NSBRI Cardiovascular Alterations Team Strategic Plan

4.0 CARDIOVASCULAR ALTERATIONS

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4.1 INTRODUCTION

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to weightlessness and other factors, such as sleep disruption, confinement and additional environmental alterations. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. In addition, there are alterations in the lymphatic, neural and hormonal control systems. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. Furthermore, the extent of cardiovascular adaptation appears to increase with duration of space flight, and the magnitude and implications of these adaptations for long-duration space flight (that is, months to years) remain largely unknown.

Specific adverse effects of space flight on the cardiovascular system include:

1) **Impaired Cardiovascular Response to Orthostatic Stress.** Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry. In many cases, the orthostatic intolerance is sufficiently severe that astronauts cannot stand erect for some time after landing and thus may interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Upon reentry into a gravitational field, blood pools in the dependent veins and arteries which leads to reduction in preload to the heart, resulting in a decrease in stroke volume, cardiac output and arterial blood pressure. Factors involved in the development of orthostatic intolerance may include structural and functional adaptations of the heart and arterial and venous blood vessels and lymphatics, alterations in volume control mechanisms, alterations leading to an inadequate or defective neural and hormonal regulatory response, alterations in local vascular reactivity, and mechanisms controlling regional distribution of blood volumes and flows. Factors, such as age, gender, genotype, as well as occupational, physical training and dietary history, may affect individual susceptibility to the development of post-flight orthostatic intolerance. Currently used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight.

2) **Occurrence of Serious Cardiac Dysrhythmias.** A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. It will be important to determine the mechanisms underlying this phenomenon in order to develop appropriate countermeasures. Potential mechanisms that might lead to reduction in the stability of the electrical substrate include electrolyte changes, changes in the neural and hormonal milieu, and alterations of cardiac myocytes, myocyte connectivity and extracellular matrix resulting from space flight. These alterations may in turn lead to changes in cardiac conduction and repolarization processes that predispose the heart to sustained rhythm disturbances.

3) **Diminished Cardiac Function.** Long-term space flight may lead to a measurable reduction in cardiac mass, probably associated with cardiac remodeling. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. Factors that may be involved in alterations in cardiac function include changes in myocyte number, size, and geometry; changes in myocardial matrix and microvasculature; alterations in myocyte and organ-level mechanical performance; changes in cardiac gene programming; stimuli and signals that lead to loss of cardiac mass and remodeling; factors affecting reversibility and recovery from these alterations.

4) **Manifestation of Previously Asymptomatic Cardiovascular Disease.** Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. Little is known about what conditions of space flight may tend to make pre-existing disease symptomatic or accelerate the progression of the underlying disease. Also, we do not know what procedures should be applied to screen astronauts for the presence of asymptomatic cardiovascular disease prior to long term missions

5) **Impaired Cardiovascular Response to Exercise Stress.** Long-term space flight may impair cardiovascular response to exercise. Current inflight exercise programs appear adequate to maintain aerobic exercise capacity.

4.2 RISKS

In concert with the above described adverse effects of space flight, the following risks in the Cardiovascular Alterations Discipline Area have been identified in the Critical Path Roadmap (Risk number in parentheses):

- Impaired Cardiovascular Response to Orthostatic Stress (14)
- Occurrence of Serious Cardiac Dysrhythmias (13)
- Diminished Cardiac Function (15)
- Manifestation of Previously Asymptomatic Cardiovascular Disease (16)
- Impaired Cardiovascular Response to Exercise Stress (17)

4.3 GOALS

The Cardiovascular Alterations Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce risk of impaired cardiovascular response to orthostatic stress*

Goal 2: *Reduce risk of occurrence of serious cardiac dysrhythmias*

Goal 3: *Reduce risk of diminished cardiac function*

Goal 4: *Reduce risk of manifestation of previously asymptomatic cardiovascular disease*

Goal 5: *Reduce risk of impaired cardiovascular response to exercise stress*

Non Risk-Based Goals

Goal 6: *Develop new cardiovascular diagnostic and therapeutic technologies for space flight applications*

Goal 7: *Develop new cardiovascular diagnostic and therapeutic technologies for medical use on Earth*

Goal 8: *Integrate Research and Analysis*

4.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The overarching intentions of the Cardiovascular Alterations Team are to:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth

The program's overall strategy is dictated by the relevant risks. The following risks are deemed to be high priority and are the focus of the team's efforts:

- Impaired Cardiovascular Response to Orthostatic Stress (14; Addressed in Goal 1)
- Occurrence of Serious Cardiac Dysrhythmias (13; Addressed in Goal 2)
- Diminished Cardiac Function (15; Addressed in Goal 3)

The remaining two risks are deemed to be of low priority:

- Manifestation of Previously Asymptomatic Cardiovascular Disease (16; Addressed in Goal 4)
- Impaired Cardiovascular Response to Exercise Stress (17; Addressed in Goal 5)

While some of the projects do address some aspects of these two risks, no one project principally addresses these risks.

