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MICROGRAVITY AND THE CARDIOPULMONARY SYSTEM: A DISCIPLINE SUMMARY

Michael D. Delp, Ph.D.
Janice V. Meck, Ph.D.

Index Terms: microgravity, bedrest, hindlimb unloading, hindlimb unweighting, countermeasures, computer modeling, orthostasis, orthostatic intolerance, autonomic nervous system, sympathetic nerve activity, baroreceptors, blood pressure control, venous pressure, heart, arrhythmias, cardiac electrophysiology, echocardiography, heart development, cell migration, vestibular, vestibulosympathetic reflex, arteries, arterioles, veins, vascular resistance, norepinephrine, nitric oxide, midodrine, cerebral circulation, cerebral autoregulation, skin blood flow, thermoregulation, cold stress, endocrine, lung, aerosol, particles, exercise, muscle strength, muscle atrophy

INTRODUCTION

Many of the various organ systems that collectively make up the cardiopulmonary system adapt to a weightless environment. Although there is little evidence to suggest cardiopulmonary adaptations during short duration or prolonged habitation in space are inappropriate or incapacitating, such adaptations present several problems upon return to a 1G environment. As identified in the NASA Critical Path, some of these problems or potential problems include alterations of the heart, orthostatic intolerance, and a diminished exercise/work capacity. Ongoing work to investigate microgravity-induced cardiopulmonary alterations are using a variety of approaches, including: research involving humans, animals, computer modeling and technology development; studies that are descriptive, mechanistic, as well as countermeasure oriented; work at the molecular, cellular, organ and whole organism levels; efforts that involve intramural and extramural integration and collaboration; and research outcomes which will provide both spaceflight specific and broader clinical benefits. With the variety of approaches and the apparent balance of inquiry, it is anticipated that the critical cardiopulmonary adaptations that occur in microgravity will soon be elucidated, and that from this knowledge, appropriate countermeasures can be designed, tested and implemented.

SUMMARY OF PRESENTATIONS

Brief summaries of the cardiopulmonary presentations at the 2001 Bioastronautics meeting are presented below (presenter name underlined) and have been grouped into eight categories, although it is acknowledged that this categorization is somewhat arbitrary because considerable overlap exists among categories.

Cardiac


Sixteen days of bed-rest has a measurable effect on cardiac repolarization processes as measured by T-wave alternans. The risk of life threatening arrhythmias during long duration space flight remains to be determined. T-wave alternans measurement is an important spin-off technology for civilian medicine. Future studies will examine effects of age and gender on the development of T-wave alternans associated with bed-rest.

BOTH GROWTH FACTOR-INDUCED CELL MIGRATION AND CELL MIGRATION INDUCED BY RANDOMIZATION OF THE GRAVITY VECTOR RELY ON METALLOPROTEINASE ACTIVATION, S. Hoffman and P. Susan.

We have used a cell line that mimics the epithelial-mesenchymal transformations that occur during early heart development to study parameters that affect cell migration into a three-dimensional collagen gel. We find that both growth factors and randomization of the direction of the gravity vector promote cell migration in this system and that, in both cases, cell migration is sensitive to inhibitors of matrix metalloproteinase (MMP) activity. Studies on specific MMPs suggest that MMP-2 and other, currently unidentified, MMPs are important in the regulation of cell migration.

From Texas A&M University, Departments of Health and Kinesiology and Medical Physiology, College Station, TX (M. Delp) and NASA Johnson Space Center, Life Sciences Research Laboratories, Houston, TX (J. Meck).
Neural-Reflex and Neurovestibular


Carotid baroreflex control of sympathetic nerve activity significantly contributes to the regulation of arterial blood pressure during acute hypotension. Aortic baroreflex control of sympathetic nerve activity predominates in its significant contribution to the regulation of arterial blood pressure during acute hypotension. Endurance exercise training impairs sympathetically neurally mediated control of vasomotion.

HUMAN SYMPATHETIC AND VAGAL NEURAL RESPONSES TO VALSALVA'S MANEUVER IN SPACE, J.F. Cox.

We provoked arterial pressure transients with 15 and 30 mmHg Valsalva straining for 15 seconds in four male astronauts before and on days 12 and 13 of the Neurolab Space Shuttle Mission. Valsalva straining provoked greater arterial pressure changes in space than on earth; vagal R-R interval responses were somewhat less, and muscle sympathetic nerve responses (expressed in terms of arterial pressure changes) were normal. Exposure to microgravity differentially affects arterial baroreflex mechanism: vagal baroreflex responses are impaired, and sympathetic baroreflex responses are normal.

SPACE TRAVEL AND ORTHOSTATIC INTOLERANCE, D. Robertson.

Orthostatic intolerance (OI) is common after space flight and resembles the disabling idiopathic OI commonly observed in otherwise healthy young individuals. OI can arise from reduced sympathetic nervous system activity and, paradoxically, also from increased sympathetic nervous system activity. Recent studies on Neurolab place the OI of microgravity in the latter hyperadrenergic category, and these studies have led to the discovery of genetic etiologies of OI such as norepinephrine transporter deficiency.


The goal of this study is to investigate the central nervous system mechanism underlying the adaptive plasticity in orthostatic responses following vestibular lesions. Blood pressure responses to nose-up body rotations of varied amplitude were recorded in alert cats prior to and following ablation of the caudal cerebellar vermis and again following subsequent bilateral vestibular neurectomy. Removal of the caudal vermis had slight to moderate effects on orthostatic responses, while subsequent vestibular lesion elicited significant impairment of orthostatic tolerance that persisted beyond the previously observed recovery period of one week.

THE VESTIBULOSYMPATHETIC REFLEX IN HUMANS: NEURAL INTERACTIONS WITH CARDIOVASCULAR REFLEXES, C.A. Ray.

Head down neck flexion increases muscle sympathetic nerve activity (MSNA). This increase in MSNA appears to be mediated by activation of the otolith organs. Semicircular canals do not increase MSNA in humans. The neural interaction between the vestibulosympathetic reflex and other cardiovascular reflexes (i.e., baro reflexes and skeletal muscle reflexes) with regard to MSNA is additive. The vestibulosympathetic reflex is a powerful activator MSNA and may help defend against orthostatic challenges in humans.

Fluid Loss and Neurovascular Effects

EVIDENCE FOR CENTRAL VENOUS PRESSURE RESETTIMG AND AGAINST ALTERATIONS IN RENAL RESPONSIVENESS TO ALDOSTERONE DURING EARLY EXPOSURE TO MICROGRAVITY, V.A. Convertino, D.A. Ludwig, J.J. Elliott, and C.E. Wade.

Reduced renal sodium retention and lower operating point for central venous pressure (CVP) appear to be mechanisms that contribute to the regulation of plasma and blood volume at reduced levels during exposure to microgravity. The natriuretic effect of microgravity appears to be caused by some mechanism(s) other than aldosterone. Inflight testing and implementation of maximal exercise as a countermeasure for reduced blood volume is recommended since this procedure restores renal sodium retention and the level at which CVP operates at 1G.
NOREPINEPHRINE RESPONSES TO TYRAMINE AND PRESSOR RESPONSES TO PHENYLEPHRINE ARE NOT REDUCED IN ASTRONAUTS AFTER SPACEFLIGHT, J. Meck, M. Ziegler, W. Waters, D. D'Aunno, P. Huang, and H. deBlock.

We have demonstrated that norepinephrine stores in sympathetic nerves are not reduced after spaceflight. In fact, the release of norepinephrine in response to tyramine is actually greater on landing day than preflight. In addition, we suggest that α-1 adrenergic receptors may be upregulated in presyncopal astronauts and down-regulated in non-presyncopal astronauts, possibly indicating differences in sympathetic activity and norepinephrine release during flight in susceptible and non-susceptible individuals.


We have demonstrated in vivo using a rat cardiopulmonary bypass model and in vitro in isolated rat mesenteric veins, that venous compliance and unstressed volume are increased and responsiveness of veins to norepinephrine are decreased in HLU rat model of microgravity. This may contribute to the impaired SV response seen in astronauts following microgravity. We plan to 1) Extend our observations by examining integrated cardiovascular function (pressure-volume loops) in the same model and 2) Understand basic molecular mechanisms of vascular hyporesponsiveness using Ca^{2+} fluorometry and vascular force measurement.

MECHANISMS OF MICROGRAVITY EFFECT ON VASCULAR FUNCTION, R.E. Purdy, S. Sangha, C. Kahwaji, J. Ma, S. Duckles, D. Krause, and N. Vaziri.

This study seeks to identify mechanisms underlying simulated microgravity-induced vascular hyporesponsiveness to norepinephrine. The evidence presented supports the hypothesis that microgravity causes a chronic elevation of the endogenous vasodilator, nitric oxide, within blood vessels, decreasing the capacity for vasoconstriction. In addition, simulated microgravity appears to impair selected signal transduction pathways associated with alpha adrenergop- mediated vasoconstriction.


We examined rat mesenteric small artery function after simulated microgravity (using hindlimb suspension). We found reduced myogenic tone after hindlimb suspension that is associated with reduced 20-HETE production. We also found that after hindlimb suspension, hemodynamic responses to heat stress (while anesthetized) were intact and there was no change in mesenteric artery sympathetic innervation.

MICROGRAVITY-INDUCED ORTHOSTATIC INTOLERANCE: AN ARTERIAL MICROVASCULAR MECHANISM, M.D. Delp.

In several vascular beds of the hindlimb unloaded rat, such as that in the hindlimb musculature and brain, the cephalic fluid shift alters the mechanical forces acting upon resistance arteries and induces a remodeling of arterial structure. These structural alterations, in turn, profoundly affect arterial function, so that vasoconstrictor responsiveness is diminished in the hindlimb circulation and enhanced in the cerebral circulation. If vascular alterations similar to those in the hindlimb unloaded rat occur in humans during spaceflight, this could partially explain the hypotension and compromised ability to elevate TPR during the assumption of an upright posture upon return to Earth, and perhaps the orthostatic intolerance of astronauts with normal blood pressures.

Specific Circulations and Organs

CEREBRAL PERFUSION IN SUBJECTS WITH ORTHOSTATIC INTOLERANCE, W. Singer, P.A. Low, V. Novak, and P. Novak.

The main symptoms of patients with orthostatic intolerance are suggestive of cerebral hypoperfusion. We could demonstrate that cerebral blood flow in the upright position is reduced in this patient group, in significant part due to hyperventilation. Cerebral autoregulation was also assessed using a new analytical method and was not significantly different from controls.
EFFECTS OF HEAD-DOWN TILT BED REST ON SWEAT GLAND FUNCTION AND MAXIMAL CUTANEOUS VASCULAR CONDUCTANCE, C.G. Crandall, M. Shibasaki, T. Wilson, J. Cui, and N. Hodges. Elevation in skin blood flow and sweating are altered following space flight. We identified that maximal cutaneous vascular conductance is impaired by head-down tilt bed rest, although sweat gland function is not altered. Chronic exercise training returns maximal cutaneous vascular conductance to pre-head-down tilt levels.

PULMONARY DEPOSITION OF AEROSOLS IN MICROGRAVITY, G.K. Prisk, J.B. West, and C. Darquenne. Aerosol deposition in the lung is important in both drug delivery to the lungs and in the adverse effects of atmospheric pollution. Measurements of total deposition in microgravity show unexpectedly high deposition of the smaller particles, perhaps providing a link to the observation that the small inhaled particles in the environment have a disproportionately high adverse effect. Current studies of aerosol transport in the lung periphery using computational fluid dynamics show irreversible transport in the direction of the lung periphery providing a protective mechanism for these findings.

Countermeasures

EFFECT OF EXERCISE AND ACCELERATION TRAINING ON RESTING AND ORTHOSTASIS INDUCED CHANGES IN HEMATOLOGICAL VARIABLES, S.R. Simonson, J.M. Stocks, S.A. Cowell, K.N. Pemberton, J. Evans, and J.E. Greenleaf. Losses of aerobic power and orthostatic tolerance are significant effects of manned spaceflight that can negatively impact crew health and safety. Daily acceleration and aerobic training may ameliorate these effects. The purpose of this pilot investigation was to determine the influence of various +Gz acceleration training protocols on the orthostatic, plasma volume, and vasoactive hormone responses to 70° head-up tilt.

PHYSIOLOGIC MAINTENANCE BY TREADMILL EXERCISE WITHIN LBNP DURING 30 DAYS BEDREST OF IDENTICAL TWINS, A.R. Hargens, D.E. Watenpaugh, S.M.C. Lee, C.J. Rogers, R.S. Meyer, A. Langemack, B. Macias, S. Kimura, G. Steinbach, E. Groppo, R. VanderLinden, W.L. Boda, D.D. O'Leary, R.L. Hughson, J.K. Shoemaker, M.G. Ziegler, S.M. Smith, and S.M. Schneider. Using identical twins as volunteers, we evaluated the efficacy of supine LBNP treadmill exercise during 30 days HDT bedrest for the following physiologic functions: 1) cardiovascular, 2) musculoskeletal, 3) exercise capacity, 4) GI function, 5) balance and posture, 6) sleep, and 7) comfort and mental status. Supine treadmill exercise within LBNP (40 min running + 5 min static LBNP for 6 days/week) maintains (as presented in this limited report): 1) orthostatic responses, 2) plasma volume, 3) upright exercise capacity, 4) spinal structure, and 5) some bone parameters. This “artificial gravity” countermeasure provides comfortable, high-intensity exercise to preserve various physiologic systems over 30 days of simulated microgravity.

ENDURANCE TRAINING DURING BED REST PREVENTS LEFT VENTRICULAR ATROPHY AND LOSS OF PLASMA AND VENTRICULAR VOLUME, M. Perhonen, J.H. Zuckerman, R. Zhang, and B.D. Levine. A decrease in upright stroke volume is the sine qua non of the cardiovascular adaptation to microgravity. This adaptation appears due to a combination of central hypovolemia and cardiac remodeling, which is likely cardiac atrophy. If both of these can be prevented the post bedrest orthostatic intolerance can be eliminated.

EVALUATION OF THE INTERIM RESISTANCE EXERCISE DEVICE FOR USE ON THE INTERNATIONAL SPACE STATION (ISS), S. Schneider, C. Lundquist, M. Rapley, W. Amonette, K. Blazine, J. Bentley, M. DeRidder, K. Cobb, and E. Mulder. My presentation describes preliminary findings comparing the effectiveness of a 16-week training program with free weights versus interim resistance exercise device. Thus far, it appears that the iRED produces increases in muscle volume, increases in muscle strength, increases in bone mineral density and lean body mass to a similar extent as training with free weights. It appears that the iRED may be used as an effective countermeasure for musculoskeletal deconditioning on ISS.
COLD STIMULATION TO IMPROVE ORTHOSTATIC TOLERANCE, J.A. Paweleczyk and D.W. Rimmer.
Moderate surface cooling can produce substantial improvements in orthostatic blood pressure. Current flight operations produce modest heat strain just prior to landing, which may exacerbate to post-flight orthostatic intolerance. Current cooling strategies are insufficient to ameliorate heat stress during the deorbit period.

**Computer Modeling**

**COMPUTATIONAL MODELS OF THE CARDIOVASCULAR SYSTEM AND ITS RESPONSE TO MICROGRAVITY AND DISEASE, R.G. Mark, R. Kamm, T. Heldt, and E. Shim.**

Computational models of the cardiovascular system have been developed and tested. Model is capable of capturing the static to dynamic response to orthostatic stress. Has been used to test hypotheses concerning the cause for orthostatic intolerance. Methods are developed to determine parameter values for specific individuals.

