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NASA Conference Publication 10068

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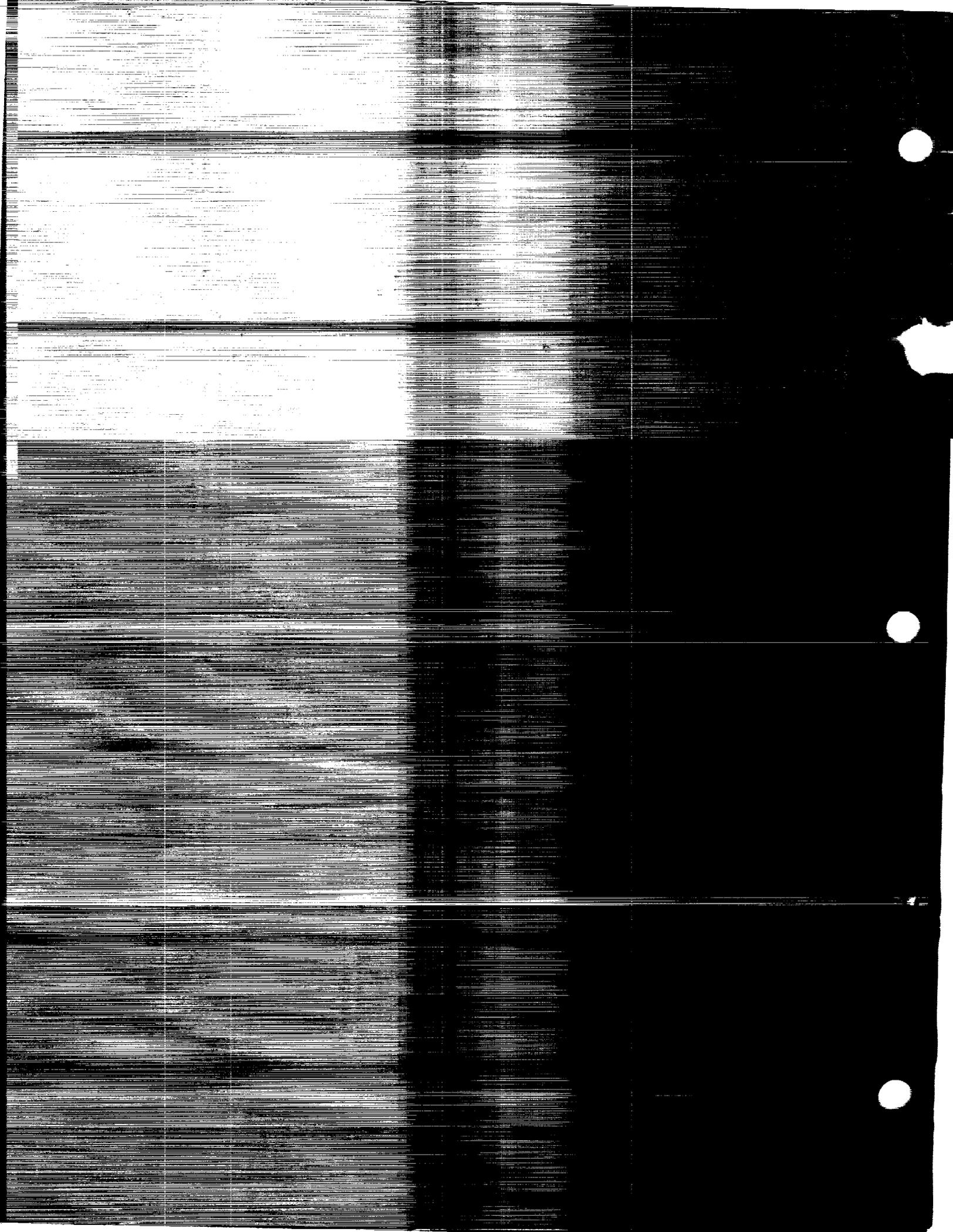
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NASA Conference Publication 10068

Proceedings of the First Joint NASA Cardiopulmonary Workshop

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Alan R. Hargens, Ph.D., Editors
NASA Lyndon B. Johnson Space Center
Houston, Texas

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December 5 - 7, 1990

The NASA logo, consisting of the word "NASA" in a bold, sans-serif font with a stylized "A".

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April 1991

THE UNIVERSITY OF CHICAGO



CONTENTS

Program	vii
Participants	ix
Introduction	xi
Discussion	xii
Carotid-Cardiac Baroreflex: Relation with Orthostatic Hypotension Following Simulated Microgravity and Implications for Development of Countermeasures	3-1
Echocardiography in the Flight Program	7-2
Pulmonary Function in Microgravity: KC-135 Experience	11-3
Central Circulatory Hemodynamics as a Function of Gravitational Stress	13-4
Glycerol-induced Hyperhydration	37-5
Spectral Analysis of Resting Cardiovascular Variables and Responses to Oscillatory LBNP Before and After 6 Degree Head Down Bedrest	51-6
Effect of Prolonged LBNP and Saline Ingestion on Plasma Volume and Orthostatic Responses During Bed Rest	61-7
Fitness, Autonomic Regulation, and Orthostatic Tolerance	71-8
Valsalva Maneuver: Insights into Baroreflex Modulation of Human Sympathetic Activity	79-9
Mechanistic Studies on Reduced Exercise Performance and Cardiac Deconditioning with Simulated Zero-Gravity	89-10
Fluid Compartment and Renal Function Alterations in the Rat During 7- and 14-Day Head Down Tilt	97-11
Local Fluid Shifts and Edema in Humans During Simulated Microgravity	109-12
Hormonal Regulation of Fluid and Electrolyte Metabolism in Zero-Gravity and Bedrest	121-13
Hormonal Regulation of Fluid and Electrolyte Metabolism During Periods of Headward Fluid Shifts	141-14
Autogenic-feedback Training: A Countermeasure for Orthostatic Intolerance	145-15
Cardiovascular Dynamics During Space Sickness and Deconditioning	155-16

Cardiovascular Measurements in Chronically Instrumented Conscious Monkeys	165
Insights into Control of Human Sympathetic Nerve Activity Derived From the Valsalva Maneuver	171

Proceedings of the
NASA Cardiopulmonary Workshop
5 - 7 December 1990

Program

Titles	Presenters
Introduction	Alan R. Hargens, Ph.D. Suzanne M. Fortney, Ph.D.
Discussion	Charles M. Tipton, Ph.D.
Carotid-Cardiac Baroreflex: Relation with Orthostatic Hypotension Following Simulated Microgravity and Implications for Development of Countermeasures	Victor A. Convertino, Ph.D.
Echocardiography in the Flight Program	John B. Charles, Ph.D.
Maximum Expiratory Flow-volume Curves During Short Periods of Microgravity	Harold J. B. Guy, M.D.
Central Circulatory Hemodynamics as a Function of Gravitational Stress	Rick D. Latham, M.D.
Glycerol-induced Hyperhydration	Marvin L. Riedesel, Ph.D.
Spectral Analysis of Resting Cardiovascular Variables and Responses to Oscillatory LBNP Before and After 6° Head Down Bedrest	Charles F. Knapp, Ph.D.
Effect of Prolonged LBNP and Saline Ingestion on Plasma Volume and Orthostatic Responses During Bed Rest	Suzanne M. Fortney, Ph.D.
Fitness and Orthostatic Tolerance	Jay C. Buckey, M.D.
Insights into Baroreflex Modulation of Human Sympathetic Activity	Michael L. Smith, Ph.D.
Mechanistic Studies on Reduced Exercise Performance and Cardiac Deconditioning with Simulated Zero Gravity	Charles M. Tipton, Ph.D.
Fluid Compartment and Renal Function Alterations in the Rat During 7- and 14-Day Head Down Tilt	Bryan J. Tucker, M.S.
Local Fluid Shifts and Edema in Humans During Simulated Microgravity	Alan R. Hargens, Ph.D.
Hormonal Regulation of Fluid and Electrolyte Metabolism in Zero-G and Bedrest	Joan Vernikos, Ph.D.
Hormonal Regulation of Fluid and Electrolyte Metabolism during Periods of Headward Fluid Shifts	Lanny C. Keil, Ph.D.

**Autogenic-Feedback Training: A Countermeasure
For Orthostatic Intolerance**

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**Cardiovascular Dynamics During Space Sickness
and Deconditioning**

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**Cardiovascular Measurements in Chronically
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INTRODUCTION

The goal of this First Joint Cardiopulmonary Workshop for Ames Research Center, Johnson Space Center, and Kennedy Space Center was to allow principal investigators to inform each other of their previous progress and future plans for their National Aeronautics and Space Administration (NASA)-funded projects. Through this meeting it was hoped that more contact, interaction, and collaboration would be fostered among investigators within the Research and Technology Objectives and Plan (RTOP). Also, it was hoped that this knowledge base could be transferred to space flight experiments and that information from actual microgravity could be used to improve ground-based human and animal models of simulated microgravity. Presently, NASA-Headquarters has recommended that RTOP tasks shift from acute to long-term studies, including more emphasis on countermeasure development. In the present environment of decreasing research support in the NASA RTOP Program, it is our goal to maximize basic understanding of mechanisms of cardiopulmonary adaptation to microgravity so that health and performance of crewmembers is optimized in space and upon return to Earth.

These proceedings include copies of papers presented at the workshop. For those papers previously published, we have included a reference and a brief description of the research performed. In some instances, additional reference material is also provided.

Alan R. Hargens
Suzanne M. Fortney

6 December 1990

DISCUSSION

After presentations by each principal investigator and discussion of their progress, Dr. Charles Tipton led additional discussion of: 1) animal and human models of microgravity simulation and 2) possible cardiopulmonary countermeasures to maintain human health in space and during return to Earth. The following discussion does not always represent all of the points or the total consensus of all Workshop participants.

Animal and Human Models

It was agreed that the optimal model for microgravity usually depends upon the question asked. However, ground-based models such as head-down tilt (HDT), horizontal posture and immersion are all valid models. Also, spinal cord lesion patients show promise as subjects for orthostatic intolerance countermeasure development. Because 5° to 6° HDT is considered the best ground-based, human model for the cardiovascular system today, investigators who use a different model should specify their reasons for using their particular model. The need to reduce psychological stress and to standardize protocols for HDT was discussed. For example, more emphasis should be placed on the control period before HDT and what measurements are critical during this time. Generally, it was agreed the upright standing or sitting is the best posture for control measurements. However, it was pointed out that often such variables as posture and stress could not be controlled during launch or in flight. It was emphasized that more teamwork and collaboration was desirable for future bed rest and in-flight studies when studies did not adversely affect each other. In this regard, Extended-Duration Orbiter (EDO) experiment and Detailed Supplementary Objective (DSO) opportunities are open to non JSC investigators but it is recommended that a JSC sponsor be recruited to monitor the EDO or DSO. Overall, it was agreed that principal investigators should justify their proposal better; i.e., clearly demonstrate the flight-relevance of their work, and that NASA should provide Requests for Proposals to give priorities for future research.

In terms of animals, the model should be selected that best addresses the mechanism under investigation. Whenever possible, however, the animal should be a species designated for future flight experimentation. Evidence was presented at this Workshop that the rat is a very good overall model for some aspects of macro- as well as the microcirculation. However, the time course of cardiovascular changes may be slower for the rat as compared to that for humans. At present, head-down tilt is considered an adequate model to study select cardiovascular responses to microgravity. It was emphasized that animals are important for their own reasons as experimental subjects for space research. Large sample sizes, an extensive data base, and low costs are key advantages for use of rodent models. However, the nonhuman primate, particularly the rhesus monkey, may be a better model for cardiac research and for certain cardiovascular parameters.

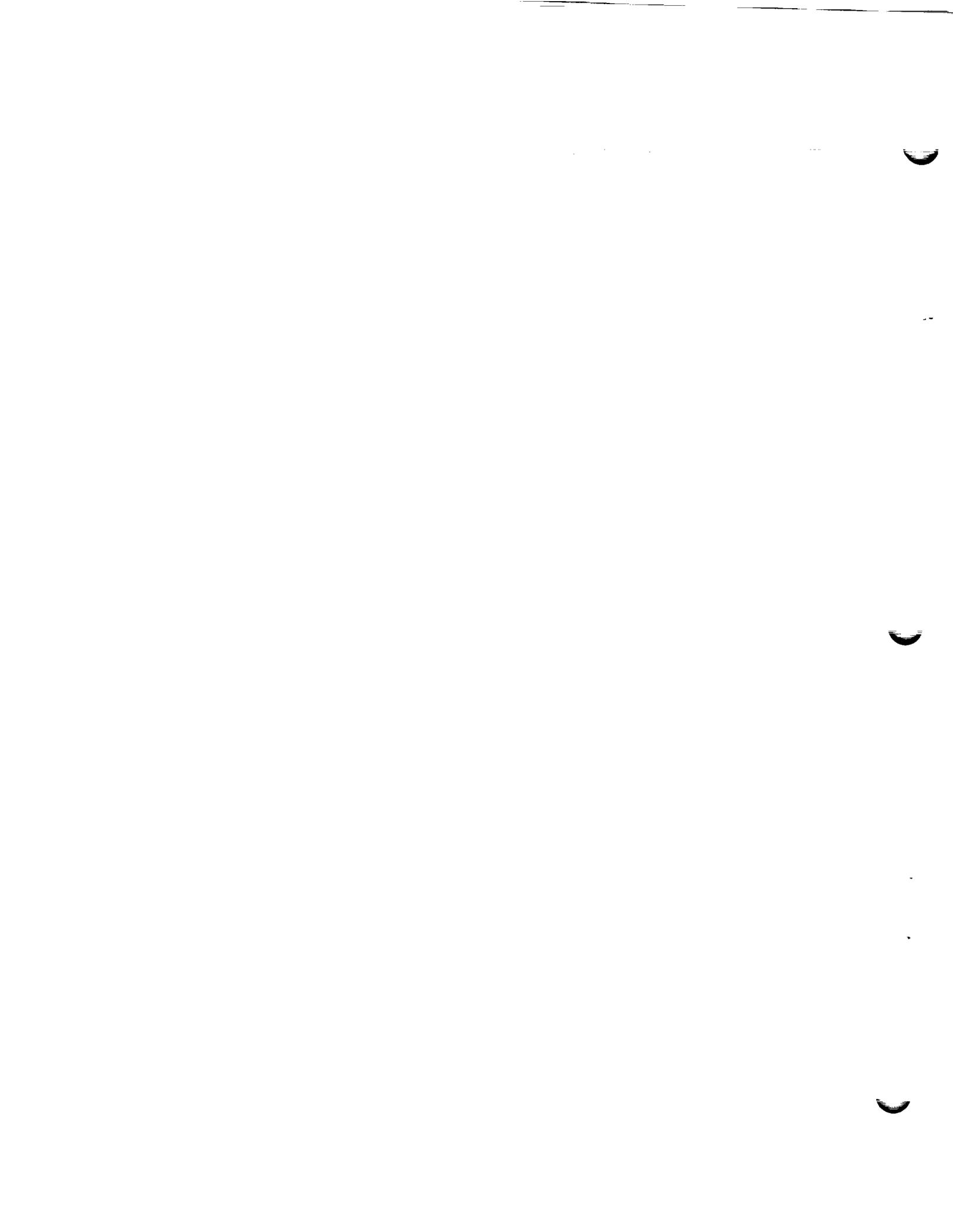
Countermeasures

Practicality and efficiency should be key factors in developing countermeasures. In this regard a minimum effective countermeasure such as high intensity, high-resistance exercise may be preferred over aerobic exercise. Specificity should also be considered, and a variety of exercises, developed into an overall exercise program, should be considered, rather than a single exercise form. For example, moderate aerobic exercise may be useful in maintaining aerobic capacity, while more intense or resistive forms of exercise may be more effective in maintaining baroreceptor function, for example. Cardiopulmonary issues during extravehicular activities (EVAs) are not being adequately addressed. Important areas of future work should include thermoregulation during EVA and pharmacologic countermeasures for postflight orthostatic intolerance. Saline ingestion is not sufficient in itself to prevent orthostatic intolerance. Although the primary cardiopulmonary problem has been identified as orthostatic intolerance and receives large amounts of funding from NASA, actual fainting occurs infrequently postflight. It may be more difficult to readapt to Earth after prolonged microgravity exposures and therefore possible loss of baroreceptor function and vascular tone in leg vessels must be investigated. It was generally agreed that all countermeasures

must be developed scientifically and that investigators within the Cardiopulmonary RTOP are excellent resources for such development.

Suzanne M. Fortney
Alan R. Hargens

12 December 1990



PRESENTED MATERIAL

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CAROTID-CARDIAC BAROREFLEX: RELATION WITH ORTHOSTATIC
HYPOTENSION FOLLOWING SIMULATED MICROGRAVITY AND
IMPLICATIONS FOR DEVELOPMENT OF COUNTERMEASURES

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P.3

Victor A. Convertino

Abstract

In a series of studies, we have examined the effects of exposure to simulated microgravity, varying states of vascular volume, and acute exercise on the function of the carotid-cardiac baroreflex in man. In the first study, exposure to simulated microgravity (6° head-down bedrest) reduced the sensitivity and buffer capacity of the vagal baroreceptor-cardiac reflex mechanisms and this impaired baroreflex function was associated with orthostatic hypotension. Since the reduction in plasma volume during BR was not correlated with impaired baroreflex function, a second study was conducted which demonstrated that the carotid-cardiac baroreflex response was not affected by either acute hypovolemia or hypervolemia. These results suggest that acute fluid replacement prior to reentry may not reverse impaired baroreflex function associated with postflight hypotension. In a third study, we demonstrated that one bout of maximal exercise increased baroreflex sensitivity and buffer capacity through 24 h post-exercise. These baroreflex changes were opposite to those observed following BR. Taken together, these data suggest that the contributions of reduced blood volume and impaired carotid-cardiac baroreflex function to orthostatic hypotension following exposure to microgravity are probably separate and additive; maximal exercise in addition to fluid replacement may provide an acute effective countermeasure against postflight hypotension.

The complete text of this manuscript is printed in Acta Astronautica, Vol. 23, pp. 9-17, 1990.

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ECHOCARDIOGRAPHY IN THE FLIGHT PROGRAM

A Report of Ultrasound Cardiography Results
from Space Shuttle Missions

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R.B

John B. Charles, Ph.D.
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Introduction.

Observations on American and Soviet astronauts have documented the association of changes in cardiovascular function during orthostasis with space flight. A basic understanding of the cardiovascular changes occurring in astronauts requires the determination of cardiac output and total peripheral vascular resistance as a minimum. In 1982, we selected ultrasound echocardiography as our means of acquiring this information. Ultrasound offers a quick, non-invasive and accurate means of determining stroke volume which, when combined with the blood pressure and heart rate measurements of the stand test, allows calculation of changes in peripheral vascular resistance, the body's major response to orthostatic stress.

Methods.

Pre- and post flight echocardiography during the Shuttle program began with STS-5 in 1982 (Nov., 1982) as part of DSO 402 (Fluid Loading Countermeasure). ("DSO" stands for "Detailed Supplementary Objective," an avenue for collecting operationally-important medical data on Space Shuttle crewmembers.) It was performed on a sporadic basis on volunteer crewmembers through 1986. Data from the first several flights was determined from two-dimensional (2D) echocardiographic images acquired with an instrument originally designed for obstetric use. In 1983, we upgraded to the ATL 4000 S/LC, which permitted 2D-guided M-mode imaging. Two of these units were acquired specifically for conversion into "flight units" (one primary unit and one backup unit) allowing data collection by trained crewmembers during Shuttle flights. The prime flight unit has flown on two Shuttle missions to date: STS 51-D (Apr., 1985) and STS-32 (Jan., 1990). Up to three more flights may be accomplished by this unit before it is retired.

Starting with STS-26 (Sept., 1988), several DSOs using echocardiography have allowed us to collect information on changes in cardiovascular function associated with flight duration (DSO 466), in-flight aerobic exercise (DSO 476), new fluid loading prescriptions (DSO 479), the use of LBNP as a countermeasure (DSO 478), and for correlation with heart rate and blood pressure immediately after landing (DSO 603). Beginning with STS-28 (Aug., 1989), we have been using a Biosound Genesis II echocardiograph with Doppler capability. This allows us to determine cardiac dimensions in conformance with our pre-existing data base and also to determine aortic flow by Doppler techniques

without the geometrical assumptions required by calculations based on M-mode measurements.

Results.

From 1982 through 1989, 54 crewmembers on 16 Shuttle missions volunteered to be subjects for pre- and post flight echocardiography. Typically, the ultrasound examination is performed during the operational Stand Test, a routine assessment of orthostatic function performed on all Shuttle crewmembers before launch (about ten days before flight), shortly after landing, and several days later. Continuous echocardiographic measurements were made while the crewmember was supine for five minutes, and then when the crewmember was standing upright for five minutes. The electrocardiogram was recorded continuously, and blood pressure was determined once per minute. The variables analyzed were: heart rate (HR), systolic and diastolic pressures (SBP and DBP), left ventricular end-diastolic and end-systolic dimensions, left ventricular wall thicknesses, right ventricular end-diastolic dimensions, left atrial and aortic dimensions, velocity of circumferential fiber shortening (VCF, and index of contractility), and (using Doppler) left ventricular inflow and outflow velocities. Hemodynamic parameters derived from these measurements included: mean and pulse arterial blood pressures (MAP and PP), left ventricular end-diastolic, end-systolic and stroke volume indexes (LVEDVI, LVESVI and LVSI), ejection fraction (EF), cardiac index (CI) and total peripheral resistance index (TPRI). The use of hemodynamic indexes normalizes for differences in body surface area between crewmembers. All crewmembers used the operational fluid loading protocol shortly before landing.

Briefly, the pre-Challenger data (collected only during the supine portion of the stand test) showed that left ventricular dimensions were reduced by an average of 25% after flights of 5-8 days duration; as a result, the stroke volume is similarly reduced.

Subsequently, DSO 466 allowed measurements to be made with the crewmember resting supine (actually left-lateral decubitus) and then while standing upright, during the operational stand test. Supine and standing HR were increased by 23% and 35% ($p < 0.0001$) on landing day compared to preflight. The HR response to orthostasis was also increased ($p < 0.0001$) on landing day. Supine DBP increased slightly, and supine and standing PP decreased slightly on landing day. There were no significant differences in supine or standing SBP or MAP on landing day compared to preflight. LVEDVI and LVSI were significantly decreased by 11.4% and 16.6% on landing day compared to preflight. TPRI was significantly greater in the standing position than in the supine position on all days except landing day.

In-flight measurements made on STS 51-D and STS-32 documented the decrease in left ventricular dimensions and increase in arterial pressure over the first 4-5 days in flight. Typically, late in-

flight measurements reproduced landing day measurements.

Discussion.

Cardiovascular physiological changes associated with short Space Shuttle flights include decreases in left ventricular end-diastolic volume and stroke volume indexes compensated for by increased heart rate to maintain cardiac output. Decreased LVEDVI follows the reduction in plasma volume known to occur in weightlessness.

Comparisons with echocardiographic data from the last Skylab crew and from Soviet Salyut crewmembers showed that the decrease in cardiac dimensions (and presumably function) occurs rapidly in-flight and changes only minimally after the first week in weightlessness.

These results revealed the nearly complete absence of a peripheral vascular resistance response to orthostasis on landing day after as little as 4-5 days in weightlessness. This suggests strongly that even crewmembers who are not syncopal are relying largely on their physiological reserve mechanisms (such as increased heart rate) to remain standing. If they were confronted with an emergency requiring increase performance, a successful outcome would be in doubt.



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Pulmonary Function in Microgravity: KC-135 Experience

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Presented to Joint ARC/JSC Cardiopulmonary Workshop December 5-7, 1990.

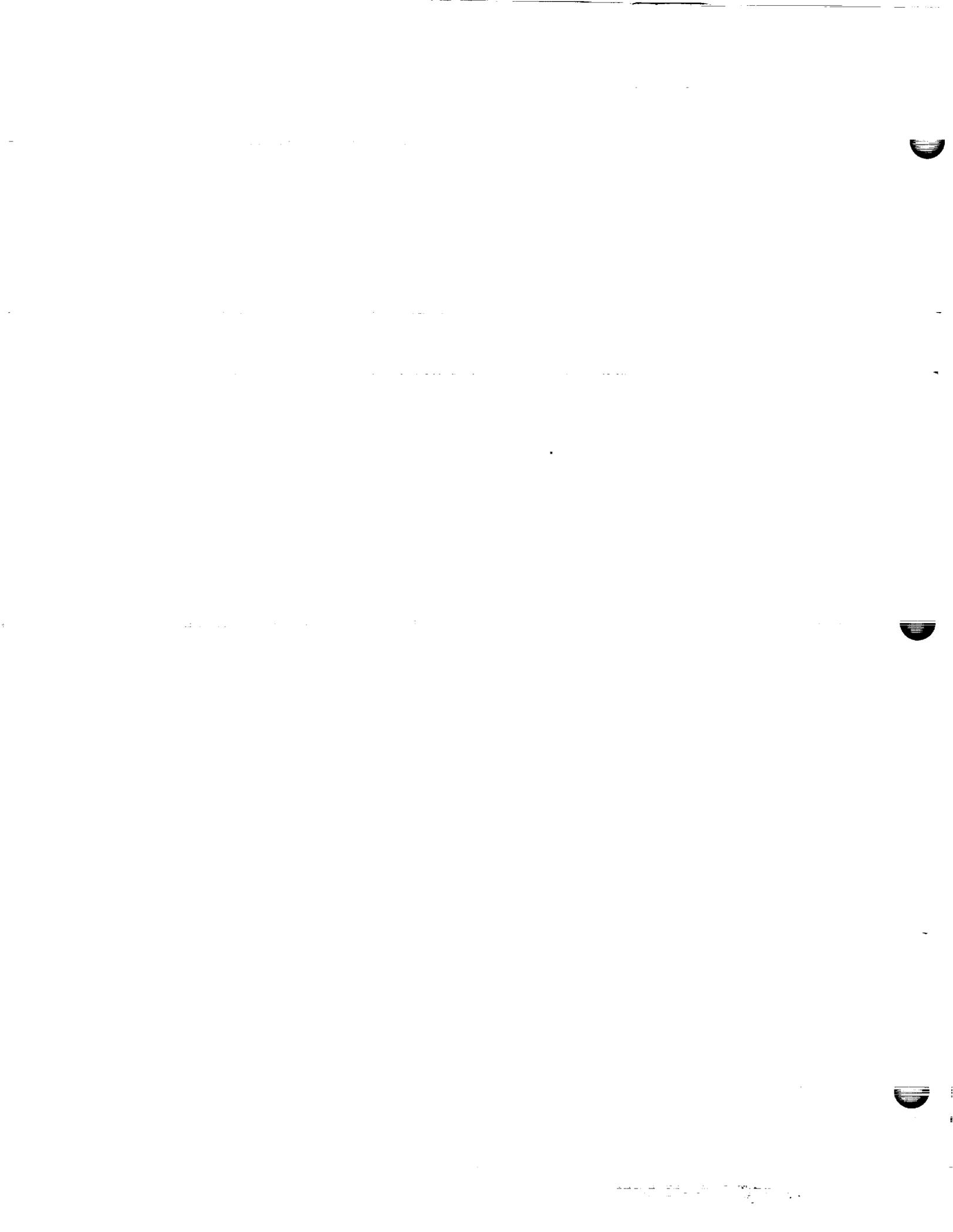
We have commenced a KC-135 program that parallels and precedes our Spacelab (SLS-1) pulmonary function experiment. Our first task was to elucidate the affect of normal gravitation on the shape of the maximum expiratory flow volume (MEFV) curve. Nine normal subjects performed multiple MEFV maneuvers at 0-G, 1-G and approximately 1.7-G. The MEFV curves for each subject were filtered, aligned at RV, and ensemble-averaged to produce an average MEFV curve for each state, allowing differences to be studied.

Most subjects showed a decrease in the FVC at 0-G, which we attribute to an increased intrathoracic blood volume. In most of these subjects, the mean lung volume associated with a given flow was lower at 0-G, over about the upper half of the vital capacity. This is similar to the change previously reported during head out immersion and is consistent with the known affect of engorgement of the lung with blood, on elastic recoil. There were also consistent but highly individual changes in the position and magnitude of detailed features of the curve, the individual patterns being similar to those previously reported on transition from the erect to the supine position. This supports the idea that the location and motion of choke points which determine the detailed individual configuration of MEFV curves, can be significantly influenced by gravitational forces, presumably via the effects of change in longitudinal tension on local airway pressure-diameter behavior and thus wave speed. (1)

We have developed a flight mass spectrometer and have commenced a study of single breath gradients in gas exchange, inert gas washouts, and rebreathing cardiac outputs and lung volumes at 0-G, 1-G, and 1.7-G. Comparison of our results with those from SLS-1 should identify the opportunities and limitations of the KC-135 as an accessible microgravity resource.