Additional non risk-based goals include those associated with the development of new cardiovascular technologies for use in space (Goal 6) and for Earth-based applications (Goal 7). Integration of Research and Analysis is Team Goal 8.

The current program is summarized in the Figure at the end of this document. Table 4.1, entitled "Current Project Research Activities," summarizes for each current Cardiovascular Alterations Team project what risks are addressed, the experimental system, the countermeasure target and the planned progression of each project along the strategic steps of Phase 1, 2 or 3 Activities.

The Cardiovascular Alternations Team has recently been enlarged by the transfer of three projects (Bers, Coolahan, McCulloch) from the former Integrated Human Function Team. This transfer was the result of an NSBRI management decision that it was better for the computer modeling and simulation projects to reside in specific teams rather than to be grouped in a separate Integrated Human Function Team. An additional cardiovascular modeling project with Dr. Mark has been part of the Cardiovascular Alterations Team since its inception and is thus already very well integrated into the team's activities. A project with Dr. Murad was also just recently incorporated into the team. As a result, the Cardiovascular Alterations Team now has 16 projects (see Figure). While we have always attempted to have horizontal communication across all team projects, with the growth of the team to 16 projects we have decided to organize the projects into groups of Human Studies, Rodent Studies, and Cardiovascular Technologies. Projects within each group will have separate group meetings in addition to meetings of the entire team.

Progress Towards Risk-Based Goals

Projects addressing risk of Impaired Cardiovascular Response to Orthostatic Stress (Goal 1). Most of the effort of the Cardiovascular Alterations Team has been focused on the problem of post-flight orthostatic hypotension, for this is a well-known current operational problem. As a matter of fact, all the team projects are involved in this effort. In animal and human studies we have studied mechanisms and proposed and tested countermeasures. We are examining a wide range of factors including neural, vestibular, hormonal, vascular, cardiac, lymphatic, and genetic factors that may contribute to the development of orthostatic hypotension. We have also developed new non-invasive techniques to study alterations in cardiovascular regulation resulting from space flight. One such technique is Cardiovascular System Identification that involves mathematical analysis of spontaneous second-to-second fluctuations in physiological signals such as heart rate, arterial blood pressure, cardiac output, and respiration to create an individualized closed loop model of cardiovascular regulation. Finally, we have developed and utilized computer simulations of the cardiovascular system to analyze data, investigate mechanisms, evaluate proposed countermeasures, and refine hypotheses to be tested experimentally. The dynamic interplay between animal, human and computer simulations has already led to the proposal of the alpha-sympathetic agonist, midodrine, as a pharmacological countermeasure to the development of orthostatic hypotension, and the successful testing of this countermeasure in animal and ground based human studies. Flight studies of this countermeasure have been approved and will begin soon. We are also developing an innovative pulsatile G-suit as a new countermeasure.

Projects addressing risk of Occurrence of Serious Cardiac Dysrhythmias (Goal 2). Several of the team projects relate to the development of life threatening dysrhythmias in space (Bers, Cohen, Coolahan, McCulloch, and Williams). The focus here has been to establish specifically whether simulated microgravity increases the risk of these ventricular tachyarrhythmias. To test this hypothesis a new non-invasive technique has been developed for the identification of subjects at risk of developing ventricular tachyarrhythmias - measurement of microvolt T-wave alternans. This technique was developed under both NASA and NSBRI support. This technique has been validated in multiple studies of patients with increased sudden cardiac death. The

technique has proven to be the best non-invasive predictor of susceptibility to ventricular tachyarrhythmias and sudden cardiac death. It has been successfully commercialized, cleared by the FDA, and approved by Medicare for reimbursement, and is in widespread clinical use. Initial bed rest data using microvolt T-wave alternans suggests that simulated microgravity increases the risk of ventricular tachyarrhythmias, and flight studies will shortly be initiated to test this in astronauts pre- and postflight. Mechanistic ground based studies will examine the effects of age and gender on susceptibility to ventricular tachyarrhythmias. Also, current studies plan to evaluate aldosterone antagonists (spironolactone) and alterations in dietary intake of electrolytes as potential countermeasures.

Projects addressing risk of Diminished Cardiac Function (Goal 3). One project (Lorell) deals primarily with the risk of diminished cardiac function and several other projects (Bers, Cohen, Coolahan, Delp, Mark, McCulloch, Shoukas, Thomas, and Williams) have this risk as a less primary focus. The aim here is to establish the development of atrophy and remodeling in ground based models and to study molecular and genetic mechanisms and functional sequelae. We require more flight data documenting the extent of space induced cardiac atrophy and remodeling that occurs during flight.

Projects addressing risk of Manifestation of Previously Asymptomatic Cardiovascular Disease (Goal 4). There are no current projects that really focus on this issue. A few projects are minimally associated with this problem (Coolahan, McCulloch, and Thomas). Although this is a lower priority risk than the first three, we are interested in the question of determining what is the optimum set of screening tests for astronauts to detect asymptomatic cardiovascular disease that may cause problems during long duration space flight. We plan to solicit proposals in this area in the future.