**DISTRIBUTED SIMULATION OF INTEGRATED HUMAN FUNCTION, J.E. Coolahan.**

The National Space Biomedical Research Institute (NSBRI) has established a new Integrated Human Function team to explore the integrated application of models and simulations of human physiology to the problems of long-term space flight. In a recently awarded NSBRI grant, the Johns Hopkins University Applied Physics Laboratory (JHU/APL) is applying distributed simulation technology developed in DoD (the High Level architecture) to link a supercomputer-based model of cardiac electrical function developed at JHU with a model of cardiac mechanical function developed at the University of California, San Diego, to investigate the interaction of mechanical and electrical cardiac activity. In subsequent years, it is planned to expand this effort to link other simulations of other human body cells, organs, and/or systems.

**Technologies**


HRF ultrasound unit scheduled for launch in 3/01. New Doppler algorithms have been validated for assessment of cardiac function in microgravity. Digital output and transmission will be essential for research and clinical use.

**RECOMMENDATIONS FOR FUTURE RESEARCH**

As part of a Cardiopulmonary group discussion, several comments and recommendations emerged. It was noted that the rodent and other animal work, as well as human bedrest studies, were contributing valuable insights into mechanisms of microgravity-induced cardiovascular dysfunction and providing a roadmap for targeting human countermeasures. However, it was acknowledged that support for cross-discipline investigations was inadequate. These included vestibular-cardiovascular, bone-cardiovascular, radiation-cardiopulmonary, and exercise-cardiovascular interactions. It was also acknowledged that the effects of the spaceflight experience itself, in addition to microgravity, should be more carefully considered; for example, of environmental factors and disruption of diurnal patterns. It was recommended that more easy access to stored blood and urine samples from astronauts and stored tissue from flight animals be made available to funded investigators. Finally, it was suggested that a Programmatic Requirement should be instituted, separate from medical operations or countermeasure evaluation requirements, to build a basic research database to document cardiovascular alterations induced by space habitation, such as long-duration Holter monitoring. However, committee or community input should be sought to determine what minimum set of baseline variables should be collected.

**SUMMARY**

Although we are gaining a better understanding of problems associated with space habitation and the cardiopulmonary system, our knowledge is still incomplete. However, it is becoming increasingly apparent that multiple factors contribute to problems associated with microgravity and the cardiovascular system, and these factors appear to vary across time, i.e., short vs. long duration space habitation. With orthostatic intolerance, for example, it is evident that there is not a single underlying mechanism across individuals. Published studies demonstrate that some orthostatically intolerant astronauts are hypotensive, while others are unable to stand despite having a normal blood pressure (Buckey et al., *J. Appl. Physiol.* 81: 7-18, 1996). As indicated in the project summaries, this may involve various combinations of hypovolemia, cardiac remodeling, peripheral and central
autonomic dysfunction, vestibular alterations, peripheral arterial remodeling, cerebral vascular alterations, and alterations in venous compliance.
INTRODUCTION
The lung presents by far the greatest surface area to the environment of any part of the body, of the order of 50 to 100 m². As a consequence, inhalation of particles can be beneficial as a means for the delivering medication, and deleterious in cases of inhaled particulate matter in the form of atmospheric pollutants. Numerous examples of polluted atmospheres exist on earth, and as the recent fire on the Mir space station showed, aerosols can readily occur in the closed environment of a spacecraft. While many inhaled particles impact in the upper airways, fine particles, those smaller than ~5 µm, are readily transported by the inspiratory airflow to the small airways of the lung. Particles in the size range of 1-5 µm are primarily deposited in the lung through the process of gravitational sedimentation, while smaller particles are affected by Brownian diffusion. The principal aim of the studies was to better understand the role of gravity in the degree and location of the deposition of inhaled particles in the human lung.

CURRENT STATUS OF RESEARCH
Methods
The studies were performed in the NASA Microgravity Research Aircraft (KC-135) and on the ground, which allowed for data to be collected in µG, normal gravity (1G) and in hypergravity (averaging ~1.6G). Using monodisperse polystyrene latex particles of known size we initially measured total pulmonary deposition over the size range of 0.5 to 3.0 µm. Subjects inhaled the particles suspended in air for a period of ~4 minutes, with a controlled breathing pattern while the aircraft alternated between µG and hypergravity. Data in 1G were collected on the ground.

In subsequent studies, we introduced small (~70 ml) boluses of aerosol laden air into a standardized test breath. By altering the timing of the bolus injection, the particles are made to probe the large central airways (by placing the bolus very late in the inspiration) of the smaller peripheral airways (by placing the bolus early in the inspiration). By measuring both the inspired and expired bolus we were able to determine deposition of the particles and dispersion of the bolus (a measure of convective gas mixing in the lungs). We could vary the size of the particles in the bolus (from 0.5 to 2.0 µm), the penetration volume at which the bolus was injected (between 150 and 1200 ml) and the length of the breathhold following the test inspiration in the standardized breathing maneuver (from 0 to 5 sec).

Results
For the larger particles studied (2 and 3 µm), total deposition of inhaled aerosol showed an almost linear increase with increasing G level, in line with a previous study. However, for the smaller particles studied, total deposition was unexpectedly high in µG, and for the 1 µm particles was more than twice that predicted by existing models of aerosol transport in the lung. This suggests that a mechanism other than Brownian diffusion was responsible for mixing the inhaled particles with the gas in the lungs, and enhancing deposition. The observation may be important in understanding the unexpectedly large health effects of very fine atmospheric particulate matter.

Both deposition and dispersion were shown to increase with increasing penetration volume and with increasing gravity. However, the deposition measurements from the bolus studies in µG did not clearly show an increase in deposition seen in the total deposition studies. Because the bolus studies are single breath tests consisting of just one inspiration and a subsequent exhalation, this suggests that the extra deposition results from the reciprocal nature of normal breathing. In support of this conjecture, studies by independent investigators in isolated rat lungs have shown a chaotic mixing of the flow streamlines in this region of the lung that increases rapidly with increasing number of breath cycles. This may provide for increased particle transport to the resident gas of the lung, and hence increased deposition. Studies with a breathhold show only a small increase in deposition suggesting that cardiogenic motion has only modest influence of particle transport.
Measurement of the dispersion of the bolus showed that, as expected, much of the convective mixing in the lung is a direct result of gravitational influences on the lung. However, there was a considerable increase in dispersion with increasing penetration volume of the bolus in μG indicating that there is a marked degree of inhomogeneity of ventilation intrinsic to the lung itself. These results are supportive of the studies of gas mixing in the lung performed by our group in spaceflight studies.

CONCLUSION

Aerosol studies in μG have shown unexpectedly high deposition. These results may be useful in understanding the reasons that cause inhaled particulate matter to have, at times, seemingly high adverse health consequences.

FUTURE PLANS

In the future we propose to examine in detail the effects of complex convective mixing in the lung. These studies will involve further, more sophisticated studies in the KC-135, coupled with modeling work using computational flow dynamics. In addition we propose to study means of improving the targeted deposition of inhaled drugs in the clinical setting.

INDEX TERMS

Aerosol, particles, deposition, dispersion, drug delivery, particulate matter, pollution.
Orthostatic intolerance (OI) is common after space flight and resembles the disabling idiopathic orthostatic intolerance commonly observed in otherwise healthy young individuals. OI can arise from reduced sympathetic nervous system activity and, paradoxically, also from increased sympathetic nervous system activity. Patients with early manifestations of pure autonomic failure demonstrate an etiology based upon reduced sympathetic nervous system activity. Patients with hyperadrenergia demonstrate an etiology based on increased sympathetic nervous activity. For many years, we have recognized that the microgravity environment induces adaptation in the cardiovascular system and its autonomic control mechanisms that lead to the presence of OI on return to gravity. Understanding the nature of OI in astronauts returning from space as well as in the relevant patient population on earth has been a priority of Vanderbilt’s Center for Space Physiology and Medicine in recent years.

Recent studies on Neurolab place the OI of microgravity in the hyperadrenergic category, and these studies have led to the discovery of genetic etiologies of OI such as norepinephrine transporter deficiency.
DIGITAL ECHOCARDIOGRAPHY IN MANNED SPACE FLIGHT: REMOTE DIAGNOSIS AND QUANTITATIVE ANALYSIS

Thomas JD, Greenberg NL, Garcia MJ, Shiota T, Firstenberg MS, Cardon LA
The Cleveland Clinic Foundation, Cleveland, Ohio

INTRODUCTION

The specific aims of the project include (1) development of infrastructure for digital acquisition, storage, and transmission -- both terrestrial and by satellite -- of echocardiograms and (2) testing compression algorithms for their impact on clinical interpretation and quantitative content, (3) validation of new quantitative approaches to assess cardiovascular mechanics in microgravity, and (4) refinement of acquisition, segmentation, display and analysis of three-dimensional echocardiograms. As part of our ongoing work with JSC engineering personnel, the ultrasound flight unit for the International Space Station (ISS) has been upgraded to software level 10.1, allowing for Doppler tissue imaging and output of DICOM loops. Currently, the ultrasound system is undergoing rack integration at Kennedy Space Center and is slated for launch on Flight 5A.1 in February 2001. Initial testing is slated to begin on the second increment beginning in April 2001, with limited research projects possible even during the assembly phase of the ISS with more dedicated science missions available thereafter.

CURRENT STATUS OF RESEARCH

Specific Aims 1) and 2) We have participated in several projects to validate the ISS Ultrasound hardware and examine the ability to perform remote diagnostics. As part of our ongoing collaboration with JSC engineering and flight surgeon personnel, we were involved in the design and analysis of a test of “Real-Time Transmission Of Ultrasound Data From The International Space Station Utilizing The ISS Communications Simulator At Johnson Space Center.” This test evaluated the impact of reducing transmission rate on image quality, both as individual fields are dropped as well as reduced bit resolution of the image. For cardiac ultrasound, optimal results were obtained at field rates of 80 or above, although rates as low as 15/sec still provided much useful information. For the abdominal examinations, lower frame-rates could be tolerated, although rates of at least 15/sec were necessary to provide meaningful, Real-time guidance to the acquisition. For strictly diagnostic purposes, however, frame-rates below 7.5 fields/sec could be tolerated for nonmoving structures. This examination demonstrated excellent image quality, particularly for the abdominal structures, with adequate image quality of the cardiac structures after some coaching regarding image orientation.

In collaboration with Medical Operations personnel on the project, “Validation of Technologies and Operations Concepts for Exploration Class Medical Operations Using the Haughton Mars Project (HMP) Testbed on Devon Island,” we participated in a blinded review of echocardiographic data obtained at the Devon Island site, where a research base was established this summer as part of the ongoing Haughton Mars Project. Echocardiograms were obtained with a SonoHeart portable ultrasound device, were digitized using a field-hardened PC, stored in MPEG2 format, relayed via the TDRSS geosynchronous satellite system down to Johnson Space Center and then routed to The Cleveland Clinic for our review. Fully diagnostic images were obtainable even in this extreme environment. We have also examined the impact of MPEG encoding during the Transmission of Echocardiographic data across NREN (in collaboration with NASA Lewis and Ames, Main, J Am Soc Echocardiogr 2000; 13(8):764-770) and participated in remote diagnosis through the Virtual Hospital Project (in collaboration with Dr. Muriel Ross and the NASA Ames Research Center (ARC) Center for Bioinformatics).

Infrastructure for review and analysis of digital echocardiographic data within the Cardiovascular Imaging Center of the Cleveland Clinic Foundation has been developed. Digital echocardiographic data storage and retrieval is possible using the ProSolv Echo Management System from Problem Solving Concepts (Carmel, IN). During the past six months, over 11,000 DICOM echocardiographic studies have been transferred and archived for long-term storage. We currently store and archive approximately 120 studies per day. Average study size is ~42 MB and the daily volume is greater than 5 GB of data per day.

Specific Aim 3) We have investigated new quantitative methodology for the assessment of left ventricular systolic and diastolic function. While this work is aimed directly at validating new echocardiographic methods for use aboard the International Space Station, all of this work is highly relevant to cardiology diagnostic methods on earth, both as pertains to patient care and in improving our understanding of cardiac pathophysiology. With our large team of engineers and clinical researchers, we have made significant progress in both basic and applied aspects of this work. Simultaneous acquisition of hemodynamic and Doppler data has been obtained in over 50 patients in the OR and catheterization laboratory (Firstenberg, Curr Surg 2000; 57: 466-472; Garcia, Am J Physiol (in press)).

Color Doppler M-mode echocardiography has been utilized to determine the influence of ventricular relaxation and preload on diastolic flow propagation and estimate both transmirtal and intraventricular pressure differences using the Euler equation. This modality provides a spatiotemporal description of ventricular filling that preserves the temporal resolution of pulsed Doppler and provides an additional spatial distribution of velocities along an ultrasound scanline.
The Euler equation describes the spatial pressure distribution ($\delta p/\delta s$) along an inflow streamline and can be solved using the spatiotemporal velocity distribution. In contrast to standard Doppler indices, the early diastolic flow propagation velocity ($v_p$) is a relatively preload independent index of LV filling. In both canines and humans, we found strong relationships between ventricular relaxation ($\tau$) and $v_p$ ($r=0.78$, $p<0.001$, J Am Coll Cardiol 35(1):201-208). We have also shown that transmitral ($y=0.95x+0.24, r=0.96, \varepsilon=0.08\pm0.54\text{mmHg}$, Am J Physiol 1996; 271 (Heart Circ Physiol 40) : H1267 - H1276; Firstenberg, J Am Coll Cardiol (in press)) and intraventricular pressure differences can be estimated noninvasively in both canines and humans using the Euler equation, Greenberg, Am J Physiol (in press).

In contrast to regular Doppler imaging, Doppler tissue imaging (DTI) records the velocity of myocardial motion rather than blood flow and is a new methodology available for the assessment of cardiac function. We have investigated the preload (in)dependence of DTI in both patients and animals. We evaluated data from patients with renal failure immediately before and after dialysis (J Am Soc Echocardiogr 1999;12(5):400). These results demonstrated significant changes in the transmitral filling indices, but little or no change in the DTI systolic and diastolic velocities. In animal experiments, we used vena cava balloon occlusions under different conditions (baseline, esmolol, dobutamine) to alter preload and measured diastolic early filling velocity ($E'$) in the septal region of the mitral annulus and evaluated these data with the corresponding end-diastolic pressures (EDP) and volumes (EDV), Firstenberg, J Appl Physiol 2000 (in press).

Following caval occlusion, under baseline conditions, $E'$ decreased with both EDV (range: 0.001 to 0.234 cm/sec/ml average: 0.080±0.085 cm/sec/ml) and EDP (range: -0.045 to 0.619 cm/sec/mmHg, average: 0.202±0.274 cm/sec/ml). Similar changes were observed during dobutamine ($E'/EDV$: range: 0.04 to 0.30 cm/sec/ml, average: 0.11±0.08 cm/sec/ml; $E'/EDP$: range: 0.04±1.21 cm/sec/mmHg, average: 0.43±0.33 cm/sec/mmHg) and esmolol ($E'/EDV$: range: 0.01 to 0.06, average: 0.04±0.017; $E'/EDP$: range: -0.05 to 0.25, average: 0.09±0.09) infusions. Overall, $dE'/dEDP$ and $dE'/dEDV$ decreased with increasing tau ($y = -0.011x+0.9$, $r=0.71$ and $y = -0.0023x+0.21$, $r=0.61$ respectively). We found that early diastolic myocardial tissue velocities are preload dependent, but this dependency is inversely related to ventricular relaxation. We have extended these techniques to a series of bedrest experiments in collaboration with Ben Levine, demonstrating the preload independence of color M-Mode and dependence of DTI under conditions of lower body negative pressure and volume infusion (Firstenberg, J Am Coll Cardiol 2000 (in press)).

