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| **Fiscal Year:** | FY 2008 | **Task Last Updated:** | FY 02/09/2009 |
| **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 | | |
| **Program/Discipline--Element/Subdiscipline:** | NSBRI--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<br>(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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| **PI Organization Type:** | UNIVERSITY | **Phone:** | 214-345-4619 |
| **Organization Name:** | The University of Texas Southwestern Medical Center at Dallas | | |
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| **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:** | 1 | **No. of PhD Degrees:** | 0 |
| **No. of PhD Candidates:** | 0 | **No. of Master' Degrees:** | 0 |
| **No. of Master's Candidates:** | 0 | **No. of Bachelor's Degrees:** | 0 |
| **No. of Bachelor's Candidates:** | 0 | **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:** | | | |

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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.<br>The original hypotheses and specific aims of the project are as follows:<br><br>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.<br><br>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.<br><br>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.<br><br>To test these hypotheses, we proposed to accomplish the following specific aims:<br><br>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.<br><br>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).<br><br>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).<br><br>2). Key Findings: In the third year of the project, we accelerated the recruitment and study of our entire cohort because of exigencies of funding within our GCRC. In particular, UT Southwestern was awarded a Clinical Translational Science Award which did not fully fund our GCRC. Although many of these problems have since been solved, we were concerned that it would have been possible that the GCRC could have closed, or severely limited services for the next year. Therefore we have studied (and expended grant funds) for the majority of next years proposed subjects as well as this years. Specifically 74 subjects were screened, 23 subjects have completed all phases of the study, and 26 subjects have completed the pre-testing and bedrest component. One subject will finish with his bedrest exposure next week, and he plus a remaining 3 subjects will complete their post re-ambulation studies over the next month thus completing our proposed cohort. Data analysis will continue aggressively and we will focus on our key outcome variables to ensure that we are adequately powered for our primary analysis. Most data have been cleaned and entered into the master experiment data base, and some preliminary results are available. Although data analysis is not yet complete, all results point in the direction of supporting our hypotheses. Subjects who exercised and received the oral volume load were protected 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.<br><br>3). Impact on objectives: None.<br><br>4). Plan for upcoming year: The plan for the next year will be to complete data analysis and begin paper writing. If underpowered for key outcome variables, we may need to study another 3-6 subjects, but we do not expect this to be likely. |
| **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"). |

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| **Task Progress:** | In the first 3 years of the project, 23 have completed all phases of the study, and all will have completed all phases of the project within the next 4 weeks. Therefore our targeted enrollment will have been achieved. As noted in the overview, this enrollment was accelerated because of financial exigencies at the UT Southwestern GCRC which have been resolved, but which forced us to spend the first quarter of next year's funds already in this year (we have asked for pre-award to account for this accelerated enrollment). We plan to perform an expeditious analysis of our primary outcome variables to ensure that we are adequately powered as predicted and that no new bedrest subjects need to be studied. One subject developed acute appendicitis after his post-bedrest invasive studies, but prior to MRI and maximal LBNP and exercise. There have been no other adverse events. Most data have been cleaned and entered into the master experiment data base, and some preliminary results are available as noted in the "main findings" section, with all results pointing in the direction of supporting our hypotheses. Most 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: 05/20/2025) |
| **Articles in Peer-reviewed Journals** | Shibata S, Hastings JL, Prasad A, Fu Q, Okazaki K, Palmer MD, Zhang R, Levine BD. "'Dynamic' Starling mechanism: effects of ageing and physical fitness on ventricular-arterial coupling." J Physiol. 2008 Apr 1;586(7):1951-62. PMID: 18258658 , Apr-2008 |
| **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. PMID: 16766646 , Nov-2006 |
| **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. PMID: 17379748 , Jul-2007 |
| **Articles in Peer-reviewed Journals** | Dorfman TA, Rosen BD, Perhonen MA, Tillery T, McColl R, Peshock RM, Levine BD. "Diastolic suction is impaired by bed rest: MRI tagging studies of diastolic untwisting." J Appl Physiol. 2008 Apr;104(4):1037-44. PMID: 18239079 , Apr-2008 |
| **Articles in Peer-reviewed Journals** | Shibata S, Hastings JL, Prasad A, Fu Q, Bhella P, Pacini E, Krainski F, Palmer D, Zhang R, Levine BD. "Congestive heart failure with preserved ejection fraction is associated with severely impaired dynamic ventricular-arterial coupling." J Am Coll Cardiol. Submitted, July 2008. , Jul-2008 |
| **Awards** | Levine BD. "American College of Sports Medicine (National) Citation Award, 2007." Jul-2007 |
| **Awards** | Levine BD. "Association of University Cardiologists, 2008." Jul-2008 |