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**CENTRAL CIRCULATORY HEMODYNAMICS AS A
FUNCTION OF GRAVITATIONAL STRESS**

Latham RD, White CD, Fanton JW, Owens RW, Barber JF,
Lewkowski BE, Goff OT

from

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Most current knowledge regarding the central hemodynamic functions in man are known for the supine posture, data having been obtained during acute cardiac catheterization procedures. Very detailed descriptions of ventricular and vascular function and their coupling have been published for this posture. Unfortunately, similar sophisticated analyses from invasive data for the upright posture in man are lacking due to the unusual conditions required for study. Tilt studies in the clinical cardiac catheterization laboratory are generally reserved for electrophysiologic studies as opposed to hi-fidelity hemodynamic recordings. Limited animal studies are available which have evaluated some aspect of ventricular/vascular function for the upright posture.

The effects of gravity upon cardiovascular performance still remains to be more precisely elucidated. Certainly, gravitational stresses at extremes of human tolerance are even less well described. Man has ventured into such hostile environments as those imposing as much as 9-10 times the force of gravity on his system to other environments in which he experiences the virtual absence of gravity. To make

recommendations regarding the health and safety operational envelopes for these environments, an understanding of how these alterations in gravitational stress effect cardiovascular function and its integration with other systems becomes more critical. Investigations must, of necessity, begin with gaining insight into the "normal" physiologic response, then advance to understanding responses to mild degrees of pathophysiology.

This study focuses on an evaluation of the central hemodynamics in a nonhuman primate model to variations in gravitational states. The baboon, phylogenetically close to man was chosen as the human surrogate. The study environments selected are head-down and head-up tilt in the physiology laboratory, centrifugation to test hypergravic stress, and parabolic flights to test transient acute responses to microgravity.

Therefore, the objectives of the present study are:

- 1) Develop the chronically instrumented conscious baboon model for hemodynamic studies,
- 2) Evaluate baroreflex function, contractility, pulsatile and steady ventricular loading characteristics, and the ventricular/vascular coupling phenomenon during postural tilt changes,
- 3) Evaluate ventricular/vascular function during centrifugation (acceleration stress),
- 4) Evaluate ventricular/vascular performance during transient microgravity induced by parabolic flight,
- 5) Compare acceleration responses pre- and post- 48 hour

head-down tilt with and without fluid loading and anti-G trousers.

This project is still in its early phases. To date, we have developed the chronically instrumented baboon model. We have also begun collecting data and performing the required analyses into ventricular/vascular function. This report will summarize the surgical technique and the hardware R&D required. Additionally, some examples of data analysis will be presented. Finally, some comments on future plans and directions will be presented.

MODEL DEVELOPMENT

The previous year has been utilized to develop the implanted animal model. Prior to surgical transducer implantation the selected baboons are acclimatized to a vest or jacket and a confinement chair used for the studies. Acceptance of these devices is prerequisite for surgical implantation. Echocardiography and radionuclide angiography noninvasive studies are also performed. Finally, a pre-surgery complete right and left heart catheterization supine and 70° head-up tilt, each with aortography is performed.

All surgical subjects undergo food and water restriction for 14 hours preoperatively. Preoperative medications include ketamine HCL (10 mg/kg im) and atropine sulfate (0.04 mg/kg iv). Maintenance anesthesia is provided by fentanyl citrate (50 mcg/kg iv) and supplemented by isoflurane

administered via a cuffed endotracheal tube connected to a volume controlled ventilator.

The surgical approach is via a left intercostal thoracotomy at the 4th intercostal space. A linear incision along the long axis of the pericardium is made, followed by placement of sutures to cradle the heart away from the mediastinum. Aortic instrumentation consists of an electromagnetic flow probe placed at the root of the ascending aorta, and a Konigsberg pressure transducer placed immediately distal to the margin of the flow probe. Another flow probe is placed around the descending aorta distal to the divergence of the brachiocephalic and subclavian arteries. Atrial instrumentation consists of a kinkless catheter tubing placed in the right atrial appendage and the body of the left atrium. Left ventricular instrumentation is comprised of a Konigsberg pressure transducer placed in the apex of the left ventricle, endocardial ultrasound crystal pairs positioned in 3 axes: anterior to posterior, free wall to septum, and base to apex. Epicardial crystals have been used for several baboons, and an additional crystal pair is positioned to measure LV free wall thickness in this situation. Additional instrumentation is limited to placement of a heavy-duty silastic occluder cuff encircling the inferior vena cava immediately posterior to the right atrium.

Intraoperative medications consist of bretylium tosylate (2-5 mg/kg/min iv) diluted to 2 mg/ml with 5% Dextrose in sterile water, lidocaine HCL, and procainamide HCL. After placement of all instrumentation, the wire leads and fluid catheters are

tunneled subcutaneously to exit the skin in the interscapular region of the back, where they are secured with mattress sutures of monofilament nylon. The percutaneous wire and catheter implants are positioned so their velour wrapping is at the level of the skin, to provide a scaffold for fibroblastic ingrowth. A thoracostomy tube is positioned at the 8th intercostal space for drainage, and serial aspirations are made for 24 hours.

Postoperative care consists of intensive care monitoring until the baboons can sit up without assistance. Analgesia is provided by oxymorphone HCL (0.1 mg/kg im) or buprenorphine HCL (0.02 mg/kg im) for a period of at least 72 hours. Baboons are closely monitored for caloric intake, and are liberally supplemented with fresh fruit on a daily basis. Antibiotic therapy with cephapirin sodium (10 mg/kg im) or gentamycin (4 mg/kg im) is usually implemented due to the 3-4 hour length of the surgical procedure. The baboons are fitted with a nylon vest which contains a pocket at the interscapular lead exit site for protecting the transducer wires.

Wound healing is monitored closely at 48 hour intervals. Initial care immediately after surgery consists of using hydrogen peroxide on the exteriorized velour to remove fibrin and cellular material. Peroxide is never used for direct wound treatment. After this initial cleansing, the velour is dried with gauze and povidone iodine solution (0.1%) is placed on the velour at the percutaneous exit site. Wound care thereafter is minimal, consisting of cleaning the velour when sebaceous secretions adherent. If lead sites become erythematous or an exudate is

apparent around the velour, the exit sites are gently cleansed with normal saline and a Q-tip swab, followed by lavage with 0.1% povidone iodine or 0.1% chlorhexidene solutions, and topical placement of povidone iodine ointment for residual antimicrobial activity.

Fluid lines are flushed at 48-72 hour intervals with heparinized saline, and serial blood cell counts are performed as a monitor of clinical status. Fluid lines are then filled with heparin after the flushing procedure. When recovery is complete, chair training resumes. A repeat right and left heart catheterization is performed to calibrate transducer elements.

The hemodynamic information desired is essential to the questions being addressed and requires rather sophisticated and extensive invasive physiologic data acquisition. The methodologies necessary to obtain certain data requires surgical implantation of transducers in the heart as well as great vessels. It is obvious that ethical and moral constraints prohibit the use of human volunteers. It is also necessary to obtain data and derive parameters of cardiovascular function that may be easily extrapolated to human physiology for these operational environments. Additionally these invasive data are necessary to provide the basis for and validation of computer model constructs for ventricular/vascular function in the microgravity environment. The evaluation baroreflex responses and describing physiologic changes with intact baroreflexes is similarly important. It is well known that quadrupeds have different cardiopulmonary and arterial baroreflex responses

compared to humans or nonhuman primates phylogenetically close to man.

INSTRUMENTATION R&D

A number of R & D efforts have been required. Several blood flow transducers were evaluated, including transit-time doppler, permanent magnet EMF and standard EMF flow probes. We determined that for the time being, standard EMF was the best probe for our studies until a custom-designed pulsed doppler flow system is constructed and tested. Additionally, we have had several custom modifications made to the Konigsberg transducers. Using totally silastic transducers we have had manufactured monofilament molded special angles to the distal portions of both the aortic and LV transducer elements. The aortic cell has a 90° bend and the LV pressure cell has a 135° angle over a 1 cm distance. The distal shank of the LV transducer was reinforced. Furthermore, silastic rings are applied to the distal portions to aid with surgical implantation stabilization. A custom-designed "kinkless" silastic tubing is used for the atrial lines. This allows placement of a small 2FR Millar catheter into the LA and LV. The leads are encased with fine velour fixed with a silastic glue. This innovation has prevented the infectious complications post-op. Specialized jackets have been designed to keep the transducer leads secure and take the pressure off exit sites.

Two other R&D products relate to centrifugation. A special designed "G" chair for the animal arm of the centrifuge has been manufactured and tested. We are also having a computer

controlled signal conditioner/biotelemetry system unit designed and assembled by NASA ARC. This unit will interface with our transducer elements and allow us to collect data remotely from the centrifuge arm. The unit may be used for study of other environments with difficult accessibility.

DATA ANALYSIS:

Data are passed through antialiasing filters (corner frequency of 100 Hz, 30 Db/octave roll-off) and digitized offline at a sample rate of 500 Hz using a Concurrent Computer (Model SLS-6300, real-time Unix 5.0) and LabWorkbench commercial software. Signals are then post-processed using both custom-designed and commercial (DaDisp, DSP Corporation) software.

Five consecutive beats are averaged for LV and Ao pressures and ascending aortic flow (ASC FLOW). Averaged beats are used to measure basic pressure and flow parameters. The first derivative of LV pressure are taken and the peak positive & peak negative values averaged for 10 beats are then determined. Average pressure and flow for simultaneous beats are submitted to Fourier analysis. Harmonics of pressure are divided by corresponding harmonics for flow to derive the aortic input impedance, and the phase angles of flow are subtracted from corresponding phase angles of pressure. The fifth to the fifteenth harmonic values are averaged to determine the characteristic impedance, Z_c (See Figs 1,2).

These same averaged beats of pressure and flow are also submitted to a 3-element Windkessel analog model of the

circulation. This model uses a Marquardt fitting algorithm to fit a calculated flow from input pressure to a measured flow. With an optimal fit, the model returns estimates for Z_c , peripheral resistance (R_p), and systemic arterial compliance (C), see Figs 3,4. These values are then compared to conventional calculations of these variables using a linear regression analysis, Figs 5-8.

A hydraulic occluder cuff is used to decrease pressures transiently. Simultaneous LV pressure and volume are submitted to a time-varying elastance model to determine the end-systolic pressure volume relationship (ESPVR). At least 7 beats and a minimum fall in systolic pressure of 10% of baseline are required for analysis. Any runs with ectopic beats are discarded. The ESPVR is fitted with a linear regression and the slope taken as the estimate of ventricular elastance, an index of contractile function, Figs 9,10. The volume intercept, V_o , is determined as well.

RESULTS

Fourteen baboons have been enrolled in some phase of model development. There has been 1 surgical death in the eldest cull animal and there have been 2 post-op hemorrhages. The hemorrhages were due to a transit-time doppler probe in one case and the aortic transducer (pressure cell) in another. Since incorporating silastic rings on the implanted transducers and using silastic electromagnetic flow probes these problems have not been seen. One animal suffered sudden death, presumed

arrhythmic. One fluid line became nonfunctional prior to use of silastic rings.

The head-down tilt studies will be conducted with the primates under sedation to alleviate anxiety. Initial trials with low dose midazolam (Versed) infusion have been performed. Unlike humans, the baboon is more resistant to the sedative pharmacological effects of this new agent such that intermittent Ketamine injections are required. Future studies will incorporate Ketamine infusion at a lower dose level.

Initial supine and tilt data are under analysis. A combination of commercially available signal analysis software (DaDisp, DSP Corporation) and custom programmed software are used to analyze data.

Some very preliminary results suggest that the pulsatile load of the baboon is not significantly changed as a function of posture changes, in contrast to peripheral resistance which increases. We previously found compliance decreased with the upright tilt under sedation. In six of the baboons' data thus analyzed the compliance values tended to be unchanged but were quite variable.

In a comparison of model vs. conventional calculations of parameters of LV loading we found that these were well correlated for both supine and head-up tilt conditions. The Z_c , however, was less well correlated with the upright posture than R_p . Compliance values tend to be overestimated by the 3-element Windkessel when compared to C determined from the RC time (τ) of aortic diastolic pressure decay.

Pre and post-ketamine studies are also under analysis. Finally, we have found in preliminary analyses that contractility by the ESPVR appears to be unchanged with 70° head-up tilt. Analyses are still in progress and in too premature status to apply statistical tools. Some examples of the types of analysis being performed are included.

CONCLUSION

We have demonstrated that we can instrument a nonhuman primate, the baboon, for sophisticated invasive hemodynamic evaluation of the cardiovascular system. We are establishing a noninvasive studies protocol such that these data may be compared with invasive findings. This year the tilt studies will be completed, as well as the centrifugation and parabolic flight tests. Data analysis is ongoing in parallel fashion. We further hope to extend development of some vascular access technology. We also expect delivery of a new cardiovascular signal conditioner/biotelemetry system for testing and evaluation. This system is scheduled to include a new custom-designed doppler probe which will provide flow velocity as well as vessel dimension.

ACKNOWLEDGEMENTS: This work has been supported in part by a grant to Dr. Latham from the USAF Office of Scientific Research, #2312/W7 and from NASA, #T-3685R. The authors are grateful to the extensive work effort given by staff of the Veterinary Research Support Branch of USAF School of Aerospace Medicine.

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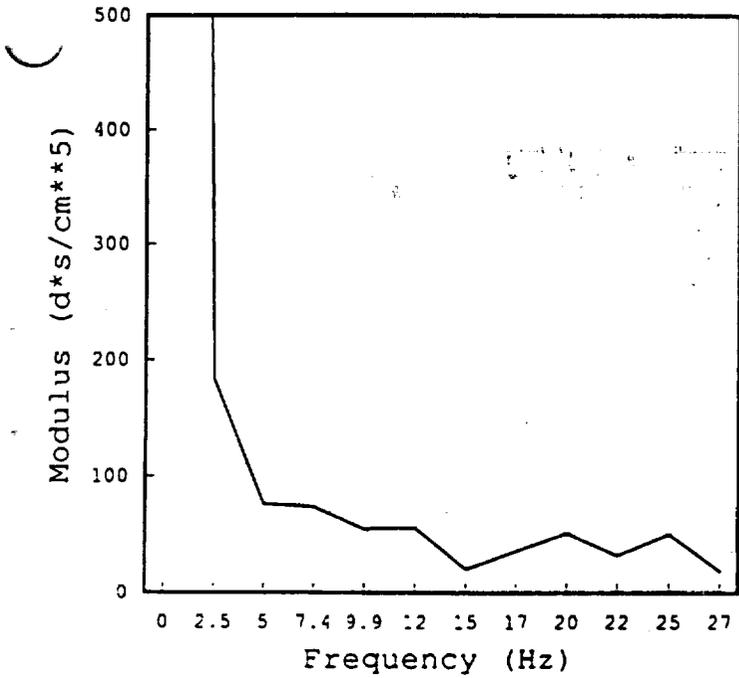
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A108 Aortic Input Impedance

SUPINE



A108 Aortic Input Impedance

UPRIGHT

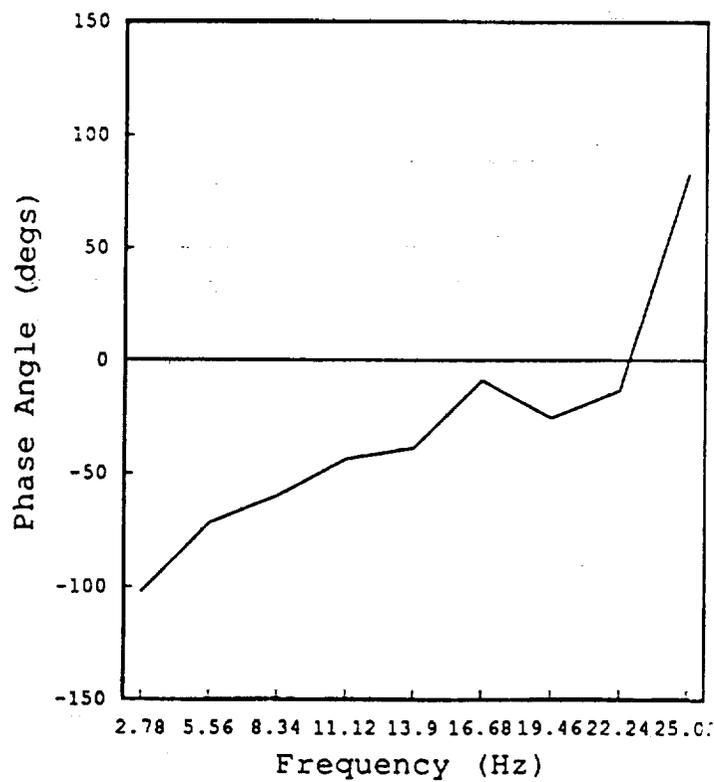
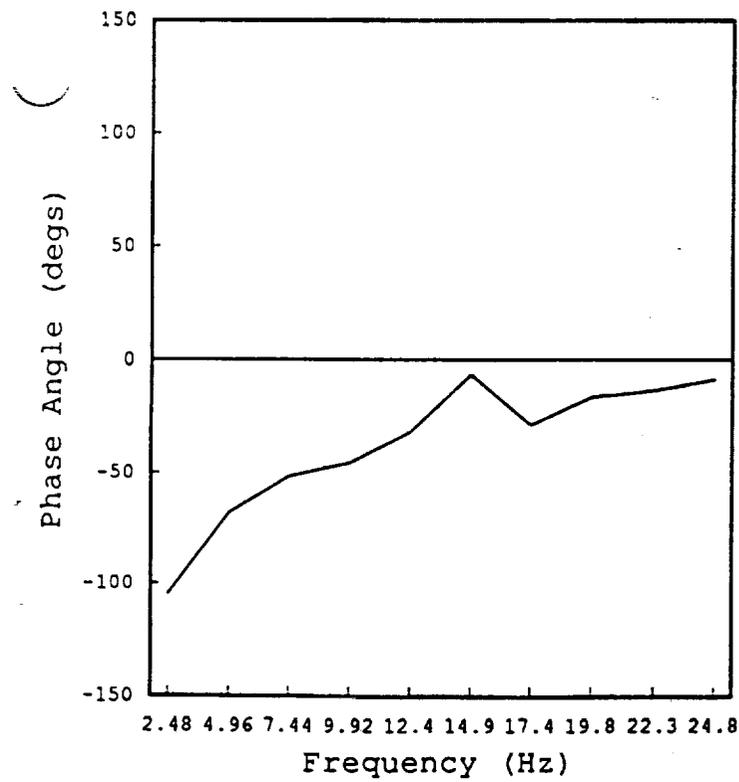
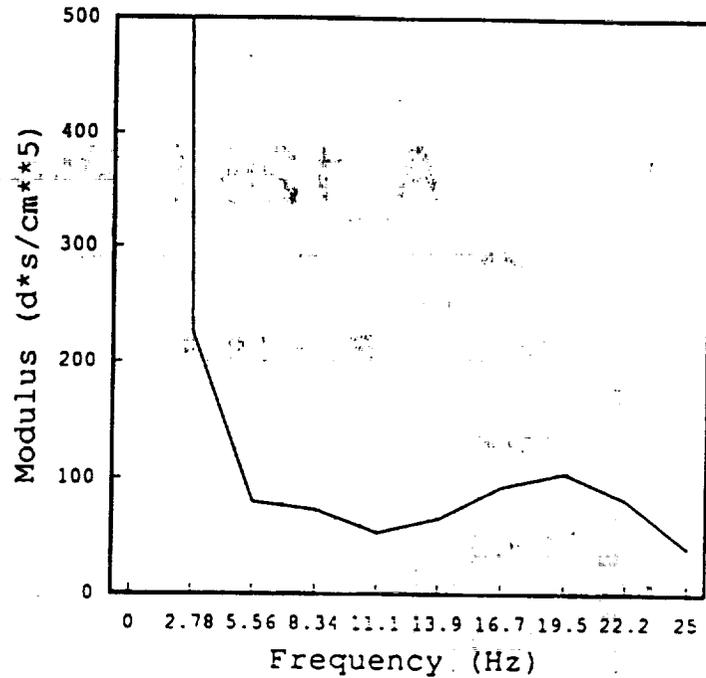


Fig. 1

A_126 UPRIGHT IMPEDANCE

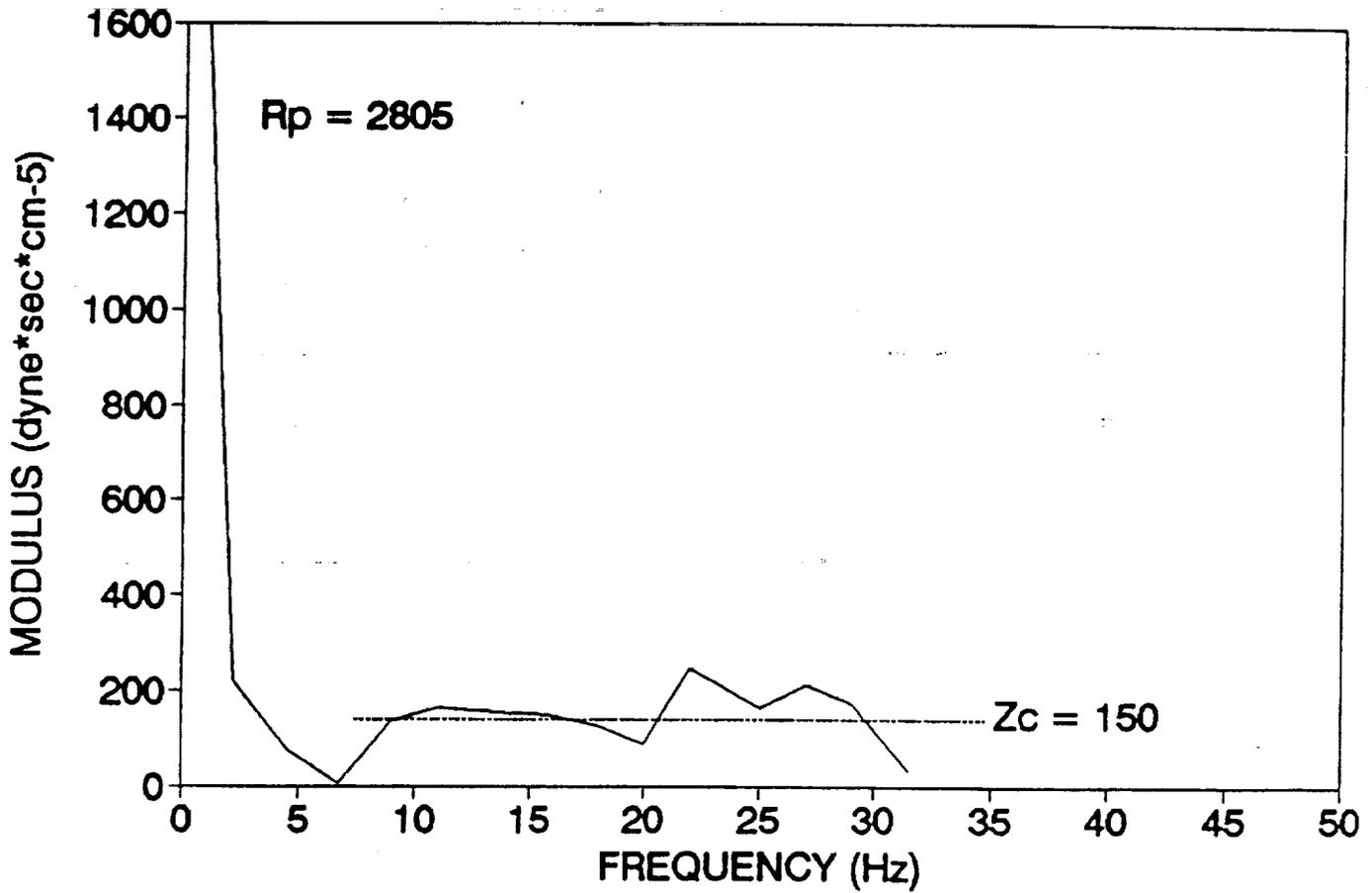
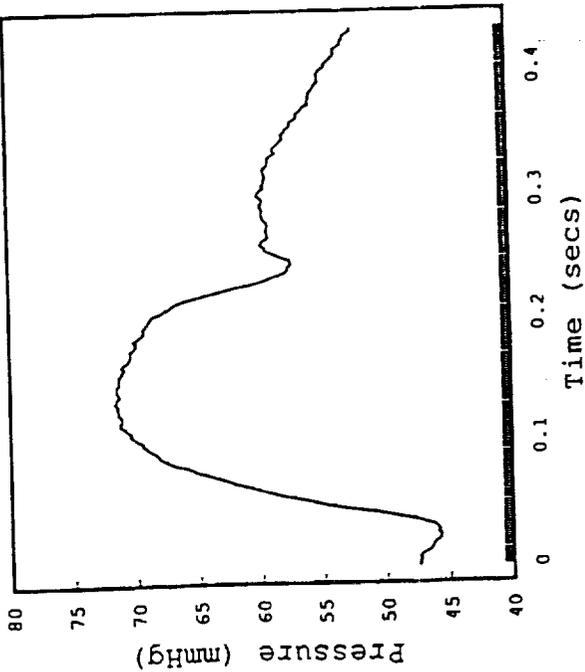
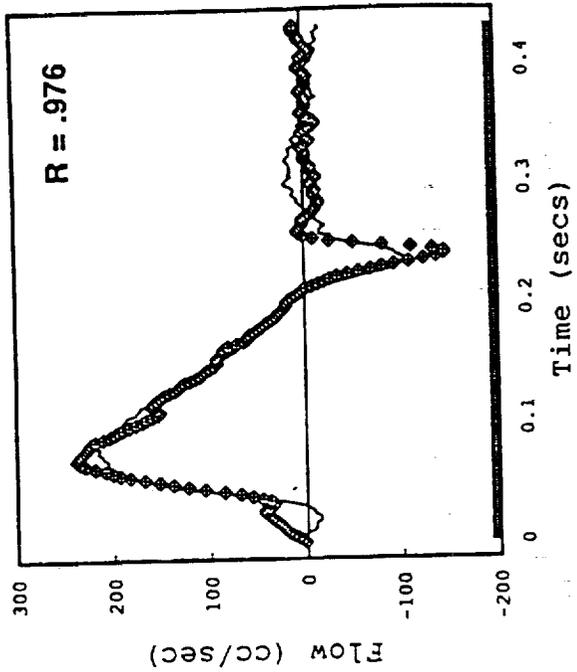