**Specific Aim 4** Our investigations continue on the use of real-time 3-dimensional ultrasound imaging for evaluation of cardiovascular physiology and pathology. Since September 1997, 813 examinations have been performed at the Cleveland Clinic on patients with a variety of cardiac diseases. Also through our collaboration with Dr. Michael Jones in the Laboratory of Animal Surgery and Medicine at the National Institutes of Health, we have conducted several series of animal investigations to address the accuracy of LV volume measurements and flow quantification using real-time 3D echocardiography. Volumetric measurements by real-time 3D echocardiography have been validated with MRI. In 34 patients, a strong relationship was found for LV volumes ($r = 0.98$, $p < 0.0001$, mean difference = -15 ± 81 ml) and ejection fractions ($r = 0.97$, $p < 0.0001$, mean difference = 0.001 ± 0.04) J Am Coll Cardiol 2000: 36(3):900-7. We also have demonstrated the geometry of the mitral annulus and tracked changes with surgical repair (Ann Thorac Surg 2000;69:717-21). Segmentation of the annular geometry is possible new computer software was developed to obtain segmentation of the mitral annulus using commercially available 3D echocardiographic review software (EchoTech). Other areas of study include assessment of aortic regurgitation, flow quantification using real-time 3D color Doppler, LA volume quantification and non-invasive Assessment of LA Function, and Quantification of LV Mass (Shiota, Am J Cardiol 1999; 84:1068-1073; Qin, Eur J Echocardiog 2000; 1:96-104; Qin, Circulation (in press); Bauer, J Am Coll Cardiol (in press); Tsujino, Ultrasound in Med & Biol (in press).

**FUTURE PLANS**

In follow-on to the foundations laid in this grant (NCC9-60), we have submitted three grants to NASA funding agencies: (1) Diagnostic Ultrasonography in Flight: Technical and Training Aspects, (2) Diagnostic 3D Echocardiography: Development Of Novel Compression, Segmentation And Registration Techniques For Manned Space Flight Application and (3) Echocardiographic Assessment Of Cardiovascular Adaptation And Countermeasures In Microgravity. These projects address key areas that we believe are critical: confidence in the ability of the ultrasound system and personnel for delivery of diagnostic information in the event of a medical contingency on orbit, automated registration of ultrasound data with previously acquired MRI and CT datasets in hopes of detecting changes as they occur in space, and development of reliable noninvasive methods to detect and quantify these changes in cardiovascular function. If successfully implemented, these projects should enable accurate diagnosis of emergencies occurring in space, contribute to the Smart Medical Care System aspect of the National Space Biomedical Research Institute, and assist in the development of countermeasures designed to maintain orthostasis and improve exercise capacity. We are also collaborating with Ben Levine on a project to quantify LV atrophy and its impact on diastolic distensibility during long-term space flight.

**INDEX TERMS (up to 10)**
Ultrasound, Echocardiography, Transmission, Compression, Cardiovascular Mechanics, 3D/4D imaging
INTRODUCTION
Orthostatic intolerance after spaceflight or bed rest is correlated with the inability to effectively increase peripheral vascular resistance (Buckey et al., *J. Appl. Physiol.* 81: 7-18, 1996). We, therefore, tested the overall hypothesis that vascular dysfunction occurs after 28 days of simulated microgravity, using an accepted rat model (hindlimb suspension).

Study #1: We specifically examined resistance artery function from the mesentery, because vasoconstriction of this vascular bed is important for orthostatic tolerance, and because others have reported that there is reduced ability to constrict this vascular bed after hindlimb suspension (McDonald et al., *J. Appl. Physiol.* 72: 2210-2218, 1992; Overton & Tipton, *J. Appl. Physiol.* 68: 355-362, 1990). Vascular function was assessed by measuring responses to vasoconstrictors, a vasodilator, pressure, and flow.

Study 2: We found in Study #1 that hindlimb suspension resulted in attenuated myogenic tone (i.e., constriction response to pressure). We then examined the mechanism by testing whether there are alterations in basal nitric oxide. In addition, we tested whether the molecule 20-HETE is involved in the mechanism of myogenic tone in rat mesenteric arteries [it has been reported to be important in renal and cerebral arteries (Harder et al., *J. Vasc. Res.* 34: 237-243, 1997)], and whether alterations in the 20-HETE pathway could account for the attenuated myogenic tone with hindlimb suspension.

Study #3: Because hindlimb-suspended rats have been reported to exhibit impaired thermoregulation (Woodman et al., *J. Appl. Physiol.* 75: 2718-2726, 1993), we examined whether 28-day hindlimb suspension attenuated the vasoconstriction response of the mesentery during heat stress. In addition, hindlimb suspension has been reported to result in attenuated baroreflex-mediated sympathetic stimulation to the mesentery (Moffitt et al., *Am. J. Physiol.* 274: R1397-R1405, 1998). We, therefore, examined whether there are concurrent alterations in the perivascular sympathetic innervation of small mesenteric arteries.

CURRENT STATUS OF RESEARCH

Methods
Study #1: Small mesenteric artery segments were isolated, cannulated, pressurized, and arterial diameter responses were measured using video microscopy. Responses to vasoconstrictors (norepinephrine, phenylephrine, serotonin, KCl), the vasodilator, acetylcholine, pressure, and flow were measured.

Study #2: The influence of basal nitric oxide on myogenic tone in arteries from control and hindlimb-suspended rats, was tested using the nitric oxide synthase inhibitor L-NAME. To examine the 20-HETE pathway, we used inhibitors of the enzyme that produces 20-HETE (17-ODYA and DDMS) and of the receptor for 20-HETE [6(Z),15(Z)-20-HEDE].

Study #3: Vascular control during heat stress was determined by Doppler flowmetry measurements of superior mesenteric artery and iliac artery blood flow velocity. Baseline measurements were made at 25°C, and heat stress to the point of cardiovascular collapse (while anesthetized) was induced by raising the ambient temperature to 42°C. Perivascular sympathetic innervation of small mesenteric arteries was determined by immunostaining the vessel wall for tyrosine hydroxylase (a marker for sympathetic nerves).

Results
Studies #1 & #2: We found no differences in responses to vasoconstrictors, acetylcholine, or flow between arteries from control and hindlimb-suspended rats. Additionally, there was no indication of vascular remodeling (i.e., distensibility, internal diameter, external diameter, wall thickness). There was, however, a significant attenuation in the myogenic response to pressure (i.e., progressive vasoconstriction to increasing pressure) both in the absence and presence of α-adrenergic stimulation (Looft-Wilson & Gisolfi, *J. Appl. Physiol.* 88: 1199-1206, 2000). This attenuation was not due to alterations in smooth muscle cell signaling events distal to G-protein activation or voltage-sensitive Ca++-channel activation (events known to be involved in the myogenic response), because
responses to the vasoconstrictors which stimulate these events were not altered. We further found no alteration in response to nitric oxide inhibition. Inhibitors of the 20-HETE pathway were found to inhibit the myogenic response from $41 \pm 13\%$ (17-ODYA) to $98 \pm 2\%$ (DDMS) and $95 \pm 1\%$ [6(Z),15(Z)-20-HEDE], indicating that this pathway is essential for maintaining myogenic tone in small mesenteric arteries. There were, however, no differences in responses to these inhibitors with hindlimb suspension.

Study #3: The rise in mean arterial pressure, rectal temperature, and superior mesenteric artery resistance, and the decline in iliac artery resistance during heat stress were similar between control and hindlimb-suspended rats. The perivascular sympathetic nerve morphology and relative innervation were also not different between the groups.

Conclusions
28-d hindlimb suspension results in attenuated myogenic tone in rat small mesenteric arteries. This impairment can potentially contribute to orthostatic intolerance, because the ability to vasoconstrict in response to an increase in pressure in this vascular bed, as would be expected during orthostasis, is compromised. Although we did not uncover the cellular mechanism for this attenuation, we found that the 20-HETE pathway is an important mechanism for the myogenic response. We tested and compared all the cellular components of the mechanism of myogenic tone that are currently known. It is possible that the early cellular events involved in transducing the pressure stimulus are altered with hindlimb suspension, leading to an impaired response. These events, however, have not been identified, and, therefore, could not be specifically tested.

Unlike the reported vascular responses to exercise after hindlimb suspension (McDonald et al., J. Appl. Physiol. 72: 2210-2218, 1992), the regional vascular responses to heat stress were not altered. The reported impairment in thermoregulation, therefore, does not seem to be due to altered regulation of mesenteric or iliac blood flow. The sympathetic innervation of this vascular bed also appears to be maintained during hindlimb suspension.

FUTURE PLANS
This project has been completed and constitutes a Ph.D. thesis.

INDEX TERMS
myogenic tone, mesenteric arteries, hindlimb suspension, orthostatic intolerance, 20-HETE, heat stress, sympathetic innervation, vasoconstriction, vascular resistance
EVIDENCE FOR CENTRAL VENOUS PRESSURE RESETTING AND AGAINST ALTERATIONS IN RENAL RESPONSIVENESS TO ALDOSTERONE DURING EARLY EXPOSURE TO MICROGRAVITY

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INTRODUCTION
Individuals exposed to microgravity or its ground-based analogs, e.g., head-down tilt (HDT), experience reduced plasma volume. Although this may not be problematic during a space mission, lower vascular volume has been linked to a decrease in maximal oxygen uptake and to orthostatic intolerance upon return to earth. The loss of body fluids cannot be readily replaced by drinking. In previous investigations, we reported that aldosterone levels increased during HDT without alterations in urine flow and sodium clearance even though blood volume was reduced. One explanation for these observations is that renal tubule cells become less sensitive to aldosterone during adaptation to microgravity. We also observed a shift in the stimulus-response relationship between central venous pressure (CVP) and peripheral vascular resistance, suggesting a possible resetting in CVP operational point (i.e., setpoint). Either one or a combination of alterations in these mechanisms could contribute to failure of fluid loading countermeasures for restoring vascular volume before return to earth. The purpose of these experiments was to test the hypotheses that exposure to a ground simulation of microgravity would 1) reduce renal sensitivity to aldosterone and 2) reduce CVP setpoint.

METHODS
Subjects. Six mature male rhesus monkeys were selected for this study. All experimental procedures and protocols were reviewed and approved by the Institutional Animal Care and Use Committee. Monkeys received two months of tilt table adaptation training prior to the experiments and were chronically instrumented with an indwelling jugular catheter that was advanced to terminate in the anterior vena cava just outside the right atrium.

Experimental design. A standard two-treatment crossover design was used, with each monkey receiving both 10° HDT and upright/prone control conditions. The treatment order was randomized, but counterbalanced, so that three monkeys received HDT followed by the control condition and three monkeys received the control condition followed by HDT. Each treatment period lasted 96 hours (4 days). Monkeys were kept unrestrained in their cages for a period of nine days between treatment periods (i.e., cross-over interval).

Saline Infusion Experiment. On day 3, each animal was lightly sedated (ketamine 0.15 mg/kg/min), placed in the prone (0°) posture, and a 5 French Foley urinary catheter was inserted for collection urine. At 0900, each animal received a continuous i.v. infusion of 0.9% saline (0.4 ml/kg/min) for 2 h. The subjects' bladders were evacuated every 30 min for measurement of urine flow rate (UVR) and urine concentrations of sodium, osmolality and creatinine. Blood samples were taken each 60 min to measure plasma concentrations of sodium (PNa), osmolality (Posm), and creatinine, and calculate renal clearances (CNa, Cosm, Ccr). Hematocrits were used to calculate percent change (%) in plasma volume. Heart rate (HR), and systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures were measured every 30 minutes. Plasma volume (PV) was measured with Evans blue dye prior to saline infusion.

Aldosterone Administration Experiment. On day 4, procedures for the saline infusion experimental protocol were repeated. However, instead of saline, each animal received a bolus i.v. infusion of aldosterone (1 mg) added to a baseline maintenance infusate (0.2 ml/kg/min 0.9% saline) for 4 h. All samples and measurements of urine and blood obtained in the saline infusion experiment were obtained following aldosterone administration. An additional volume of blood (6 ml each) was withdrawn at 0, 60, 120, and 240 min after aldosterone administration for determination of plasma renin activity (PRA), aldosterone (Ald), vasopressin (AVP), and atrial natriuretic peptide (ANP). HR, SBP, DBP, and MAP were measured every 30 minutes. CVP was measured before and during an 18-h period following Ald administration.
RESULTS

**Dietary intake.** Average daily (24 h) fluid intake during HDT (400 ± 137 ml) was not statistically different (t = 0.58, P = 0.595) from that of the control condition (421 ± 171 ml). Daily calorie and sodium intakes were 126 ± 19 kcal and 105 ± 17 mg in the control condition compared to 152 ± 25 kcal and 107 ± 22 mg during HDT (t = 0.566, P = 0.596).

**Saline Infusion Experiment.** Baseline PV was decreased by HDT and CVP during HDT (2.3 ± 0.3 mmHg) was lower [F(1,5) = 7.22, P = 0.011] than during control (4.5 ± 1.4 mmHg). CVP demonstrated an overall main effect (increase) during saline infusion [F(1,5) = 11.65, P = 0.002] that was similar between Control (2.3 ± 0.8 mmHg) and HDT (2.7 ± 0.8 mmHg) conditions [F(1,5) = 0.78, P = 0.485]. At 18 h post-infusion, control and HDT CVP values were similar to pre-infusion baseline values for control (4.5 vs 4.3 mmHg) and HDT (2.3 vs 2.7 mmHg). Ccr was unaltered by saline infusion [F(1,5) = 0.51, P = 0.614] or HDT [F(1,5) = 0.42, P = 0.827]. UVR, CNa and Cosm demonstrated an overall main effect (increase) due to saline infusion [F(1,5) = 7.88, P = 0.009]. However, we could not distinguish a statistical difference between HDT and Control conditions for UVR, CNa and Cosm during saline infusion [F(1,5) = 0.45, P = 0.531]. HDT caused a parallel shift to the left in the stimulus-response relationship between CVP and UVR. Neither heart rate or arterial blood pressures showed statistically discernable effects of treatment [F(1,5) = 0.60, P = 0.474], time [F(4,20) = 1.55, P = 0.227], or their subsequent interaction [F(4,20) = 0.62, P = 0.656].