Projects addressing risk of Impaired Cardiovascular Response to Exercise Stress (Goal 5). Although several of the projects address exercise, this is not a primary focus of any of the current projects. The reason for this situation is that the current in-flight exercise regimen appears to be adequate to maintain aerobic exercise capacity.

Progress Towards Non Risk-Based Goals

Progress towards Development of New Cardiovascular Technologies for Space flight (Goal 6) and Earth-based Applications (Goal 7). The progress of the Cardiovascular Alterations Team has been heavily dependent on the development of new technologies which allow us to better understand, measure and alter physiological processes. Technologies that we have developed and applied include computer simulation technologies, Cardiovascular System Identification technology for the non-invasive quantification of closed cardiovascular regulation, measurement of Microvolt T-Wave Alternans to assess cardiac electrical stability, and ultrasound technologies for the non-invasive assessment of cardiovascular function. One of these technologies (Microvolt T-Wave Alternans) has already been successfully commercialized for clinical use here on Earth. We are just beginning to develop a novel pulsatile G-suit as a countermeasure to the development of orthostatic hypotension. Future progress of the Cardiovascular Alterations Team will continue to be dependent, in part, on the development of new diagnostic and therapeutic technologies. In the future we plan to solicit proposals which specifically focus on the development of novel cardiovascular technologies with applications to both space and Earth medicine.

Progress towards Integration (Goal 8) The cardiovascular team strives to have a dynamic interplay/integration between projects focused on animal studies, human studies, and

cardiovascular simulations (Table 4.2 and Figure 4.1). This intra-team interaction has been facilitated by team retreats and telecons. With the recent enlargement of our team from 12 to 16 projects discussed above, going forward we will have projects within each of the three areas (animal studies, human studies, and cardiovascular simulations) also meet separately in addition to the team wide meetings.

In addition to our intra-team integration we interact with a number of other NSBRI teams including Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems. Two of our project leaders (Cassone, Thomas) are integrated into the functioning of other teams (Human Performance, Smart Medical Systems). We plan to further promote this inter-team interaction for the following reasons:

- In addition to microgravity, other conditions of space flight may also adversely affect the cardiovascular system, including sleep disruption, reduced physical stress, environmental factors, and psycho-social stresses.
- Countermeasures proposed by and/or affecting the other teams may include pharmacological, nutritional, and physical interventions (including artificial gravity) and modifications of behavior, activity and environment.

Additional Issues

Below are some important cross-cutting issues which affect multiple projects.

Experimental Models. Additional data from space flight is required to evaluate the degree of correspondence of data from ground-based animal and human models with space flight data. Previously, we have had very limited opportunity to obtain data for this validation, but we are now beginning to obtain both animal and human flight data.

Cardiovascular Space Flight Database. There is an urgent need to obtain and make available to investigators a systematic database of cardiovascular data from astronauts before, during and after space flight. We will be working with a NASA-NSBRI initiative to develop a cardiovascular physiological flight database from data collected routinely during ongoing flights.

Experimental Approaches. Investigations are required which range from the molecular, genetic and cellular level to the organ system level to the level of the entire organism. Our projects do span this spectrum and we are using computer simulations as a means of integrating the experimental data across these different levels of organization.

Individual Susceptibility. Investigation of factors that make an individual more susceptible to the adverse effects of space flight on the cardiovascular system may include age, gender, genotype, and dietary, occupational and physical conditioning history. We have begun to address these issues but more activity in this area is required.

4.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Presented here are the objectives underlying each goal and the strategic activities that we plan to use to achieve the goals and objectives of our program. The timelines for achievement of the activities underlying each goal are presented in Table 4.3.

Goal 1: *Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress*

Objective 1A: Assess Risk and/or Determine Level of Acceptable Risk

- Continue to collect data from ongoing flights to determine incidence and level of risk of orthostatic intolerance particularly during long term flights

Objective 1B: Determine Mechanisms

- Understand alterations in nitric oxide and prostacyclin systems
- Understand alterations in circadian physiology
- Study alterations in CV regulation using CV System Identification
- Develop accurate computer models of CV System
- Study effects of microgravity on blood vessels, lymphatics
- Study effects of adrenergic agents (midodrine)
- Study effects of soluble guanylyl cyclase gene disruption
- Study effects of vestibular stimulation
- Develop and apply relevant ultrasound technology
- Assess volume, electrolyte and hormonal responses
- Assess effects of sleep disruption
- Assess effects of gender and age
- Develop pulsatile G suit
- Assess effects of artificial gravity

Objective 1C: Develop Countermeasures

Preliminary

- Evaluate pharmacologic alteration of nitric oxide and prostacyclin systems
- Evaluate circadian intervention
- Use CV System Identification to evaluate countermeasures
- Utilize CV models to simulate effects of countermeasures
- Evaluate vascular and lymphatic interventions
- Evaluate adrenergic agents (midodrine)
- Evaluate soluble guanylyl cyclase intervention
- Evaluate vestibular intervention
- Utilize ultrasound technology to evaluate countermeasures
- Evaluate volume regulatory and electrolyte interventions
- Evaluate sleep control intervention
- Evaluate gender and age dependent interventions
- Evaluate exercise countermeasure
- Evaluate pulsatile G suit
- Evaluate artificial gravity countermeasure

