**National Space Biomedical Research Institute**
Team: Cardiovascular Alterations – Team Executive Summary
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## Background/Scope

The overall purpose of the cardiovascular system is to pump and distribute sufficient quantities of blood to meet the metabolic and thermoregulatory demands of the body both at rest and during physical exertion. This function may be impaired by a physiological or pathophysiological adaptation to microgravity, or by the development or manifestation of previously subclinical cardiovascular disease. Previous research regarding the cardiovascular system in space has focused predominantly on blood pressure control and mechanisms of orthostatic hypotension after return to Earth. This focus has been driven by the presence of a high incidence of orthostatic intolerance – typically defined (somewhat artificially) as the inability to stand quietly for 10 minutes either actively, or passively on a tilt table. Indeed the study of hydrostatic gradients (and their removal), as well as their importance for the regional distribution of blood flow and its regulation by both long-term and short-term cardiovascular control mechanisms remains of fundamental importance for cardiovascular science.

The primary manifestation of the cardiovascular adaptation to spaceflight is a small stroke volume in the upright position on return to Earth. This phenomenon is due to both loss of plasma volume and atrophy of cardiac muscle, so that cardiac filling is inadequate, especially when standing quietly. Autonomic compensatory responses to this small stroke volume are appropriate, but may be overwhelmed by limited reserve in some astronauts. Moreover, reduced cardiovascular reserve may limit the amount of blood available for thermoregulation, which could be especially challenging during extravehicular activity. However, recent work both in space and using ground-based models has advanced this field considerably. As a consequence, specific and highly effective hazard controls have been developed for either preventing or managing orthostatic hypotension, at least under typical Earth landing conditions. It remains uncertain whether orthostatic intolerance is clinically relevant under less restrictive conditions such as during normal physical activity when active muscles pump blood back to the heart, or even during brief but highly intense exertions such as might be caused by an emergency situation, since blood pressure has never been measured under such conditions after either short-duration or long-duration spaceflight. It also is uncertain whether the less severe gravitational gradients of the moon or Mars are sufficient to impair blood flow distribution or cause orthostatic intolerance, though this problem is considered unlikely. Thus, it remains unclear whether hazard controls that are effective upon return to Earth under well controlled conditions would be similarly adequate on Mars when medical support will be much less comprehensive, or under an emergency on Earth.

Because cardiovascular disease often presents catastrophically, the development of cardiovascular diseases in astronauts on a mission to Mars can seriously compromise mission success. Therefore two of the key objectives of the Cardiovascular Alterations Team are to develop strategies to minimize the risk of subclinical cardiovascular disease in astronauts and to determine whether long-duration spaceflight poses specific risks to the cardiovascular system that might become manifest during flight. The Cardiovascular Alterations Team is currently engaged in determining the effect of long-duration spaceflight on the heart and blood vessels during actual flight experiments that when concluded in the ISS era, will provide definitive answers to whether spaceflight alters cardiac structure, compromises cardiac systolic and/or diastolic function, or alters the risk for cardiac arrhythmias. The Team is also working on parallel ground-based experiments designing novel therapies for prolonged deconditioning that can be directly applicable to the flight environment. These strategies include exercise training regimens as well as pharmacologic and nutritional interventions. The Team works closely with colleagues in flight medicine at NASA Johnson Space Center to develop screening programs for astronauts and to limit the risk of developing cardiovascular disease during a long-duration space mission.

## Goals

Goal 1: Determine conclusively whether long-duration spaceflight leads to clinically and physiologically significant changes in cardiac and vascular structure and function.

Goal 1a: determine whether long-duration spaceflight with current hazard controls increases the risk for clinically significant orthostatic intolerance due to orthostatic hypotension during: a) return to Earth (1G); and b) exposure to environments with less than 1G gravitational stress.

Goal 2: Determine conclusively whether long-duration spaceflight causes a real risk for developing cardiac arrhythmias. The key issue regarding cardiac arrhythmias is to define the answer to two questions: 1). Is there something unique and specific about the spaceflight environment that increases the risk for: a.) observed arrhythmias, b.) clinically significant arrhythmias, and c.) most importantly life-threatening arrhythmias; and 2). If so, are there specific changes in the structure and function of the heart (either morphological or electrophysiological) induced by spaceflight that can induce arrhythmias in normal hearts, or is it rather an expression of pre-existing cardiovascular disease.

Goal 3: Establish effective countermeasures to “cardiovascular deconditioning” that will maintain cardiac structure and function, and allow preservation of work thermoregulatory capacity sufficient to meet mission demands.

Goal 3a: Determine the limits of thermal stress to which humans can compensate while working in a hypobaric environment that mimics extravehicular activity.

Goal 4: Using animal models, determine whether the radiation exposure during long-duration spaceflight will injure coronary endothelium and accelerate atherosclerosis;

Goal 5: Determine the optimal strategy of cardiovascular screening to reduce the risk of flying astronauts with pre-existing but subclinical cardiovascular diseases that could become manifest during a prolonged exploration-class mission.

## Support of NASA Needs

Goals 1 and 2: A detailed investigation of cardiac structure and function using both ground-based Magnetic Resonance Imaging in conjunction with ground-based and in-flight echocardiography is currently under way involving Cardiovascular Alterations (CA) Team members. This project also includes the best currently available technology for assessing arrhythmia risk in healthy hearts and includes many of the members of the NSBRI CA Team. Importantly, it also includes, as consultants, some of the most widely respected cardiac electrophysiologists in the world which will help greatly with interpreting the clinical significance of the findings. The completion of these experiments may well result in retiring of these risks that have been on the books for decades.