**Aldosterone Administration Experiment.** UVR was slightly reduced from 51 ± 3 ml/h in the control condition to 42 ± 3 ml/h in HDT. Filtered sodium load, Ccr, Cosm, urinary Na/K ratio, Posm, and PNa remained relatively unchanged by HDT (P = 0.266). CNa and Na excretion increased with HDT (P = 0.055). Urine Na concentration and renal fractional excretion of Na also increased due to HDT (P = 0.020 and 0.069, respectively). Overall, UVR, filtered Na load, Ccr, Posm, and PNa were unaffected by Ald administration (P = 0.20). Cosm, CNa, Na excretion and Na/K ratio decreased with Ald infusion (P = 0.011). Urine Na concentration and renal fractional excretion of Na demonstrated indistinguishable changes due to Ald infusion (P = 0.253 and 0.152, respectively). None of the Ald effects (interactions) on renal functions were altered by HDT. Although PV tended to increase after Ald infusion, neither HR, MAP or %?PV showed statistically discernable effects of treatment [F(1,5) = 1.897, P = 0.227], time (F(4,20) = 2.108, P = 0.118), or their subsequent interaction (F(4,20) = 0.833, P = 0.520). A large main effect of time was seen for Ald (F(2,10) = 94.07, P = .0001) as a result of Ald administration. Plasma Ald spiked immediately after infusion and then returned to baseline levels. PRA and AVP were unaffected by HDT treatment (F(1,5) = 0.713, P = 0.437) or time (F(3,15) = 0.660, P = 0.589), with no subsequent interaction effects (F(3,15) = 1.489, P = 0.258). A large main effect of treatment condition was observed for ANP (F(1,5) = 19.89, P = .0066) with lower values resulting from HDT.

CONCLUSIONS

Contrary to our first hypothesis, the data suggest that exposure to microgravity increases renal excretion of sodium by a natriuretic mechanism other than a change in renal responsiveness to aldosterone. Since the response relationship between CVP and UVR was shifted to the left with HDT, and CVP returned to its pre-infusion levels following volume loading in HDT and control conditions, our results are consistent with our second hypothesis that a lower CVP during exposure to microgravity may reflect a new operating point about which vascular volume is regulated. These results may explain ineffective fluid intake procedures currently employed by astronauts.
MICROGRAVITY-INDUCED ORTHOSTATIC INTOLERANCE:
AN ARTERIAL MICROVASCULAR MECHANISM

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INTRODUCTION

It appears that the precision with which the cardiovascular system tightly regulates arterial pressure and cerebral perfusion during orthostasis is due in part to its capacity to appropriately adapt to the prevailing mechanical environment, which on Earth is largely determined by the head-to-foot hydrostatic pressure gradient created by 1G. Consequently, when the head-to-foot gravitational vector is removed during spaceflight, there is a cephalad fluid shift and a putative elimination of arterial pressure gradients. There is little evidence to suggest that cardiovascular function is compromised in microgravity or that cardiovascular adaptations to this new environment are inappropriate. However, adaptive responses to a weightless environment do appear inappropriate upon return to 1G. These "maladaptations" of the cardiovascular system are manifest primarily as orthostatic intolerance and reduced aerobic capacity.

Studies of humans following spaceflight and bedrest indicate that one of the predominant mechanisms underlying orthostatic intolerance is hypotension resulting from an inability to adequately elevate total peripheral resistance (TPR) (Arbeille et al. Acta Astronautica 36, 1996; Buckey et al., JAP 81, 1996; Mulvagh et al. J Clin Pharm 31, 1991; Vernikos et al. J Clin Pharm 31, 1991). Although this inadequate elevation of TPR could originate from both neural and vascular alterations, there is evidence in humans to suggest a peripheral vascular mechanism (Schmid et al. Hypogravic and Hypodynamic Environments, p. 211-223 (SP-269) 1971; Shoemaker et al. JAP 84, 1998; Whitson et al. JAP 79, 1995). Additionally, there is indirect evidence in humans to suggest that alterations in autoregulatory control of cerebrovascular tone may serve to attenuate brain perfusion during orthostasis (Zhang et al. JAP 83, 1997). In order to further study these phenomenon, the hindlimb unloaded (HU) rat has been used as a model to study weightlessness because, like that in humans, HU elicits a headward fluid shift and cardiovascular deconditioning characterized by orthostatic hypotension and a diminished capacity to elevate TPR. The purpose of these studies was to determine whether HU alters the structure and contractile function of resistance arteries from skeletal muscle, visceral tissue, and the cerebrum.

CURRENT STATUS OF RESEARCH

Methods: HU rats were placed in a head-down position by elevating the hindlimbs to an approximate spinal angle of 40-45° from horizontal; this was maintained for 2 wk. At the end of the experimental period, resistance arteries were isolated from the gastrocnemius and soleus muscles, mesentery, spleen and brain (basilar artery). The vessels were cannulated with micropipettes and pressurized. To assess vasomotor responsiveness of skeletal muscle arterioles, concentration-response relationships to several vasoconstrictors (norepinephrine and KCl) and vasodilators (isoproterenol, adenosine, acetylcholine and sodium nitroprusside) were determined. To examine vascular structure, isolated resistance arteries were pressurized, bathed in Ca²⁺-free buffer solution, fixed, embedded in paraffin, and sectioned. Media layer cross-sectional area, outer and inner media perimeter, and media wall thickness were determined from the vessel cross-sections.
Results: HU resulted in an increased basilar artery media (smooth muscle) wall thickness and a decreased luminal cross-sectional area (Figure 1); the increase in medial cross-sectional area and wall thickness resulted from smooth muscle hypertrophy (Wilkerson et al. JAP 87, 1999). There was no effect of HU on the structure of mesenteric or splenic resistance arteries. Conversely, HU resulted in a thinning of the medial layer in gastrocnemius feed arteries and arterioles (Figure 2; Delp et al. AJP-HCP 278, 2000). The functional consequence of this smooth muscle atrophy was a diminished myogenic and agonist-induced vasoconstrictor responsiveness (Delp JAP 86, 1999).

Figure 1. Basilar artery from control (A) and HU (B) rat.

Figure 2. Feed artery (A, B) and first-order arteriole (C, D) from control (A, C) and HU (B, D) rat.

Conclusion: In several vascular beds of the HU rat, such as that in the hindlimb musculature and brain, the fluid shift alters the mechanical forces acting upon resistance arteries and induces a remodeling of arterial structure (Delp et al. AJP-HCP; Wilkerson et al. JAP). These structural alterations, in turn, profoundly affect arterial function, so that vasoconstrictor responsiveness is diminished in the hindlimb circulation (Delp JAP; McDonald et al. JAP 72, 1992) and enhanced in the cerebral circulation (Geary et al. JAP 85, 1998). Others have also reported vasoconstrictor responsiveness is diminished in the splanchnic circulation (Looft-Wilson & Gisolfi JAP 88, 2000; Overton & Tipton JAP 68, 1990), but this alteration is not the result of an arterial structural remodeling, presumably because these vascular beds are located at or near the hydrostatic indifference point of the rat. There is evidence to suggest that the diminished constrictor responsiveness of visceral arteries result from an up-regulation of inducible nitric oxide synthase activity (Vaziri et al. JAP 89, 2000). If vascular alterations similar to those in the HU rat occur in humans during spaceflight, this could explain the compromised ability to elevate TPR during the assumption of an upright posture upon return to Earth.

FUTURE PLANS: Determine further the functional consequences of smooth muscle hypertrophy in cerebral resistance arteries and the mechanisms of diminished splanchnic vasoconstriction.

INDEX TERMS: cardiovascular; hindlimb unloading; unweighting; simulated microgravity
14 DAYS HEAD-DOWN TILT BED REST DOES NOT ALTER MAXIMAL FOREARM CUTANEOUS VASCULAR CONDUCTANCE

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INTRODUCTION

We, as well as others, have shown that thermoregulatory responses are compromised following head-down tilt (HDT) bed rest and space flight (2, 4-7). For example, we (2) found that after 14 days of HDT bed rest, forearm skin vascular conductance was reduced at any given internal temperature during passive heating (Figure 1). These data indicate that following microgravity exposure the individual is hotter before the cutaneous vascular begins to dilate, and once this dilatation has begun, for the same increase in internal temperature there is less of an increase in skin blood flow.

Maximal cutaneous blood flow can be altered as evidenced by reduced maximal flows in the elderly (8) and in individuals with hypertension (1). Others have reported that leg maximal conductance is reduced following simulated microgravity exposure (3), but these reductions were likely confined to the muscle. It remains unclear whether simulated microgravity impairs maximal cutaneous vasodilation, which may contribute to reduced elevations in cutaneous vascular conductance during a heat stress following simulated or actual microgravity exposure. Thus, the purpose of this protocol was to test the hypothesis that 14 days of HDT bed rest impairs maximal forearm cutaneous vascular conductance and identify whether supine ergometry exercise training during bed rest would prevent this impairment from occurring.

CURRENT STATUS OF RESEARCH

Methods: Seventeen healthy subjects (14 males; 3 females) participated in this protocol. Data were obtained prior to, and on day 14 of HDT bed rest. For the female subjects, pre-HDT data were collected 28 days prior to the scheduled post-HDT data collection in an attempt to control for potential effects of the menstrual cycle on maximal cutaneous vascular conductance. Eleven of the seventeen subjects exercised (supine cycle ergometry) 3 times a day for 30 min per exercise bout at a heart rate representing 75% of pre-bed rest maximum. Six subjects did not exercise during HDT bed rest. Repeated baseline forearm blood flow measurements were obtained in thermoneutral conditions (Tsk = 32±0.2°C; via thermocouple attached to forearm) using venous occlusion plethysmography. The forearm was then heated to 42°C using a cylinder water spray device that sprayed a fine mist of heated water from jets surrounding the subject’s forearm. Maximal forearm skin blood flow was obtained via plethysmography following 45 min of heating (9). In both thermal conditions blood pressure was obtained by auscultation from the opposite arm. Forearm vascular conductance was calculated as forearm blood flow-mean arterial blood pressure⁻¹. Units for forearm vascular conductance in the present paper are reported as ml-100ml⁻¹·min⁻¹·100mmHg⁻¹. Data were analyzed via 2-way ANOVA with main factors of bed rest (i.e. pre and post-HDT; repeated variable) and exercise (i.e. exercise and non-exercise groups; non-repeated variable). Data are reported as mean±SEM. The α level for statistical significance was set at P≤0.05.

Results: Fourteen days HDT bed rest significantly reduced baseline (i.e. normothermic) forearm vascular conductance (pre-HDT: 3.87±0.3; post-HDT: 2.9±0.2; P=0.003). No statistical interaction between bed rest and exercise main factors was identified (P=0.25), thereby suggesting that the decrease in forearm vascular conductance due to HDT was unaffected by the exercise protocol (exercise group: 3.7±0.2 to 2.9±0.2; non-exercise group:...
4.1±0.8 to 3.0±0.5). HDT bed rest did not significantly reduced maximal forearm cutaneous vascular conductance (pre-HDT: 21.4±1.4; post-HDT: 20.3±1.8; P=0.32). Likewise, no statistical interaction between bed rest and exercise main factors was identified (P=0.59; exercise group: 21.5±2.0 to 20.9±2.6; non-exercise group: 21.3±1.2 to 19.3±2.3). However, five of the six subjects from the non-exercise group showed a decrease in maximal forearm cutaneous vascular conductance following bed rest, while the sixth subject showed a large increase in this value (Figure 2). No noticeable trends were observed in the exercise group (Figure 3).

Conclusions: These findings suggest that reductions in baseline forearm vascular conductance following prolonged HDT exposure previously reported by us and others is not altered by supine exercise training during HDT. Moreover, HDT bed rest does not alter maximal forearm cutaneous vascular conductance, however a reduction in this variable was observed in five of the six subjects in the non-exercise group.

FUTURE PLANS
Four additional subjects are scheduled to participate in this study. Two of these subjects will be assigned to the non-exercise group. From these studies we have also collected data investigating the effects of HDT bed rest on sweat gland function. These data will be analyzed upon completion of the bed rest protocol.

INDEX TERMS
Thermoregulation, skin blood flow, head-down tilt bed rest, maximal forearm blood flow, cutaneous vascular conductance, microgravity exposure, humans, exercise.

CITED REFERENCES
HINDLIMB UNWEIGHTING AFFECTS RAT VASCULAR CAPACITANCE FUNCTION

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INTRODUCTION
Microgravity is associated with an impaired cardiac output response to orthostatic stress. A decreased venous filling pressure due to increased venous compliance may be an important contributing factor in this response.

CURRENT STATUS OF RESEARCH
Methods
We used a constant flow, constant right atrial pressure cardiopulmonary bypass procedure to measure total systemic vascular compliance (\(C_T\)), arterial compliance (\(C_A\)), and venous compliance (\(C_V\)) in seven control and seven 21-day hindlimb unweighted (HLU) rats. These compliance values were calculated under baseline conditions and during an infusion of 0.2 \(\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}\) norepinephrine (NE). The change in reservoir volume which reflects changes in unstressed vascular volume (\(V_0\)) that occurred upon infusion of NE was also measured.

Results
\(C_T\) and \(C_V\) were larger in HLU rats both at baseline and during the NE infusion (\(p < 0.05\)). Infusion of NE decreased \(C_T\) and \(C_V\) by approximately 20% in both HLU and control rats (\(p < 0.01\)). \(C_A\) was also significantly decreased in both groups of rats by NE (\(p < 0.01\)), but values of \(C_A\) were similar between HLU and control rats both at baseline and during the NE infusion. Additionally, \(V_0\) was attenuated in HLU rats compared to control rats (\(p < 0.05\)).

CONCLUSION
The larger \(C_V\) and attenuated \(V_0\) in HLU rats could contribute to a decreased filling pressure during orthostasis and thus, may partially underlie the mechanism leading to the exaggerated fall in cardiac output and stroke volume seen in astronauts during an orthostatic stress following exposure to microgravity.

FUTURE PLANS
We plan to repeat the calculation of compliance and unstressed volume using bilateral carotid occlusion to stimulate the sympathetic nervous system instead of using an exogenous sympathomimetic. In this future study, we plan to use female rats and male rats to examine gender differences in the response.

INDEX TERMS
microgravity, compliance, vein, sympathetic nervous system, orthostatic intolerance, hindlimb unweighting, capacitance
SIMULATED WEIGHTLESSNESS INDUCES REVERSIBLE CHANGES IN CARDIAC REPOLARIZATION PROCESSES IN HUMANS


INTRODUCTION
Episodes of ventricular tachycardia have been recorded during space flight. However, it is has not been established whether space flight alters the susceptibility of the heart to ventricular dysrhythmias. NASA has supported the development of the technique of measuring microvolt level T wave alternans (TWA). TWA is measured during exercise or other physiologic stress sufficient to elevate the heart rate. The development of sustained TWA with an onset heart rate of 110 bpm or less has been associated with increased risk of sustained ventricular arrhythmias or sudden cardiac death in patients with cardiac disease. The goal of the present study was to determine if head-down tilt bed rest alters the occurrence of TWA.

CURRENT STATUS OF RESEARCH
Methods
Eleven subjects underwent a 16 day head-down tilt bed rest study. TWA was measured during bicycle exercise prior to bed rest, immediately following bed rest, and 2-3 days post bed rest. The tracings were read in a blinded fashion.

Results
Three subjects who had no sustained TWA prior to bed rest developed sustained TWA following bed rest, all with an onset heart rate above 110 bpm. Sustained TWA disappeared 2-3 days later. Three subjects demonstrated non-sustained TWA or recovery TWA only during the measurement made immediately following bed rest. One patient had sustained TWA with an onset heart rate of 120 bpm prior to bed rest, following bed rest sustained TWA disappeared, and reappeared 2-3 days later.