Mature

- Test midodrine countermeasure in human ground studies
- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation and Validation

- Flight test midodrine countermeasure
- Flight test other countermeasures successful in mature countermeasure development

Operational Implementation

- Implement midodrine countermeasure
- Implement other countermeasures successful in evaluation and validation of counter-measures

Goal 2: *Reduce Risk of Occurrence of Serious Cardiac Dysrhythmias*

Objective 2A: Assess Risk and/or Determine Level of Acceptable Risk

- Obtain and analyze ECG data from prior and future flights to determine incidence of dysrhythmias

Objective 2B: Determine Mechanisms

- Microvolt T-wave alternans (MTWA) studies in patient populations to validate MTWA as a non-invasive measure of susceptibility to ventricular dysrhythmias
- Measure effects of microgravity on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of electrolyte alterations on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of alterations in volume regulatory hormones on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Measure effects of age and gender on susceptibility to ventricular dysrhythmias as measured by MTWA in humans
- Develop animal model of microgravity altered susceptibility to ventricular dysrhythmias
- Develop computer models of cardiac electrical activity in humans

Objective 2C: Develop Countermeasures

Preliminary

- Test aldosterone antagonist (spironolactone) as potential countermeasure in human studies
- Measure MTWA in pre and post flight astronauts
- Evaluate dietary countermeasure in human studies
- Evaluate pharmacologic countermeasures in animal studies
- Evaluate countermeasures developed for Goal 1 in human studies

Mature

- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation and Validation

- Flight test countermeasures successful in mature countermeasure development

Operational Implementation

- Implement countermeasures successful in evaluation and validation of countermeasures

Goal 3: *Reduce Risk of Diminished Cardiac Function*

Objective 3A: Assess Risk and/or Determine Level of Acceptable Risk

- Obtain and analyze relevant data from prior and future flights to characterize and quantify to what extent space flight causes cardiac atrophy and remodeling, whether the alterations are reversible and whether they pose a long-term risk to astronauts.

Objective 3B: Determine Mechanisms

- Develop myocyte and cardiac computer models
- Measure effects of microgravity on cardiac mass
- Measure effects of microgravity on myocyte function
- Measure effects of microgravity on cardiac remodeling
- Measure role of calcium, hormones, genes, muscle degradation
- Develop ultrasound techniques to measure cardiac function

Objective 3C: Develop Countermeasures

Preliminary

- Use computer models to simulate potential countermeasures
- Evaluate growth hormone countermeasure
- Evaluate adrenergic countermeasure

- Evaluate dietary and exercise countermeasures
- Evaluate other pharmacological countermeasures
- Evaluate countermeasures developed for Goal 1 in human studies

Mature
- Select and test most promising countermeasures and develop and test in human ground studies

Evaluation & Validation
- Flight test countermeasures successful in mature countermeasure development

Operational Implementation
- Implement countermeasures successful in evaluation and validation of countermeasures

Goal 4: *Reduce Risk of Manifestation of Previously Asymptomatic Cardiovascular Disease*
Objective 4A: Assess Risk and/or Determine Level of Acceptable Risk
- Propose non-invasive screening protocol to detect asymptomatic cardiovascular disease and test in ground-based study where subjects are followed for several years for manifestations of cardiovascular disease.

Goal 5: *Reduce Risk of Impaired Cardiovascular Response to Exercise Stress*
- Since current inflight exercise regimens appear to accomplish this goal, we do not plan further activity in this area.

Goal 6: *Develop new cardiovascular diagnostic and therapeutic technologies for space flight applications*
Objective 6A: Solicit proposals

Goal 7: *Develop new cardiovascular diagnostic and therapeutic technologies for medical use on Earth*
Objective 7A: Solicit proposals

Goal 8: *Integrate Research and Analysis*
Objective 8A: Integrate Research Within the Cardiovascular Alterations Team.
- Continue scheduled discussions

Objective 8B: Integrate Research With Other Teams, Using Modeling as well as Other Approaches
- Integrate cardiovascular models with models of other organ systems to simulate integrated physiologic behavior of multiple systems
- Create models of individualized physiologic function from data collected on a single astronaut at a single point in time
- Develop shared research protocols with other teams such as Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems.

Objective 8C: Integrate Research with Scientists Outside of NSBRI

4.6 SUMMARY

During space flight the cardiovascular system undergoes adaptive changes in structure and function in response to weightlessness and other factors, such as sleep disruption, confinement and additional environmental alterations. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. In addition, there are alterations in the lymphatic, neural

and hormonal control systems. While these adaptations appear to be associated with generally adequate cardiovascular performance during conditions of short-duration space flight, they are not appropriate upon reentry into a gravitational environment. Furthermore, the extent of cardiovascular adaptation appears to increase with duration of space flight, and the magnitude and implications of these adaptations for long-duration space flight (that is, months to years) remain largely unknown.