Fig 2

A106 Aortic Pressure - Upright
Time of Cardiac Cycle = .43 secs



A106 Flow - Upright
Time of Cardiac Cycle = .43 secs



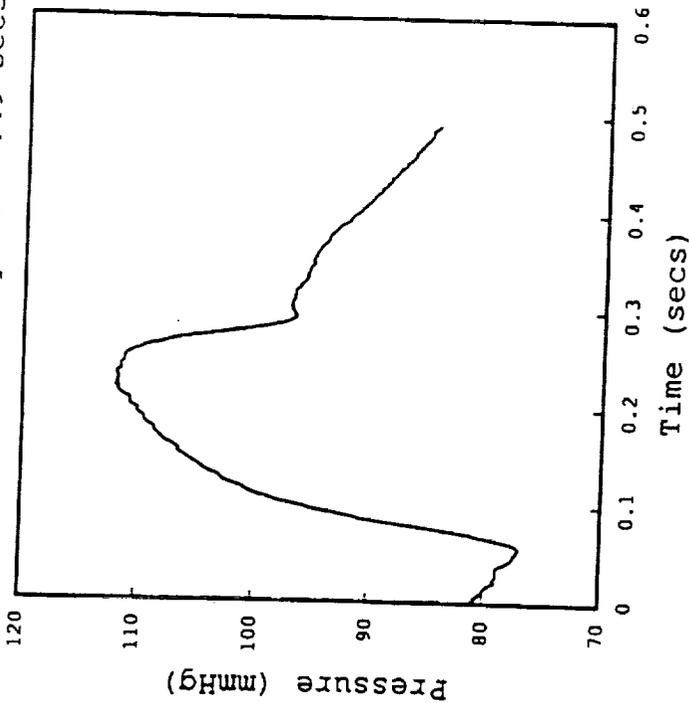
— Fitted Flow ♦ Measured Flow

PARAMETER FINAL VALUE COEFFICIENT VARIANCE

Z_c	76.43 d*s*cm ⁵	.0230
R	2475 d*s*cm ⁵	.0440
C	1.85 cc/mmHg	.0202

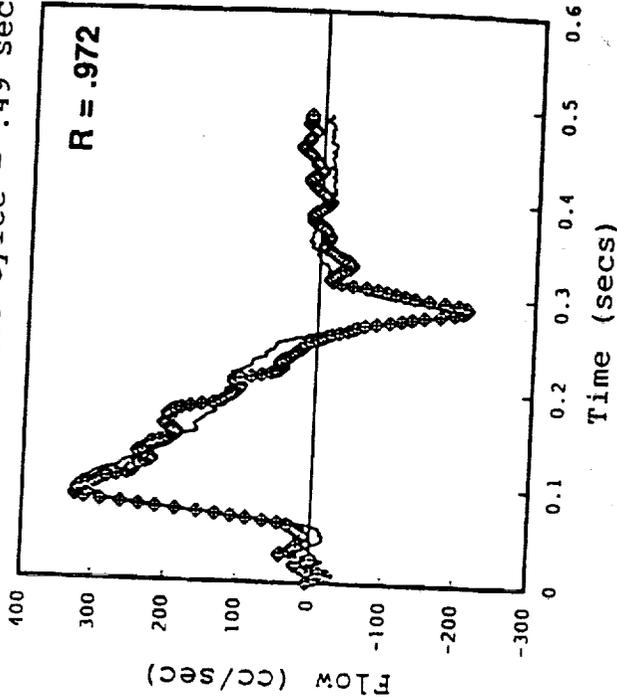
A106 Aortic Pressure - Supine

Time of Cardiac Cycle = .49 secs



A106 Flow - Supine

Time of Cardiac Cycle = .49 secs



— Fitted Flow ♦ Measured Flow

<u>PARAMETER</u>	<u>FINAL VALUE</u>
Z_c	43.21 $d^*s^*cm^{-5}$
R	2668 $d^*s^*cm^{-5}$
C	1.83 cc/mmHg

COEFFICIENT VARIANCE

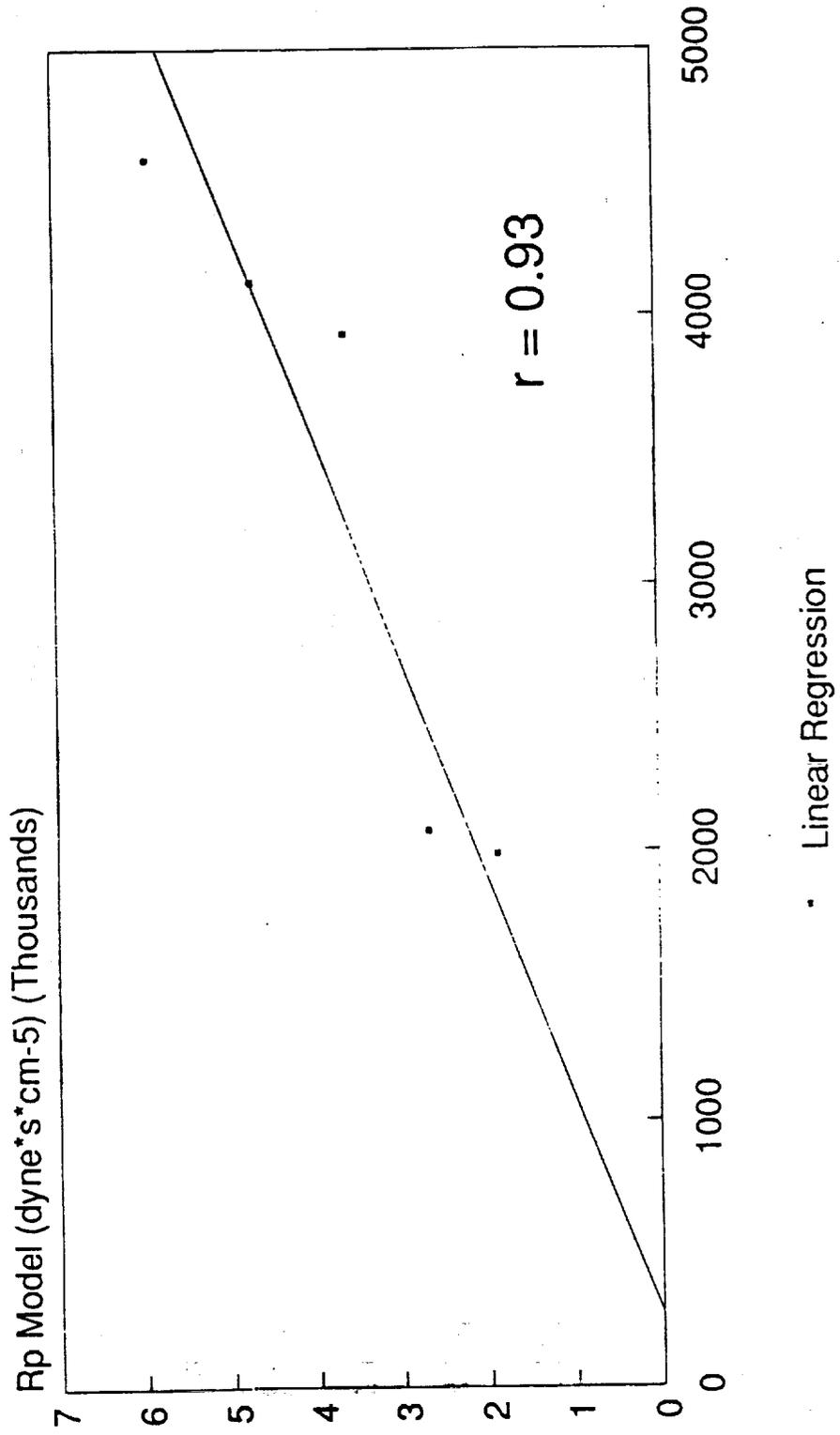
.0312

.0387

.0176

Fig 4

Supine Rp Comparison (Model vs. Calculated)



Upright Rp Comparison (Model vs. Calculated)

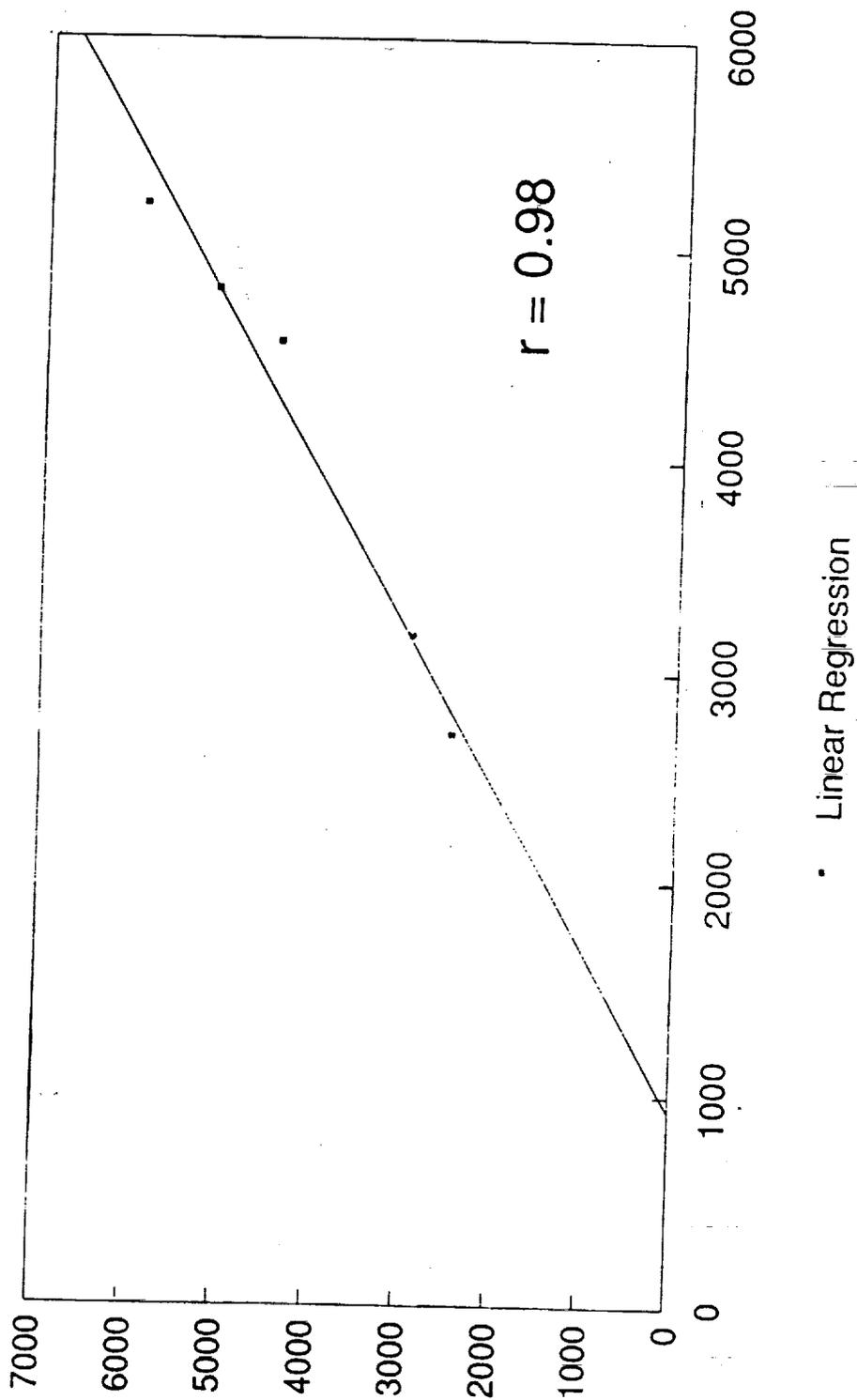
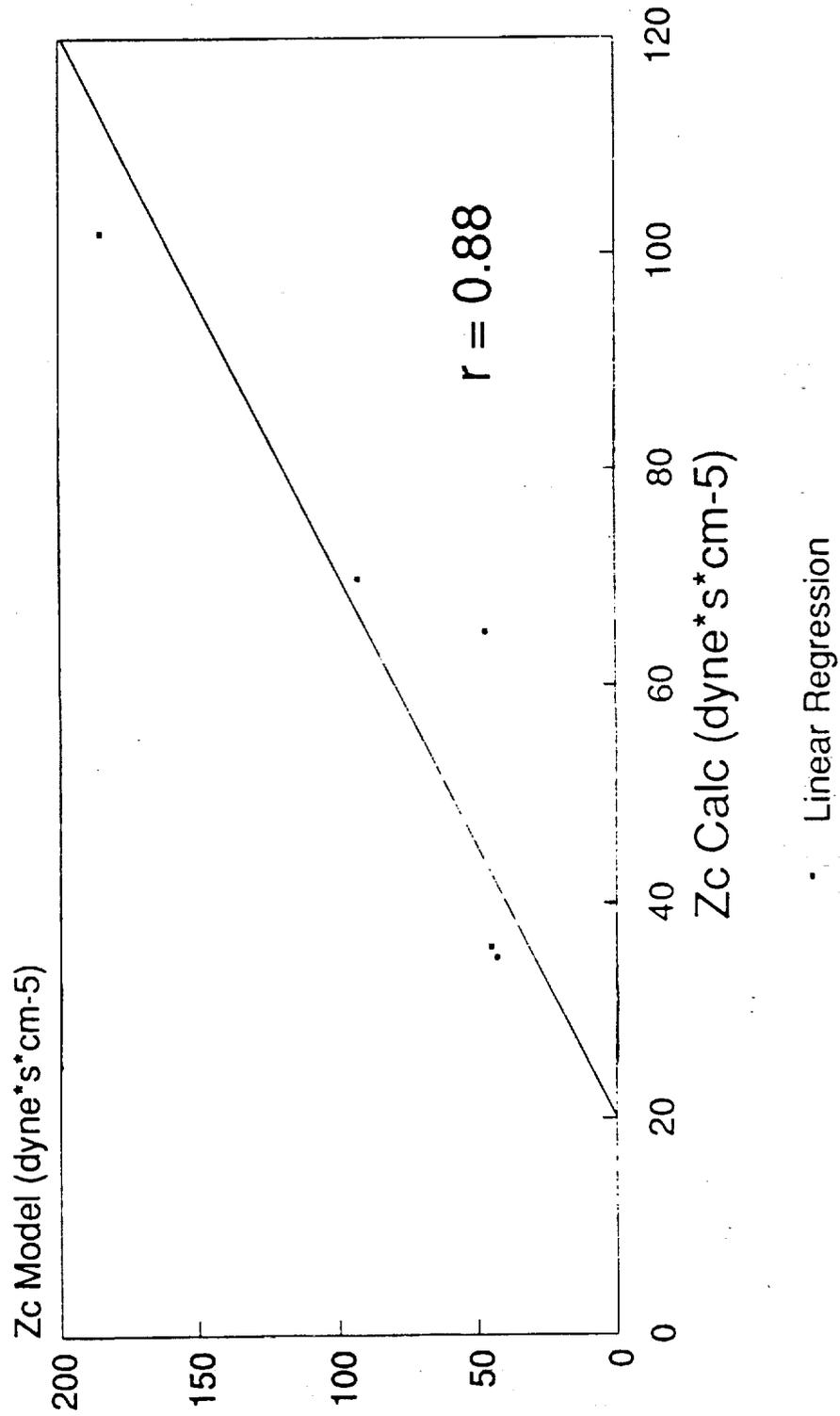


Fig.6

Supine Zc Comparison (Model vs Calculated)



Upright Zc Comparison (Model vs Calculated)

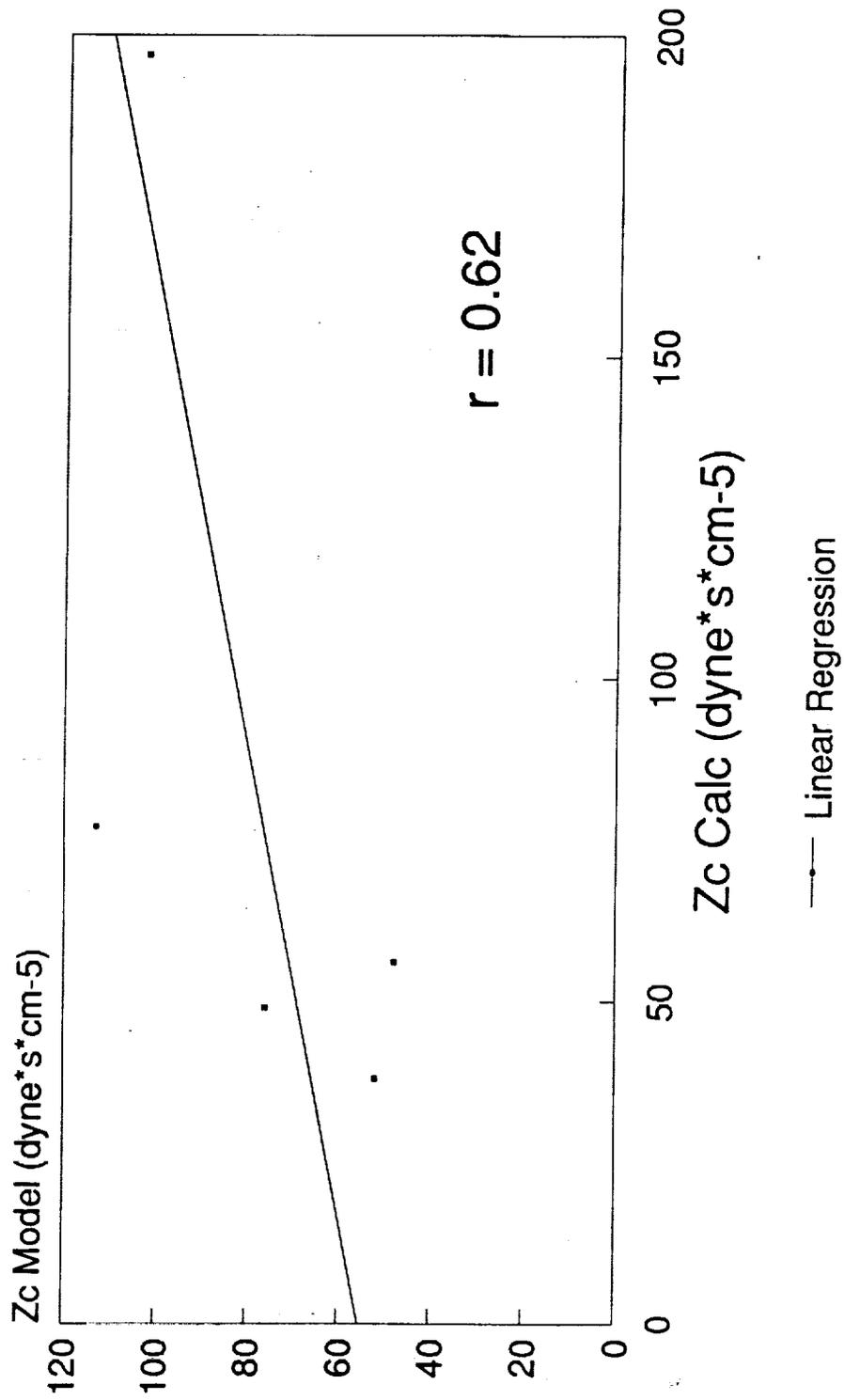


Fig. 8

A_126 SUPINE ESPVR

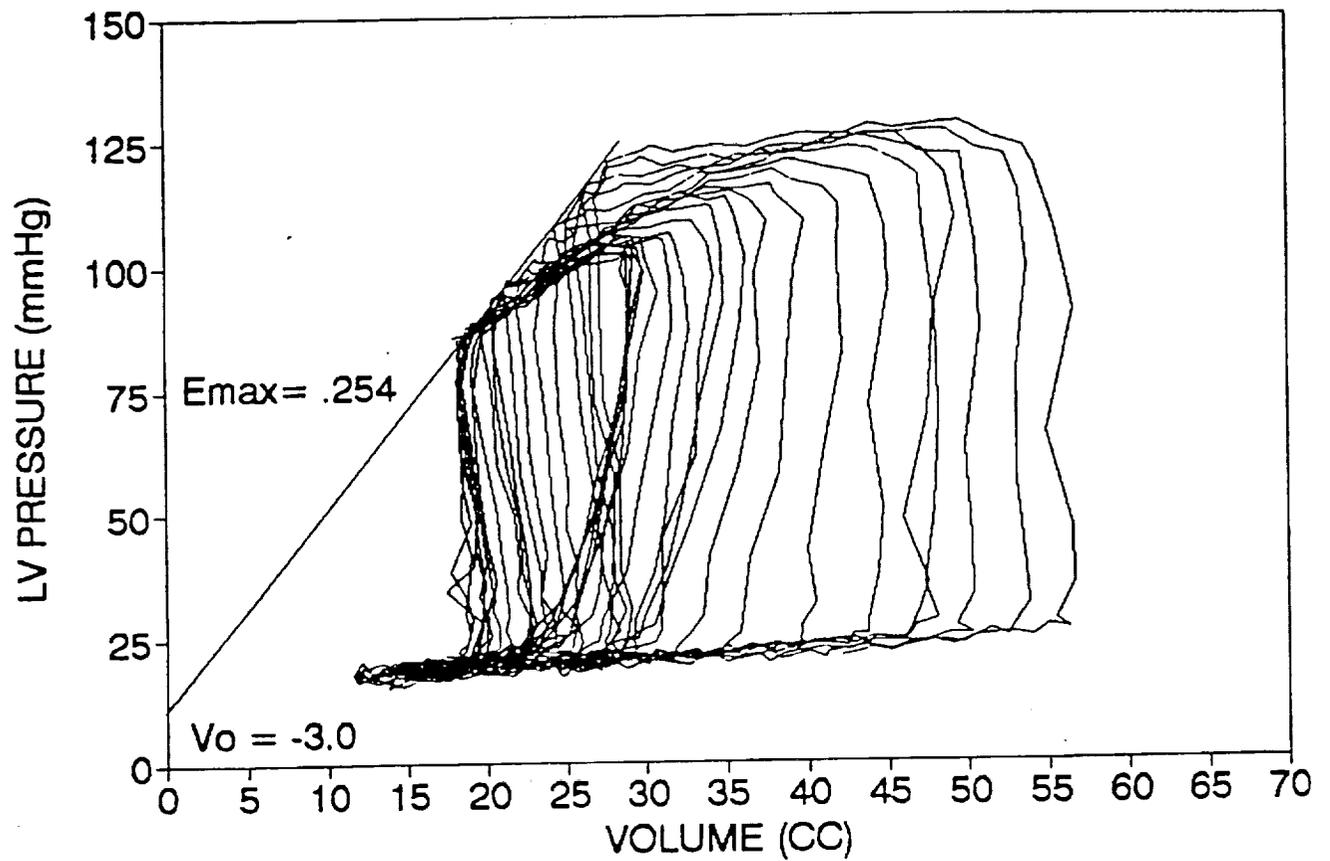


Fig. 9

A_126 ESPVR - UPRIGHT

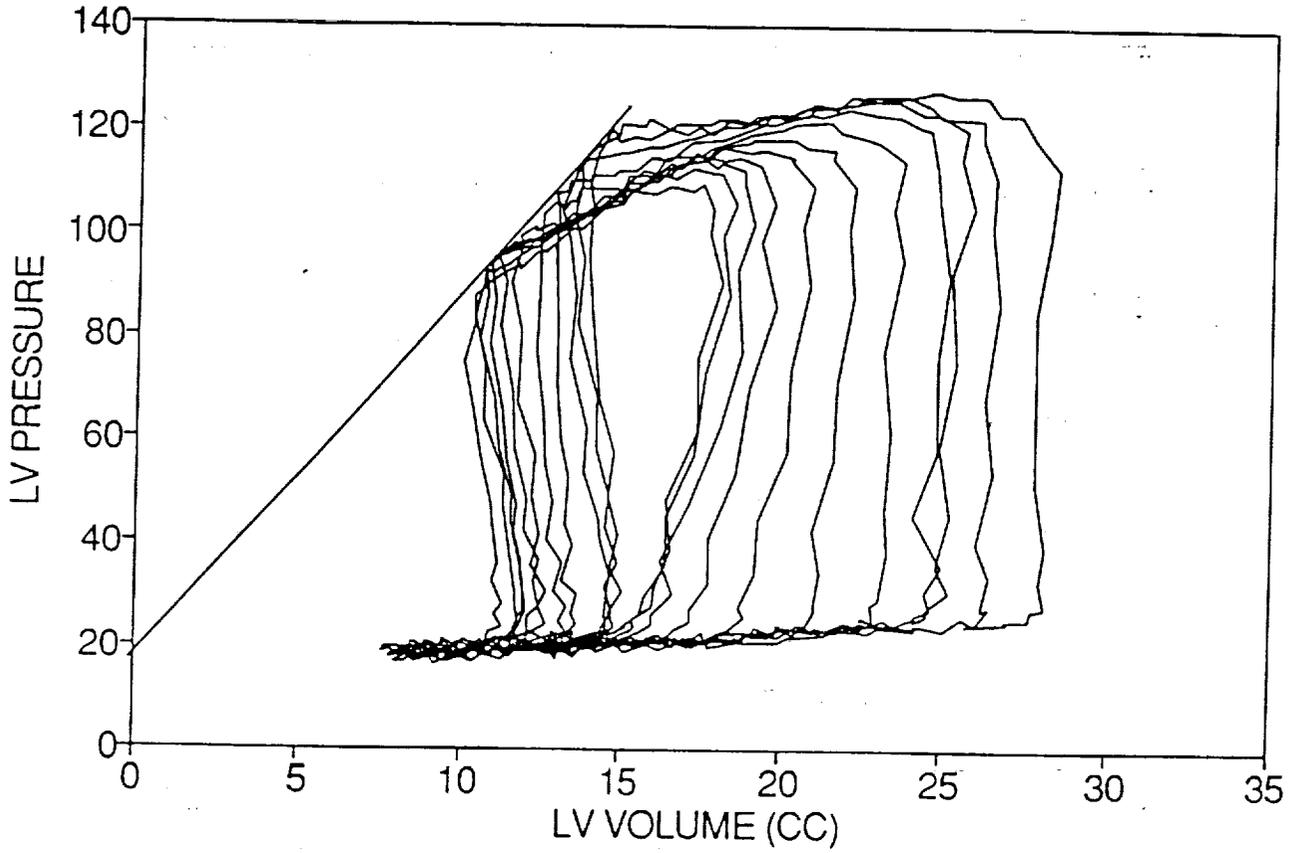


Fig . 10

"Glycerol-induced Hyperhydration"

by

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Maintenance of euhydration is essential for maximum work performance. Environments which induce hypohydration reduce plasma volume and cardiovascular performance progressively declines as does work capacity (Fortney et al., 1981). Hyperhydration prior to exposure to dehydrating environments appears to be a potential countermeasure to the debilitating effects of hypohydration. The extravascular fluid space, being the largest fluid compartment in the body, is the most logical space by which significant hyperhydration can be accomplished. Volume and osmotic receptors in the vascular space result in physiological responses which counteract hyperhydration.

Our hypothesis is that glycerol-induced hyperhydration (GIH) can accomplish extravascular fluid expansion because of the high solubility of glycerol in lipid and aqueous media. A hypertonic solution of glycerol is rapidly absorbed from the gastrointestinal tract, results in mild increases in plasma osmolality and is distributed to 65% of the body mass (Lin, 1977). A large volume of water ingested within minutes after glycerol intake results in increased total body water because of the osmotic action and distribution of the glycerol (Riedesel et al. 1987). The resulting expanded extravascular fluid space can act as a reservoir to maintain plasma volume during exposure to dehydrating environments. We have conducted experiments to be presented later which demonstrate advantages of GIH for subjects exercising in a hot environment (Lyons et al. 1990). The fluid shifts associated with exposure to microgravity result in increased urine production and is another example of an environment which induces hypohydration. Our goal is

to demonstrate that GIH will facilitate maintenance of euhydration and cardiovascular performance during space flight and upon return to a 1 g environment.

The experimental protocol for the GIH experiments involved the subjects checking into the hospital at 1900 h and drinking one liter of water at 2000 h to ensure euhydration. No food or water after midnight and at 0715 h a catheter was placed in a cubital vein. At 0730 subjects drank glycerol, 1 g/kg, in orange juice, 3.4 ml/kg. In the first study subjects drank 1.5 liter of 0.1% NaCl during the next two hours and 300 ml of 0.1% NaCl during the third hour. The control run involved the same protocol including the same volume of fluid intake except without glycerol either 48 h prior to or after the experimental run.

The glycerol intake markedly decreased the urine volumes (Figure 1). Another experiment with the same protocol involved 1.5, 1.0 and 0.5 g/kg glycerol intake. The serum glycerol values varied with the glycerol dosages (Figure 2). The 0.5 g/kg dosage did not result in significant changes in water retention. The amount of water retained after 4 h was similar for the 1.0 and 1.5 g/kg glycerol dosages. Therefore subsequent studies have involved the 1.0 g/kg dosage. Apparently the rates of glycerol catabolism and excretion are dose dependent such that the 1.5 g/kg doesn't result in a greater water retention than the 1.0 g/kg. The mean volume of water retained after 4 h has been 10.2 ml/kg (S.E. = 0.5) when subjects ingested 1 g/kg glycerol and drank 1.5 to 1.8 liter of water within 1 to 3 h of time zero. It is also of interest to note that whereas the retention of water was for 4 h the increased plasma osmolality following the glycerol intake had returned to control values within 2 h (Figure 3). This indicates that glycerol and water have moved from the plasma to the intracellular space and the water retained is intracellular.

The next study asked the question, does the GIH provide an advantage for subjects exercising in the heat? The subjects were heat acclimated prior to participation. At 48-h or longer intervals the 6 men and 2 women participated in random order in three separate 4.5-h

experiments. Each experiment included a 1.5-h bout of exercise at 60% of maximum oxygen consumption in a moderate dry heat (42° C). One experiment involved limited fluid intake (5.4 ml/kg) which was similar to ad libitum fluid intake in pilot studies under similar conditions. The other two experiments involved ingesting a large volume of fluid in an attempt to hyperhydrate the subjects prior to the exercise. One attempt at hyperhydration involved ingestion of glycerol (1 g/kg) in orange juice plus a large volume of water (21.4 ml/kg) at time zero plus additional glycerol (0.1g/kg) in orange juice at hourly intervals after the first two hours. The subjects drank 50 ml of water at hourly intervals after the second hour (Table 1). The second involved drinking the same volume of water and orange juice (Table 1).