Conclusion
Sixteen days of bed rest alters the occurrence of TWA, tending to induce TWA in subjects who have no TWA prior to bed rest. None of the subjects had sustained TWA with an onset heart rate ≤ 110 bpm which is the level at which it would be considered clinically significant. These results suggest that even short term bed rest alters cardiac electrical repolarization processes.

FUTURE PLANS
We plan to study the effects of gender and age on the occurrence of TWA in association with bed rest, and to study changes in TWA associated with space flight.

INDEX TERMS
arrhythmias, ventricular arrhythmias, T wave alternans, cardiac electrophysiology, cardiac electrical, dysrhythmias, ventricular dysrhythmias
ARTERIAL BAROREFLEX CONTROL OF SYMPATHETIC NERVE ACTIVITY DURING ACUTE HYPOTENSION: EFFECT OF FITNESS

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INTRODUCTION
Human investigations of arterial baroreflex control of muscle sympathetic nerve activity (MSNA) have been limited exclusively to the carotid baroreflex because of technical limitations. In their investigations, which used aortic and carotid baroreceptor activation and deactivation via pharmacologic challenge (phenylephine and nitropusside) counteracted by neck pressure and neck suction, only the carotid- and aortic-cardiac baroreceptor reflex was examined. We have developed a non-pharmacologic method of providing a repeatable hypotensive challenge to humans during which we can examine carotid and aortic baroreflex control of MSNA. A question of interest to NASA is whether aerobic fitness affects the baroreflex control of MSNA.

CURRENT STATUS OF RESEARCH
Methods
Acute hypotension was induced non-pharmacologically in fourteen healthy subjects, seven high-fit (FH) mean VO₂max 67.8 ± 2.3 ml/kg/min and seven average-fit (AF) 49.2 ± 2.1 ml/kg/min by releasing a unilateral arterial thigh cuff following 9-minutes of resting ischemia under two conditions: control (aortic (ABR) and carotid (CBR) baroreflex deactivation) and suction (ABR deactivation alone). Prior to and for 14-s following arterial thigh cuff occlusion direct measures of blood pressure and central venous pressure and post ganglionic muscle sympathetic nerve activity (MSNA) were recorded during both experimental conditions.

Results
The application of neck suction to negate the CBR during cuff release significantly attenuated the MSNA response (increased 134.3 ± 1.9 units/14-s) compared to control (increased 195.2 ± 43.4 units/14-s) and caused a greater decrease in MAP (19.4 ± 1.7 vs. 15.2 ± 1.7 mmHg, p<0.05). Furthermore, during both trials FH subjects exhibited a greater decrease in MAP compared to AF subjects despite an augmented baroreflex control of MSNA.

Conclusion
These data indicate that while the CBR contributes importantly to the MSNA response during acute hypotension, the ABR appears more dominant. Additionally, we suggest that an impaired control of vascular reactivity hinders blood pressure regulation in HF subjects.

FUTURE PLANS
Evaluation of MSNA and end-organ receptor

INDEX TERMS
Blood pressure control, neck suction, baroreceptor activation
NOREPINEPHRINE RESPONSES TO TYRAMINE AND PRESSOR RESPONSES TO PHENYLEPHRINE ARE NOT REDUCED IN ASTRONAUTS AFTER SPACEFLIGHT

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INTRODUCTION
Astronauts who become presyncopal after spaceflight have subnormal standing plasma norepinephrine (NE) levels and low peripheral resistance. To pursue this finding we studied 11 astronauts before and after spaceflight. We measured plasma NE responses to small and moderate intravenous tyramine injections (T1 & T2), and after 10 minutes of upright tilt; and pressor responses to small and moderate phenylephrine injections (P1 & P2). Astronauts self-selected into presyncopal and nonpresyncopal groups during tilt testing on landing day.

CURRENT STATUS OF RESEARCH
Methods
We studied 11 astronauts, 9 men and 2 women, aged 36 to 51, before and after flights lasting 5 to 16 days aboard the American Shuttle. Studies were performed ten days before launch, two to four hours after landing, and three days after landing. Subjects abstained from caffeine, alcohol, maximum exercise and vasoactive medications for 24 hours prior to each study session. Subjects were instrumented for electrocardiogram, manual blood pressure and beat-to-beat finger blood pressure (Finapres). Intravenous catheters were inserted into antecubital veins in both arms. One catheter was used for infusions of drugs and the other for withdrawal of blood samples. Two-dimensional and M-mode echocardiography were used to determine aortic cross-sectional area at the aortic cusp, and aortic flow was measured with continuous wave Doppler ultrasound. The arm with the hand on which the Finapres was attached was strapped to an armboard adjusted so that the finger remained at heart level during upright tilt.

After a 20 minute supine rest period, a baseline blood sample was drawn for plasma norepinephrine levels. While continuous measurements of beat-to-beat arterial pressure and aortic flow were made, a dose of 2.0 mg/1.73m² body surface area (BSA) of tyramine (an indirect sympathomimetic) was injected intravenously. Exactly four minutes after the injection, another blood sample was drawn for a norepinephrine level. After another three minutes, if arterial pressure and heart rate were returned to baseline, the procedure was repeated with a 4 mg/1.73m² BSA dose of tyramine.

Following an additional rest period for return of heart rate and arterial pressure to return to baseline, a 0.13 mg/1.73m² of phenylephrine was injected while continuous measurements were made for four minutes, or until heart rate and arterial pressure returned to baseline. Then the procedure was repeated with a 0.26 mg/1.73m² injection of phenylephrine.

Finally, a tilt test was performed. The subject was secured to the tilt table with a system of straps. After two minutes supine, the table was tilted to the 80° upright position, while measurements continued. At the end of ten minutes upright, or as soon as presyncopal symptoms occurred, a final blood sample was drawn for norepinephrine and the test was terminated.

Statistics
The effects of interest were group (presyncopal and nonpresyncopal), and day (preflight, postflight). A repeated measured analysis of variance was used. Student’s t-tests were performed to document differences in variables when there was a significant main effect.
Results
Five astronauts became presyncopal on landing day. NE release with tyramine on landing day was equal to or greater than preflight in both groups. However, during upright tilt, NE release was significantly lower in presyncopals (Fig. 1). Mean arterial pressure (MAP) responses to phenylephrine were not reduced in either group on landing day (Fig. 2).

Conclusion
Postflight orthostatic hypotension is not due to inadequate NE stores or impaired $\alpha_1$-adrenergic responses, but is related to inadequate NE release by the sympathetic nervous system. Support: NRA-OLMSA 01-051

FUTURE PLANS
We will continue to collect data on all upcoming flights. These findings will be pursued in a new grant.
THE VESTIBULOSYMPATHETIC REFLEX IN HUMANS:
NEURAL INTERACTIONS WITH CARDIOVASCULAR REFLEXES

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INTRODUCTION
Alteration in sympathetic outflow has been suggested as a factor for post-spaceflight orthostatic intolerance. However, the mechanism(s) responsible for changes in sympathetic outflow after spaceflight has not been elucidated. There has been increasing evidence suggesting that the vestibular system participates in the regulation of sympathetic nerve activity. Our laboratory has conducted a series of studies that clearly indicate that the vestibular system (i.e., otolith organs) does indeed regulate muscle sympathetic nerve activity (MSNA) in humans. However, the integrative response of the vestibulosympathetic reflex with other cardiovascular reflexes on MSNA has not been definitively studied.

CURRENT STATUS OF RESEARCH
Methods
Subjects performed three experimental trials. The first trial examined MSNA responses during activation of the vestibulosympathetic reflex elicited by head-down rotation with the subject in the prone position. The second trial examined MSNA responses to activation of another cardiovascular reflex (baroreflexes and skeletal muscle reflexes). The third trial examined MSNA responses during simultaneous activation of both the vestibulosympathetic reflex and one other cardiovascular reflex (i.e., combination trial). The order of these three trials was randomized. Cardiopulmonary and arterial baroreflexes were elicited by lower body negative pressure (LBNP) performed at -10 and -30 mmHg. Isometric handgrip performed at 30% MVC for 2 minutes was used to stimulate the skeletal muscle reflex.

Leg MSNA (microneurography), arterial pressure (Finapres), and heart rate (EKG) were measured continuously during the experimental trials. The sum of the individual trials (trials 1 and 2) were compared with the combination trial (trial 3) to determine the nature of the interaction of the two neural reflexes.

Results
In all studies, head-down rotation elicited significant increases in MSNA. Likewise, LBNP and isometric handgrip elicited significant increases in MSNA. In all studies, MSNA responses in the combination trial (i.e., head-down rotation plus another cardiovascular reflex) were not different from the sum of the individual trials (Figs 1 and 2).

Figure 1. The change in muscle sympathetic nerve activity (MSNA) from baseline during head-down rotation (HDR) and lower body negative pressure (LBNP) performed alone, the algebraic sum of HDR and LBNP, and when HDR and LBNP were performed together. The algebraic sum and the HDR and LBNP combination trial were not different from each other during either the –10 or –30 LBNP protocol. These findings suggest that an additive interaction exists between the vestibulosympathetic reflex and baroreflexes.
Figure 2. The change in muscle sympathetic nerve activity (MSNA) from baseline during head-down rotation (HDR) and isometric handgrip (IHG) performed alone, the algebraic sum of HDR and IHG, and when HDR and IHG were performed together. The algebraic sum of the individual trials and the combination trial (HDR + IHG) were not different from each other. These findings suggest that an additive interaction exists between the vestibulosympathetic reflex and exercise pressor reflex. *The response is significantly different from baseline, P < 0.05.

Conclusion
The interaction between the vestibular system and these cardiovascular reflexes on MSNA is additive. The additive interaction between the baroreflexes and vestibulosympathetic reflex indicate that the vestibular system may assist in defending against orthostatic challenges in humans by elevating MSNA beyond that of the baroreflexes. Additionally, the further increase in MSNA via otolith stimulation during isometric handgrip when arterial pressure is markedly elevated indicates that the vestibulosympathetic reflex is a powerful activator of MSNA.

FUTURE PLANS
To test the effect of bed rest, an earth-based model that simulates microgravity, on sympathetic responses to head rotations.

INDEX TERMS
Vestibulosympathetic reflex
Autonomic function
Sympathetic nervous system
Orthostatic intolerance
HUMAN SYMPATHETIC AND VAGAL NEURAL RESPONSES TO VALSALVA’S MANEUVER IN SPACE

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INTRODUCTION

Early concerns that exposure to microgravity would lead to massive organ (particularly cardiovascular) system failure, proved unfounded. However, published evidence indicates clearly that in most astronauts, responses to standing are different after space missions than they were before. With standing, astronauts’ heart rates tend to be faster, their blood pressures may fall, and most cannot stand passively for ten minutes without developing symptoms or signs of presyncope. In earlier research (Fritsch et al., 1992; Fritsch-Yelle et al., 1994), we tested and validated the hypothesis that exposure to microgravity impairs vagal-cardiac responses to graded carotid baroreceptor stimulation provoked by neck pressure changes. For the Neurolab Space Shuttle Mission, we tested the hypothesis that microgravity also impairs sympathetic-muscle responses to baroreceptor changes provoked by graded Valsalva straining.

METHODS

We recorded the electrocardiogram, finger photoplethysmographic arterial pressure, respiration, and peroneal nerve muscle sympathetic activity in four healthy male astronauts, ages 38 – 44 yr, before, during, and after the 17 day Neurolab Space Shuttle Mission. Astronauts performed two 15 s Valsalva maneuvers at 15 and 30 mmHg each, in random order.

RESULTS

Arterial pressure changes, which both trigger and reflect autonomic responses, were substantially greater in space than on Earth. For example, the average systolic pressure reduction during straining at 30 mmHg was 27 pre-flight, and 49 mmHg in-flight. Changes of vagal-cardiac neural outflow (as reflected by electrocardiographic R-R intervals) during and after Valsalva straining tended to be less during, than before the space mission. Average systolic pressure and R-R interval responses to Valsalva straining are depicted in Figure 1. [Each Lissajous figure began with the pressure reduction after the initial Phase 1 pressure elevation (lowest R-R interval), and continued to the peak pressure increase after release of straining.] These data document a much greater excursion of systolic pressure during Valsalva maneuvers, and arguably, a less steep increase of R-R intervals during the pressure rise after release of straining.

![Figure 1](image-url)
Increases of muscle sympathetic nerve activity during straining were also much greater in space than on Earth; however, sympathetic baroreflex gain, taken as the integrated sympathetic response divided by the maximum diastolic pressure reduction during straining, was the same in space and on Earth. Figure 2 shows linear regressions of four second average changes of muscle sympathetic nerve activity, plotted as functions of changes of diastolic pressure, during Valsalva straining. Each relation begins with the same point (the lowest point), and proceeds from lower right to upper left. Responses measured before the mission are shown as open circles, connected by a fine line, and responses measured in space are shown as closed circles, connected by a heavy line. These data document a greater reduction of arterial pressure during Valsalva straining during than before the space mission. They show clearly, however, that the gain of muscle sympathetic nerve responses (slopes of the relations) is nearly identical in space and on earth.

![Graph showing changes of sympathetic activity and diastolic pressure](image)

**Figure 2**

**DISCUSSION**

This study complements earlier research on the influence of microgravity on arterial baroreflex mechanisms. Prior research documented significant impairment of vagally-mediated carotid baroreceptor-cardiac baroreflex responses (Fritsch et al., 1992; Fritsch-Yelle et al., 1994). The Neurolab data, obtained from four astronauts before and during the mission, indicate clearly that microgravity modifies hemodynamic and autonomic responses to Valsalva straining. The most conspicuous difference is that arterial transients provoked by straining are much greater in space than on earth. Presumably, greater pressure changes reflect the fact that blood volume is reduced in space (Leach et al., 1996). We did not perform statistical analyses of these data because of the small number of subjects. However, changes provoked by microgravity were the same in all four astronauts: pressure reductions and sympathetic responses during straining were larger in space than on Earth. However, the gain of the reflex response was nearly identical. We conclude from this and earlier research that exposure of healthy humans to microgravity augments arterial pressure and sympathetic responses to Valsalva straining, and differentially reduces vagal, but not sympathetic baroreflex gain.

**References**


THE CEREBELLAR VERMIS MEDIATES RECOVERY OF COMPENSATORY CARDIOVASCULAR RESPONSES FOLLOWING REMOVAL OF VESTIBULAR INPUTS

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INTRODUCTION
Post-spaceflight orthostatic intolerance is a serious health risk for astronauts. Plastic changes in the vestibular system during spaceflight may contribute to the development of this condition. A previous study carried out in our lab showed that vestibular lesions can result in orthostatic intolerance, but that other sensory inputs can eventually be used to compensate for this deficit¹. This study was designed to investigate the role of the caudal vermis of the cerebellum in compensation for the effects of vestibular lesions on cardiovascular regulation. The results may provide insight into the etiology of post-spaceflight orthostatic intolerance, and may reveal general mechanisms involved in adaptation to altered gravitational environments.