Adverse effects of space flight on the cardiovascular system include: 1) Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance, which limits their ability to function during reentry and after landing and possibly could interfere with the ability of astronauts to egress from the spacecraft under emergency conditions. Currently used countermeasures, such as oral administration of salt and water prior to reentry and application of anti-gravity suits, do not adequately prevent orthostatic intolerance, especially following long-duration space flight. 2) A number of anecdotal reports suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. If space flight does in fact significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. 3) Long-term space flight may lead to a measurable reduction in cardiac mass. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. 4) Long-duration space flight may exacerbate previously undetected cardiovascular disease, such as coronary artery disease. 5) Long-term space flight may impair cardiovascular response to exercise.

The aim of the Cardiovascular Alterations Team is to minimize these risks using the following approach:

- Characterize and quantify the adverse effects of space flight on cardiovascular structure and function
- Determine the mechanisms of these adverse effects
- Develop effective countermeasures to these adverse effects
- Develop new cardiovascular technologies for use in countermeasure development and for spin-off applications on Earth

This approach involves an integrated team effort involving projects ranging from the molecular, cellular, organ system, and whole animal investigations as well as computer simulations.

The team has already achieved advanced development of one countermeasure for orthostatic hypotension, the alpha agonist midodrine. The team has progressed from ground-based studies to having two flight studies approved, one of which will be testing the midodrine countermeasure, the other of which will focus on alterations in vascular control mechanisms.

The team has successfully developed two new technologies. One of these technologies, measurement of microvolt T-wave alternans is a non-invasive means of assessing risk of ventricular arrhythmias and sudden cardiac death. This technology is being used to determine whether microgravity predisposes astronauts to ventricular dysrhythmias. This technology has been successfully commercialized, cleared by the FDA, reimbursed by Medicare, and is in widespread clinical use to reduce sudden cardiac here on Earth, which claims 350,000 lives in the United States each year. The other technology developed by the team is Cardiovascular System Identification that non-invasively quantifies closed-loop cardiovascular regulation. This technology is being used to assess mechanisms of post flight orthostatic hypotension, and also

has applications for diagnosis and management of heart failure, diabetes and hypertension on Earth.

The team has developed effective cardiovascular computer models that have been used to analyze and integrate data from multiple studies and evaluate potential countermeasures.

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Figure 4.1 – Relationship and Integration of Projects