Table 1. Fluid Ingestion Regimens

	<u>Large Fluid Intake</u>		<u>Limited Fluid Intake</u>
	<u>Glycerol</u>	<u>No Glycerol</u>	
Time Zero	1 g GLY/kg in 3.3 ml/kg OJ	3.3 ml/kg OJ	3.3 ml/kg OJ
Within 1 h	21.4 ml/kg of water	21.4 ml/kg of water	
Each hour after 2 h	0.1 g GLY/kg in 0.1 ml/kg OJ plus 50 ml water	0.1 ml/kg OJ plus 50 ml water	50 ml water
Total Fluid intake in 4 h	28.4 ml/kg	28.4 ml/kg	5.4 ml/kg

GLY = glycerol, OJ = orange juice.

The mean accumulated sweat output for the 90 min of exercise was 1450 ± 160 ml with the glycerol ingestion compared to $1130 \text{ ml} \pm 100$ ml following just the large volume of water ($P < 0.05$) (Figure 4). During the 60- to 90-min interval of exercise in the heat, the glycerol ingestion resulted in a mean sweat output of 700 ± 90 ml and the large volume of water without glycerol at time zero resulted in a mean volume of $470 \text{ ml} \pm 40$ ml ($P < 0.01$). This difference amounted to a 33% increase in sweat following the pre-exercise GIH.

After 30 min of exercise, the mean rectal temperature was lower ($P < 0.05$) following glycerol ingestion when compared to the other two fluid regimens. The limited fluid intake and large volume of water at time zero resulted in similar mean rectal temperatures during the 90 min of exercise (Figure 5).

The next experiment was designed to determine whether or not we could extend the GIH to 48 h. This experiment involved 7 male subjects and once again at time zero they ingested a large volume of fluid (21.4 ml/kg) either with or without glycerol, 1 g/kg. On both the control and glycerol intake days, the total water plus orange juice intake over the 48-h period was 50.8 ml/kg. On days they ingested glycerol, the glycerol intake was 1 g/kg at 0700 h, 0.10 g/kg at 0800 h, 0.303 g/kg at 1000 h and 1100 h, and 0.379 g/kg at 1400 h and 1600 h. Previous studies and pilot experiments had indicated that these rates of water and glycerol intake would provide GIH for 48 h. The fluid intake and urine volumes are presented in figure 6.

Our current studies involve cardiovascular responses to lower body negative pressure (LBNP) prior to and after bedrest with and without GIH. Prior to bedrest subjects undergo a maximum oxygen consumption test (VO_2max), underwater weighing to determine percent body fat and three pre-syncope LBNP tests. The 4 male subjects had VO_2max values greater than 40 ml $\text{O}_2/\text{kg}/\text{min}$ and less than 20% body fat. The LBNP box involved a seal with a kayak skirt at the

waist and a foot rest rather than a bicycle saddle for support of the subject. During the LBNP tests the electrocardiogram was recorded continuously and the arterial blood pressures were recorded manually at 1-min intervals. The reproducibility of the LBNP responses is illustrated in figure 7.

The standard LBNP test conducted on days -1, 4, 5, 6, & 7 of the bedrest involved 5 min at each level of negative pressure, -10, -20, -30, -40, -50, and -60 mm Hg. Glycerol and fluid intake was administered on days 5 and 6 of the bedrest as described above for the 48-h GIH. The heart rate, systolic and diastolic blood pressure were analyzed by analysis of multiple variance and the Dunnett's test for multiple comparison of treatments.

Subjects had less tolerance for LBNP on bedrest day 4 when compared to pre-bedrest (day -1), ($p < 0.05$). The heart rate and blood pressure responses on bedrest days 4, 5, 6, and 7 were similar ($p > 0.05$). The GIH on days 5 and 6 did not improve cardiovascular responses to the standard LBNP test. This may have been expected because the standard LBNP test is only of 30 min duration. In the heat stress experiment described in the previous paragraphs, the increased sweating after GIH was greater during the 30 to 60-min and 60 to 90-min intervals than during the 0 to 30-min interval of heat stress.

Experiments for the immediate future will involve bedrest, a "soak" procedure (2-h exposure to cycling LBNP, 1 min to -60 and 1 min to zero LBNP). The "soak" procedure will be conducted 1.5 h after the GIH on day 5 of the bedrest. Pre-syncope LBNP will be conducted on days -1, 4, 5, and 6 of the bedrest. These experiments will also include monitoring of cranial blood flow by the transcranial doppler technique during all LBNP tests.

Additional future studies will include measurements of ^{14}C tagged glycerol and tritiated water in the laboratory rat after GIH to determine the distribution of glycerol and water among various body fluid compartments. We are also interested in testing the extent to which we can

increase the amount of hyperhydration by changing the timing and dosages of glycerol and water intake.

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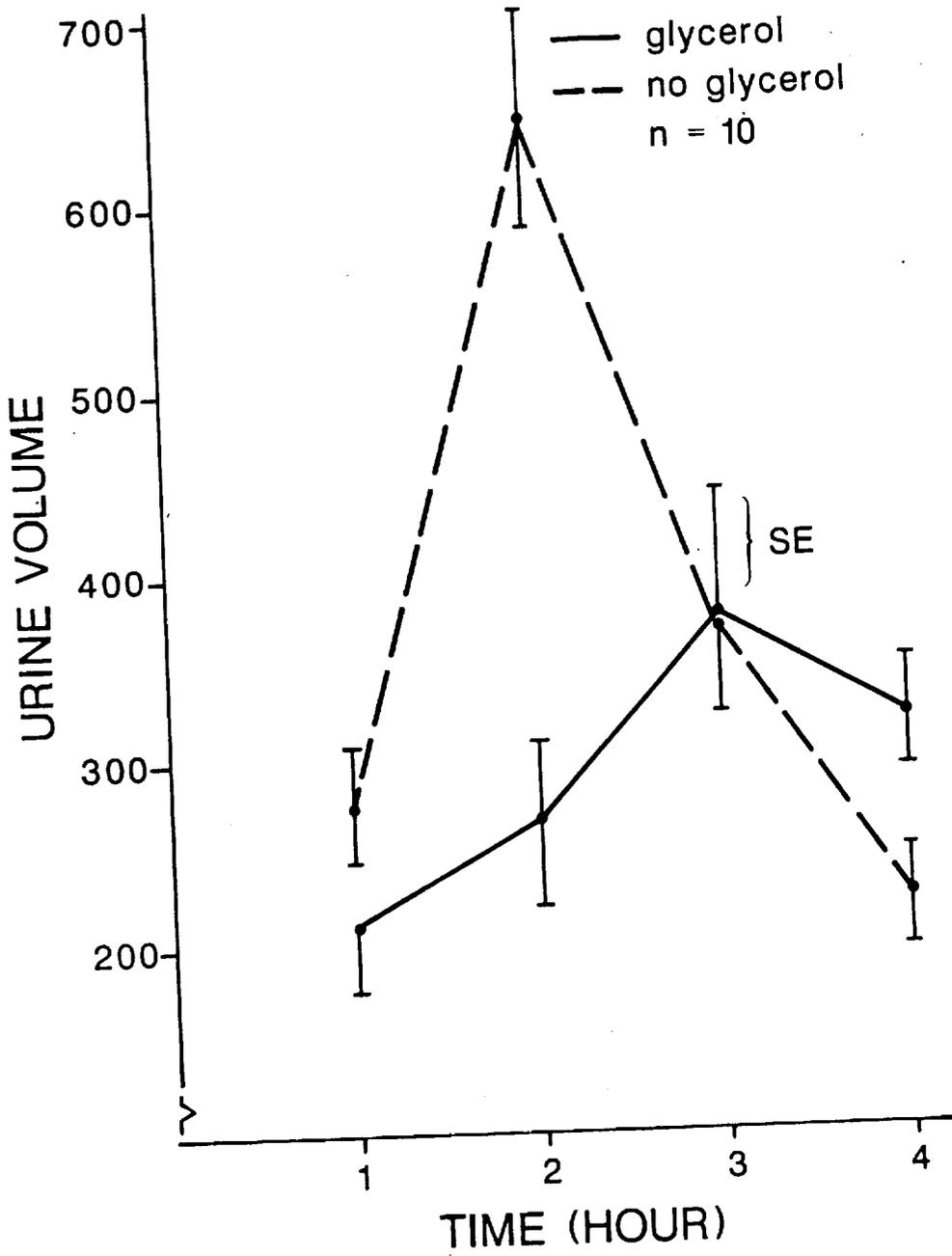


Figure 1. Mean volume of urine voided at each hour (ingestion of 0.1% NaCl, 21.4 ml/kg, during first two hours and 300 ml during third hour).

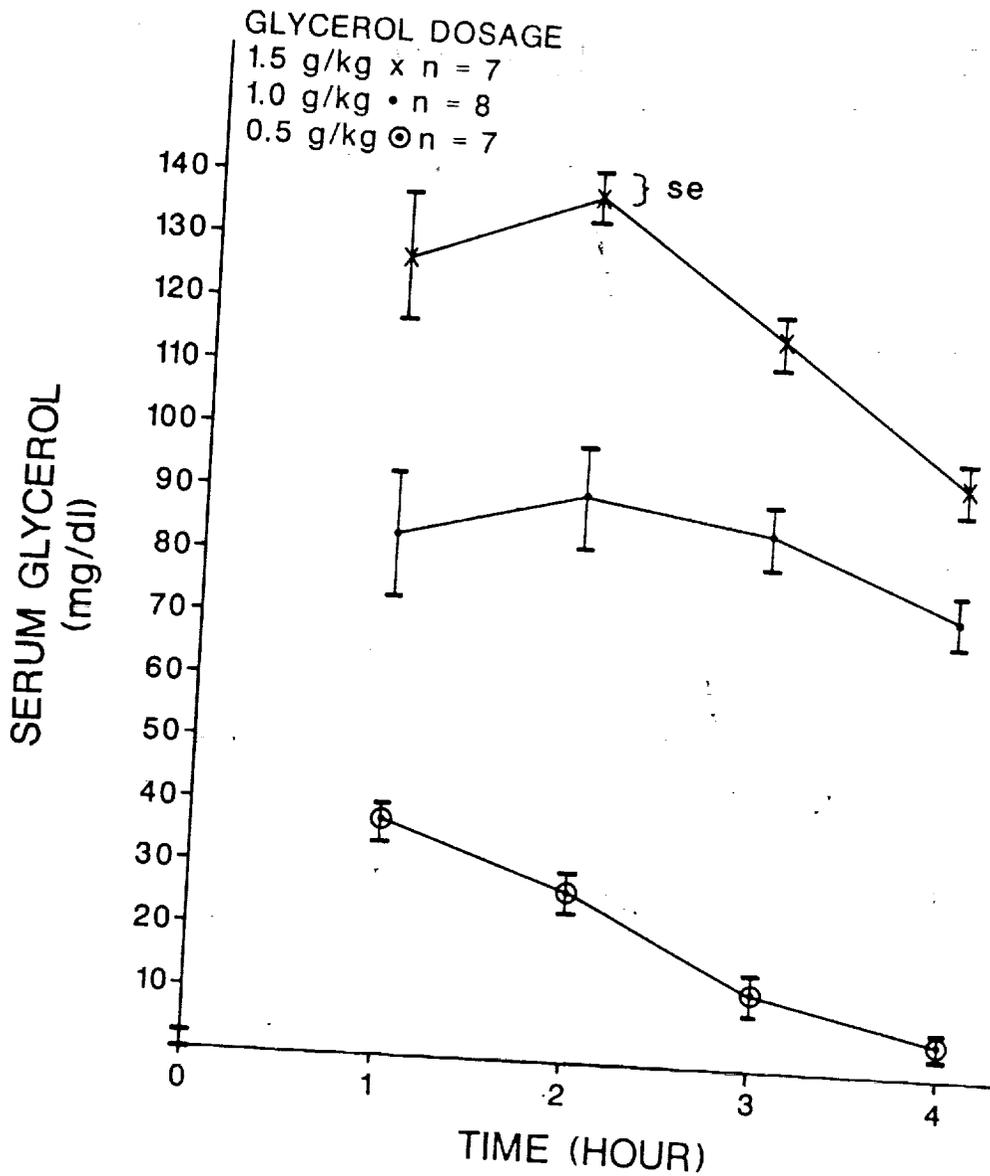


Figure 2. Serum glycerol after glycerol ingestion (ingestion of 0.1% NaCl, 21.4 ml/kg, during first 40 min.).

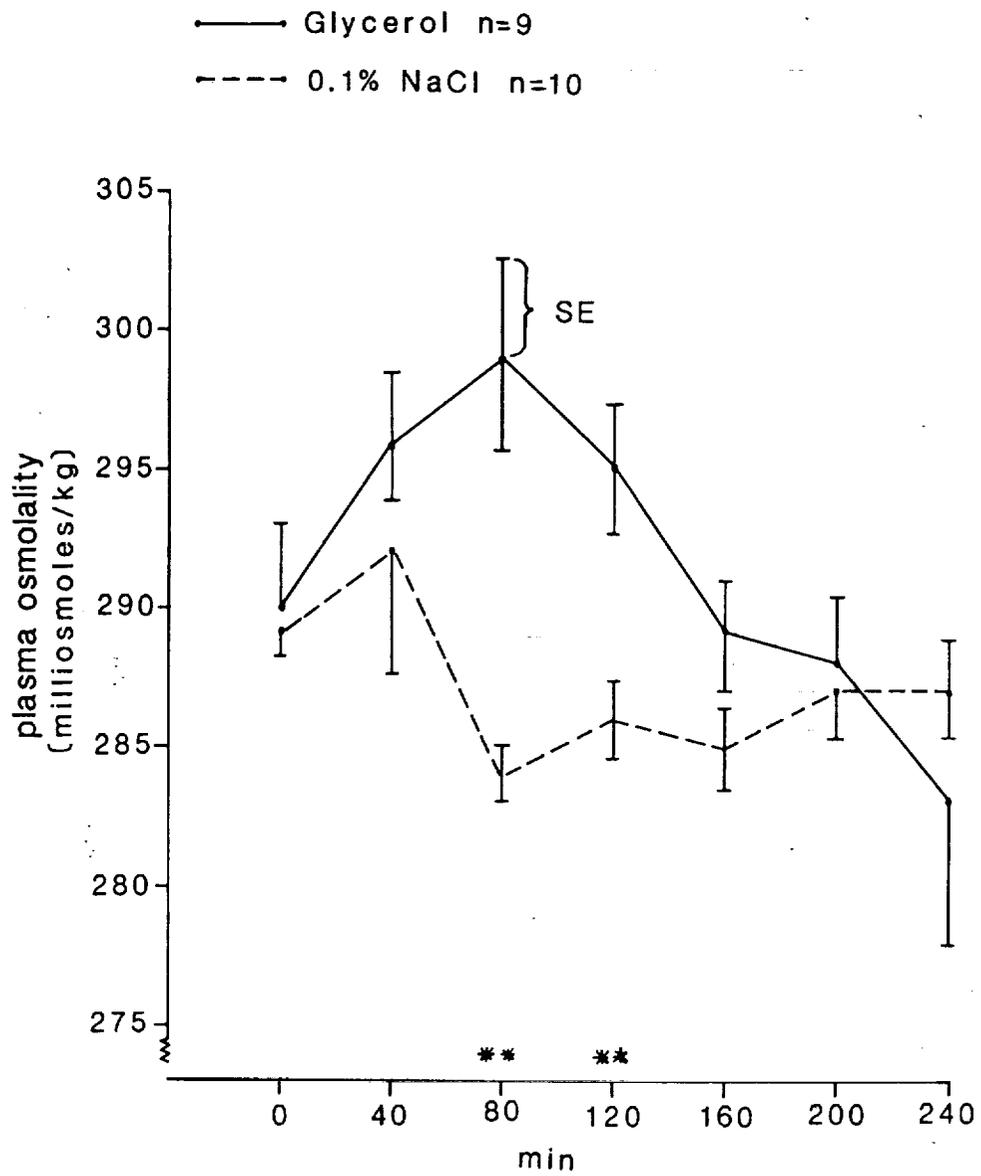


Figure 3. Plasma Osmolality (same fluid ingestion as Figure 2).

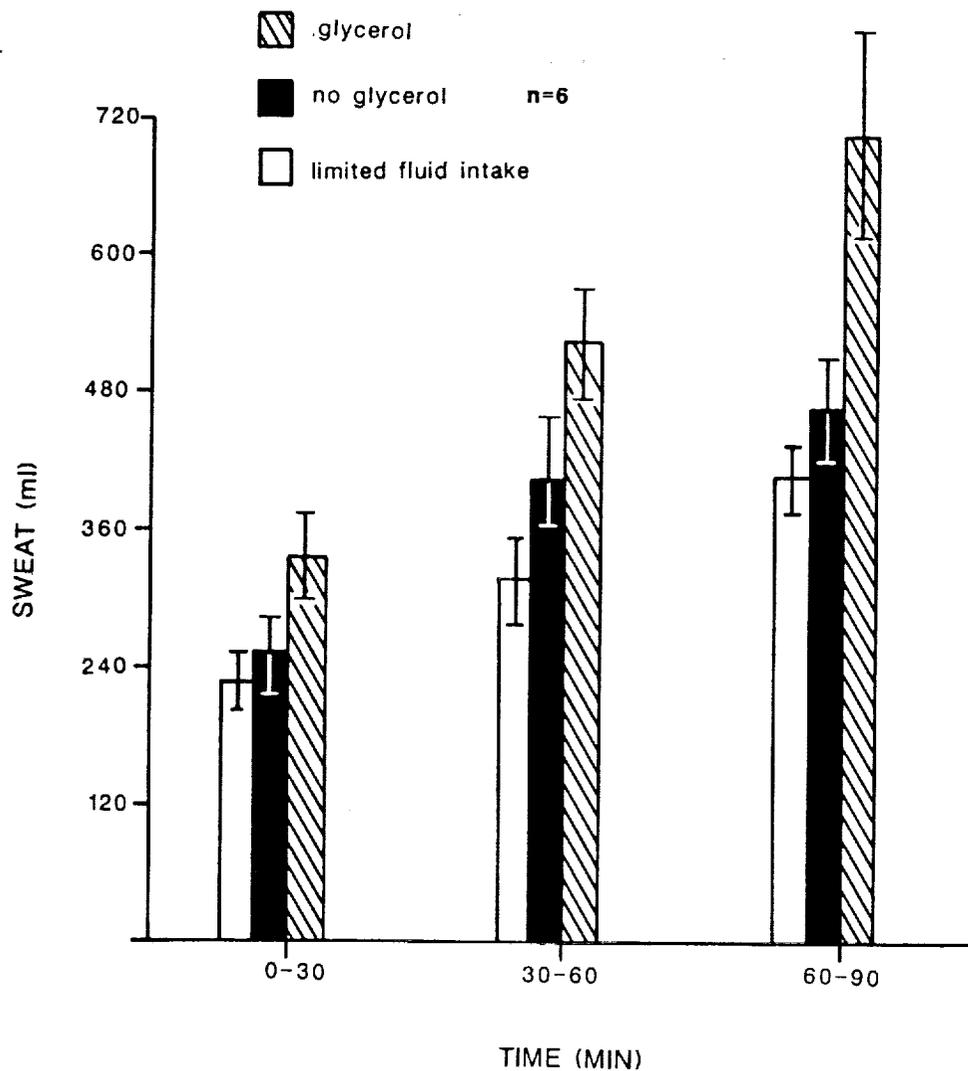


Figure 4. Mean sweat output for six subjects at 30-min. intervals during moderate exercise (60% VO_2max) in the heat (42°C, 100 m/min. air velocity, 25% relative humidity). Significance between glycerol and other two fluid regimens at 30-60 min. ($p < 0.05$) and 60-90 min. ($p < 0.01$). Fluid regimen same as Table 1.

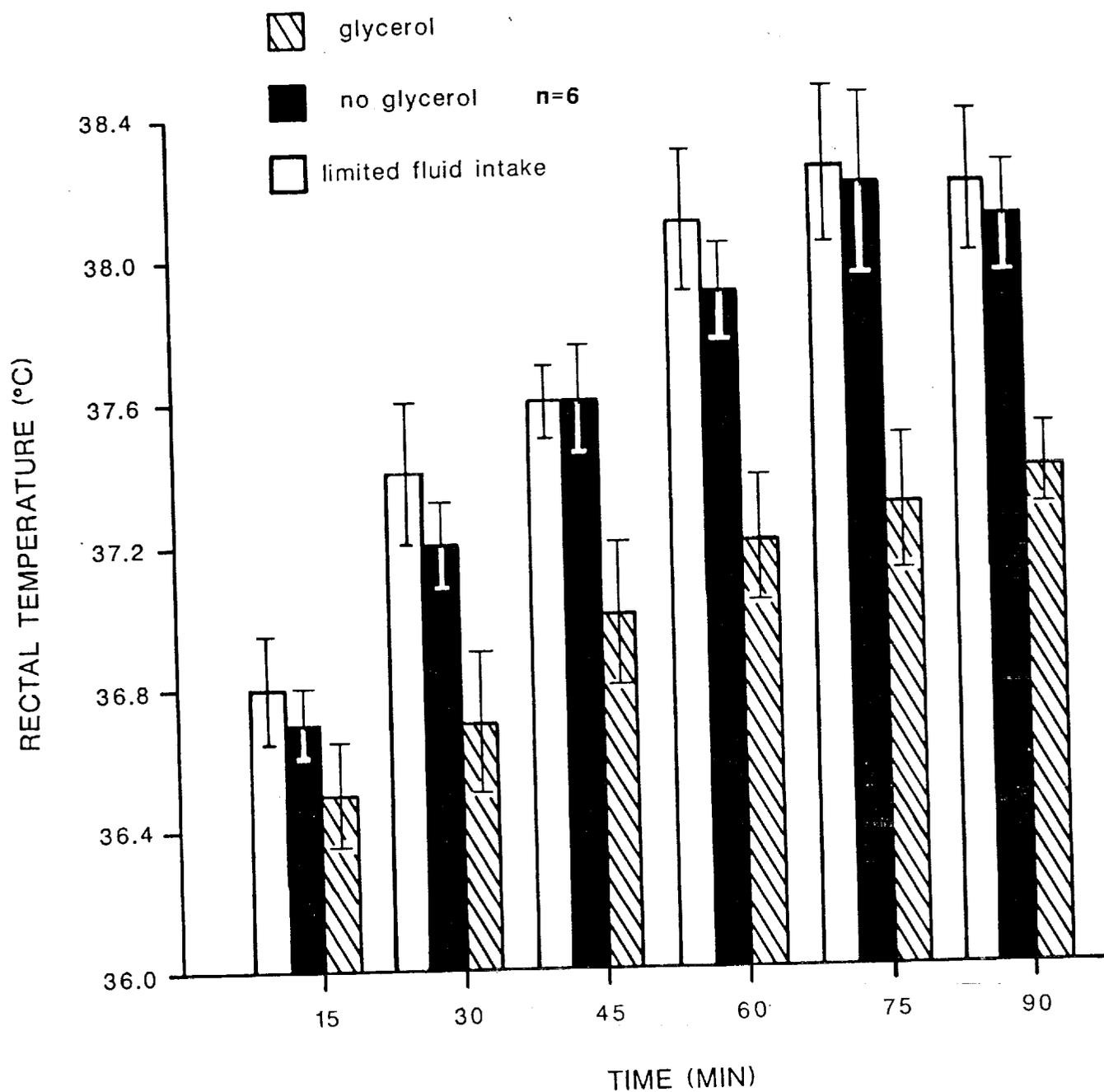


Figure 5. Mean rectal temperature at 15-min. intervals during moderate exercise (60% VO_2max) in the heat (42°C, 100 m/min. air velocity, 25% relative humidity). Significance between glycerol and other two fluid regimens after 15-min. interval ($p < 0.01$). Fluid regimen same as Table 1.

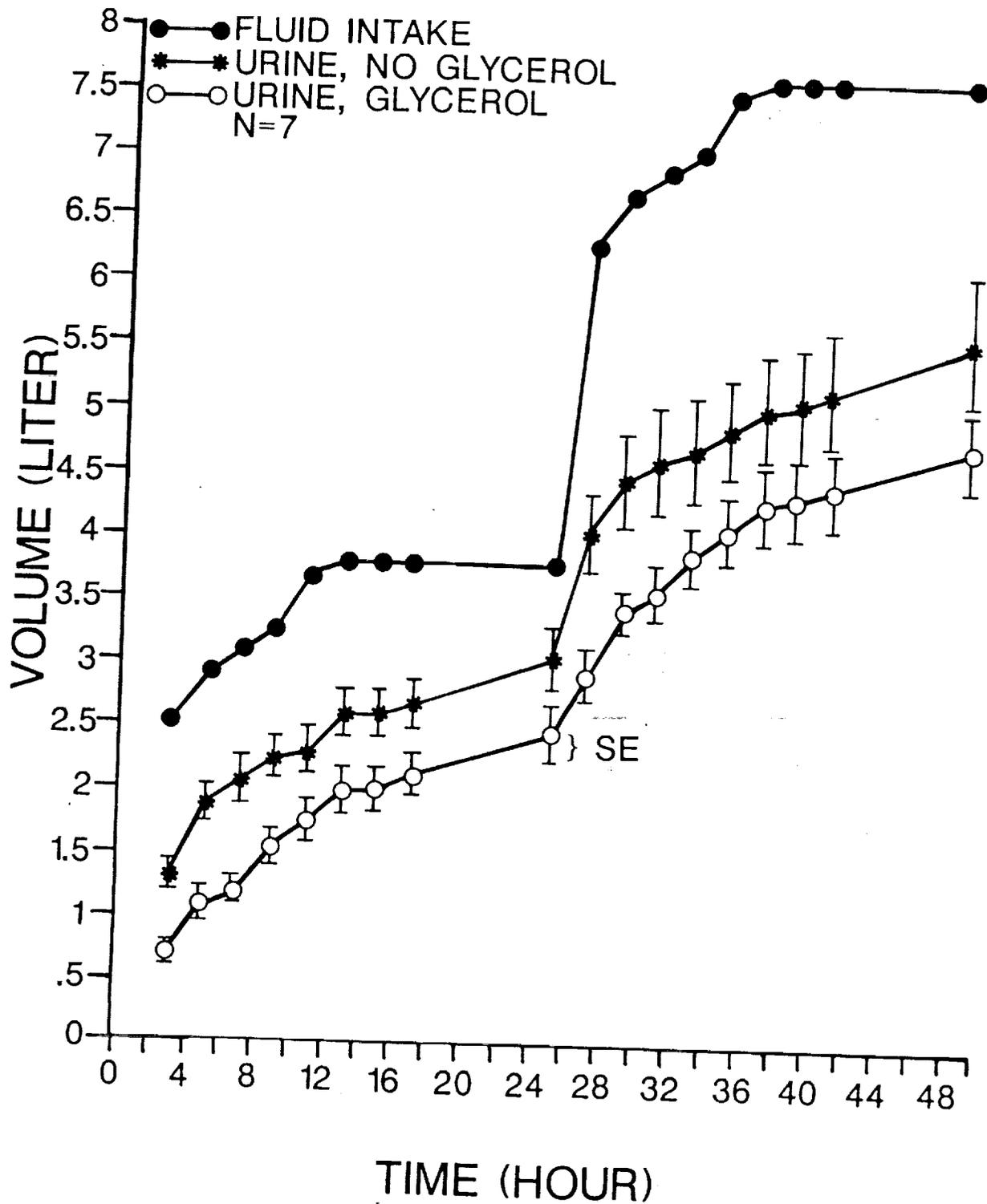


Figure 6. Accumulated fluid intake and urine output with and without glycerol. Significance in urine output between glycerol and no glycerol was $p < 0.05$ at each hour.