CURRENT STATUS OF RESEARCH
Methods
Blood pressure and heart rate was measured in cats trained to lie in a prone position on a table capable of generating 20, 40, and 60° nose-up body rotations. Each animal’s head was fixed in space by means of a screw inserted into a metal bolt mounted on the skull. Blood pressure was monitored with the use of a self-contained telemetric transducer (Data Sciences International, St. Paul, MN) composed of a gel-filled catheter that was introduced into the femoral artery and passed proximally into the abdominal aorta and a transmitter that was secured in the peritoneal cavity. Heart rate was determined from the blood pressure trace. In addition, a patch electrode was secured to the thoracic musculature on either side of the heart in a subset of animals to obtain ECG traces, thus providing a second means for monitoring heart rate. Data were recorded in the animals in an intact state, following ablation of the caudal cerebellar vermis, and again following bilateral vestibular neurectomies. We utilized two testing situations to determine the relative importance of visual cues with regard to blood pressure control during tilt: one in which visual cues regarding position in space were available, and another in which all such cues were eliminated.

Results
Data have been collected in four animals thus far. Baseline data are currently being collected in a fifth animal and will be available at the time of presentation. A sixth animal is currently being trained and will likely have undergone the partial cerebellectomy by the time of presentation. Ablation of the caudal cerebellar vermis had variable effects on orthostatic tolerance. At least one animal showed no significant impairment following partial cerebellectomy, while two others showed at least some increase in blood pressure lability during tilt subsequent to the lesion. Recovery of orthostatic tolerance induced by complete removal of vestibular inputs was impaired or precluded in the cerebellar-lesioned animals.

CONCLUSION
Removal of the caudal vermis appears to hinder the recovery of orthostatic tolerance following bilateral vestibular neurectomy that was observed during a previous experiment carried out in our lab¹. The direct effects of the cerebellar lesion itself on orthostatic tolerance were variable and may indicate that, at least in some animals, the caudal vermis of the cerebellum has a more or less active role in effecting compensatory cardiovascular responses to orthostatic challenges. Our observations do support our hypothesis that the caudal vermis of the cerebellum is a part of the neuronal circuit mediating cardiovascular responses to increased orthostatic stress. A better understanding of the cerebellum’s role in this circuit as well as increased knowledge of the circuit in general may provide insight into cardiovascular regulation during and after exposure to microgravity.

FUTURE PLANS
Continued elaboration of the neural circuit described above will be the focus of future experiments. Goals for future experiments include elaborating on the findings described above, investigating the potential role of the fastigial nucleus in the circuit, and identifying other components of this circuit using anatomical techniques.
INDEX TERMS
Cerebellum
Vestibular
Cardiovascular
Orthostatic
Autonomic
Plasticity

Reference
BOTH GROWTH FACTOR-INDUCED CELL MIGRATION AND CELL MIGRATION INDUCED BY RANDOMIZATION OF THE GRAVITY VECTOR RELY ON METalloPROTEINASE ACTIVATION

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INTRODUCTION

The precardiac mesoderm is the developmental precursor of both the myocardial and endocardial lineages in the heart. The endocardial lineage forms from cells that detach from the epithelioid precardiac mesoderm, migrate as mesenchymal cells into the underlying basement membrane, then undergo a reverse transformation into endothelial cells. This epithelial–mesenchymal transformation and subsequent migration into the underlying basement membrane can be mimicked using a cell line (QCE-6 cells which are derived from the precardiac mesoderm) cultured on top of three-dimensional collagen gels.

CURRENT STATUS OF RESEARCH

Methods
QCE-6 cells were cultured on top of three-dimensional collagen gels in the presence or absence of growth factors and inhibitors of the matrix metalloproteinase MMP-2. Cell migration into the gels was monitored by direct microscopic observation. MMP-2 present in the culture medium and in the collagen gel was detected by Western blotting and by gelatin zymography. Standard experiments were performed using collagen gels formed in 24-well plates. For experiments involving randomization of the gravity vector, collagen gels were formed in the “culture space” of a Rotary Cell Culture System. Experimental chambers were then rotated in the vertical orientation (randomization of the gravity vector) while control chambers were rotated in the horizontal orientation (constant direction of gravity vector).

Results
When QCE-6 cells are cultured on top of a collagen gel under control conditions, they do not enter the gel. In the presence of added growth factor (bFGF) MMP-2 expression is induced and the cells migrate into the gel. MMP-2 expression appears to be a critical intermediate in the induction of migration by bFGF because the addition of TIMP-2, an inhibitor of MMP-2, blocks bFGF-induced cell migration. Interestingly, exposure of QCE-6 cells cultured on collagen gels to randomization of the direction of the gravity vector also induces migration into the gel. The mechanism underlying this migration appears to be similar to the one induced by bFGF, given that migration induced by randomization of the gravity vector is also accompanied by increased production of MMP-2 and is blocked by inhibitors of MMP-2.

Conclusion
Randomization of the gravity vector may affect cell behavior by inducing signaling cascades that are induced by growth factors such as bFGF under standard culture conditions.

FUTURE PLANS
The role of MMP-2 and other matrix metalloproteinases in cell migration induced by growth factors or by randomization of the gravity vector will be analyzed in detail by experimentally perturbing their expression and their enzymatic activity.

INDEX TERMS
Heart development
QCE-6 cells
Cell migration
Collagen gel
Growth factor
bFGF
Matrix metalloproteinase
MMP-2
TIMP-2
Randomization of the gravity vector
CEREBRAL PERFUSION IN SUBJECTS WITH ORTHOSTATIC INTOLERANCE

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INTRODUCTION

Orthostatic intolerance is characterized by symptoms of lightheadedness, tiredness, palpitations, blurred vision and occasionally, by loss of consciousness during standing, which are relieved upon recumbency. These symptoms are suggestive of cerebral hypoperfusion, yet they occur in the absence of orthostatic hypotension. We therefore evaluated cerebral vasoregulation in patients with OI. The specific objectives were 1) to evaluate if excessive cerebral vasoconstriction occurs in OI during head-up tilt 2) to find out whether hypocapnia could be the mechanism for this phenomenon 3) to investigate whether an impaired cerebral autoregulation (CA) is present in these patients. We hypothesized that cerebral hypoperfusion is present and related to changes in CO₂ and is not due to impaired CA. Therefore, we undertook a series of studies to evaluate the effect of head-up tilt on respiration, CO₂, cerebral blood flow and systemic cardiovascular responses in OI patients and healthy controls. We also evaluated the effect of correction of CO₂ on the recorded abnormalities. Finally, we evaluated CA using the Valsalva maneuver (VM) combined with a new analytical method.

CURRENT STATUS OF RESEARCH

Methods

Subjects: Thirty patients suffering from orthostatic intolerance (OI) and seventeen healthy subjects participated in the study. OI was defined as an excessive orthostatic heart rate (HR) increment of at least 30bpm and an absolute standing HR of at least 100bpm for >60% of the duration of the 10 min tilt-table test associated with symptoms of OI including dizziness, lightheadedness and blurry vision.

Protocols: After a period of rest, participants underwent a head-up tilt to 80° for 10 minutes. Eight patients underwent an additional tilt study with hyperventilation for 4 minutes, followed by CO₂ rebreathing for 5 minutes. Participants also performed three VM in the supine position with recovery periods of at least 3 minutes between maneuvers.

Data Acquisition and Analysis: Time series of RR-intervals, systolic (SBP), diastolic (DBP) and mean (MBP) blood pressure (BP) were acquired beat-to-beat. HR was calculated from RR-intervals. BP was measured from the finger using a photoplethysmographic method (Finapres). Impedance Cardiography was measured using BOMED NCCOM3 R-7, Irvine, CA. Respiration was measured using a nasal thermistor and sampled at 4 Hz. Endtidal CO₂ was derived from the expiratory air flow using Puritan Bennett 254 airway gas monitor calibrated with 5% CO₂.

Cerebral blood flow velocity (CBFV) was measured using transcranial Doppler (TCD) (Multigon Industries, New York). The left middle cerebral artery was insonated from the anterior temporal window. The TCD-probe (2 MHz) was positioned to record the maximal velocity and fixed in the desired angle using a specially designed teflon probe holder. Systolic (CBFV_S), diastolic (CBFV_D) and mean (CBFV_M) CBFV were detected from the analog signal on a beat-to-beat basis. Cerebrovascular resistance (CVR) was estimated as MBP/CBFV_M.

CA was assessed using a new analytical method: The resistance area product (RAP) of cerebral vascular resistance was calculated on a beat-to-beat basis from the slope of the best linear fit between the upstroke of the raw signal of BP and CBFV of each cardiac cycle. An autoregulatory index (ARI) was then calculated as the slope of the linear fit between beat-to-beat values of RAP and MBP during the VM. A higher ARI stands for a greater change of RAP with the same change of BP and therefore better CA.

Results

Clinical Characteristics: Gender and age distribution of patients (25 women and 5 men, aged from 21 to 44 years; mean 31.3±1.2 years) and controls (13 women and 4 men; aged from 20 to 41 years; mean 30±1.6 years) were statistically not different. All patients experienced typical symptoms of orthostatic intolerance such as dizziness, lightheadedness and fatigue. None of the controls reported symptoms of orthostatic intolerance during head-up tilt.
Head-up Tilt: All OI patients had increased supine HR (p<0.001) and cardiac output (CO, p<0.01) when compared with the control group. In response to head-up tilt, OI patients had a significantly greater HR (p<0.001), CO (p<0.001), and lower CO₂ (p<0.01) than controls. CBFV was significantly lower during tilt in OI. In contrast, CVR increased during tilt in OI patients (p<0.01), but not in controls. TPR significantly increased with tilt in controls (p<0.05) but not in OI and TPR values during tilt were lower (p<0.01) than in controls.

In controls, respiratory frequency and CO₂ did not significantly change during tilt. In contrast, OI patients underwent a significant degree of hypocapnia during tilt (p<0.01). The mean respiratory frequency during tilt of 0.25 Hz in OI did not differ significantly from that of controls (0.23 Hz), although the range of respiratory frequencies was wider during tilt in OI (from 0.06 to 0.39 Hz) than in controls (0.12 to 0.31 Hz). In OI patients, spontaneous rhythmic breathing was interrupted by episodes of deep breaths, faster respiratory rate, irregular respiration or apneas.

To quantify the relationship between CO₂ and CBFV and HR we regressed changes in CO₂ against changes in CBFV_M and in HR in these patients with OI and in controls. CBFV_M significantly correlated with the level of CO₂ with coefficient of determination >0.8 (p<0.0001) in all patients. Linear regression was used to quantitate the relationship. For OI, the relationship between CBFV_M and CO₂ had a coefficient of determination of 0.93, and the slope was 1.46 cm/s/mmHg. A significant regression was also found between HR and CO₂; coefficient of determination was 0.86, and slope -0.54 cm/s/mmHg. Corresponding values for controls were: CBFV_M vs CO₂: R² = 0.86, p<0.001; HR vs CO₂, R² = 0.72, p<0.0001. There was no significant difference in the slopes for OI and controls.

Hyperventilation during head-up tilt induced significant reductions of CBFV and CO₂ and a significant increase in HR and CVR. BP was not significantly different. CBFV and CVR rapidly improved within the first 2 minutes of CO₂ rebreathing. HR was also significantly lower during CO₂ rebreathing.

Cerebral Autoregulation: Changes of RAP closely followed changes of MBP during the VM in all participants except for one control with poor correlation between these parameters who was excluded from further analysis. R² was greater than 0.5 for all other participants (R² = 0.75±0.14). The correlation was significantly better in patients (R² = 0.81±0.08) than controls (R² = 0.64±0.15, p<0.05). ARI was not significantly different between patients (0.0131±0.0063 cm⁻¹s) and control group (0.0140±0.0040 cm⁻¹s).

Conclusion
Cerebral vasoconstriction occurs in OI during orthostasis, which in significant part is due to hypocapnia resulting from hyperventilation with an increase in depth but not rate of respiration. CA however is not impaired in patients with OI.

FUTURE PLANS
We plan to further explore mechanisms of cerebral vasoregulation in patients with orthostatic intolerance and to further validate our improved method to evaluate dynamic CA.

INDEX TERMS
OI, POTS, cerebral autoregulation, vasoregulation, hypocapnia, blood flow velocity, hyperventilation, transcranial Doppler, head-up tilt

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MICROGRAVITY-INDUCED VASCULAR HYPORESPONSIVENESS: NITRIC OXIDE-DEPENDENT AND -INDEPENDENT MECHANISMS

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INTRODUCTION

Space-flight-adapted astronauts exhibit orthostatic intolerance. Recent evidence points to a decreased capacity to elevate peripheral resistance on standing as a major underlying mechanism. We have used the hindlimb unweighted (HU) rat to simulate microgravity, and to explore mechanisms by which vascular function could be impaired. 20 days of HU results in a marked reduction of contraction of abdominal aorta, carotid and femoral artery to norepinephrine. Our recent results have identified an up-regulation of the expression of nitric oxide synthase isoforms in vascular and nonvascular tissues, representing a chronic increase in nitric oxide-dependent vasodilator mechanisms. In addition, we have found the HU reduces or eliminates selected second messenger signaling steps associated with vascular contraction to norepinephrine.

CURRENT STATUS OF RESEARCH

Methods

Wistar rats were prepared with tail harnesses that were tethered to the top of the cage. The tether was shortened to elevate the hindlimbs 0.5cm from the cage floor when fully extended, tilting the body approximately 35°. After twenty days, tissues from these rats and their time-paired caged controls were isolated for in vitro analysis. Blood vessels were cut into 3mm rings and mounted in organ baths for isometric contraction/relaxation measurements. Blood vessels, heart, kidney and brain were subjected to Western blot analysis to determine protein mass of the endothelial constitutive, inducible and neuronal isoforms of nitric oxide synthase (ecNOS, iNOS and nNOS, respectively). Tissue content of nitrates and nitrites, the stable metabolites of nitric oxide, were isolated, chemically converted to nitric oxide and measured by chemiluminescence.

Results

Endothelium removal in the HU carotid artery ring restored the norepinephrine-induced contraction of this vessel to control levels. The sensitivity of the HU carotid artery to acetylcholine-induced relaxation was 10-fold greater than control. Protein mass of ecNOS in the HU carotid artery was greater than control. None of these HU-induced effects was seen in either abdominal aorta or femoral artery. Thus, up-regulation of endothelium-dependent nitric oxide function occurs in the carotid artery, but not abdominal aorta or femoral artery. Blockade of either cyclooxygenase or thromboxane A₂ (TP) receptors markedly depressed the already weak contraction of HU carotid artery to norepinephrine, but had no effect in control artery rings. Such blockade had no effect in endothelium-denuded HU arteries. Thus, HU treatment up-regulates endothelial nitric oxide vasodilator activity and prostaglandin-dependent vasoconstrictor activity. The overall effect of HU is a reduction in the contractile response of carotid artery to norepinephrine.

In femoral artery, HU treatment reduced the maximal contraction to norepinephrine. In order to test for a contribution of iNOS to the HU effect, vessels were exposed to 0.3 µM L-arginine and norepinephrine concentration-response curves were obtained in the presence and absence of the iNOS selective inhibitor, aminoguanidine. Aminoguanidine had no effect in control vessels, but increased the contraction to norepinephrine in the HU vessels. In phenylephrine-precontracted vessels, L-arginine induced an aminoguanidine-sensitive relaxation that was greater in HU than control vessels. These experiments strongly suggest that HU treatment up-regulates the expression of iNOS in the femoral artery, leading to an increased tissue concentration of nitric oxide. In turn, the vasodilator action of nitric oxide decreases the ability of the femoral artery to contract to norepinephrine. Western blot analysis of the femoral artery demonstrated that iNOS protein mass is increased by HU treatment.