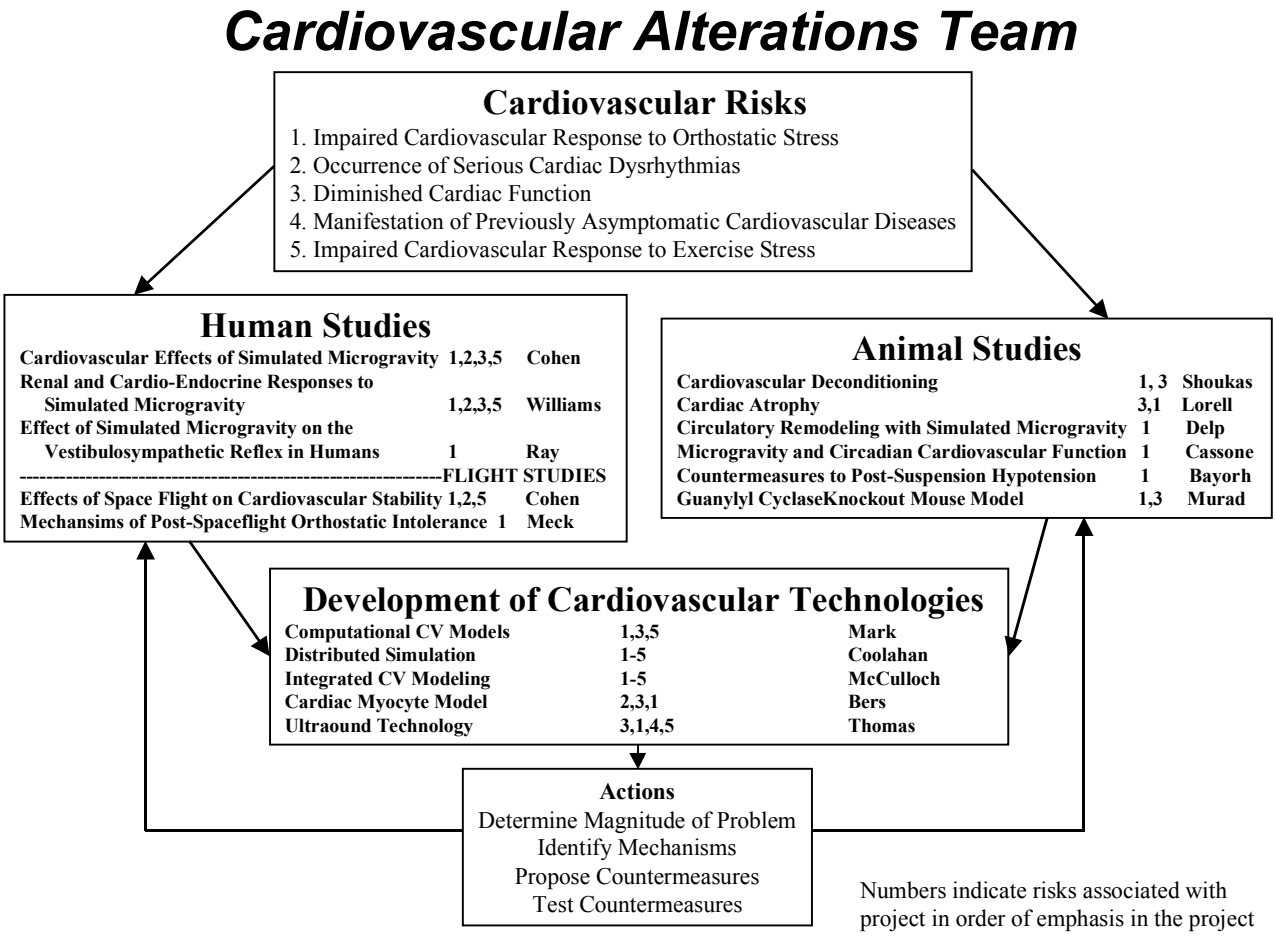

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Table 4.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BAYORH/Possible Countermeasures to Post-Suspension Hypotension in the Head-Down Tilt Rat Model	Orthostatic hypotension	Pharmacological (Nitric oxide and prostacyclin inhibitors)	Head-down tilt rat model	Alterations in nitric oxide and prostacyclin systems	Interventional pharmacological studies	Test countermeasures in human studies
BERS/Integrative Cardiac Myocyte Model: Ion channels, Ca and Contraction	• Dysrhythmias • Cardiac function • Orthostatic hypotension	Simulation of effects of wide variety of potential countermeasures	Computer simulation of cardiac myocyte	Develop computer mode of cardiac myocyte	Simulate effects of space flight and potential countermeasures on myocyte function	Use computer model to analyze data from animal and human countermeasure studies
CASSONE/Microgravity and Circadian Cardiovascular Function	Orthostatic hypotension	• Environmental • Pharmacologic	Tail suspended rat	Effects of alterations in circadian physiol and microgravity on nervous and CV systems	Interventional studies: • Environmental • Pharmacological	Test countermeasures in human studies
COHEN/Cardiovascular Effects of Simulated Microgravity in Man	• Orthostatic hypotension • Exercise • Cardiac function • Dyshythmias	• Pharmacological (Midodrine and Spironolactone) • Diet (Electrolytes)	• Head down tilt bed rest - humans • Sleep disruption • Groups vary by age and gender	Effects of microgravity on: • CV regulation (CV System Identification) • Dysrhythmias (T-Wave Alternans)	Ground based testing in humans of • Midodrine • Spironolactone • Diet (Electrolytes)	Ground based testing in humans of • Midodrine • Spironolactone • Diet (Electrolytes)

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
COHEN/Effects of Space Flight on Cardiovascular Stability	• Orthostatic hypotension • Exercise • Dysrhythmias	• Pharmacological (Midodrine and Spironolactone) • Diet (Electrolytes)	Pre and post flight humans	Effects of microgravity on: • CV regulation (CV System Identification) • Dysrhythmias (T-Wave Alternans)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes)	Pre and post flight in humans of • Midodrine • Spironolactone • Diet (Electrolytes) • Spironolactone
COOLAHAN/Distributed Simulation of Integrated Human Function	• Orthostatic hypotension • Dyshythmias • Cardiac function • CV Disease • Exercise	Simulation of effects of wide variety of different potential countermeasures including exercise	Computer model of the cardiovascular system integrated with other systems	Develop and validate accurate model of myocyte and heart	•Develop integrated CV model •Develop integrated model incorporating other systems •Simulate effects of space flight and potential CMs	Analyze data from animal and human tests of countermeasures
DELP/Circulatory Remodeling with Simulated Microgravity	Orthostatic hypotension • Cardiac function • Exercise	Peripheral vascular countermeasures	• Hindlimb unloading (HU) of rats • Shuttle flight (STS-107) of rats	Measure effects and mechansims of HU and shuttle flight on: cerebral & peripheral vascular beds, lymphatics, cardiac mass	Evaluate data to identify and then test potential countermeasures	Test countermeasures in human studies

Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
LORELL/Cardiac Unloading: Biologic Mechanisms and Countermeasures for Cardiac Atrophy	• Cardiac function • Orthostatic hypotension	• Pharmacological countermeasures to: reduce cardiac atrophy, suppress muscle degradation, & restore cardiac function • Identify molecular targets to modify cardiac muscle growth and degradation	• Heterotopic cardiac transplantation rodent model: intact heart & adult myocyte •Transgenic mouse models and cultured myocytes	Study: cardiac remodeling, myocyte function, & role of calcium, hormones, muscle degradation, genes, kinases	Test: • Low dose growth hormone • Adrenergic agonist	Test countermeasures in human studies
MARK/Computational Models of the Cardiovascular System and its Response to Microgravity and Disease	• Orthostatic hypotension • Cardiac function • Exercise	Simulation of effects of wide variety of different potential countermeasures	Computer model of the cardiovascular system	Develop and validate accurate model of cardiovascular system	Simulate effects of space flight and potential countermeasures	Analyze data from animal and human tests of countermeasures
MCCULLOCH/Integrated Modeling of Cardiac Mechanical and Electrical Function	• Orthostatic hypotension • Dysrhythmias • Cardiac function • CV Disease • Exercise	Simulation of effects of wide variety of different potential countermeasures including exercise	Three dimensional finite element model of the heart	Develop and validate accurate three dimensional finite element model of the heart	Simulate effects of space flight and potential countermeasures	Analyze data from animal and human tests of countermeasures
MECK/Mechanisms of Post-Space Flight Orthostatic Intolerance	Orthostatic hypotension	Pharmacological (Nitric oxide system, Adrenergic system)	Pre and post flight astronauts	Study effect of space flight on: responses to adrenergic agents & nitric oxide system	Propose and test countermeasures in ground based models	Test countermeasures in human studies

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Table 4.1. Project Research Activities (continued)

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
MURAD/A soluble guanylyl cyclase mouse knock-out model	Orthostatic hypotension	Pharmacological (affecting soluble guanylyl cyclase (sGC))	Tail-suspended knockout mouse	Study effect of sGC gene disruption on the CVsystem	Study effect of sGC gene disruption on development of orthostatic hypotension	Propose and test pharmacologic countermeasures
RAY/Effect of Simulated Microgravity on the Vestibulosympathetic Reflex in Humans	Orthostatic hypotension	Countermeasures affecting vestibulosympathetic reflex	Human bed rest studies	Study effects of vestibular stimulation and bed rest on sympathetics	Propose and evaluate feasibility of countermeasures in human studies	Test countermeasures in human studies
SHOUKAS/Mechanics of Cardiovascular Deconditioning	• Orthostatic hypotension • Cardiac function	• Pharmacological (Adrenergic agents) • Pulsatile G-suit	• Hindlimb unloading (HU) of rats • Shuttle flight (STS-107) of rats	Measure effects and mechansims of HU and shuttle flight on: • vascular beds • cardiac fctn	• Identify and test pharmacologic countermeasures in rodent model • Develop pulsatile G-suit	Test countermeasures in human studies
THOMAS/ Echocardiographic Assessment of CV Adaptation and Countermeasures in Microgravity	• Orthostatic hypotension • Cardiac function • CV disease • Exercise	N/A	• Core lab analysis of ultrasound data •Development of new ultrasound techniques	Study effects of interventions & countermeasure s using ultrasound techniques	Study effects of interventions & countermeasures using ultrasound techniques	Study effects of interventions & countermeasures using ultrasound techniques
WILLIAMS/Influence of Gender and Age on Renal and Cardio-Endocrine Responses to Simulated Microgravity	• Orthostatic Hypotension • Exercise • Cardiac Function • Dysrhythmias	• Pharmacological (Midodrine and volume regulating hormones) • Diet (Electrolytes)	• Head down tilt bed rest Head down tilt bed rest - humans • Sleep disruption • Groups vary by age and gender	Assess volume, electrolyte, hormonal responses	•Midodrine •Spironolactone •Diet (Electrolytes)	•Midodrine •Spironolactone •Diet (Electrolytes)

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Table 4.2. Integration Activities

	Bayorh	Bers	Cassone	Cohen	Coolahan
Internal Communication	•Animal studies group •All	•CV technology group •All	•Animal studies group •All	•Human studies group •All	•CV technology group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)
Sample Sharing	•Tissue (Animal studies group) •Data (All)	•Computer Code (CV technology group) •Data (All)	•Tissue (Animal studies group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)	•Computer Code (CV technology group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Animal Studies(Animal studies group) •Human and Computer Studies (All)	Human Studies (Humans studies group) Animal and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

Table 4.2. Integration Activities (continued)

	Delp	Lorell	Mark	McCulloch	Meck
Internal Communication	•Animal studies group •All	•Animal studies group •All	•CV technology group •All	•CV technology group •All	•Human studies group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)
Sample Sharing	•Tissue (Animal studies group) •Data(All)	•Tissue(Animal studies group) •Data (All)	•Computer Cod e(CV technology group) •Data (All)	•Computer Code (CV technology group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	•Computer Studies (CV technology group) •Human and Animal Studies(All)	Human Studies (Humans studies group) Animal and Computer Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

Table 4.2. Integration Activities (continued)