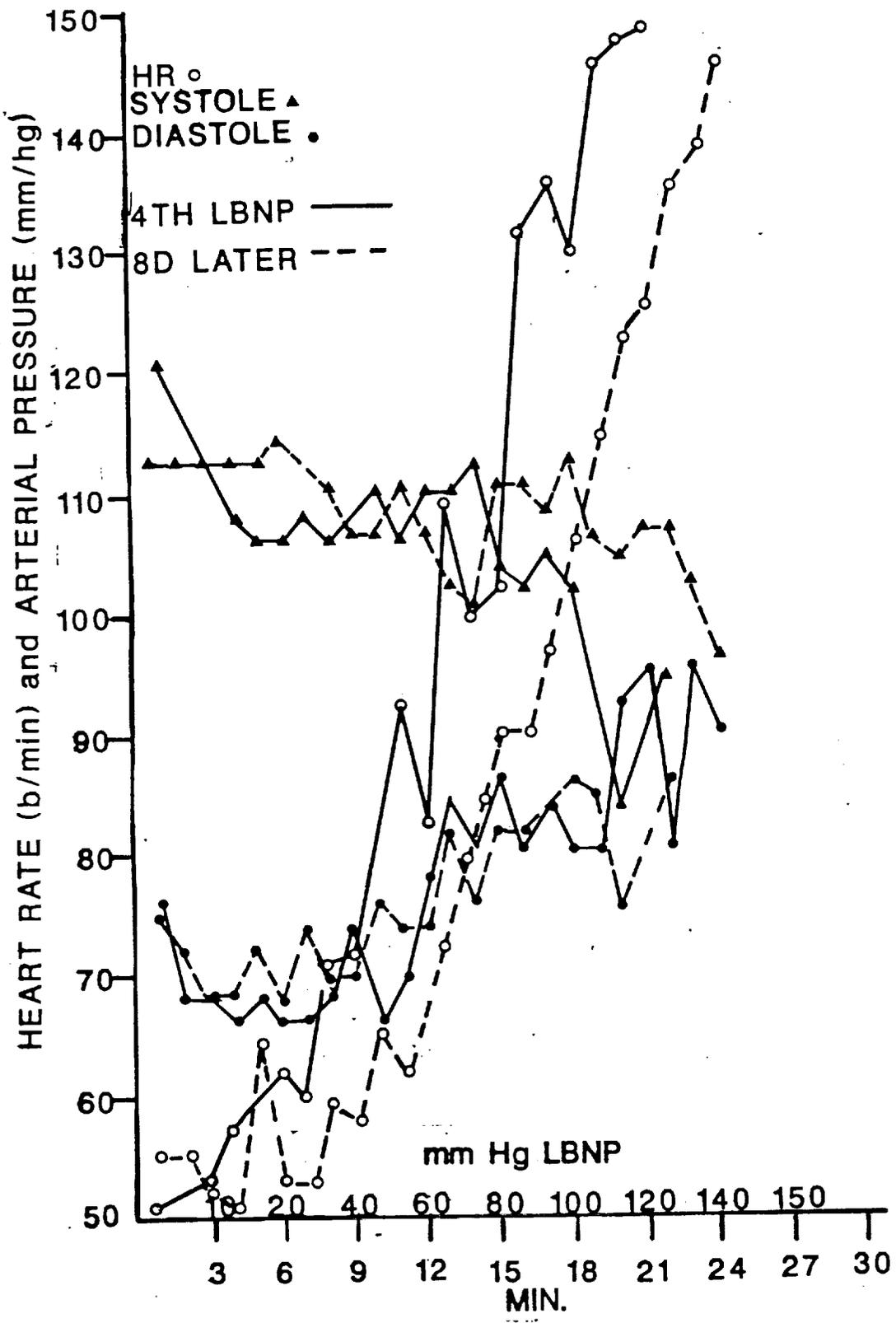


Figure 7. Heart rate and blood pressure responses to lower body negative pressure for a given subject at the same time of day on separate days.

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SPECTRAL ANALYSIS OF RESTING CARDIOVASCULAR VARIABLES AND RESPONSES
TO OSCILLATORY LBNP BEFORE AND AFTER 6° HEAD DOWN BEDREST

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SUMMARY

A major focus of our research program is to develop noninvasive procedures for determining changes in cardiovascular function associated with the null gravity environment. We define "changes in cardiovascular function" to be 1) the result of the regulatory system operating at values different from 'normal' but with an overall control system basically unchanged by the null gravity exposure or 2) the result of operating with a control system that has significantly different regulatory characteristics after an exposure.

To this end, we have used a model of weightlessness that consisted of exposing humans to 2 hrs. in the launch position, followed by 20 hrs. of 6° head down bedrest. Our principal objective was to use this model to measure cardiovascular responses to the 6° head down bedrest protocol and to develop the most sensitive "systems identification" procedure for indicating change. A second objective, related to future experiments, is to use the procedure in combination with experiments designed to determine the degree to which a regulatory pathway has been altered and to determine the mechanisms responsible for the changes.

From the viewpoint of systems identification, we recently have focused on the use of oscillatory lower body negative pressure (LBNP) and spectral analysis of the resulting cardiovascular responses before and after the bedrest protocol mentioned above. The application of this approach to the bedrest study was prompted by a systematically designed series of experiments that have previously demonstrated its effectiveness in several areas. In the past, we have used oscillatory (sinusoidal) acceleration or LBNP as provocative tests to determine:

1. The overall frequency response characteristics of integrated cardiovascular regulation in response to blood volume shifts induced by sinusoidal whole-body acceleration in dogs (Knapp, et al. 1978, 1982).
2. The relative contributions (amplitude and time of response) of both cardiac and peripheral vascular mechanisms in the regulation of pressure and flow during oscillatory blood volume shifts in dogs (Marquis, et al 1978).
3. The differences in the cardiovascular control mechanisms of endurance trained (treadmill) and untrained dogs in response to oscillatory blood volume shifts (Charles, et al 1983).

4. The chronotropic frequency response characteristics of humans during sinusoidal $\pm 1g_z$ acceleration (Knapp, et al 1983).
5. The relative contributions of cardiac and peripheral mechanisms to blood pressure regulation in dogs during sinusoidal LBNP (Aral, et al 1986).
6. The chronotropic frequency response characteristics of humans during sinusoidal LBNP (Knapp, et al 1987).
7. The differences in stroke volume and heart rate in response to sinusoidal LBNP in the same human subject in salt replete and depleted states (Knapp, et al 1990).

We now seek to evaluate the effectiveness of the oscillatory LBNP (and spectral analysis) protocol to evaluate cardiovascular regulation in humans before and after head down bedrest. We also seek to place the sensitivity of the technique in perspective with other protocols that do not use provocative tests. Our current studies are designed to answer the following specific questions:

1. Can the frequency response characteristics of cardiovascular regulation in normal supine humans be identified by spectral analysis of responses to oscillatory LBNP? How do the results compare to those from the spectral analysis of resting variables?
2. Can bedrest-induced changes in cardiovascular function be identified by spectral analysis of responses to oscillatory LBNP? How do the results compare to those from the spectral analysis of resting variables? If they are more sensitive, does the enhancement justify the extra effort involved with the provocative test?
3. Which spectral analysis technique is the most sensitive to track subtle changes in cardiovascular function during bedrest? Can the details of the spectra provide information about the mechanisms of cardiovascular control and do changes in the spectra associated with bedrest reflect changes in control mechanisms?

In an effort to answer these questions, we have been investigating several approaches to determine the spectral content of resting variables alone and in response to sinusoidal LBNP. At present, we are:

1. measuring the spectral content of resting variables using autoregression and chirp Z transform analysis.
2. measuring the excursions (peak-to-peak differences) in cardiovascular responses as a function of LBNP frequencies.
3. measuring the spectral content of each response to each LBNP input frequency using discrete Fourier transforms, chirp Z transforms (for increased spectral resolution) and autoregression analysis.

4. measuring the spectral content of cardiovascular responses to step changes in LBNP by autoregression.

Preliminary results from some of the above listed approaches are presented below.

SINUSOIDAL LBNP RESPONSES

We are completing a study designed to determine the overall frequency response characteristics of integrated cardiovascular regulation in ten normal supine humans in response to oscillatory LBNP. Another goal of this study was to examine the effects of short term (22 hrs.) head down bedrest (plus Lasix, 40 mg P.O.) on the frequency response characteristics in the same subjects. The response of a typical subject before bedrest to sinusoidal LBNP (0 to -60 mm Hg) at .01 Hz (period = 100 sec) is shown in Figure 1. The variables from top to bottom are: LBNP, arterial pressure (AP, Finapres), ascending aortic flow (AF, Exerdop), central venous pressure (CVP, Cobe), stroke volume (SV, beat-by-beat calculation from the AF), heart rate (HR) and total peripheral vascular resistance (TPR, beat-by-beat calculation from $(AP - CVP)/(SV \times HR)$). From this figure several observations can be made: AP was well regulated during the test (the three places without data are a servo control of the system). There were oscillations of AF, SV and CVP that were both large and minimally regulated, i.e. their magnitudes decreased as the level of LBNP increased and vice versa. The oscillations in HR and TPR were also large and were reactive in nature, that is, their magnitudes increased as LBNP level increased and vice versa. Oscillations in cardiac output (not shown) were more similar to those of SV than HR, varying from 5.1 L/min at atmospheric pressure to 3.2 L/min at peak LBNP. In all subjects at the low frequencies (.004 to 0.01 Hz), LBNP induced decreases in SV of ~50% which were associated with large oscillations in HR and TPR, resulting in very small (~2 mm Hg) oscillations of AP.

The Fourier transform results (first harmonic and phase angle with respect to LBNP) for this group of subjects are shown in Figures 2 - 7 for both pre- and post-bedrest states.

PRE-BEDREST: The SV oscillations (Figure 2) lagged the LBNP input by -20° at the lowest frequency, i.e. minimum values of SV occurred -20° after the -60 mm Hg LBNP dips. Oscillations were ± 17 ml at .004 Hz and dropped to ± 4 ml at .1 Hz at which time the phase lag had increased by an additional 100° . The CVP oscillations (Figure 3) which lagged the LBNP input by -10° at the lowest frequency, had associated half amplitude oscillations of ~2.5 mm Hg, dropping to 1 mm Hg at the highest frequency while the phase lag only increased an additional 20° . Peak values of calf circumference (CC, Figure 4) lagged the -60 mm Hg LBNP dip by -30° ($+150^\circ$, Figure 4) at the lowest frequency (this peak in CC occurred -20° after the minimum in CVP). The lag in CC with respect to LBNP increased by an additional 20° at the highest frequency while the half amplitude dropped from 1.1% to 0.3%. Peak values of TPR occurred -10° after the -60 mm Hg LBNP dip ($+170^\circ$, Figure 5) at the lowest frequency and increasingly lagged up to

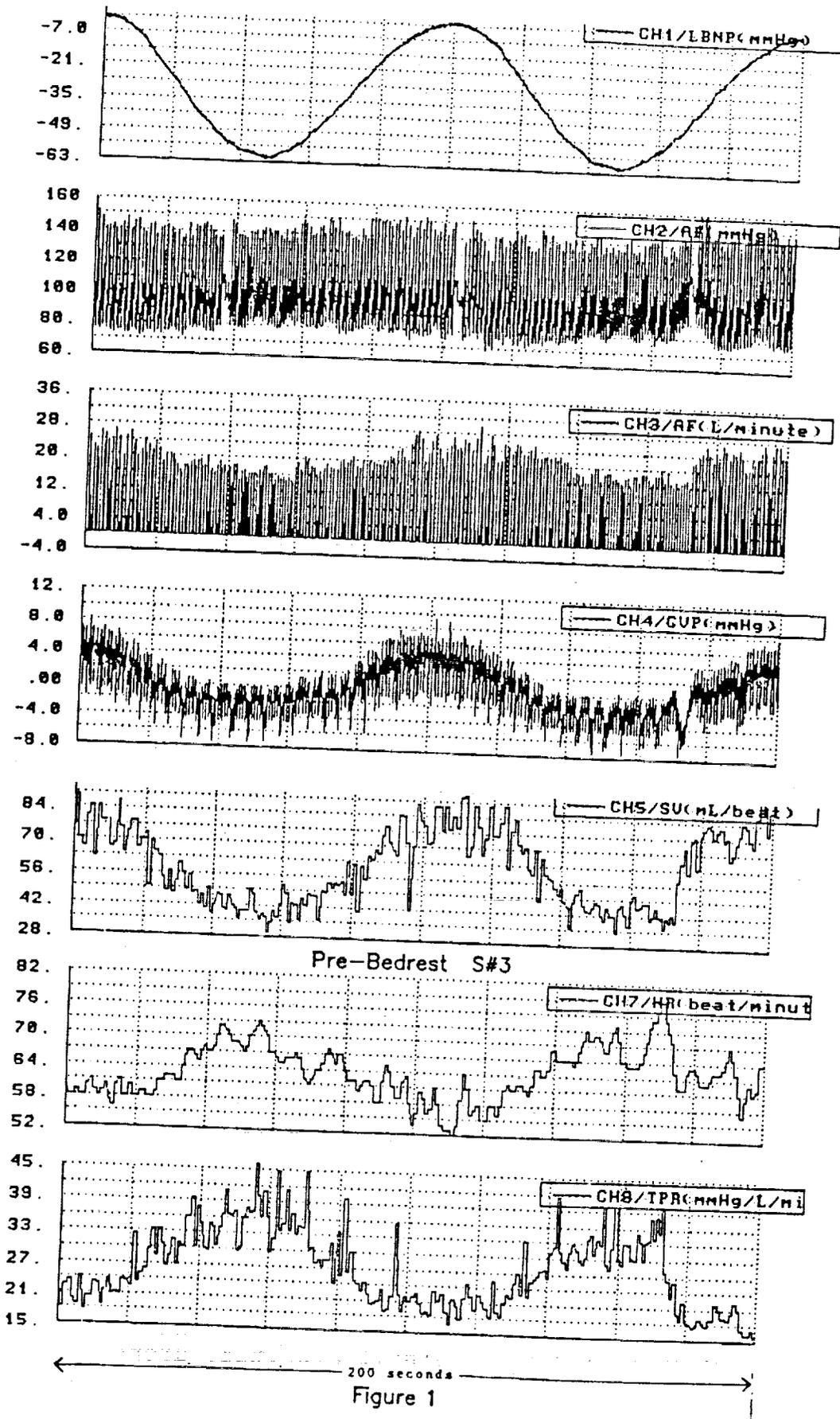


Figure 1

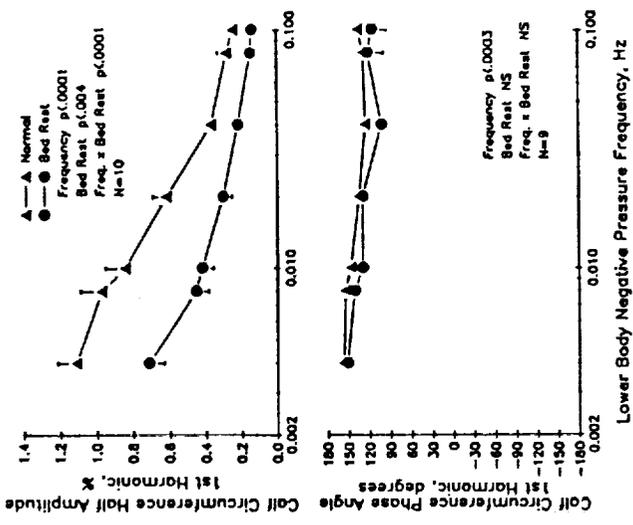


Figure 2

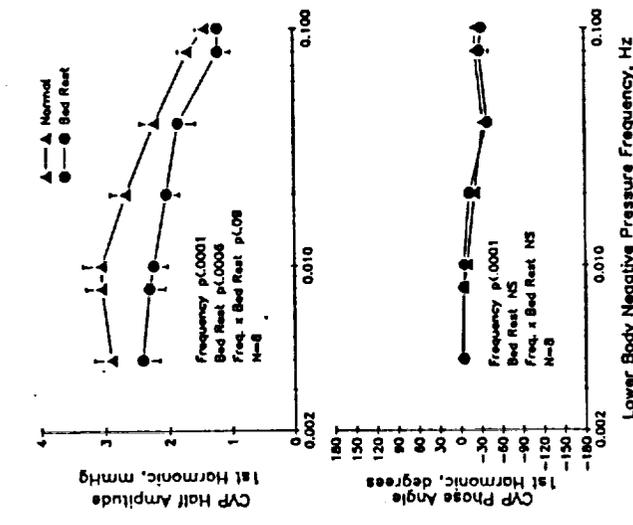


Figure 3

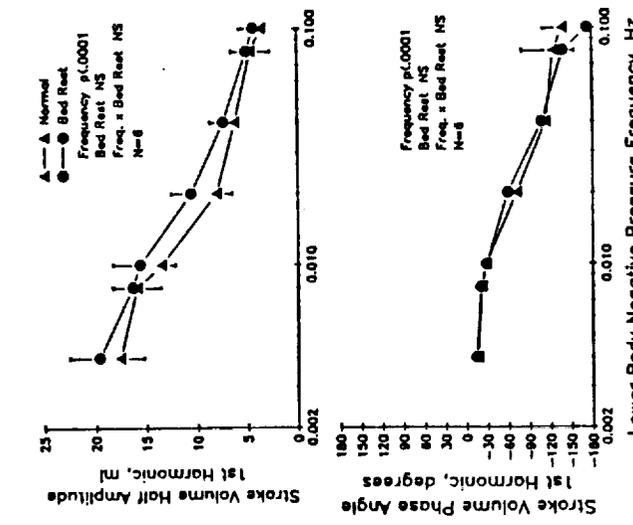


Figure 4

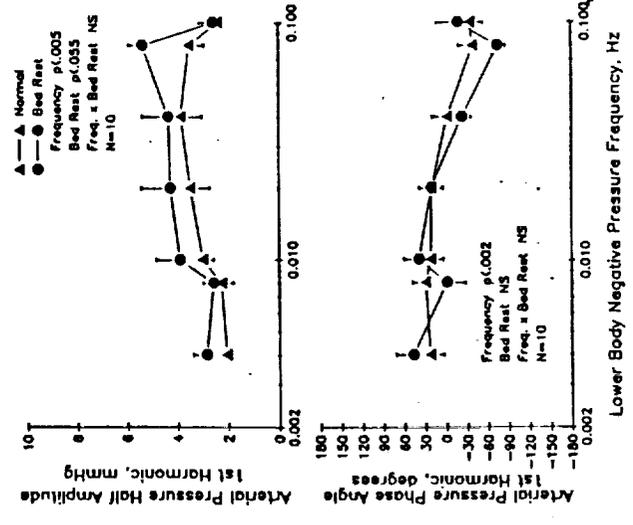


Figure 5

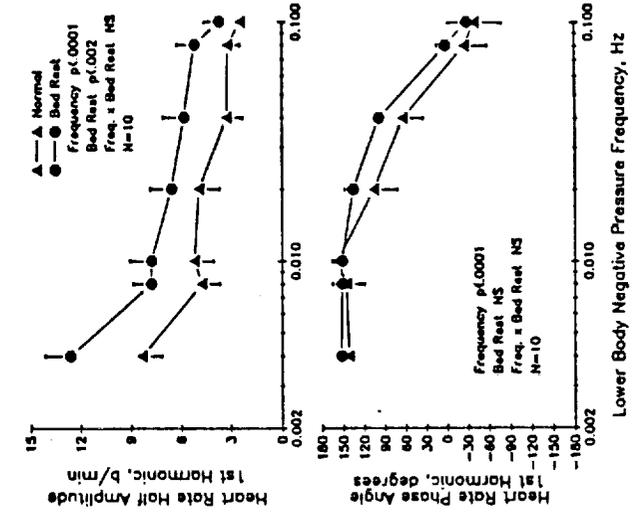


Figure 6

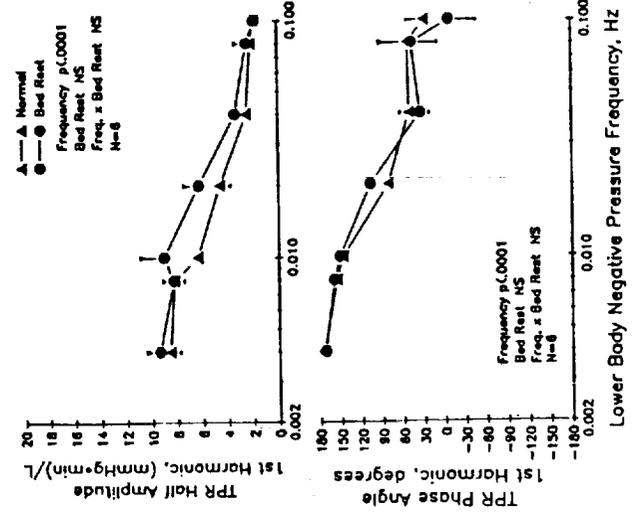


Figure 7

an additional 140° at the highest frequency. The half amplitude of TPR decreased from 8 mm Hg/(L/min) to 2 mm Hg/(L/min) across the range. Peak values of HR (Figure 6) lagged the -60 mm Hg LBNP dip by -30° ($+150^\circ$, Figure 6) at the lowest frequency and increasingly lagged up to an additional 180° at the highest frequency while the half amplitude of HR oscillations decreased from 8 b/min to 3 b/min. The AP half amplitudes (Figure 7) increased with increasing frequency up to 0.04 Hz and then decreased slightly. Peak AP led the -60 mm Hg LBNP dip by -30° at the lowest frequency, switching to a phase lag after 0.04 Hz.

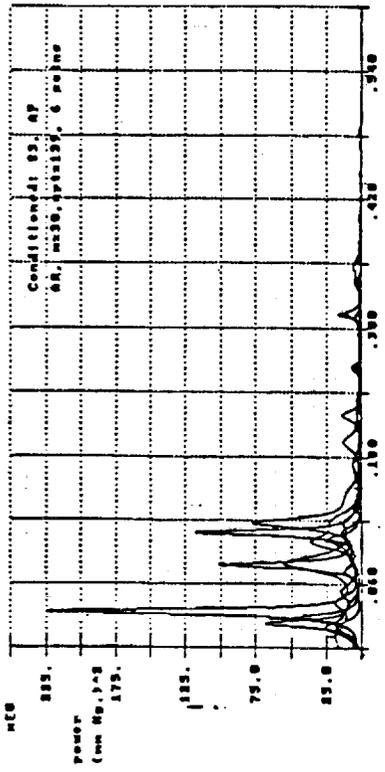
POST-BEDREST: The post-bedrest results from this group of subjects indicated several interesting responses: The AP, HR, SV and TPR half amplitudes were larger than those in the pre-bedrest state and the half amplitudes of CVP and CC were smaller. The phase relationships of these variables with respect to the LBNP input were not significantly affected by the short term bedrest.

The principal conclusions from this study were that in normal male subjects: 1) AP was well regulated at LBNP input frequencies below .01 Hz due to the appropriate timing of large amplitudes of oscillations of both HR and TPR which counteracted the large relatively passive oscillations of SV. 2) AP oscillations were largest between .01 and 0.08 Hz due to the inappropriate phasing of relatively small amplitudes of oscillations in SV, HR and TPR. 3) The half amplitudes of oscillations of AP were increased by bedrest even though the amplitude of the vascular volume being shifted was reduced as indicated by the decreased half amplitudes of CVP and CC. 4) The increased half amplitude of AP oscillations in post- vs pre-bedrest were therefore due to the inappropriate timing of larger oscillations of HR, SV and TPR in response to smaller oscillations of vascular volume.

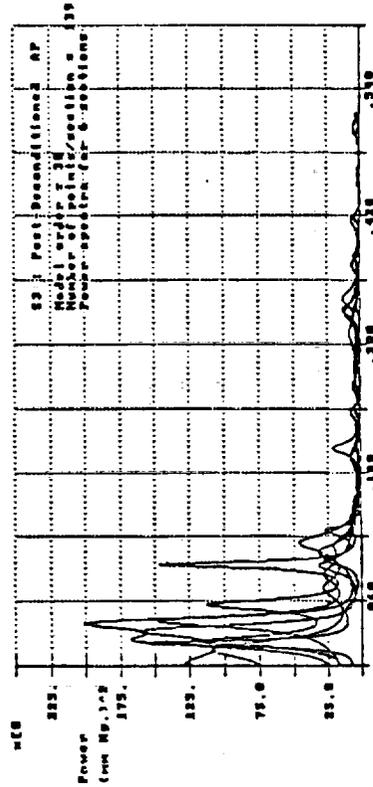
CARDIOVASCULAR SPECTRA FROM RESTING SUBJECTS

Based on the fact that an increase in heart rate and peripheral resistance has been a consistent finding in bedrest and spaceflight studies, we hypothesized that these deconditioning procedures produce a net increase in peripheral neural sympathetic activity. Previous studies (Akselrod, Rimoldi) by other investigators have demonstrated that changes in neural activity are manifest in changes in arterial pressure (Rimoldi) and heart rate (Akselrod, Rimoldi) spectra. We are currently using autoregressive techniques to calculate the spectral content in data records of resting arterial pressure, heart rate, respiration rate, stroke volume, peripheral resistance, central venous pressure and cardiac output in the same subject before and after our 22 hrs. of 6° head down bedrest. Arterial pressure and heart rate from a supine, freely breathing subject, are shown in Figure 8. The top row shows 6 spectra obtained from consecutive, individually detrended, 2.5 min segments of arterial pressure (left) and heart rate (right). Each data point in the AP time record was obtained by integrating arterial pressure over a beat (one R-R interval). Each data point for HR was obtained by taking the reciprocal of the R-R interval. In the pre-bedrest data (top row), power in AP was localized in two ranges ($<.06$ Hz and between .06 - .14 Hz) while power in HR spectra was localized in the region $<.04$ Hz and between .06 - .18 Hz. The

