Fiscal Year:	FY 2006	**Task Last Updated:**	FY 01/08/2007
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		
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Zip Code:	75231-5129	**Congressional District:**	5
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	NSBRI
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No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	2
No. of Bachelor's Candidates:	2	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
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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 first year of the project, 27 subjects have been screened for the study, five have completed all phases of the study, and the sixth subject has just started bedrest. Three of the completed subjects were in the exercise arm, and two subjects were in the sedentary arm. There have been no adverse events, and all recruited subjects have completed all the study procedures with high quality data. 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. Both 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 year's 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. Our GCRC has just been renovated, and we hope to be able to study more subjects in parallel as one short term bedrest funded by Dr. Crandall comes to a close.
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 year of the project, 27 subjects have been screened for the study, five have completed all phases of the study, and the sixth subject has just started bedrest. Three of the completed subjects were in the exercise arm, and two subjects were in the sedentary arm. There have been no adverse events, and all recruited subjects have completed all the study procedures with high quality data. 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. Both 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)
Awards	Levine BD. "ACSM John Sutton Clinical Lecture, Michael J. Joyner Teaching Award, Royal Danish Academy of Cardiovascular Sciences, June 2006." Jun-2006