	Murad	Ray	Shoukas	Thomas	Williams
Internal Communication	•Animal studies group •All	•Human studies group •All	•Animal studies group •All	•CV technology group •All	•Human studies group •All
Integrated Experiment Development	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human Studies (Human studies group) •Animal and Computer Studies (All)	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	•Human and Animal Studies(All) •Computer Studies (CV technology group)	•Human Studies (Human studies group) •Animal and Computer Studies (All)
Sample Sharing	•Tissue (Animal studies group) •Data (All)	•Blood and Urine (Human studies group) •Data (All)	•Tissue (Animal studies group) •Data(All)	•Data (All) •Computer Code (CV technology group)	•Blood and Urine (Human studies group) •Data (All)
Synergistic Studies of Opportunity	•Animal Studies (Animal studies group) •Human and Computer Studies (All)	Human Studies (Humans studies group) Animal and Computer Studies (All)	•Animal Studies Animal studies group) •Human and Computer Studies (All)	•Human and Animal Studies (All) •Computer Studies (CV technology group)	Human Studies (Humans studies group) Animal and Computer Studies (All)
Development of Computer Model of Integrated Human Function	•CV technology group	•CV technology group	•CV technology group	•CV technology group	•CV technology group

Human Studies Group = Cohen, Meck, Ray, Williams, and collaborators from other Teams
Animal Studies Group = Bayorh, Cassone, Delp, Lorell, Murad Shoukas, and collaborators from other Teams
CV Technology Group = Bers, Coolahan, Mark, McCulloch, Thomas, and collaborators from other Teams
Collaborators from other Teams include members of Human Performance, Neurobehavioral, Neurovestibular, Rehabilitation, Technology Development, and Smart Medical Systems Teams

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Table 4.3a. Achieving Goal 1: Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze relevant data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Study alterations in CV regulation using CV System Identification • Study effects of adrenergic agents (midodrine) • Assess volume, electrolyte and hormonal responses													
• Understand alterations in nitric oxide and prostacyclin systems • Understand alterations in circadian physiology • Develop accurate computer models of CV System • Study effects of microgravity on blood vessels, lymphatics • Study effects of soluble guanylyl cyclase gene disruption • Study effects of vestibular stimulation • Develop and apply relevant ultrasound technology • Assess effects of sleep disruption • Assess effects of gender and age • Develop pulsatile G suit													
• Assess effects of artificial gravity													
Phase 2: Preliminary Countermeasure Development Research													
• Evaluate adrenergic agents (midodrine)													
• Evaluate pharmacologic alteration of nitric oxide and prostacyclin systems • Evaluate circadian intervention • Use CV System Identification to evaluate countermeasures • Utilize CV models to simulate effects of countermeasures • Evaluate vascular and lymphatic interventions • Evaluate soluble guanylyl cyclase intervention • Evaluate vestibular intervention • Utilize ultrasound technology to evaluate countermeasures • Evaluate volume regulatory and electrolyte interventions • Evaluate sleep control intervention													

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Table 4.3a. Achieving Goal 1: Reduce Risk of Impaired Cardiovascular Response to Orthostatic Stress (continued)

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 2: Preliminary Countermeasure Development Research													
• Evaluate gender and age dependent interventions • Evaluate exercise countermeasure • Evaluate pulsatile G suit													
• Evaluate artificial gravity countermeasures													
Phase 3: Mature Countermeasure Development Research													
• Test midodrine countermeasure in human ground-based studies													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test midodrine countermeasure													
• Flight test other countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement midodrine countermeasure													
• Implement other countermeasures in Phase 4													

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Table 4.3b. Achieving Goal 2: Reduce Risk of Serious Cardiac Dysrhythmias

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze ECG data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Microvolt T-wave alternans (MTWA) studies in patient populations													
• Measure effects of microgravity on MTWA • Measure effects of electrolyte alterations • Measure effects of alterations in volume regulatory hormones • Measure effects of age and gender • Develop animal model • Develop computer models of cardiac electrical activity													
Phase 2: Preliminary Countermeasure Development Research													
• Measure MTWA in pre and postflight astronauts													
• Test aldosterone antagonist as countermeasure in human studies • Evaluate dietary countermeasures in human studies • Evaluate pharmacologic countermeasures in animal studies • Evaluate countermeasures developed for Goal 1 in human studies													
Phase 3: Mature Countermeasure Development Research													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement countermeasures successful in Phase 4													

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Table 4.3c. Achieving Goal 3: Reduce Risk of Diminished Cardiac Function

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Obtain & analyze relevant data from prior and future flights													
Phase 1: Focused Mechanistic Research													
• Develop myocyte and cardiac computer models													
• Measure effects of microgravity on cardiac mass • Measure effects of microgravity on myocyte function • Measure effects of microgravity on cardiac remodeling • Measure role of calcium, hormones, genes, muscle degradation • Develop ultrasound techniques to measure cardiac function													
Phase 2: Preliminary Countermeasure Development Research													
• Use computer models to simulate potential countermeasures • Evaluate growth hormone countermeasure • Evaluate adrenergic countermeasure • Evaluate dietary and exercise countermeasures • Evaluate other pharmacological countermeasures • Evaluate countermeasures developed for Goal 1 in human studies													
Phase 3: Mature Countermeasure Development Research													
• Select and test most promising countermeasures and develop and test in human ground studies													
Phase 4: Countermeasure Evaluation & Validation													
• Flight test countermeasures successful in Phase 3													
Phase 5: Operational Implementation of Countermeasure Strategy													
• Implement countermeasures successful in Phase 4													