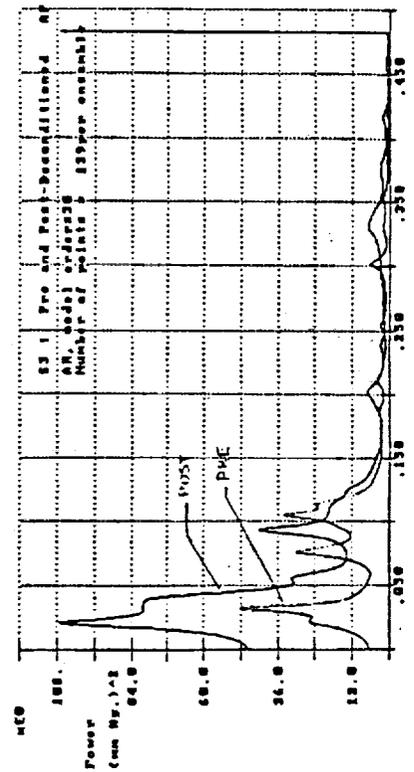
Arterial Pressure, S#3



Pre-Bedrest

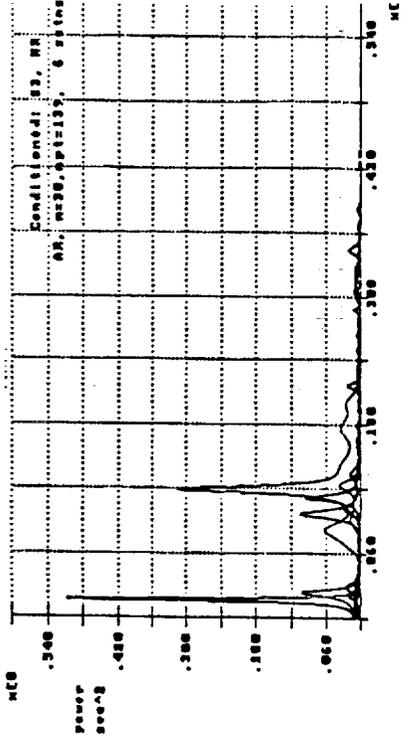


Post-Bedrest

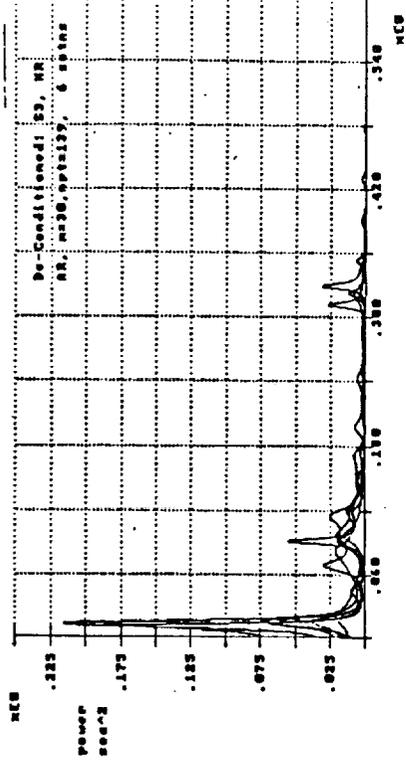


Pre- & Post-Bedrest

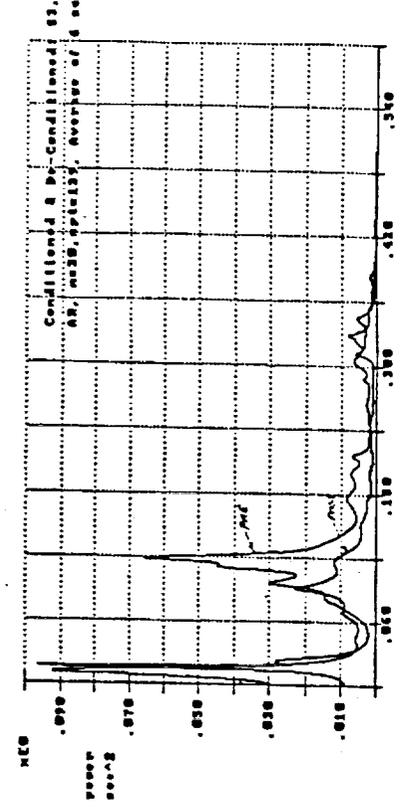
Heart Rate, S#3



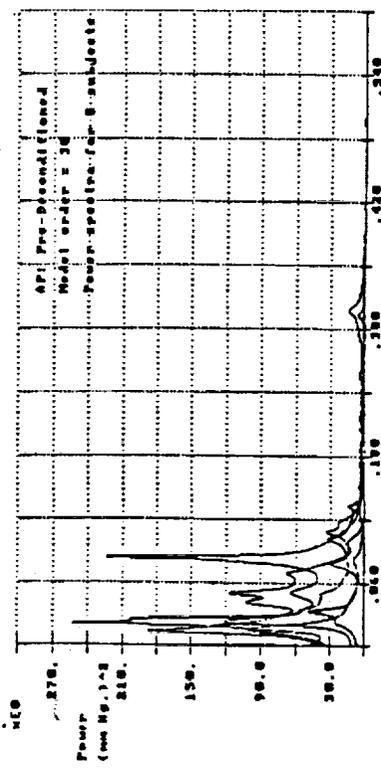
Pre-Bedrest



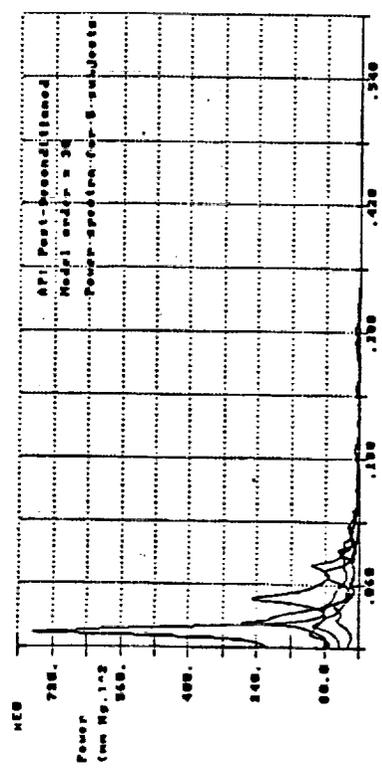
Post-Bedrest



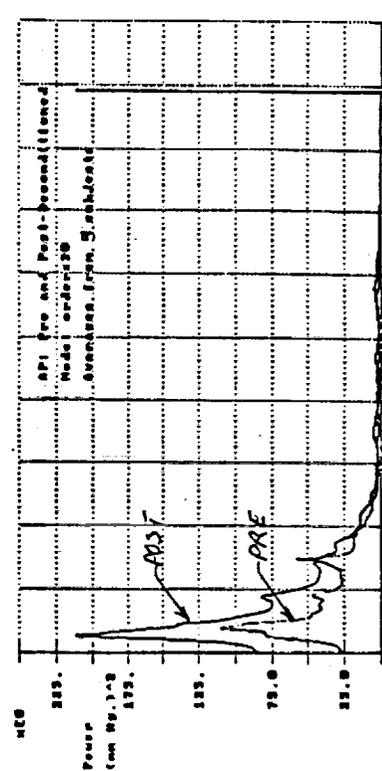
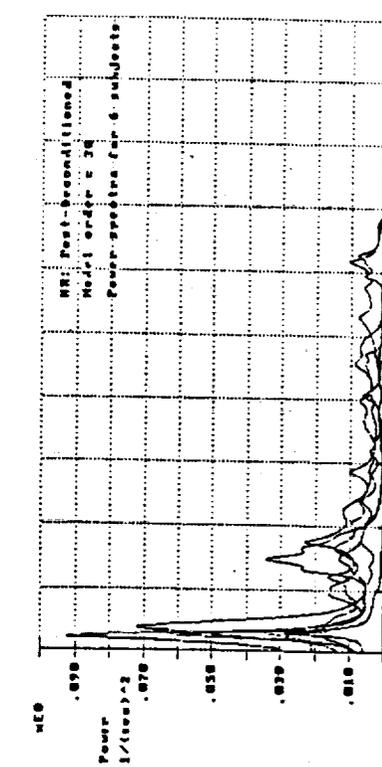
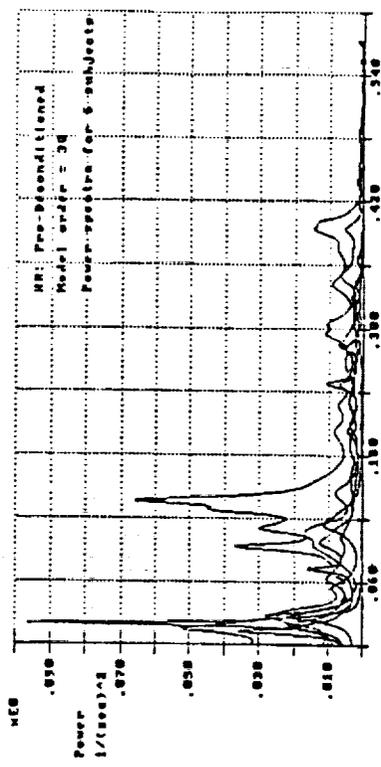
Pre- & Post-Bedrest



Pre-Bedrest



Post-Bedrest



Pre- & Post-Bedrest

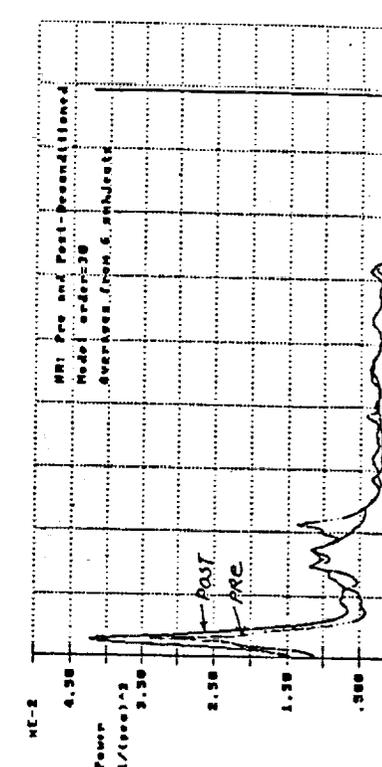


Figure 9

respiratory power (data not shown) for this subject was distributed between 0.08 and 0.4 Hz. The post-bedrest spectra are shown in the second row where increases in AP power are seen at the lowest frequencies. The six spectra for each state were then averaged (to enhance statistical stability) and are shown in the last row for both pre- and post-bedrest. The AP spectral power (area under the curve) was found to increase after bedrest for frequencies below .06 Hz. In this subject, power in the HR spectrum was decreased by bedrest.

Data for the group of subjects are shown in Figure 9. In the top two rows, spectra (one for each subject) are overlaid in plots of AP (left) and HR (right), pre- (first row) and post- (second row) bedrest. Each subjects' spectrum is the average of the 6, 2.5 min segments (in Figure 8). These plots reflect power in the same frequency ranges as those shown for the individual subjects in Figure 8. The pre- and post-bedrest averaged spectra for the group are shown in the bottom row where again, as in the single subject, AP power was increased in both low frequency ranges by bedrest. There did not appear to be a significant effect of bedrest in the HR spectra. Analysis of the remaining subjects and variables and comparison of results with those from the LBNP provocative tests are continuing.

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**EFFECT OF PROLONGED LBNP AND SALINE INGESTION ON
PLASMA VOLUME AND ORTHOSTATIC RESPONSES DURING
BED REST**

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Laura Steinmann

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SCIENCES)*

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Intolerance", and JSC Director's Discretionary Funds .

ABSTRACT

Orthostatic intolerance remains a significant problem following space flight despite frequent use of the saline fluid-loading countermeasure and volitional use of an anti-gravity suit during re-entry and landing. The purpose of this project is to examine the plasma volume (PV), endocrine, and orthostatic responses of bed-rested subjects following 2-hr and 4-hr treatments of lower body negative pressure (LBNP) and saline ingestion. Ten healthy men (25 to 41 yrs) underwent 13 days of 60° head-down bed rest. The men were randomly assigned into 2 groups. Group A underwent a 4-hr LBNP/saline treatment on bed rest day 5 and the 2-hr treatment on day 11. Group B underwent the 2-hr treatment on day 6 and the 4-hr treatment on day 10. Blood volume was determined before and after bed rest using radiolabelling. Changes in PV between measurements were calculated from changes in hematocrit and estimated red cell volume. Urinary excretion of anti-diuretic hormone (ADH) and aldosterone (ALD) were measured each day during the study. Orthostatic responses were measured using a ramp LBNP protocol before bed rest, before each treatment, and 24 hours after each treatment. Both 2-hr and 4-hr treatments resulted in a restoration of PV to pre-bed rest levels which persisted at least 24 hours. This increase in PV was associated with significant increases in urinary excretion of ADH and ALD. Twenty-four hours after the 4-hr treatment, the heart rate and pulse pressure response to LBNP were significantly lower and stroke volumes during LBNP were increased. Twenty-four hours after the 2-hr treatment, there was no evidence of improvement in orthostatic responses. These results suggest that a countermeasure which simply restores PV during space flight may not be sufficient for restoring orthostatic responses.

INTRODUCTION AND BACKGROUND:

LBNP has been used as a procedure to assess orthostatic responses postflight in the Apollo program (1), and in flight during the Skylab program (2). In the Soviet space program LBNP is routinely used inflight both as an assessment procedure and as a countermeasure for postflight orthostatic intolerance (3,4). Cosmonauts perform the LBNP countermeasure while wearing a flexible LBNP suit (the Chibis suit). The LBNP exposures are begun 5 to 21 days before landing, depending on the mission duration, and are combined with fluid and salt ingestion. There is no data

available from the Soviet flight experience which would reveal the precise mechanism by which their LBNP countermeasure acts to improve orthostatic responses.

American research into the possible use of LBNP as a countermeasure began in the 1960s. Lamb and Stevens (5), Stevens et. al (6), and McCally et. al (7) performed studies indicating that prolonged exposures (8-12 hrs daily) to LBNP during bed rest could maintain body fluid balance (5), plasma volume (6), and orthostatic responses (6,7). Hyatt and West (8) were the first to combine the LBNP exposure with fluid ingestion. They reported a restoration of plasma volume and significantly reduced heart rate and blood pressure changes during LBNP, in men after 7 days of bed rest. They concluded that the improvement in orthostatic responses was most likely the result of the increased plasma volume and that further work was required to determine the minimum exposure duration required to provide such improvements.

PURPOSE AND HYPOTHESES:

The operational purpose of this project is to determine whether the LBNP/saline countermeasure proposed by Hyatt and West (8) may be reduced to 2 hours and still maintain the beneficial effects on plasma volume and orthostatic responses. In answering this question, we hope to gain a better understanding of potential mechanisms for the loss of orthostatic function during a simulated space flight-- 13 day bed rest--and a greater understanding of the specific mechanisms by which prolonged LBNP during bed rest may reverse some of these changes.

We hypothesize that during prolonged LBNP exposures, fluid is redistributed from the thoracic region of the body to the lower body, thus stimulating cardiopulmonary mechanoreceptors. The unloading of these receptors due to the decrease in central blood volume results in an increased secretion of ADH and ALD. Increased levels of ADH and ALD result in fluid and electrolyte retention during the 24 hour period after the LBNP/saline countermeasure. In addition, the accumulation of fluid in the lower body during LBNP may result in the filtration and sequestration of fluid in the lower body tissues. This fluid is later reabsorbed, and in the presence of elevated ADH and ALD may contribute to the plasma volume expansion. The restoration of plasma volume will result in a larger stroke volume,

lower heart rates, higher blood pressures, and a larger cardiac output during a graded orthostatic stress such as LBNP.

METHODS AND PROCEDURES:

Ten men (25 to 40 yrs; 169 to 182 cm. height; 66 to 90 kg weight; and 45 to 59 ml/min/kg maximum oxygen consumption) participated in this study.

The study protocol involved a crossover design with the subjects randomly assigned to two groups, group A and group B. The experimental protocol is shown in **Figure 1**. Each subject was exposed to one 4-hr and one 2-hr LBNP/saline treatment, with half the subjects exposed to the 4-hr treatment first and the 2-hr treatment second (group A), and the other half exposed to the 2-hr treatment first and the 4-hr treatment second (group B). During each treatment, the subject was exposed to a continuous negative pressure exposure of -30 mm Hg and ingested one liter of isotonic saline between exposure minutes 30 and 90.

Blood volume was calculated as the sum of red cell volume (RCV) and PV measurements obtained before and on the last day of bed rest. RCV was determined with 51 chromium sulfate and PV was determined with 125 iodinated human serum albumin. PV was calculated for each bed rest day from the daily RCVd ($\text{RCVd} = \text{pre bed rest RCV} - \text{the accumulative loss of red cells due to daily blood draws}$) and the daily hematocrit value; where $\text{PV} = (\text{RCVd}/(\text{hct}/100)) - \text{RCVd}$.

Pre-syncopal LBNP tests (graded LBNP exposures in 3 min. stages which continued until pre-syncopal symptoms were observed) were done before and after bed rest. LBNP response tests (graded LBNP exposures in 5 min. stages from 0 to -60 mm Hg in 10 mm Hg steps) were performed pre-bed rest, before each treatment, and 24 hours after each treatment.

FIGURE 1 : BEDREST PROTOCOL					
BEDREST DAY	BLOOD DRAWN	HORMONES DETERMINED	BLOOD VOLUME	LBNP PROCEDURE	
				GROUP A	GROUP B
- 2	YES		YES	PSL-LBNP	PSL-LBNP
- 1	YES	YES		LBNP	LBNP
1	YES				
2	YES	YES			
3	YES	YES			
4	YES	YES		LBNP	LBNP
5	YES	YES		4HR LBNP	
6	YES			LBNP	2HR LBNP
7	YES				LBNP
8	YES	YES			
9	YES			LBNP	LBNP
10	YES				4HR LBNP
11	YES	YES		2HR LBNP	LBNP
12	YES			LBNP	
13	YES		YES	PSL-LBNP	PSL-LBNP
R1	YES	YES		LBNP	LBNP
R2	YES	YES		LBNP	LBNP

Each subject underwent a 13-day, 6° head-down bed rest, two days of ambulatory control before bed rest, and two days of ambulatory recovery after bed rest. Throughout bed rest fluid, salt, and food intake were maintained at 2500 ml of rehydration fluid/day, 4 grams of salt/day, and 2500 Kcal/day. Twenty-four hour urine collections were obtained each day of the study from which volume, electrolytes, ADH, and ALD concentration were measured. Venous blood samples were obtained without stasis each morning and before each LBNP test. Hematocrit and hemoglobin concentration were determined from each sample.

RESULTS AND DISCUSSION:

A. Pre-syncope LBNP Results--Pre vs. Post Bed Rest

The effect of 13 days of bed rest on LBNP tolerance is shown in Figure 2; where "LBNP tolerance" is defined as the LBNP pressure tolerated for at least one minute without pre-syncope symptoms. Not all subjects had a decrease in LBNP tolerance during bed rest and

there was no significant correlation between changes in LBNP tolerance and changes in blood volume (measured via radiolabelling on the morning of PSL-LBNP testing). However, there was a significant correlation between the the change in LBNP tolerance during bed rest and the pre-bed rest LBNP tolerance (Figure 3). Subjects with high LBNP tolerance had a greater decrease in LBNP tolerance during bed rest than subjects with low LBNP tolerance.

FIGURE 2

Lowest Pressure Attained, Pre vs. Post Bed Rest

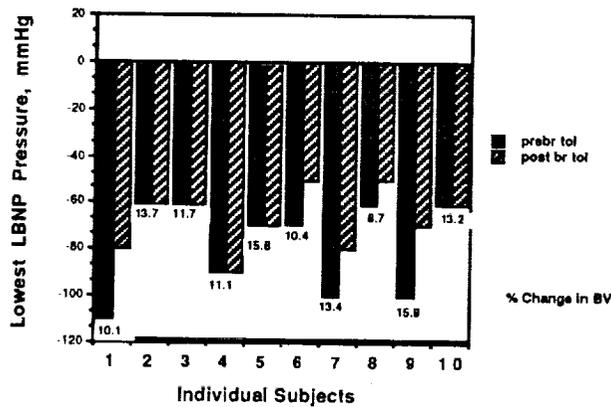
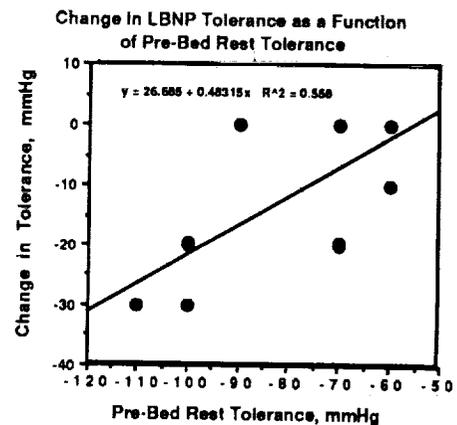


FIGURE 3



B. Changes in Plasma Volume During Bed Rest--Effect of the 2-hr and 4-hr LBNP and saline ingestion treatments.

The changes in PV determined from each morning blood sample are shown in Figure 4 for Group A and in Figure 5 for Group B. In both groups, PV decreased initially during bed rest and returned towards the pre-bed rest level for one to two days following each LBNP treatment.

FIGURE 4

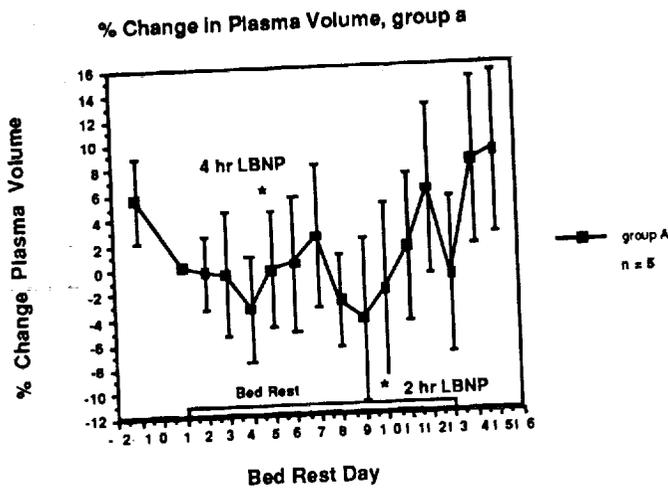
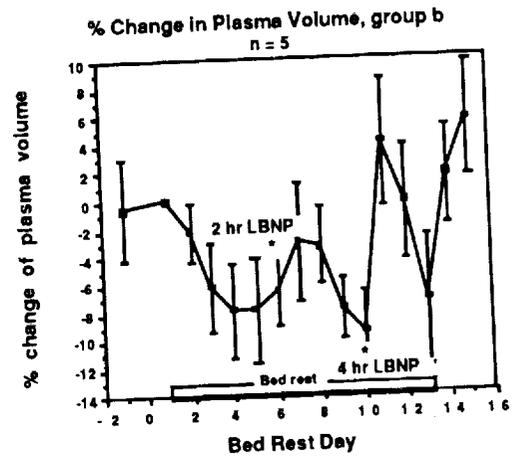


FIGURE 5



C. ADH, ALD, and PV during Bed Rest: effect of LBNP and saline ingestion:

There were no significant differences between the two groups in any of the treatment or bed rest responses (analysis of variance). Therefore, the data from both groups was combined to compare the effect of the LBNP and saline ingestion treatments on PV, endocrine, and orthostatic responses. PV was calculated from blood samples drawn immediately before each LBNP response test and ADH and ALD secretion were determined from 24-hr urine samples (Table 1). PV was significantly reduced from pre-bed rest levels before each LBNP treatment, but, 24 hours after each treatment PV was no longer significantly different from pre bed rest. On the day of each LBNP treatment, there was a significant increase in the secretion of both ADH and ALD (compared to pre-treatment) which may have contributed to the plasma volume expansion.

TABLE 1

Variable	PreBR	Pre 4hr	Post 4hr	Pre 2hr	Post 2hr
PV (ml)	3157(161)	*2918(132)	3144(173)	*2987(131)	3109(146)
UV (ml)	2506(250)	2538(155)	+2923(111)	2258(162)	+2788(191)
ADH (ng)	136(33)	114 (15)	+177 (26)	93 (18)	+155 (42)
ALD (ng)	16(4)	*35(4)	+54(5)	*37(7)	+46(7)

* = Different from pre bed rest, $P < 0.05$.

+ = Different from pre treatment (pre 4hr or pre 2hr), $P < 0.05$.

D. Orthostatic Responses during Bed Rest--effect of LBNP and saline treatments:

The results in Table 2 illustrate the orthostatic responses (mean \pm S.E.) for all 10 subjects by presenting specific cardiovascular variables during the final (-60 mm Hg) LBNP exposure level. Heart rates were significantly higher than pre bed rest during all pre and post LBNP treatment tests, although post treatment, the heart rates were lower than pre treatment. Pulse pressure was significantly reduced during bed rest without LBNP treatment but not after treatment. Stroke volume was reduced significantly during bed rest without treatment, but not following treatment. Cardiac output (measured by continuous wave Doppler at the suprasternal notch) was not affected by either bed rest or LBNP treatment.

TABLE 2

<u>Variable</u>	<u>Pre-BR</u>	<u>Pre-4hr</u>	<u>Post-4hr</u>	<u>Pre-2hr</u>	<u>Post-2hr</u>
Heart rate (bpm)	111(5)	*134 (4)	*128 (5)	*144 (5)	*134 (5)
Pulse Pressure (mm Hg)	25 (3)	*16(2)	19 (2)	*18 (3)	19 (3)
Cardiac Output (l/min)	4.2 (0.4)	3.7 (0.2)	3.8 (0.4)	3.6 (0.3)	4.0 (0.3)
Stroke Volume (ml/beat)	39 (5)	*27 (2)	29 (3)	*27 (3)	29 (3)

* = Different from pre bed rest value, $P < 0.05$.

Figures 6 and 7 illustrate the mean \pm S.E. heart rate response to the entire LBNP ramp test (0 to -60 mm Hg) and they compare this response pre bed rest, during bed rest before treatment (pre 2-hr and pre 4-hr) and 24 hours after the 4-hr and 2-hr treatments.

After the 4-hr treatment, the heart rate response was significantly elevated from pre-bed rest, but significantly improved from pre treatment (pre 4-hr). The effectiveness of the treatment to lower heart rate diminished with increasing LBNP exposure.

After the 2-hr treatment, the heart rate response was significantly elevated from pre bed rest and there was no significant improvement after the treatment.

FIGURE 6

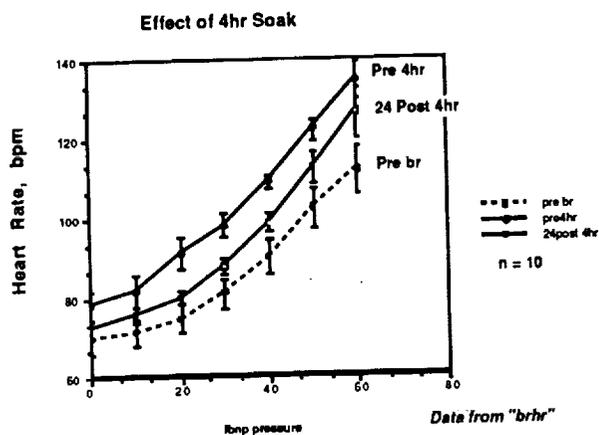
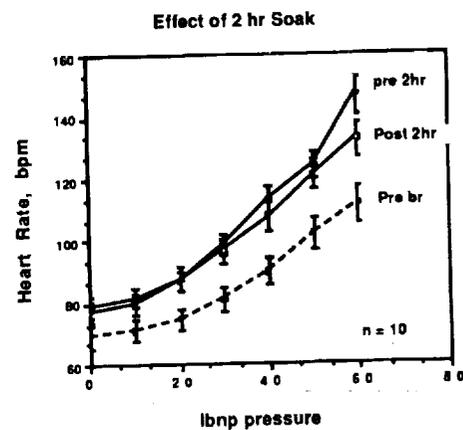


FIGURE 7



CONCLUSIONS:

- 1) The loss of tolerance to LBNP after 13 days of bed rest is most marked in individuals with high LBNP tolerance pre bed rest.
- 2) Prolonged LBNP exposures during bed rest effectively increase PV for at least 24 hours and this expansion may be related to an increased secretion of ADH and ALD.
- 3) 4-hr LBNP exposures combined with salt water ingestion may provide some improvement of orthostatic responses for approximately 24 hours. 2-hr exposures are less effective.

SIGNIFICANCE:

Prolonged LBNP and saline ingestion may provide an effective means to restore PV during space flight. However, with this particular protocol (LBNP pressure and fluid ingestion) a 2 hour LBNP exposure is not sufficient to restore orthostatic responses.

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Research Summary for:

NASA Grant NAG9-297

"Fitness, Autonomic Regulation and Orthostatic Tolerance"
Principal Investigator: Jay C. Buckey, M.D.

Work on this grant has consisted of two major studies of cardiovascular regulation in athletes along with several smaller supporting studies. This summary will give a brief overview of two major studies, and then conclude with an analysis of what the findings from these studies mean practically, and how they can be applied to current problems with post-flight orthostatic intolerance.

BACKGROUND

Orthostatic intolerance has been a consistent finding after spaceflight. The factors modulating the severity of this intolerance, however, have not been clear. Also, the adaptation leading to postflight orthostatic intolerance has been called "cardiovascular deconditioning", implying that exercise might help to prevent orthostasis. But the relationship between aerobic fitness and orthostatic intolerance is controversial. For example, the U.S. Air Force encourages its fighter pilots to avoid excessive aerobic training, out of a concern that it might reduce G tolerance. On the other hand, aerobic exercise is being studied as a possible countermeasure for the orthostatic intolerance seen after spaceflight.

To deal with this controversy, this project had two main goals. One was to determine whether aerobically trained individuals do indeed have greater orthostatic intolerance, and if so, what are the mechanisms. The second was to determine the differences between those individuals with orthostatic intolerance and those without, to see if any mechanisms for the intolerance could be elucidated. Dr. Benjamin Levine at UT-Southwestern was the leader of the team performing the studies done for this project.

STUDY 1: CROSS-SECTIONAL STUDY OF ORTHOSTATIC INTOLERANCE IN HIGHLY AEROBICALLY TRAINED INDIVIDUALS

(see enclosed paper Levine et al. "Physical Fitness and Cardiovascular Regulation: Mechanisms of Orthostatic Intolerance" for complete data.)

The first study was a cross-sectional study of individuals with varying degrees of fitness. Three groups were identified, a high fit group (Max. $VO_2=60$ ml/min/kg), a mid-fit group (Max. $VO_2=48.9$ ml/min/kg) and a low-fit group (Max. $VO_2=35.7$). The large range of fitness levels allowed for correlations to be drawn between fitness and various cardiovascular variables--including orthostatic intolerance. Graded lower body negative pressure (LBNP) was used to measure orthostatic tolerance, and as a test of cardiovascular regulation. Cardiac output, stroke volume, heart rate, blood pressure, arm flow, plasma volume and maximal leg

conductance were measured during supine rest. The changes in cardiac output, stroke volume, heart rate, blood pressure, and arm flow were measured during LBNP.