Goal 3: The current CA Team is testing the specific strategy of rowing ergometery in a periodized "elite athlete" based training program, with or without use of a nutriceutical to reduce bone resorption. Preliminary data strongly support this approach, including maintaining upright, 1G maximal cardiac output and exercise capacity.

Goal 3a: To address this goal, a new project has been added to the CA Team led by former payload specialist Dr. Jim Pawelczyk. This project will use ground-based simulation of extravehicular activity (EVA), including a high-resolution EVA mobility unit under hypobaric conditions to determine the limits of compensable thermal stress for humans and the cardiovascular reserve that would be required to meet these demands. The CA Team is also collaborating simultaneously with a new project funded directly by NASA examining changes in thermal tolerance during simulated lunar gravity exposure (PI: David Keller, Ph.D.).

Goal 4: Two new projects have been added to the Team which will use animal models to determine whether deep space-like radiation will injure coronary endothelium, impair vascular function and possibly accelerate atherosclerosis.

Goal 5: This is a key new "gap" that should be addressed in a future solicitation.

**Deliverables**

<u>1-5 Year Timeframe</u>

Goals 1 and 2: Complete current flight experiment. Retire arrhythmia risk by Year 5, though this outcome depends on rapidity with which the experiment can be implemented and numbers of subjects recruited. Retire alterations in cardiac structure and function risk also by Year 5, though with the same caveat; retire orthostatic intolerance risk, both for post-flight orthostatic hypotension in 1-G environment, and for lesser degrees of gravitational stress (Mars and moon).

Goal 3: Complete currently funded NSBRI experiments and deliver highly developed countermeasure to NASA for flight testing and implementation. Implement new science project to determine limits of compensable thermal stress in an EVA-like environment.

Goal 4: Implement new science projects by Dr. Shoukas and Dr. Dennis Kucik. By Year 5, determine if additional studies are required for this issue.

<u>6-10 Year Timeframe</u>

Goal 4 and 5: Establish optimal screening tools, using the best preventive medicine strategies to reduce the risk of developing subclinical disease to as low as possible. Determine whether low-dose radiation increases the risk of atherosclerosis in experimental models.

## Cross-Links

The NSBRI Cardiovascular Alterations Team currently consists of Benjamin Levine, M.D., Art Shoukas, Ph.D., James Thomas, M.D., James Pawelczyk, Ph.D., and Dennis Kucik, M.D., Ph.D., and also includes one postdoctoral fellowship grant by Shigeki Shibata, M.D., Ph.D., working in Dr. Levine's lab. There already exists a robust collaboration among these Team members: 1) Dr. Thomas is currently a collaborator on Dr. Levine's NSBRI bed-rest project. This project also collaborates with the Musculoskeletal Alterations Team on bed-rest experiments both in Dallas and in Cleveland; 2) Dr. Thomas is a collaborator on Dr. Levine's NASA-supported flight experiment (along with co-PI Dr. Mike Bungo) previously entitled CARDIAC: Cardiac Abnormalities in Rhythm and Diastolic function due to Inactivity, Atrophy and Confinement. This study now is called the Integrated CardioVascular Flight Investigation and includes a formal collaboration among the NASA/JSC Cardiovascular Lab (with Steve Platt, Ph.D.), and flight medicine (Drs. Doug Hamilton and Smith Johnston); 3) Dr. Shoukas is currently sharing a Ph.D. student from Johns Hopkins, Eric Tuday, with Dr. Steve Platt, studying the effects of long-term bed rest and gender on arterial stiffness; 4) Four Team members are collaborators on Dr. Levine's NIH grant entitled: Aging, Fitness, and Failure: Mechanisms of Diastolic Dysfunction; 5) Dr. Levine is working with the education and outreach group to develop a DVD translating the exercise intervention developed for spaceflight countermeasure to help women with the Postural Orthostatic Tachycardia Syndrome. It is hoped that this effort will lead to a large international registry for this condition.

It should be emphasized that two of our members are actively practicing clinical cardiologists, and therefore, bring extensive clinical as well as research experience to the Team. When combined with the strong animal and basic science contribution of Dr. Shoukas, Dr. Kucik and their teams, the CA Team is highly integrated, both vertically (basic to clinical science) and horizontally (rapid transfer of clinical research knowledge to direct care of astronauts).

## Enabling Capabilities and Gaps

Key "Gaps" and targets for new solicitations:

1) Optimal screening procedures for short-duration (3-5 years) cardiovascular risk, partnering with the preventive cardiology community. These should include sophisticated modern imaging tools as well as genetic screening. Genetic tools are most highly developed for specific conditions like channelopathies and hypertrophic cardiomyopathy, though extensive risk modeling has not been attempted with an astronaut-type population. Strategies applicable to both new astronaut recruits, as well as to experienced, more senior astronauts who may have developed disease during their tenure should be explored, and include the efficacy of medical therapy on subclinical disease in an astronaut population;

2) Implementation of integrated countermeasures – the CA Team will deliver a well validated countermeasure to NASA by the end of this year. Opportunities to test this specific intervention in a spaceflight environment should be explored.

## Earth-Based Benefits

Dr. Levine's POTS countermeasure DVD will have great impact on the ~500,000 women who have been diagnosed with this condition.