Studies of the isolated middle cerebral artery of control and HU rats were undertaken. Vessel segments were cannulated and pressurized, and vessel diameter was measured by videomicroscopy. Myogenic tone was assessed and found to be markedly increased in the HU vessels. In part, this was due to a decrease in the contribution of nitric oxide in the HU vessels, compared to control. This finding is consistent with the possibility that the increase in pressure at the level of the brain vasculature stimulated an adaptation of the cerebrovascular autoregulation to protect the brain from overperfusion. The increased myogenic tone would contribute to that protection by decreasing vessel diameter and reducing brain blood flow.
Experiments were carried out to determine whether HU is associated with a generalized increase in the role of nitric oxide. Protein masses of NOS isoforms were determined by Western blot analysis in both vascular and nonvascular tissues. In thoracic aorta, heart and kidney, iNOS was increased. The level of nNOS was also increased in both kidney and brain. There was no change in ecNOS in any of the tissues studied. In the kidney, nitric oxide is associated with regulation of natriuresis and diuresis. The observation that iNOS and nNOS are elevated in HU kidneys is consistent with the suggestion that nitric oxide levels are also elevated, leading to natriuresis, diuresis and hypovolemia, a known characteristic of both simulated and real microgravity. In the brain, nitric oxide is one factor that regulates sympathetic outflow. That nNOS is increased in the brain of HU rats, suggests that the resultant elevated nitric oxide could lower sympathetic outflow. In order to determine if the HU-induced changes in iNOS had in vivo hemodynamic effects, the blood pressure responses to I.V. injections of norepinephrine and the iNOS inhibitor, aminoguanidine were measured. Blood pressure increased more in control, than in HU rats in response to norepinephrine. In contrast, HU rats exhibited a greater aminoguanidine-induced blood pressure elevation than controls. The reduced pressor response of HU rats to norepinephrine is consistent with the known vascular hyporesponsiveness associated with simulated microgravity. The greater pressor response to aminoguanidine in HU suggests that nitric oxide production in the vasculature, via the activity of iNOS, was greater in HU compared to control. Thus, nitric oxide-dependent vasodilation would make a greater contribution to the ambient blood pressure. The results with aminoguanidine suggest that iNOS levels are generally elevated in the vasculature of HU compared to control rats.

Studies in the abdominal aorta address nitric oxide-independent mechanisms by which HU depresses the maximal contractile response of blood vessels to vasoconstrictor agents. It was found that HU treatment depresses the contraction to norepinephrine, but not serotonin. This suggested that HU may affect either receptor or second messenger events associated with vascular stimulation by norepinephrine, but not serotonin. Use of receptor antagonists did not reveal any HU-mediated changes at the receptor level. However, use of signal transduction inhibitors revealed certain second messenger pathways that are altered by HU when norepinephrine, but not serotonin, is the agonist. Both indomethacin and genistein markedly inhibited the norepinephrine-induced contraction in control, but not in HU, aorta. Both inhibitors had equal blocking effects in control and HU aortas when serotonin was used. This suggests that both a vasoconstrictor prostaglandin and a tyrosine kinase second messenger pathway contribute to norepinephrine-induced contraction in control, but not HU, aorta. Because HU treatment reduced or eliminated these vasoconstrictor mechanisms when norepinephrine was used, but not when serotonin was used, HU may have uncoupled these pathways from the alpha-adrenergic receptor. Using aorta rings stimulated with norepinephrine and shock frozen, Western blot analysis was used to assess HU effects on phosphorylated MAP kinase (pMAPK) levels. Tyrosine kinases are known to be involved in the phosphorylation and, therefore, activation of MAPK. The protein mass of pMAPK in control tissues was nearly double that in HU tissues. Genistein reduced the pMAPK level in control tissues to that of the HU tissues, but had no effect on pMAPK in HU tissues themselves. These differences in pMAPK levels, and the effects of genistein, mirror the results of the contractile studies described above. They support the view that HU eliminates the tyrosine kinase-associated component of the norepinephrine-induced contraction by uncoupling this pathway from the alpha adrenoceptor.

FUTURE PLANS
In vivo experiments will be carried out to assess orthostatic hypotension in control and HU rats. Animals will be instrumented with radiotelemetric blood pressure probes and intravenous cannulas for drug administration. At the completion of 20-day HU treatment, both control and HU rats will be placed in a tilt restrainer and blood pressure will be monitored in the horizontal and head-up vertical positions. Pressor responses to norepinephrine and aminoguanidine will also be tested in these two positions. Novel compounds, peripheral benzodiazepine receptor ligands, been shown to inhibit iNOS expression. Control and HU rats will be injected with these compounds throughout the 20-day HU treatment and the blood pressure experiments described above will be repeated. Vascular and nonvascular tissues from control and HU animals, treated with these compounds, will be subjected to Western blot analysis to determine iNOS protein levels.

INDEX TERMS: abdominal aorta, aminoguanidine, blood pressure, cardiovascular, carotid artery, cerebrovascular autoregulation, femoral artery, hindlimb unweighted rat, middle cerebral artery, nitric oxide, nitric oxide synthase, microgravity, orthostatic intolerance, simulated microgravity, tyrosine kinase
Orthostatic intolerance (OI) is commonly seen in astronauts returning to the normal gravitational environment. OI is a serious safety concern in current missions and may turn out to be a limiting factor in long duration space exploration by humans. To quantitatively supplement some of the current experiments investigating the mechanisms underlying post-space flight OI, we developed a computational model of the cardiovascular system which is capable of simulating the short-term (0-2 min) dynamic response to sudden orthostatic stress.

The model consists of a 12 compartment lumped parameter representation of the hemodynamic system coupled to set-point models of the two major neural reflex mechanisms, the arterial baroreflex and the cardiopulmonary reflex. The systemic circulation is split into four parallel pathways to allow for blood regional blood pooling in the periphery. Furthermore, we implemented non-linear venous compliances and venous valves to accurately simulate the rate of fluid shifts during orthostatic stress. The control system consists of a single arterial baroreflex and a cardiopulmonary reflex. Deviation of locally sensed pressures from pre-defined set-point values generate error functions that, in conjunction with static gain values, determine the strength of the four effector mechanisms (heart rate, left and right ventricular contractility, venous tone, and arteriolar resistance).

We validated the model under baseline (supine) conditions and after the onset of gravitational stress by comparing the model’s predictions to a limited set of population-averaged data found in the medical literature. By appropriately modifying some of the model’s parameters we systematically simulated a number of proposed hypotheses of the mechanisms underlying post-flight orthostatic intolerance. The modeled hypotheses included hypovolemia, cardiac atrophy, increased leg venous compliance, decreased gain of the heart rate baroreflex, and a reduced ability to constrict venous and arterial smooth muscle. By simulating a tilt test response under these altered baseline conditions, we were able to compare the simulator’s predictions to astronaut stand test data post-spaceflight. Our simulations indicate that although hypovolemia is the biggest single contributor, no single mechanism can account for the altered post-spaceflight heart rate dynamics. Rather, our simulations suggest that a superposition of reduced vasoconstriction of arterial and venous smooth muscle and hypovolemia can account for the dynamics of the heart rate response seen in astronauts post-flight.
MIDODRINE REDUCES ORTHOSTATIC INTOLERANCE FOLLOWING 16 DAY HEAD-DOWN TILT BED REST


INTRODUCTION
Post flight orthostatic hypotension is one of the primary cardiovascular risks associated with space flight, and constitutes a current operational hazard. To investigate the mechanisms leading to the development of orthostatic hypotension we utilized a head-down tilt bed rest as a model of microgravity. We utilized the technique of Cardiovascular System Identification (CSI) to assess changes in closed-loop cardiovascular control during the course of the study. Cardiovascular System Identification involves analysis of second-to-second fluctuations in physiologic signals such as heart rate, arterial blood pressure, and respiration in order to construct a closed-loop model of cardiovascular regulation. The coupling mechanisms in the CSI model are represented by impulse response functions. We also evaluated in a double blind fashion, the efficacy of a single oral dose of the alpha agonist midodrine, administered at the very end of bed rest, for preventing the development of orthostatic hypotension.

CURRENT STATUS OF RESEARCH
Methods
We implemented a 16 day head-down tilt bed rest protocol with strict dietary control in order to simulate microgravity conditions. Subjects underwent a tilt-stand test prior to the bed rest period, at the end of the bed rest period, and 2-3 days post bed rest. CSI measurements were obtained prior to bed rest, during the bed rest period, immediately following bed rest, and 2-3 days post bed rest. A subset of the subjects were randomized to receive a 5 mg oral dose of midodrine or placebo at the very end of bed rest in a double blind fashion.

Results
We studied 15 male subjects. CSI measurements made at the end of bed rest compared to measurements made pre-bed rest indicated that the autonomically mediated heart rate baroreflex was significantly diminished with the peak amplitude reduced by 56%. The largely mechanically mediated couplings, between respiration and arterial blood pressure, and between impulse heart rate and arterial blood pressure, also changed significantly. The autonomically mediated coupling between respiration and heart rate did not change significantly. Of the subjects receiving midodrine 71% were able to complete the tilt-stand test immediately following bed rest without becoming presyncopal, whereas only 25% of the control subjects were able to complete the test (p < 0.04).

Conclusion
In a 16 day bed rest study, CSI identified alterations in closed-loop cardiovascular control; in particular the heart rate baroreflex was significantly reduced. A single dose of midodrine administered orally at the end of bed rest substantially reduces orthostatic intolerance.

FUTURE PLANS
Future plans include studying effects of gender and age in the development of orthostatic intolerance using the methods developed in this study. Midodrine will also be tested in these studies. We have proposed using CSI and testing the effectiveness of midodrine in flight studies as well.

**INDEX TERMS**
Orthostatic hypotension, orthostatic intolerance, cardiovascular system identification, midodrine.
INTRODUCTION: Presently, exercise protocols and equipment for space flight are unresolved, although recent calculations suggest that all exercise in space to date has lacked sufficient loads to maintain preflight cardiovascular and musculoskeletal mass and function. Previously we found that lower body negative pressure (LBNP) produces a footward “gravitational” force equal to the product of the pressure differential and waist seal cross-sectional area of the LBNP chamber. An additional static force approximately equivalent to one Earth body weight is generated over the lower body by each 52 mm Hg of LBNP during supine posture. This artificial-gravity concept may help maintain the cardiovascular and musculoskeletal systems of crew members during prolonged exposure to microgravity. Currently-available bungee cord assisted, treadmill exercise is limited by harness discomfort, lower than normal loads, abnormal postflight gait, and the absence of gravitational blood pressures within the vascular system. Recently we found that supine LBNP treadmill exercise reproduces footward forces as well as the VO$_2$ and heart rate responses of upright exercise on Earth. Also, we have reported that supine LBNP exercise maintains upright exercise capacity after short (5day) and moderate (14day) periods of head-down tilt (HDT) bed rest.

PURPOSE: This project evaluates a novel method to create artificial gravity using supine LBNP treadmill exercise to prevent loss of physiologic function in microgravity simulated by 30 days of HDT bedrest. Identical twins were used as volunteers so that statistical power could be maximized.

CURRENT STATUS OF RESEARCH

Methods: Six sets of identical twins (all male, 22-31 years, N=12) remained in 6° HDT bedrest for 30 days to simulate prolonged microgravity. Six subjects were randomly selected to exercise supine in an LBNP chamber for 40 minutes six days per week (EX group), while their twin brothers served as non-exercise controls (CON). Pressure within the exercise LBNP chamber was adjusted to increase load, hence increasing exercise intensity. During supine treadmill exercise, LBNP (52-63 mmHg) was applied to produce footward forces equivalent to those for upright running on Earth at 1.0-1.2 times body weight (BW) and subjects performed an interval exercise protocol (40-80% peak exercise capacity [VO$_2$ pk]). Five minutes of resting LBNP immediately followed each exercise session. During orthostatic tolerance tests using 60 degrees head-up tilt plus graded LBNP (HUT/LBNP), orthostatic tolerance time, heart rate (HR) and middle cerebral artery blood flow velocity (MFV) were measured pre- and post 30 days bedrest. Pre- and post-bedrest, subjects completed an upright treadmill stress test to volitional fatigue. Submaximal (74±6% pre-BR VO$_2$pk) exercise responses (oxygen consumption VO$_2$, HR, minute ventilation $V_E$, and respiratory exchange ratio RER) and VO$_2$pk were compared using repeated measures ANOVA. Regional bone mineral density (BMD) and bone mineral content (BMC) were determined using Dual Energy X-ray Absorptiometry (Lunar Corp. DPX-IQ) on each subject before and after HDT bedrest. Using MRI, cross-sectional area (CSA) of iliopsoas spinal muscle at L4/5 was compared between CON and EX groups before and after 30 days bedrest. Lumbar spines were loaded with 50% BW using an MRI-compatible compression harness before and after 30 days HDT. The curvature response of the lumbar spine to normal loading conditions was compared between CON and EX groups. Statistical significance was set at p < 0.05.

Results: Orthostatic tolerance time decreased significantly after 30 days bedrest in the CON group, but was relatively maintained in the EX group (Fig 1, * signifies p<0.05). During the HUT/LBNP orthostatic tolerance test, HR increased more in CON (22 bpm) than EX (15 bpm). Compared with the pre-bedrest, MFV remained greater during HUT in the EX group than in the CON group. Upright treadmill test time to
fatigue decreased in the CON group but not in the EX group (Fig 2). Other exercise parameters were significantly degraded in the CON group, but maintained in the EX group (Table 1).

Table 1. Exercise Parameters

<table>
<thead>
<tr>
<th></th>
<th>VO₂ (L/min)‡</th>
<th>HR (bpm)‡</th>
<th>V̇E (L/min)‡</th>
<th>RER‡</th>
<th>VO₂pk (L/min)</th>
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<tbody>
<tr>
<td><strong>CON Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>2.67±0.14</td>
<td>173±8</td>
<td>80.2±4.3</td>
<td>1.05±0.01</td>
<td>3.56±0.25</td>
</tr>
<tr>
<td>Post</td>
<td>2.50±0.14</td>
<td>188±5*†</td>
<td>93.4±6.8*†</td>
<td>1.15±0.01*†</td>
<td>2.87±0.20*†</td>
</tr>
<tr>
<td><strong>EX Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.52±0.15</td>
<td>170±8</td>
<td>76.7±6.3</td>
<td>1.05±0.03</td>
<td>3.50±0.26</td>
</tr>
<tr>
<td>Post</td>
<td>2.50±0.13</td>
<td>166±7</td>
<td>74.1±4.9</td>
<td>1.03±0.02</td>
<td>3.31±0.23</td>
</tr>
</tbody>
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*Significantly different (p<0.05) than pre-bedrest  †Significantly different than EX Group  ‡Submaximal exercise response

BMD in the spine (L2-L4) and BMC in the arms and legs of CON subjects decreased significantly after 30 days of bedrest. These parameters remained unchanged in the EX group. Iliopsoas (L4/5) CSA decreased significantly more in CON group (1.9 ± 1.2 cm²) than in the EX group (no change). During 50% BW load application (similar to upright posture), normal spinal curvature was preserved in the EX group but not in the CON group.

Conclusions: Our treadmill exercise protocol within LBNP plus a short period of post-exercise LBNP maintains orthostatic responses, upright exercise capacity and submaximal exercise responses during bedrest. This high intensity weight-bearing, artificial-gravity exercise also preserves bone parameters in the arms, legs and spine. Other important physiologic adaptations to gravity are maintained as well. These results document the efficacy of our apparatus and exercise protocol for maintaining physiologic structure and function during long-duration microgravity as simulated by 30 days of HDT bedrest.