Baroreceptor function was measured two ways. A neck collar made of silastic was placed around the neck to stimulate the carotid baroreceptors. A short R-wave triggered protocol during held expiration was used to measure "open-loop" baroreceptor function, and a prolonged (2 minute) protocol using random sequence of negative and positive pressures was used to measure "closed-loop" gain. The "open-loop" procedure and equipment used for the baroreflex testing was the same as the one used after Shuttle flights as part of DSO #467.

The study produced several interesting results. The highly fit individuals did have lower orthostatic tolerance, when compared to the mid and low fit subjects together (LBNP \times time=1175 mmHg-min high-fit, 2003 mid-fit, 1883 low-fit). But, orthostatic tolerance (as measured by LBNP) did not correlate with VO₂. A multivariate function predicting tolerance was developed, and it included terms both related and unrelated to physical fitness. This indicates that orthostatic tolerance is a complex function of many different variables, and that no linear relationship between fitness and orthostatic tolerance exists. It is also clear, however, that orthostatic tolerance is not better in the fit individuals, which calls into question using regular aerobic training to counter orthostatic intolerance.

The baroreceptor data was also intriguing. Typically, the baroreceptor curves use R-R interval as the dependent variable. Differences in R-R interval can be expected since the fit individuals will have lower heart rates. This change in baseline heart rate does not necessarily reflect a change in baroreflex responsiveness. The important consideration, when investigating orthostatic intolerance, is what would the change in blood pressure be for a given change in heart rate. Since a fit individual also has a greater stroke volume than an unfit one, the same heart rate change will lead to a much greater change in cardiac output in the fit person. To compensate for this, the baroreceptor curves were plotted in a novel way, using the effective change in blood pressure (the triple product of heart rate, stroke volume and total peripheral resistance) as the dependent variable. No differences in baroreceptor function between groups were seen, but "closed-loop" gain of the carotid baroreceptor did correlate with orthostatic intolerance.

Although fitness was not a strong predictor of orthostatic tolerance, the data could be analyzed in a different way. How did the subjects who did experience pre-syncope differ from those who did not? When this analysis was done, one striking finding emerged (Figure 1). The people who did have pre-syncope not only had a greater stroke volume, but had a greater decrease in stroke volume during LBNP. This suggested that the fainters were having a greater

decrease in filling pressure than the non-fainters. Could this be due to a difference in ventricular compliance between the groups?

STUDY #2: VENTRICULAR PRESSURE/VOLUME RELATIONSHIPS IN ATHLETES (see enclosed paper Levine et al. "Left Ventricular Pressure/Volume and Frank-Starling Relations in Endurance Athletes: Implications for Orthostatic Tolerance and Exercise Performance" for complete data.)

The question about compliance led to the second major study on this grant. Perhaps there is another, less studied, mechanism behind the orthostatic intolerance seen in very highly aerobically trained individuals. Differences in myocardial compliance between highly fit and unfit individuals would lead to strikingly different Frank-Starling relationships. The highly fit athlete not only has a larger resting stroke volume than the non-athlete, but is also able to increase stroke volume during exercise to a greater extent than the non-athlete. This suggests that the athlete's heart operates on the steep portion of the Starling curve. While this may be an advantage during exercise, allowing for greater increases in stroke volume for a given change in filling pressure, this could also be a major disadvantage during orthostatic stress. Stroke volume would drop to a greater degree with a fall in filling pressure.

To test this hypothesis, two groups of subjects were studied. One consisted of highly trained endurance athletes (Max. $VO_2=68$ ml/min/kg), and the other sedentary subjects (Max. $VO_2=41$ ml/min/kg). Left ventricular end-diastolic pressure was measured with a Swan-Ganz catheter. This pressure was varied using two interventions, lower body negative pressure to -15 and -30 mmHg, and saline infusion at 15ml/kg and 30ml/kg. Cardiac volume was measured with two techniques. Stroke volume was calculated from acetylene rebreathing cardiac outputs and end-diastolic volume was calculated from echocardiography.

The results from this study are shown in Fig. 2. The fit subjects have a much greater change in stroke volume for a given change in pulmonary capillary wedge pressure. The echocardiographic data produced the same result; the athletes had greater decreases in end-diastolic volume with LBNP. The athletes also had significantly less orthostatic tolerance as measured by LBNP. This suggests that basic cardiac structural differences (i.e. a change in myocardial compliance) may be significant contributors to orthostatic tolerance.

CONCLUSIONS AND RELEVANCE

Orthostatic intolerance and aerobic fitness

In both these studies, the fit individuals had diminished orthostatic tolerance compared to unfit controls. This supports the data from many other studies showing a decrease in orthostatic intolerance with aerobic fitness. It is significant, however, that this is not a simple, linear relationship. The interactions between orthostatic tolerance and fitness are complex, many highly fit individuals have excellent tolerance, while many unfit subjects pass out easily.

Nevertheless, several inferences can be made. While proscribing aerobic exercise for astronauts in space or on the ground would be excessive, using regular intense aerobic exercise as a countermeasure for orthostatic intolerance does not make sense. The relationship between fitness and orthostatic tolerance may be U shaped. Very highly fit subjects are on the steep portion of the Frank-Starling relationship, moderately fit subjects have the best tolerance, and very unfit subjects (such as would occur after bedrest or spaceflight), like the highly fit subjects, also have hearts on the steep portion of the Starling curve. In the very unfit subject, plasma volume and stroke volume are so low that very small changes in filling pressure would lead to orthostatic instability. This may explain why the bouts of maximal exercise proposed by Convertino are effective during bedrest in reducing post-bedrest orthostatic intolerance. The bed-rested subjects may experience a transient increase in plasma volume and stroke volume after the exercise thereby moving "up" the Frank-Starling curve.

Extensive, regular aerobic conditioning in space may be useful for bone or muscle atrophy, and for maintaining endurance, but not for combatting orthostatic intolerance. This does not mean that exercise itself has no role, since static exercise and bouts of maximal aerobic exercise (as mentioned above) have been shown to improve orthostatic tolerance.

Mechanisms of orthostatic intolerance

Often, studies on orthostatic intolerance focus on differences in cardiovascular regulation. Various tests have been used to study the heart rate, cardiac output and peripheral responses to orthostatic stress to see if the response is blunted. For example, the first study in this series used extensive measurements of baroreceptor function to test the hypothesis that baroreceptor responsiveness was impaired in the fit subjects. Despite this, no striking differences in baroreceptor function were noted between groups. This does not mean that the baroreceptors have no role, since closed loop gain did correlate with orthostatic tolerance, but does indicate that any orthostatic intolerance seen in fit individuals cannot immediately be ascribed to baroreceptor differences.

Another possibility to explain differences in orthostatic responses, could be a greater decreases in filling pressures with orthostatic stress. This can be ascribed to basic structural changes in the cardiovascular system (i.e. compliance of the myocardium), rather than a change in neurohumoral regulation. In athletes, this reasoning provides a very useful way of thinking about orthostatic intolerance. The Frank-Starling relationship shows that high stroke volumes during exercise and the large drop in stroke volume with standing are really two sides of the same coin. The shift in the athletes to the steep portion of the Starling curve provides an advantage during exercise and a disadvantage with orthostatic stress.

The athletes produced several structural changes in their cardiovascular systems. They have a greater blood volume at the same central venous pressure as unfit subjects, indicating a much greater venous capacity. Also, their maximal vascular conductance is greater, indicating a greater ability for vasodilation.

Analysis of baroreceptor function

One other result from the set of studies performed on this grant has been a new way to analyze baroreceptor function curves. Typically, R-R interval is plotted as a function of carotid distending pressure to produce a curve describing carotid baroreceptor function. R-R interval is used since it reflects the change in vagal outflow.

This approach has a problem when studying orthostatic intolerance in individuals with different resting values of heart rate, stroke volume and total peripheral resistance. Similar changes in R-R interval in two subjects with greatly differing levels of TPR, for example, would result in widely different changes in blood pressure. This means that to interpret the baroreflex curves, the effective change in blood pressure that would result from a change in R-R interval is important.

One limitation to this approach is the assumption that stroke volume and total peripheral resistance stay relatively constant during a baroreflex testing session. This was checked during a supporting study done as part of this grant. Stroke volume was measured using Doppler echocardiography during the sequence of R wave triggered changes in carotid distending pressure used in the studies. Stroke volume changed less than 5% during the baroreflex test (see enclosed abstract "The Effect of Carotid Baroreceptor Stimulation on Stroke Volume").

Overall, the approach of using the effective change in blood pressure proved useful in normalizing baroreflex curves for greatly different basal values of stroke volume and total peripheral resistance. Obviously, this is a simplified approach that applies an analysis more appropriate for steady flow to a system with pulsatile flow. Nevertheless, it does allow for more meaningful comparisons between groups, and has been used during a study of

changes in baroreceptor function with posture (see enclosed abstract "Effect of posture on the carotid baroreflex").

SUMMARY

The studies performed on this grant have provided new information about fitness and orthostatic intolerance. Orthostatic intolerance is more prevalent in highly trained athletes, but it is not a simple, linear function of VO₂ max. The mechanism may have more to do with myocardial compliance, as reflected in the different Frank-Starling relationships (LV end-diastolic pressure vs. LV diastolic volume) between elite athletes and sedentary controls. These points are described in detail in the enclosed paper by Levine, "Regulation of central blood volume and cardiac filling in endurance athletes-utilization of the Frank-Starling mechanism as a determinant of orthostatic tolerance."

Publications from NASA Grant NAG9-297

Papers:

Levine BD, Buckey JC, Fritsch JM, Yancy CW, Watenpaugh DE, Snell PG, Lane LD, Eckberg DL, Blomqvist CG: Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. J. Appl. Physiol. (in press).

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Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG: Left ventricular pressure/volume and Frank-Starling relations in endurance athletes: implications for orthostatic tolerance and exercise performance. Circulation (submitted).

Abstracts:

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Figure 1

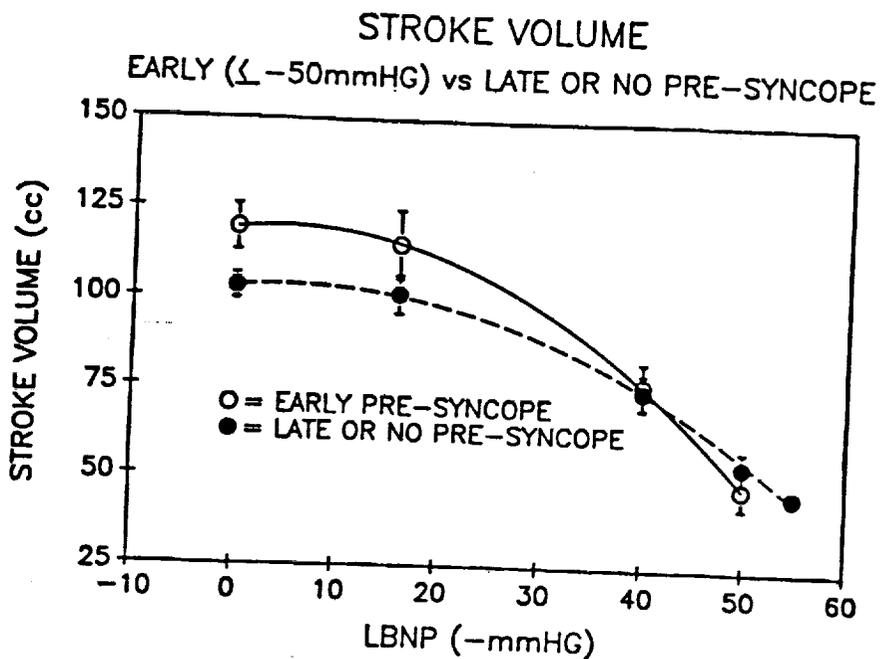
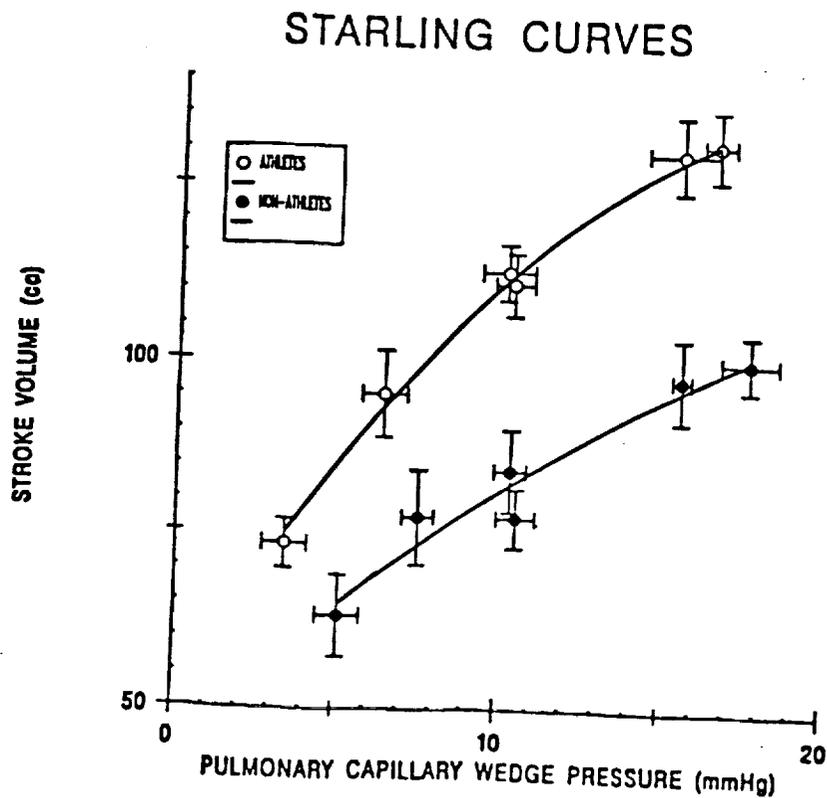


Figure 2



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Valsalva maneuver: Insights into baroreflex
modulation of human sympathetic activity

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METHODS

We recorded R-R intervals, tidal volumes, arterial pressures, expiratory pressures, and muscle sympathetic nerve activity on electrostatic and FM recorders. Two protocols were followed. **Protocol #1:** Nine subjects performed five Valsalva maneuvers at each of three expiratory pressures (10, 20, and 30 mmHg) during which muscle sympathetic activity was recorded. The order of pressure levels was randomized. **Protocol #2:** Six subjects performed five Valsalva trials at 30 mmHg during which right atrial pressure was recorded from a saline-filled catheter connected to a pressure transducer. The same parameters listed above were measured except muscle sympathetic nerve activity. This protocol was used to determine the time course of return of right atrial pressure to baseline levels after a strain, and the relation of this time course to the return of arterial pressure.

RESULTS

A sample tracing of one Valsalva trial from one subject is depicted in Fig. 1. The typical phases of the Valsalva maneuver and their sympathetic responses are shown clearly. These include phase 1 elevation of arterial pressure and inhibition of sympathetic activity at the onset of straining; phase 2 reduction of pressure and increase of sympathetic activity as straining continues; phase 3 abrupt decrease of pressure and increase of sympathetic activity after release of straining; and phase 4 elevation of pressure and inhibition of sympathetic activity during resumption of controlled-rate breathing.

Relation between sympathetic nerve activity and arterial pressure. Average changes of peak muscle sympathetic nerve activity during straining and arterial pressure during phase 4 are listed in Table 1. Absolute sympathetic nerve activity correlated only modestly with absolute diastolic pressure during straining ($r = 0.55$, $p < 0.05$); whereas, beat-to-beat change of sympathetic nerve activity correlated well with beat-to-beat change of diastolic pressure ($r = 0.79$, $p < 0.01$). Peak sympathetic activity during straining correlated significantly with phase 4 increases of systolic and diastolic pressures ($r > 0.80$; $p < 0.0001$).

Post-strain sympathetic inhibition. Several measurements were made to determine what physiologic adjustments account for post-strain sympathetic inhibition. The time to return of baseline systolic pressure, sympathetic activity, and the occurrence of the first post-straining sympathetic burst correlated significantly with the intensity of straining. The time of return to baseline sympathetic nerve activity was consistently greater than the return to baseline arterial pressure (Fig 3).

Six subjects were studied to determine the time of return to baseline right atrial pressure after Valsalva straining. The time of return to baseline right atrial pressure (27.3 ± 3.0 s) was not different ($p = 0.40$) from time of return to baseline systolic arterial pressure (24.5 ± 2.2 s), and therefore was not predictive of the return to baseline sympathetic nerve activity.

SUMMARY

Valsalva's maneuver, voluntary forced expiration against a closed glottis, is a well-characterized research tool, used to assess the integrity of human autonomic cardiovascular control. Valsalva straining provokes a stereotyped succession of alternating positive and negative arterial pressure and heart rate changes mediated in part by arterial baroreceptors. Arterial pressure changes result primarily from fluctuating levels of venous return to the heart and changes of sympathetic nerve activity.

We measured muscle sympathetic activity directly in nine volunteers to explore quantitatively the relation between arterial pressure and human sympathetic outflow during pressure transients provoked by controlled graded Valsalva maneuvers. Our results underscore several properties of sympathetic regulation during Valsalva straining. First, muscle sympathetic nerve activity changes as a mirror image of changes in arterial pressure. Second, the magnitude of sympathetic augmentation during Valsalva straining predicts phase 4 arterial pressure elevations. Third, post-Valsalva sympathetic inhibition persists beyond the return of arterial and right atrial pressures to baseline levels which reflects an alteration of the normal relation between arterial pressure and muscle sympathetic activity. Therefore, Valsalva straining may have some utility for investigating changes of reflex control of sympathetic activity after spaceflight; however, measurement of beat-to-beat arterial pressure is essential for this use. The utility of this technique in microgravity can not be determined from these data. Further investigations are necessary to determine

whether these relations are affected by the expansion of
intrathoracic blood volume associated with microgravity.

TABLE 1. Peak sympathetic nerve activity during straining and arterial pressure elevations after Valsalva straining

	Valsalva pressure, mmHg		
	10	20	30
Sympathetic activity, arbitrary units/10 s	1905±203	3086±374	4801±505
Change of systolic pressure, mmHg	10.4±1.2	17.9±1.4	25.5±1.8
Change of diastolic pressure, mmHg	3.6±0.7	7.8±1.0	13.1±1.1

All values are mean ± SEM. All changes were significantly different from zero ($P < 0.001$; $n = 7$). Pressure changes reflect the Phase 3 to 4 change; sympathetic increases reflect peak increase during Phase 2.

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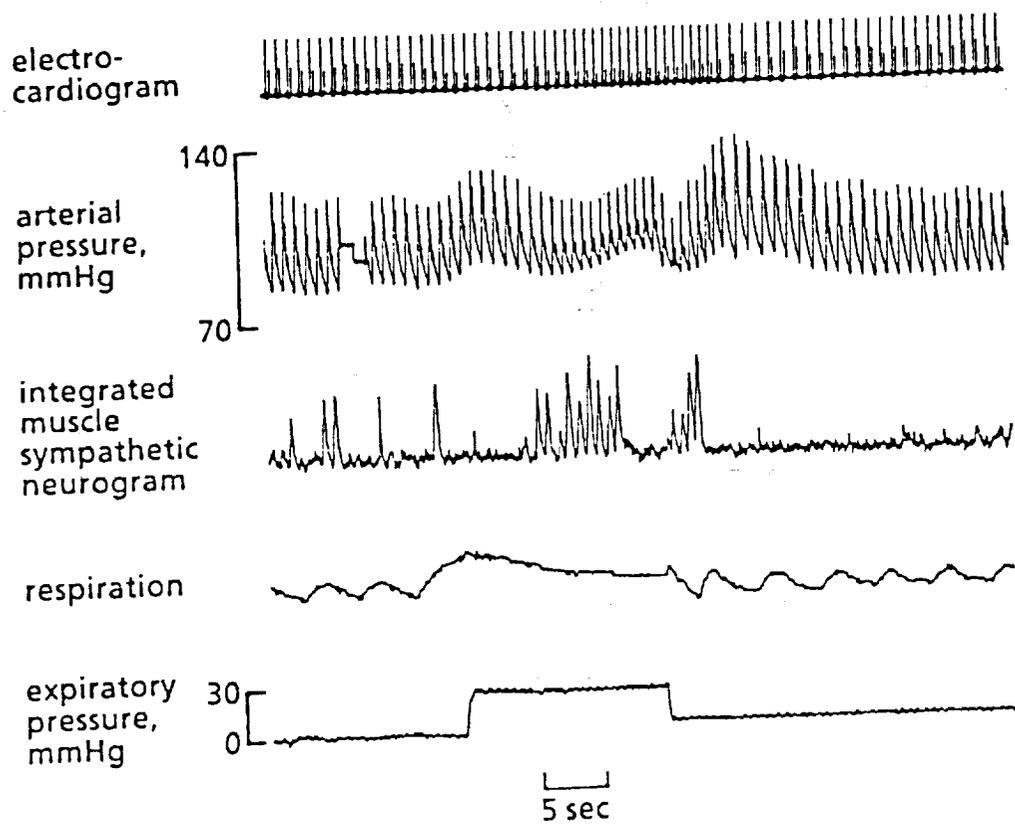


Figure 1. Original recording from a single trial for one subject.

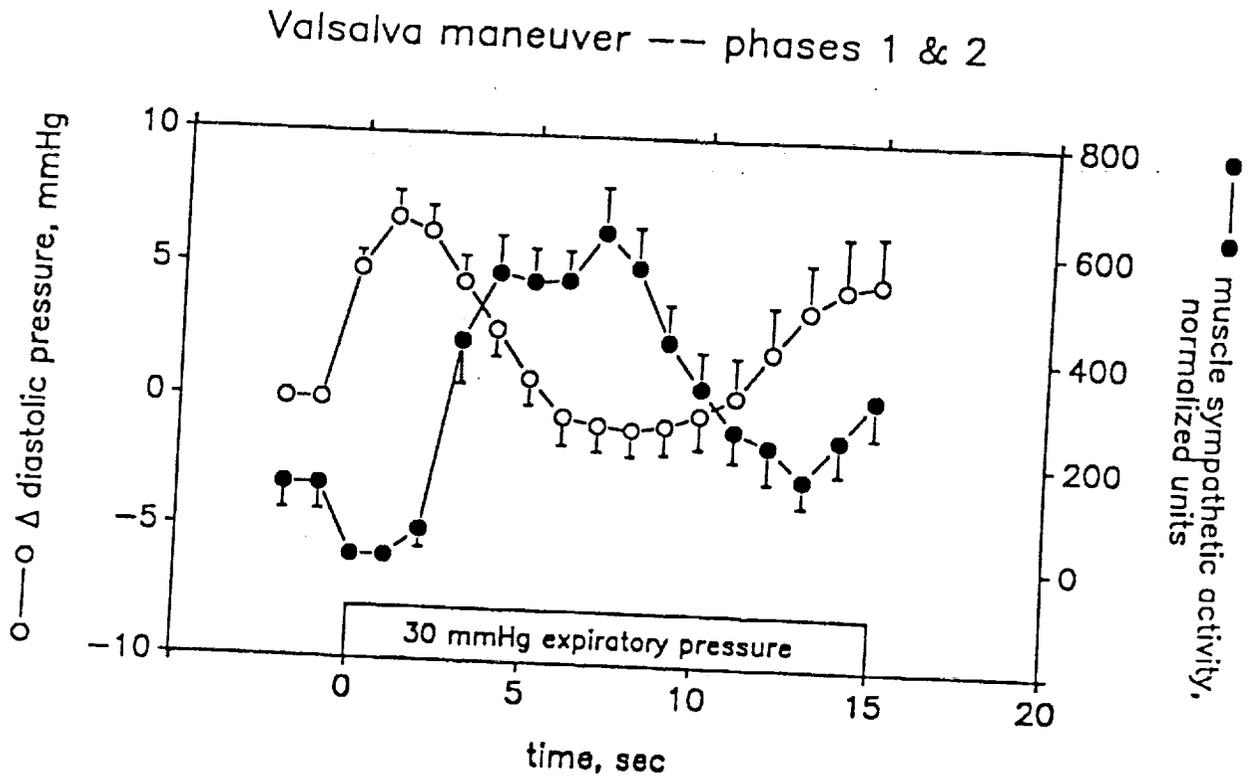


Figure 2. Average changes of muscle sympathetic nerve activity and diastolic pressure during 1-s time bins during 30 mmHg Valsalva maneuvers in 7 subjects. Brackets encompass one SEM. Muscle sympathetic activity was offset 1.3 s to account for nerve conduction latency.

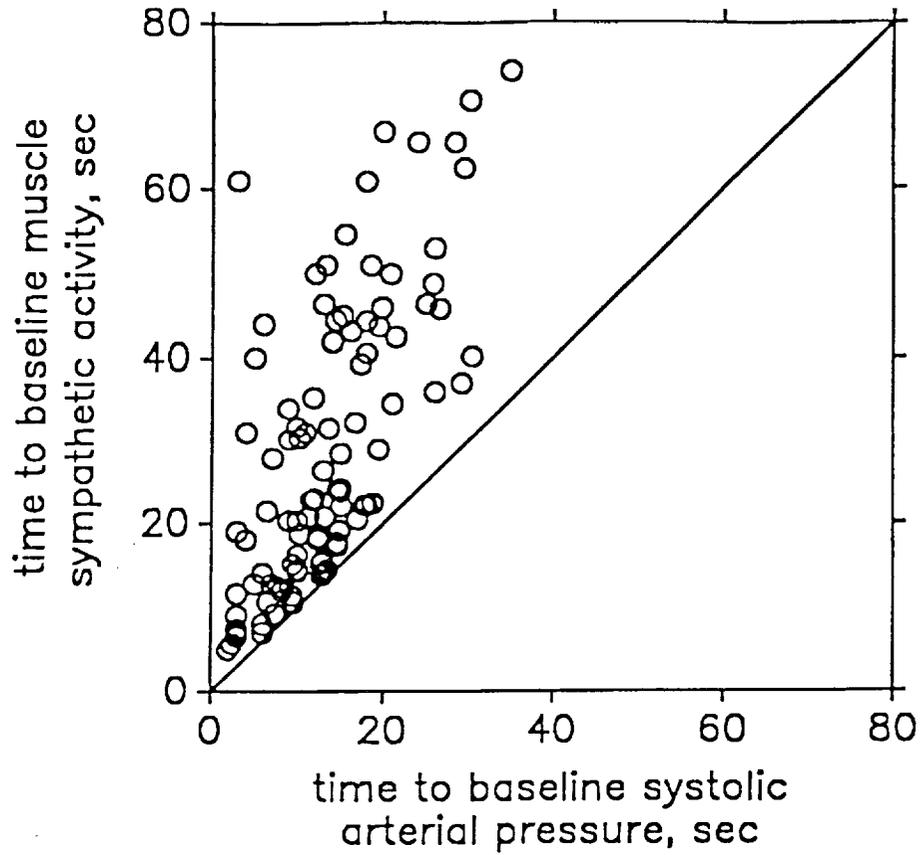


Figure 3 Relation between post-strain latency of return to baseline muscle sympathetic activity (ordinate) and post-strain latency of return to baseline systolic pressure (abscissa). These data indicate clearly that post-strain sympathetic inhibition extends beyond the return of arterial pressure to to baseline levels.



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**Mechanistic Studies on Reduced Exercise Performance
and Cardiac Deconditioning with Simulated Zero Gravity**

(NASA-NAG 2-392)

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Part I: Current Activities

A. Introduction

As indicated by the title, the primary purpose of this sponsored research is to study the physiological mechanisms associated with the exercise performance of rats subjected to conditions of simulated weightlessness. A secondary purpose is to study related physiological changes associated with other systems. To facilitate these goals, a rodent suspension model was developed (Overton-Tipton) and a $\dot{V}O_2$ max testing procedure was perfected.

Three methodological developments have occurred during this past year deserving of mention. The first was the refinement of the tail suspension model so that (a) the heat dissipation functions of the caudal artery can be better utilized and (b) the blood flow distribution to the tail would have less external constriction (Figure 1). The second was the development on a one-leg weight bearing model for use in simulated weightlessness studies (Figure 2) concerned with change in muscle mass, muscle enzyme activity and hindlimb blood flow.

