MICROGRAVITY AND THE CARDIOPULMONARY SYSTEM: 
A DISCIPLINE SUMMARY
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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 Bioastronautic 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 RESETTNG 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.
Vascular
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 Ca²⁺ 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 adrenoceptor-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. Pawelczyk 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 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 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.