FUTURE PLANS: Two more sets of identical twins will be studied.

INDEX TERMS: countermeasures, artificial gravity, exercise, cardiovascular, muscle, bone, bed rest, long-duration microgravity, orthostatic tolerance, spine

ACKNOWLEDGEMENTS: Supported by NASA grant 199-26-12-34, NIH grant to the UCSD GCRC M01 RR00827, Canadian Space Agency, Natural Sciences and Engineering Research Council of Canada, and the Heart and Stroke Foundation of Ontario. Special thanks to DynaMed, Inc. for the use of a Dynawell spinal compression harness.
COLD STIMULATION TO IMPROVE ORTHOSTATIC TOLERANCE

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INTRODUCTION
Post-flight orthostatic intolerance remains a persistent problem after spaceflight, and may be exacerbated by increasing flight duration. The most commonly employed countermeasure (oral saline fluid loading) has proven to be modestly successful in laboratory settings but has failed to eliminate the problem after spaceflight. The ideal countermeasure would provide restoration of cardiac filling pressure and volume (hence stroke volume) while promoting vasoconstriction in gravity-dependent regions of the circulation. The resultant increase in cardiac output and systemic vascular resistance, represents a comprehensive solution to the problem.

We have considered skin cooling as a potential countermeasure to ameliorate orthostatic tolerance, using the current liquid cooling garment (LCG) as an experimental model. Accordingly, we measured core temperature during de-orbit preparation and landing activities to determine the efficacy of the current LCG in launch/entry suits. Ongoing studies in a ground-based model will identify the characteristics and efficacy of cooling in volume-depleted subjects.

CURRENT STATUS OF RESEARCH
Data were obtained from the four payload crew during deorbit preparation, reentry, landing, and post-landing of the STS-90 Neurolab mission flown April 17 - May 3, 1998. A radio-telemetered thermistor pill (HTI, Inc.) was swallowed on the morning of landing day, approximately 4 hours prior to landing. Each pill was calibrated individually. Core temperature was measured at one-minute intervals and recorded by an ambulatory receiver/data logger. Data were compared to a separate in-flight data segment obtained 2 days earlier at the same relative clock time. The LCGs worn under the LES were commercial heavyweight polypropylene long underwear outfitted with perfusion tubes. Thin polypropylene was worn under the LCG for subject comfort. Two crewmembers utilized thermoelectric cooling units that removed heat at a rate of 1.4 kcal/min (99 W); the other two crewmembers shared a unit that rejected heat at a combined rate of 2 kcal/min (140 W). Water was circulated through the units at a rate of 37.8-45.4 L/hr.

Figure 1 reveals that the thermoelectric cooling units failed to remove sufficient metabolic heat to maintain thermal balance during deorbit preparatory and landing activities. With the benefit of hindsight, these results are not surprising; the cooling units were designed with capacities equivalent no greater than basal metabolic rate. Deorbit preparation requires a large amount of crew activity to deploy equipment (such as crew seats) and pack mission equipment. Much of this work is done while wearing thermal underwear and LCGs without cooling, further adding to heat strain. Metabolic load during this period has not been quantified; unfortunately this measurement is unlikely to be made in the near future because mission operations must take priority over scientific research during this critical phase of space flight.

Additional experiments currently underway will determine the magnitude, time course, and mechanism of the reflex cardiovascular adjustments that occur with skin cooling. In a 2x2 design, 12 subjects receive four separate LBNP
exposures to presyncope with and without cooling (LCG with a water temperature of 15°C) before and after experimental hypovolemia (removal of 500 mL of whole blood). Early results reveal large improvements in orthostatic tolerance following skin cooling. Cooling increases central venous pressure, stroke volume, and mean arterial pressure, though the duration of the effect varies with the duration of cooling. We speculate that very short exposures to cooling (<2 min) are sufficient to cause reflex adjustments stimulated by peripheral cold thermoreceptors; however, presyncope rapidly ensues when cooling is stopped. Longer exposure (>40 min) is sufficient to reduce core temperature and occasionally induce shivering, which maintains the improvement in orthostatic tolerance for many minutes after cooling is stopped. More complete results from this study will be available at presentation.

CONCLUSION
We offer several recommendations based on available data. First, estimation of metabolic heat production during deorbit preparation and landing is required. Second, the capacity of thermoelectric cooling devices must be increased to remove this heat. Third, liquid cooling should be applied for relatively long periods of time to induce changes in core and skin temperature. With these changes, surface cooling appears to be an extremely powerful technique to improve post-flight orthostatic tolerance.

FUTURE PLANS
1. Recent data suggest that the effect of cold stimulation is confined to the upper body. We will therefore be examining the distribution of sympathetic responses evoked by surface cooling.
2. More thorough assessment of the dose-response characteristics of cooling
3. Evaluation of cold thermoreceptor activity evoked by surface cooling.

INDEX TERMS
Cold stress, sympathetic nervous system, orthostatic tolerance
EFFECT OF EXERCISE AND ACCELERATION TRAINING ON RESTING AND ORTHOSTASIS INDUCED CHANGES IN HEMATOLOGICAL VARIABLES

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INTRODUCTION
Losses of aerobic power and orthostatic tolerance are significant effects of manned spaceflight that can negatively impact crew health and safety. Daily acceleration and aerobic training may ameliorate these effects. The purpose of this investigation was to determine the influence of passive intermittent +Gz acceleration (PAS) training, constant +Gz acceleration + interval exercise (CAE) training, and intermittent +Gz acceleration + interval exercise (IAE) training on the orthostatic, plasma volume, and vasoactive hormone responses to 70º head-up tilt. It was hypothesized that all three acceleration-training protocols would improve orthostatic tolerance and the addition of aerobic conditioning would not alter this effect. This improved orthostasis would result in a smaller decrease in plasma volume (PV) and a greater increase in plasma renin activity (PRA) and smaller increases in plasma vasopressin (PVP) and norepinephrine (NEPI) in response to tilt testing.

CURRENT STATUS OF RESEARCH
Methods
Three subjects underwent PAS training on the Ames Research Center human powered centrifuge (HPC) for 30 min [warm-up, 24 min of 2 min acceleration intervals (+1.0 Gz to 50% Gzmax, +2.4 ± 0.1 Gz), and cool-down] 5d/wk for 3 wk. The other 3 underwent constant +Gz acceleration (CAE, 50% of HPC maximal acceleration, +2.3 ± 0.2 Gz) while performing supine interval training on a cycle ergometer [warm-up (40% peak oxygen uptake (VO2peak)), 24 min of 2 min intervals (40% - 90% VO2peak), cool-down] 5d/wk for 3 wk. A crossover design was used with 3 wk of ambulatory deconditioning between protocols. A third group of 6 men then underwent IAE training consisting of linked intermittent +Gz acceleration and cycle ergometry [warm-up (40% peak acceleration tolerance (+Gzpeak)), 24 min of 2 min intervals (40% - 90% +Gzpeak), cool-down] 5d/wk for 3 wk. Before and after each training protocol, peak (peak) VO2, workload (WL), and heart rate (HR) were determined supine. Resting (r) HR and blood pressures (SBP, DBP, and MAP) after 40 min of supine rest and orthostatic responses to 70º head-up tilt (t), to presyncope or 60 min were measured pre- and post-training (data reported for last 2 min of tilt). Maximal human powered +Gz acceleration tolerance was determined using the HPC.

Results
Both the CAE (1766 ± 88 to 1967 ± 49 kpm) and IAE (1750 ± 43 to 2017 ± 48 kpm) protocols improved work capacity (p ≤ 0.05). PAS training increased HRr (63 ± 4 to 71 ± 5 bpm) and HRt,
(71 ± 8 to 89 ± 7 bpm) while CAE and IAE had no effect on HR, but IAE eliminated the tilt induced decrease in MAP (30.7 ± 14.0 vs. −8.9 ± 4.8 %). PAS (3424 ± 185 to 3461 ± 97 mL) and IAE (3592 ± 125 to 3787 ± 120) increased resting PV, while CAE (3616 ± 215 to 3533 ± 130 mL) decreased it. None of the protocols appears to have impacted the endocrine response to 70°-head-up tilt.

Conclusion
PAS and IAE training are more similar than either is to CAE training. Intermittent acceleration appears to have a greater training effect than constant load acceleration.

FUTURE PLANS
This study assessed the training response in ambulatory subjects. The next step is to determine if acceleration training is an effective countermeasure for bed rest-induced orthostatic intolerance.

INDEX TERMS
Acceleration, Human Powered Centrifuge, Orthostasis, Hemodynamics, Endocrine

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ENDURANCE TRAINING DURING BED REST PREVENTS LEFT VENTRICULAR ATROPHY AND LOSS OF PLASMA AND VENTRICULAR VOLUME

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Bed rest deconditioning is associated with a loss of plasma volume (PV), and left ventricular (LV) atrophy. In contrast, endurance training leads to increased resting blood and plasma volume and LV hypertrophy. In order to determine whether endurance training during bed rest can prevent the deconditioning induced atrophy and associated changes in hemodynamics, we assigned 14 previously sedentary subjects (37 ± 2 yr) into two groups: exercise (n=10) and non-exercise (n=4), during complete bed rest with -6 dg. head-down-tilt for 18 days. The exercise group trained on a supine ergometer for 30 min at 75% HRmax, 3 times/day. This regimen was chosen based on preliminary calculations with the goal of normalizing stroke work between bed rest and ambulatory periods. We measured LV mass and end-diastolic volume (LVEDV) before and after bed rest using cine magnetic resonance imaging. PV was measured by Evans Blue technique, and cardiac output (Qc) and stroke volume (SV) by an acetylene rebreathing technique. Results: LV mass increased by 7 ± 3% (p<0.05) in the exercise group while it decreased slightly (3 ± 2%, n.s.) in the non-exercise group. PV and SV decreased (p<0.05) by 9 ± 1% and 15 ± 1%, respectively in the non-exercise group; Qc (10 ± 4%, p=0.07) and LVEDV (10 ± 5%, p=0.09) also tended to decrease in the non-exercise group. In contrast, PV was maintained at the pre bed rest level after bed rest (-1 ± 4%, n.s.) in the exercise group and no significant changes were observed in Qc, SV or LVEDV. Conclusion: Endurance training of sufficient intensity and duration, maintains plasma volume and ventricular filling during bed rest, accompanied by significant LV hypertrophy. Although the optimal "dose" of exercise has not been defined (i.e., mode, intensity, duration) this study demonstrates that endurance exercise may be an effective prophylaxis against the "cardiovascular deconditioning" associated with bed rest.
EVALUATION OF THE INTERIM RESISTANCE EXERCISE DEVICE FOR USE ON THE INTERNATIONAL SPACE STATION (ISS)

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INTRODUCTION
Heavy resistance exercise training has been proposed as a countermeasure to prevent muscle atrophy and bone demineralization during long duration spaceflight. The STS-106 crew recently delivered a new, elastomer-based interim resistive exercise device (iRED) to ISS for use during at least the first 2 years of station occupancy. Crewmembers will be required to perform both upper and lower body exercises, for approximately 60 minutes/session, 6 days per week, with the seventh day consisting of active rest. Very little is known about the force curve characteristics or training responses to the iRED.

CURRENT STATUS OF RESEARCH
Methods
A total of 32 subjects will be recruited for a 16-week training study. The subjects will be randomly divided into 4 groups while balancing the major outcome variable of the study; 1 repetition maximal (1RM max) strength for the squat exercise among the groups. Eight subjects will serve as controls and perform no resistive exercise. Eight subjects will train 3 times each week for 3 sets using the iRED (iRED3). Eight subjects will train 3 times each week for 6 sets using the iRED (iRED6). Eight subjects will train 3 times each week for 3 sets using free weights (FW3).

Before and after the 16-week training program, thigh muscle volume will be measured using magnetic resonance imaging (MRI); 1RM max strength for squat, heel raise and dead lift exercises will be assessed using free weights; lean body mass and vertebral bone mineral density will be determined by dual energy X-ray absorptiometry (DEXA).

We hypothesize that training with the iRED will be less effective than training with free weights, as the total work during each given exercise contraction will be less, due to hysteresis in the force curves characteristic of this elastomer device. Increases in 1RM strength, muscle volume, lean body mass, and bone mineral density will be smaller in the iRED3 group compared to the FW3 group. Increasing the total training volume in the iRED6 group may increase the effectiveness of the iRED training program.

Results:
We are not yet far enough into the study to report any group differences. We currently are training 3 FW3, 4 iRED3 and 4 iRED6 subjects, and monitoring 3 control subjects. These subjects should complete the 16-week program by late November 2000. The remaining subjects should begin training in January 2001 and complete the study by late April 2001.

Conclusion:
It is too early to make any definitive conclusions regarding training with the iRED. The subjects appear to be getting stronger in both the free weight and iRED groups as their daily training weights are increasing as the study progresses.

FUTURE PLANS:
We hope to finish this study early next year and next conduct a bed rest study using the iRED and the training protocol that produces the best benefit/training time. This approach will confirm that this exercise
device and protocol will not only increase muscle strength in a 1 g environment but also prove effective in preventing muscle atrophy and loss of strength during bedrest, a spaceflight simulation.

INDEX TERMS:
Muscle atrophy, bone demineralization, resistive exercise, muscle strength
Distributed Simulation of Integrated Human Function
Dr. James E. Coolahan

The long-term objective of the Distributed Simulation of Integrated Human Function project for the National Space Biomedical Research Institute (NSBRI) is to demonstrate the ability to simulate Integrated Human Function (IHF) over time by providing a technical framework to permit simulations of different human physiological functions, executing in separate locations, to interact to produce synergistic results. The hypothesis of this research is that interoperable simulations of human physiological functions applicable to the space flight environment executing interactively can produce integrated results that cannot be produced by these simulations executing independently. The specific aims of this research are: to develop, at the Johns Hopkins University (JHU), a computational model of the human ventricular myocyte and a finite element model of the geometry and fiber structure of the human heart; to develop a distributed simulation of human cardiac function, incorporating the simulation of the human cardiac ventricular cell resident at JHU, and a simulation of coupled mechanical and electrical function resident at the University of California, San Diego (UCSD); and, working with the NSBRI IHF team, to select other appropriate models that can be represented over time using simulations, and integrate them into (a) a distributed simulation of cardiovascular function; and (b) a multi-function distributed simulation of cardiovascular, bone, and muscle systems representative of the IHF simulations that will be needed for long-term space flight. The research will leverage the significant body of research in constructing distributed interoperable simulations that has been performed in connection with the development of the High Level Architecture (HLA) for simulations developed by the U. S. Department of Defense. The initial distributed simulation of human cardiac function will be constructed by developing a Federation Object Model (FOM) describing the objects, attributes, and interactions of the respective JHU and UCSD simulations, and incorporating a structured Federation Development and Execution Process (FEDEP) to ensure proper systems integration. An HLA Runtime Infrastructure (RTI) will provide the means for distributed execution across the coast-to-coast network implementation. The FOM developed for this initial application will be extended in subsequent years to incorporate simulations of other aspects of cardiovascular system function, and ultimately, related elements of bone and muscle systems, so that a multi-system distributed simulation will be executed in the final year of the project.