption may be particularly severe after long duration space flight with uncertain recovery. Despite in depth study, the optimal countermeasure for each system has not been defined. More importantly, previous work has focused predominantly on one organ system at a time, ignoring the interaction among systems, and preventing the development of a specific countermeasure for an individual astronaut that might be effective for the heart, muscles and bones. The global objective of this proposal is to test an integrated countermeasure that will be effective against cardiovascular deconditioning, skeletal muscle atrophy, and bone demineralization, and that ultimately can be applied practically abroad the International Space Station or a mission to Mars. The original hypotheses and specific aims of the project are as follows: Hypothesis 1: An “optimized” exercise training program combining dynamic plus intermittent resistance exercise can prevent the cardiovascular atrophy and deconditioning associated with prolonged bed rest. Hypothesis 2: This dynamic plus resistance exercise training program, when combined with potassium-magnesium-citrate supplementation will attenuate the increased risk for stone formation, and diminish bed rest-induced bone loss to a greater extent than the effect of exercise training or supplementation alone. Hypothesis 3: This dynamic plus resistance exercise training program during bed rest will also attenuate structural and functional alternations in skeletal muscle induced by prolonged bed rest, thereby preserving strength and endurance. To test these hypotheses, we proposed to accomplish the following specific aims: Specific Aim 1: To perform an exercise countermeasure using rowing ergometry combined with resistance training to obtain the most intensive stimulus to cardiac hypertrophy in the shortest period of time. The functional importance of cardiac atrophy for orthostatic tolerance after prolonged bed rest will be determined from a novel combination of classical, invasive cardiovascular physiology to measure the static component of diastole (Frank-Starling and LV pressure/volume curves), in conjunction with innovative, non-invasive imaging techniques to measure the dynamic component of diastole. A novel oral volume loading strategy will also be applied just prior to orthostatic tolerance testing. Specific aim 2: To assess the effect of exercise training combined with supplementation with potassium magnesium citrate (KMgCit) in preventing microgravity-induced increases in bone resorption, urinary calcium excretion, and risk of stone formation. These specific aims will be accomplished by precise metabolic control and evaluation, plus non-invasive evaluation of bone structure and function (bone quality by ultrasound) . Specific Aim 3: To demonstrate the effectiveness of dynamic and resistance exercise training in attenuating the loss of structure and functional capacity of skeletal muscle during prolonged bed rest. This aim will include measures of whole muscle size and function (magnetic resonance imaging/spectroscopy), functional exercise testing (strength and endurance), biochemistry (enzyme activities, ubiquitin-proteasome pathway induction), and histology (muscle fiber type and morphometry, and capillary density). 2). Key Findings: In the second year of the project, 19 new subjects have been screened for the study (total = 46), twelve have completed all phases of the study, a 13th subject is in the middle of bedrest, and the 14th will start next week. Nine of the completed subjects were in the exercise arm, and three subjects were in the sedentary arm. There have been no adverse events. Two subjects left the study after completing all initial evaluations -- one because she elected to join a different research study from a pharmaceutical company, and a second because of a sudden, unexpected death in the family. We already have the next subject recruited and his pre-bedrest studies are scheduled. Most data have been cleaned and entered into the master experiment data base, and some preliminary results are available. Although we will not perform a preliminary data analysis to avoid reducing statistical power, all results point in the direction of supporting our hypotheses. Subjects who exercised and received the oral volume load have had complete protection against orthostatic intolerance with maximal LBNP tolerance virtually identical to baseline levels despite 5 weeks of head down tilt bedrest. Cardiac muscle mass as well as the mass/volume ratio have been preserved, and both Starling and pressure-volume curves are superimposable. Muscle strength has been preserved, and urinary calcium loss has been attenuated, though we do not know which patients have gotten KMgCit or placebo. 3). Impact on objectives: Based on the first two years' data and performance, we have not changed any of our hypotheses, and not altered the protocol. 4). Plan for upcoming year: The plan for the next year will be to continue a high rate of subject recruitment. We have permission to enroll 2 patients simultaneously, and therefore expect the experiment to be completed on time and within budget.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The information obtained from these experiments will be relevant for patients after prolonged confinement to bed rest, or chronic reduction in physical activity, as well as for patients with disease processes that alter cardiac stiffness such as obesity, hypertension, heart failure or ischemic heart disease, plus normal aging and osteoporosis. Indeed, we are already using this strategy to treat patients with chronic orthostatic intolerance and the Postural Orthostatic Tachycardia Syndrome with outstanding results. Rowing and strength training have been incorporated into my standard clinical algorithm for management of these patients, all of whom have very small hearts. This work has led to the elaboration of a new name for this important clinical syndrome: "The Grinch Syndrome" (because their hearts are "two sizes too small").

Task Progress:	In the first 2 years of the project, 46 subjects have been screened for the study, twelve have completed all phases of the study, and a thirteenth subject will start bedrest next week. Nine of the completed subjects were in the exercise arm, and three subjects were in the sedentary arm. This rate exceeds that of the first year of the project and is consistent with completion of the project with the time frame proposed. There have been no adverse events. Most data have been cleaned and entered into the master experiment data base, and some preliminary results are available. Although we will not perform a preliminary data analysis to avoid reducing statistical power, all results point in the direction of supporting our hypotheses. Subjects who exercised and received the oral volume load have had complete protection against orthostatic intolerance with maximal LBNP tolerance virtually identical to baseline levels despite 5 weeks of head down tilt bedrest. Cardiac muscle mass as well as the mass/volume ratio have been preserved, and both Starling and pressure-volume curves are superimposable. Muscle strength has been preserved, and urinary calcium loss has been attenuated, though we do not know which patients have gotten KMgCit or placebo.
Bibliography Type:	Description: (Last Updated: 12/13/2023)
Articles in Peer-reviewed Journals	Dorfman TA, Levine BD, Tillery T, Peshock RM, Hastings JL, Schneider SM, Macias BR, Biolo G, Hargens AR. "Cardiac atrophy in women following bedrest." J Appl Physiol. 2007 Jul;103(1):8-16. Epub 2007 Mar 22. PMID: 17379748 , Jul-2007
Articles in Peer-reviewed Journals	Shibata S, Zhang R, Hastings J, Fu Q, Okazaki K, Iwasaki K, Levine BD. "Cascade model of ventricular-arterial coupling and arterial-cardiac baroreflex function for cardiovascular variability in humans." Am J Physiol Heart Circ Physiol. 2006 Nov;291(5):H2142-51. Epub 2006 Jun 9. PMID: 16766646 , Nov-2006