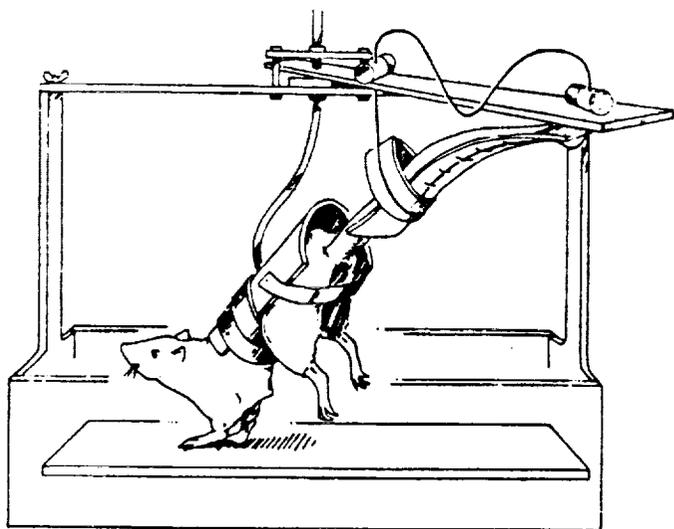


Figure 1

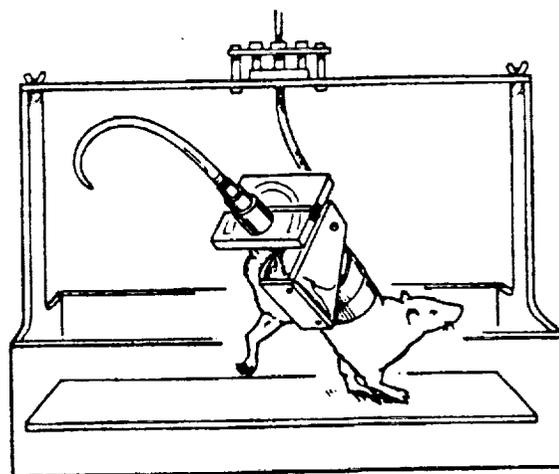


Figure 2

With the assistance of a visiting Professor, Dr. Roger Coomes and Mr. Craig Stump, a NASA Pre-Doctoral Fellow, the chemical body composition of 30 rats was determined and used to develop a prediction equation for percent fat using underwater weighing procedures to measure carcass specific gravity and to calculate body density, body fat and fat free mass. The mathematical least square equation that had the best fit was $Z = a/x + bY + c$ where: $a = -2136.4$, $x = \text{specific gravity} \cdot 10^5$, $b = 0.05555$, $y = \text{body mass in grams}$ and $c = -10.09180$. The correlation coefficient between the measured fat percentage and the predicted fat percentage was 0.834.

1. A comparative study on the effects of two suspension methods on select anatomical, biochemical and physiological variables.
 - a. We wanted to determine if exercise performance results were different depending upon the method selected.
 - b. Select results (\bar{X} , * intergroup statistical significance) from controls between the Morey-Holton and the Overton-Tipton models were as follows:

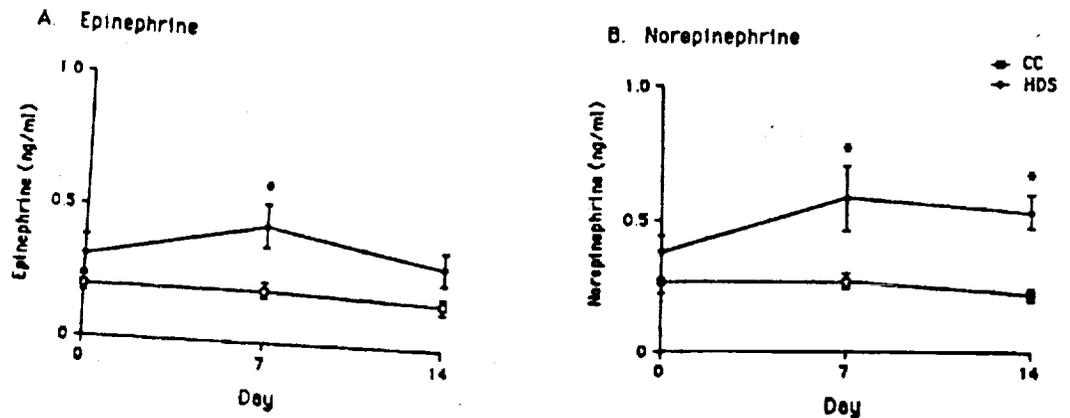
Group	N	% Change in Plasma NE (2 Days)	% Change in Plasma NE (9 Days)	% Change in Body Mass (14 Days)	% Change in VO ₂ max (14 Days)	% Change in Run Time (14 Days)
Cage Control	3-10	11	5	3	5	16
Morey-Holton	6-10	53*	47*	-5	-7	-26*
Overton-Tipton	7-9	71*	212*	-14*	0	-19*

2. Relevant findings from the one-leg weight (4) bearing model were:
 - a. The decrease in soleus muscle mass with suspension can be minimized or prevented by having one hindlimb support the mass of the animal.
 - b. The decrease in the activity of aerobic enzymes of the soleus muscle with suspension can not be prevented by having one hindlimb support the body mass of the animal.
 - c. The increase in resting blood pressure observed with a one-leg hindlimb suspension model may be associated with the integration of the afferent inputs by the medulla.
3. Conclusions:
 - a. We now have suspension techniques suitable to measure the effects of posture and weight bearing on a variety of physiological, biochemical, and anatomical parameters.
 - b. We can now better estimate the body compositional changes with simulated weightlessness.

B. The Influence of Sympathetic Nervous System

1. Time course of changes in catecholamines.

- a. To determine the changes in the Overton-Tipton model before initiating sympathectomy studies, a study with 10 control and 11 suspended rats was conducted. The results are listed in Figure 3 (\bar{X} , SE, * intergroup and intragroup difference that was statistically significant).



2. The effects of chemical sympathectomy and simulated weightlessness on exercise performance.

- a. To determine whether exercise performance would be altered after the "removal" of the sympathetic nervous system.
- b. Select $\dot{V}O_2$ max results with saline or guanethidine sulfate injections in male or female rats (\bar{X} , SE, * intragroup, ⊗ intergroup statistical significance, $ml \cdot mm^{-1} \cdot kg^{-1}$ or $ml \cdot min^{-1} \cdot kg$ FFM⁻¹).

Group	N	Pre-Suspension	After 7 Days	After 14 Days	After 14 Days (FFM)
SHAM (males)					
Cage Control	6	84±3	86±3	85±2	102±6
Suspended	6	84±2	87±1	80±2*	94±6
SYMX (males)					
Cage Control	6	81±1	82±2	77±2	88±4
Suspended	8	86±2	98±2*⊗	94±1*⊗	108±6*
SHAM (females)					
Cage Control	8	83±2	85±2	78±2	92±2
Suspended	7	89±1	84±2	88±2⊗	94±3
SYMX (females)					
Cage Control	6	88±4	89±3	88±3	104±3
Suspended	7	85±2	95±4*	94±4⊗	109±4

4. The combined influences of sympathectomy, adrenal demedullation and simulated weightlessness on exercise performance.
 - a. Although the results are in the analysis stage, the data (presented) are in form for publication.
 - b. Trends suggest that absolute $\dot{V}O_2$ max is significantly decreased when demedullation is coupled with sympathectomy. Changes in relative $\dot{V}O_2$ max are not as apparent.
5. Conclusions: The presence of circulating epinephrine (and its receptors) appears to be essential to avoid the marked decrease in $\dot{V}O_2$ max that occurs with weightlessness.

C. Effects of Simulated Weightlessness for 28 Days on Performance and Fat-free Mass

1. To determine whether longer durations would affect both exercise performance and fat-free mass.
 - a. Select results (\bar{X} , SE, * intragroup, ⊗ intergroup statistical significance) pertaining to % fat, $\dot{V}O_2$ max ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ or FFM⁻¹) or run time (min) of female rats.

Group	N	% Fat	Start	$\dot{V}O_2$ max		Run Time	
				End	End (FFM)	Start	End
Cage Control	9	12±1	99±3	92±2*	109±8	15±.6	13±.7*
Suspended	8	7±2*	96±3*	90±4	102±8	15±.8	10±.5*⊗

2. Conclusions: Simulated weightlessness causes more of a change in fat mass than in fat-free mass. Consequently, the decline in $\dot{V}O_2$ max is due to other mechanisms than a decrease in the active muscle mass.

D. The Effect of Prior Endurance Training on Exercise Performance of Rats Exposed to Conditions of Simulated Weightlessness for 28 Days

1. To determine whether trained rats would exhibit greater decreases in exercise performance than nontrained rats with suspension.
2. Results are after 6 weeks of training (\bar{X} SE, ⊗ intergroup statistical significance).

	N	Body Mass (g)	$\dot{V}O_2$ max ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$)	Run Time (Minutes)
Nontrained	12	344±16	82±2	12±.4
Trained	10	330±10	98±1⊗	16±.4*

3. The influence of simulated weightlessness for 28 days on the exercise performance of nontrained and trained animals.
 - a. Rational was the same as listed in above.

b. Results are (\bar{X} SE, * intragroup, ⊗ intergroup statistical significance) for body mass (gram), $\dot{V}O_2$ max ($ml \cdot min^{-1} \cdot kg^{-1}$) and run time (min).

Group	N	Body Mass		$\dot{V}O_2$ max		Run Time	
		Start	End	Start	End	Start	End
NT-Cage Control	12	344±16	431±11*	82±2	75±4	12±.4	11±.4
NT-Suspended	9	341±16	309±16*	81±4	77±3	12±.5	8±.2*⊗
T-Cage Control & Detraining	10	330±10	419±11*	91±1	84±3	16±.4	15±.5
T-Suspended	10	344±7	285±15*⊗	95±2	81±3*	16±3	10±1.1*⊗

4. Conclusions: Prior exercise training is associated with a faster decline in performance measures than nontrained rats during this time period. It is unknown whether the same trends would continue longer durations.

E. Published Results on the Effects of Simulated Weightlessness on Select Physiological Parameters.

1. Baroreflex control of heart rate (LBNP; sympathomimetic agents) was not significantly altered by 9 days of simulated weightlessness (3).
2. Suspended rats exhibited a reduced pressor response to phenylephrine injections than cage control rats. Also with this finding was a significant elevation in mesenteric vascular resistance (3).
3. Suspended rats had greater decreases, but not statistically, in plasma volume than nonsuspended rats (3).
4. Blood flow results obtained from Doppler probes indicated that:
 - a. Suspension was associated with an increase in iliac and mesenteric vascular resistance during exercise (3).
 - b. Iliac blood flow was significantly decreased after 48 hours suspension (4).
 - c. The decrease in iliac blood flow with suspension was prevented by having one hindlimb support the weight of the animal (4).
5. The effects of simulated weightlessness on the rise in core temperature with a gradual heat challenge indicated that the suspended rats reached 40.5°C sooner than their nonsuspended controls. We speculate that these results occur because of a reduction in hindlimb blood flow and a decline in plasma volume.

Part II: Future Projects and Their Relevance to Current or Future NASA Projects

- A. The influence of 42-56 days of simulated weightlessness on exercise performance as evaluated by $\dot{V}O_2$ max, run time and mechanical efficiency.
- B. The influence of 42-56 days of simulated weightlessness on resting and exercise cardiac hemodynamics, plasma volume, blood gas changes, and baroreflexes.

- C. The influence of an elevated plasma volume on the prevention of $\dot{V}O_2$ max changes with short (14 day) and long (42-56) durations of simulated weightlessness.
- D. The influence of short (14 days) and long (42-56) durations of simulated weightlessness on tissue norepinephrine turnover rates.
- E. The influence of front leg exercise training by suspended rats on their whole body $\dot{V}O_2$ max values.
- F. The influence of short (14 days) and long durations (42-56 days) of simulated weightlessness on the exercise performance of hypophysectomized rats.

Part III. Publications Associated Directly or Indirectly with NASA-NAG 2-392

A. Manuscripts Published in 1990

- 1) Kregel, K.C., D.G. Johnson, C.M. Tipton, and D.R. Seals. Arterial baroreceptor reflex modulation of sympathetic cardiovascular adjustments to heat stress. Hypertension 15:497-504, 1990.
- 2) Kregel, K.C., C.M. Tipton, D.R. Seals. Thermal adjustments to nonexertional heat stress in mature and senescent Fisher 344 rats. J. Appl. Phys. 68:1337-1342, 1990.
- 3) Overton, J.M. and C.M. Tipton. Effect of hindlimb suspension on cardiovascular responses to sympathectomized and lower body negative pressure. J. Appl. Physiol. 68:355-362, 1990.
- 4) Stump, C.S., J.M. Overton, and C.M. Tipton. Influence of a single hindlimb support during simulated weightlessness in the rat. J. Appl. Physiol. 68:627-634, 1990.

B. Abstracts Published in 1990

- 5) Coomes, R.K., L.A. Sebastian, C.S. Stump, P.K. Edwards, and C.M. Tipton. Influence of two methods of head-down suspension (HDS) on the stress response of rats: Preliminary Results. ASGSB Bulletin. 4(1) 73, 1990.
- 6) Kregel, K.C., J.M. Overton, D.G. Johnson, C.M. Tipton, and D.R. Seals. Cardiovascular sympathoadrenal and thermal adjustments to nonexertional heat stress in the conscious rat. FASEB J. 4(3):A889, 1990.
- 7) Stump, C.S., C.R. Woodman, and C.M. Tipton. Exercise induced glycogen depletion in select rat hindlimb muscles after two weeks of hindlimb suspension. Med. Sci. Sports Exerc. 22(2):S52, 1990.
- 8) Woodman, C.R., K.C. Kregel, and C.M. Tipton. Thermal responses to non-exertional heat stress following simulated weightlessness in the conscious rat. FASEB J. 4(3):A569, 1990.
- 9) Woodman, C.R., C.S. Stump, L.A. Sebastian, and C.M. Tipton. Influences of 28 days of hindlimb suspension on the $\dot{V}O_2$ max of trained and nontrained rats. ASGSB Bulletin, 4(1):65, 1990.



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P.12

**Fluid compartment and renal function alterations in the rat
during 7 and 14 day head down tilt**

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Exposure to conditions of microgravity for any extended duration can modify the distribution of fluid within the vascular and interstitial spaces, and eventually intracellular volume. Whether the redistribution of fluid and resetting of volume homeostasis mechanisms is appropriate for the long term environmental requirements of the body in microgravity remains to be fully defined. The event that initiates the change in fluid volume homeostasis is the cephalad movement of fluid which potentially triggers volume sensors and stretch receptors (atrial stretch with the resulting release of atrial natriuretic peptide) and suppresses adrenergic activity via the carotid and aortic arch baroreceptors. All these events act in concert to reset blood and interstitial volume to new levels, which in turn modify the renin-angiotensin system. All these factors have an influence on the kidney, the end organ for fluid volume control. How the fluid compartment volume changes interrelate with alterations in renal functions under conditions of simulated microgravity is the focus of the present investigation which utilizes 25-30° head-down tilt in the rat.

A previous investigation by our laboratory studied the effects of head-down tilt (HDT) during the first seven days of suspension utilizing both chronic cannulation, thereby allowing repeated measures in the same rat, and renal micropuncture methods (1). In this study we examined the changes in extracellular fluid volume and renal function during the time course of HDT in the rats. The measurements of extracellular fluid volume and whole kidney function were performed in awake rats, thus permitting evaluation of the time course alterations in renal function in conscious non-surgically stressed rats. The HDT group was compared to suspended but non-tilted controls. In addition to the awake

studies, renal micropuncture techniques were utilized to ascertain the changes in the determinants of glomerular ultrafiltration at the single nephron level in rats exposed to seven days of HDT (1). Plasma renin activity, plasma catecholamine concentrations, and urinary catecholamine excretion were also measured to ascertain whether any of the changes in glomerular dynamics observed could be correlated with these factors which regulate systemic and renal vascular resistance (1).

In this first study, extracellular fluid space (ECF) significantly increased within 24 hr after the onset of HDT and then returned gradually to pre-tilt values by the end of the 7 day HDT (figure 1). Glomerular filtration rate (GFR) also increased significantly ($19 \pm 8\%$) within 24 hours with a gradual decline and finally a significant reduction ($-7 \pm 1\%$) by day 7 of head-down tilt (figure 1). The changes in GFR were most likely renal plasma flow dependent since the GFR changes paralleled the alteration in renal plasma flow except after seven days HDT where GFR was reduced and renal plasma flow was not different from control values (figure 1). In general, urine flow increased by 24 hours of HDT and remained elevated throughout the 7 days of simulated microgravity (figure 2). Both urinary sodium and potassium excretion changes were less consistent during the seven day HDT (figure 2).

At the end of seven day HDT another group of rats were submitted to renal micropuncture studies to ascertain which of the determinants of glomerular filtration contributed to the reduction in filtration rate. In superficial nephrons, single nephron glomerular filtration rate (SNGFR) decreased from 43 ± 2 to 31 ± 3 nl/min which was due solely to reductions in the glomerular ultrafiltration coefficient (1). These data are

consistent with the awake rat renal function measurements in which parameters other than renal plasma flow were responsible for the reduction in glomerular filtration rate. This first study was successful in delineating some of the specific alterations in renal function that occur in this model of cephalad fluid shift and relative hypokinesia, findings which are similar to human studies in situations of simulated microgravity (2).

In more recent studies, initiated this year with the start of NAG 2-659, two separate groups of rats were utilized to examine blood volume changes, extracellular fluid volume, and renal function alterations during 14 day HDT and 7 days post-tilt recovery. The major focus of this study was to further define the applicability of this model for longer term studies simulating the changes that occur in humans under conditions of microgravity and recovery and to correlate the changes in fluid compartment volumes to alterations in renal function to ascertain if the kidneys were responding to maintain volume homeostasis.

In the first group of rats, chronic cannulation of the femoral artery and vein was performed and the animals were allowed one week to recover. The rats were separated into four subgroups (n=6 in each group) and either tail suspended for 1, 7, or 14 days or left in the normal orthostatic position. Blood volume was measured in each of the four subgroups of awake rats utilizing ^{51}Cr labeled endogenous erythrocytes and the changes in volume with duration of HDT was compared to non-tilted controls. Although not significant, blood volume tended to increase from 5.4 ± 0.1 to $5.6 \pm 0.1\%$ of body weight after 24 hrs HDT (figure 3). By day 7, blood volume significantly decreased to $5.0 \pm 1\%$ of body weight and decreased further to $4.8 \pm 0.1\%$ by day 14 of HDT similar to observations made in humans (figure 3). There were no differences in body weight,

systemic hematocrit, or plasma protein concentrations among the four subgroups indicating that the observed blood volume changes were independent of these factors.

In the second group of rats cannulation of the femoral artery and vein and bladder was performed as in prior studies for chronic monitoring of extracellular volume, systemic electrolytes and plasma protein concentration as well as renal function (GFR, renal plasma flow, urine flow rate, urinary sodium and potassium excretion). Serial measurements of these parameters were performed twice prior to HDT and then at 24 hrs, 3, 7, 10, and 14 days during HDT. After the 14 day HDT period was completed, all rats were returned to normal orthostatic position and, after a 45 min waiting period, the measurements were repeated. Measurements were also performed at 24 hrs, 3, and 7 days post-HDT. All values were compared to pre-tilt control measurements in the same rat on a paired basis. Similar to our previous findings, extracellular fluid volume increased from 28.2 ± 3.1 to 31.4 ± 3.5 % of body weight after 24 hrs of HDT and then steadily decreased to 24 ± 2.1 % of body weight by day 7 (figure 4). By day 14, ECF returned to values not different from control (27.3 ± 1.2 % of body weight). During post-tilt recovery, ECF did not differ from pre-tilt control values (figure 4). GFR increased during HDT from 2.1 ± 0.1 in control to 2.3 ± 0.2 after 24 hrs HDT and to 2.8 ± 0.2 ml/min after 3 days HDT (figure 5). By day 7, GFR was not different from control (2.2 ± 0.1 ml/min) and GFR at day 14 HDT was 2.3 ± 0.2 ml/min, also not different from pre-tilt values (figure 5). It was surprising that GFR remained at values not different from control despite the decrease in blood volume and 7 and 14 days HDT. Post-tilt GFR values were not different from pre-tilt values measured in this group of rats (figure 5). Renal plasma flow increased by day 3 of HDT

but did not significantly deviate from control values at the other measurement time points (figure 6). In early HDT, there seems to be a mild volume expansion with concomitant increase in GFR and renal plasma flow, but after the initial expansion phase, ECF and renal function return to values not different from pre-tilt measurements with a decrease in blood volume.

These definition phase studies provide a low cost, ground based alternative for investigation of fluid compartment volume alterations and renal function in microgravity conditions. The results are quite similar to the studies in humans where some of the same parameters were measured in HDT. However, the rat also provides a model for more invasive studies, such as renal micropuncture, as well as a vehicle for therapeutic trials to modify cardiovascular and renal response due to long term exposure to microgravity. Also, this model can easily be extended to examine volume homeostasis and renal function under conditions of 30-90 days of simulated microgravity.

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Figure 1

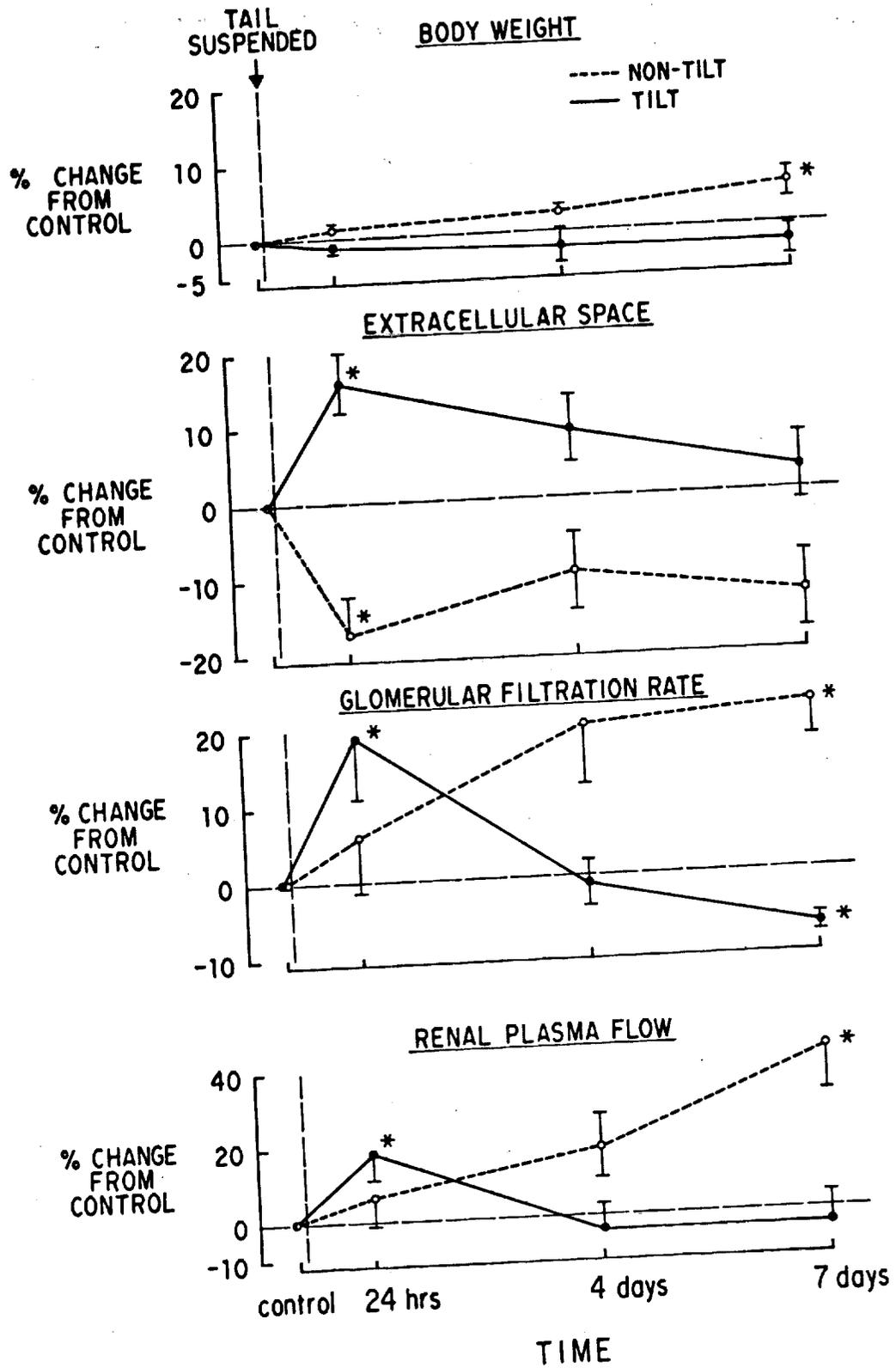
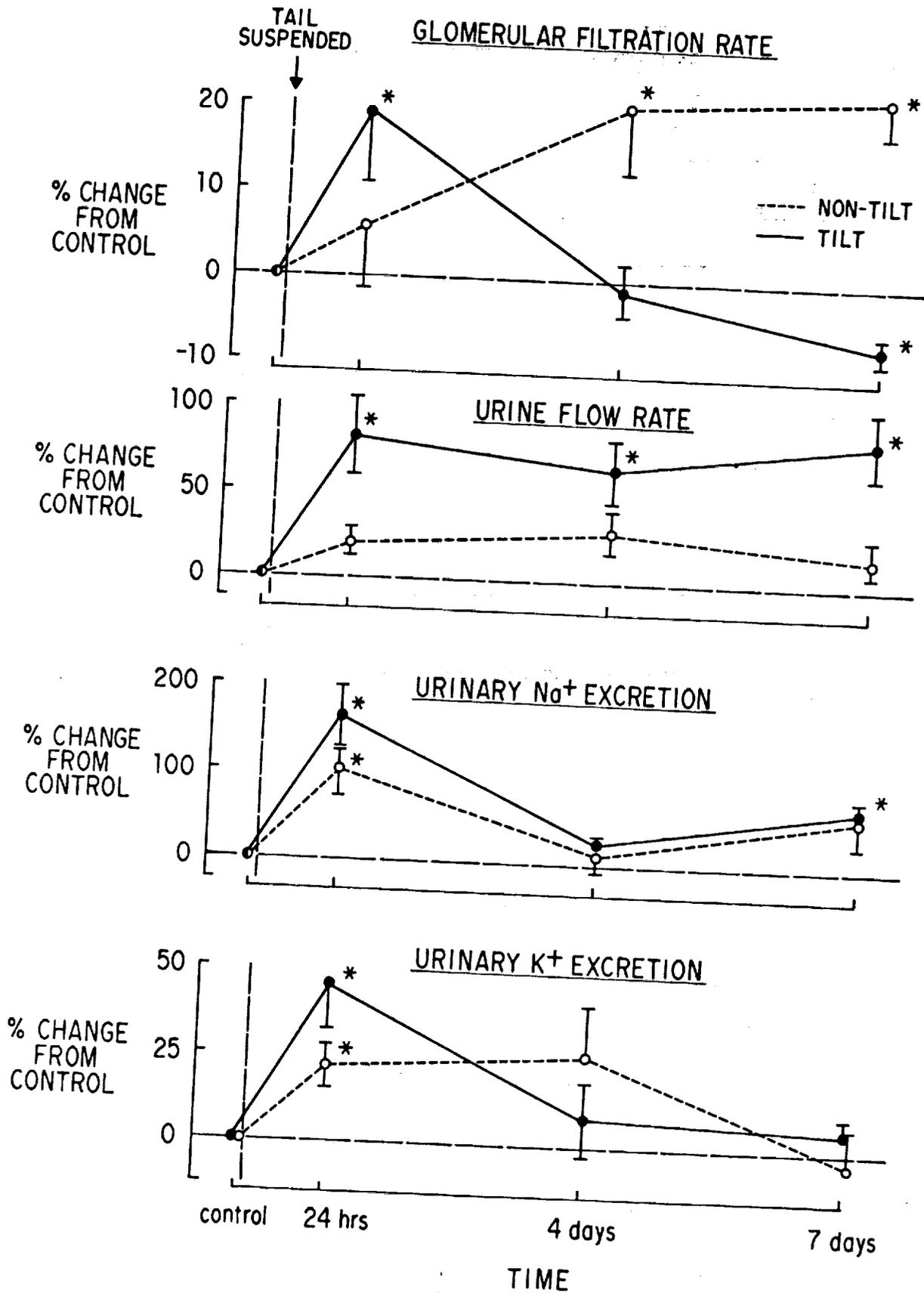


Figure 2



BLOOD VOLUME CHANGES IN HEAD DOWN TILT

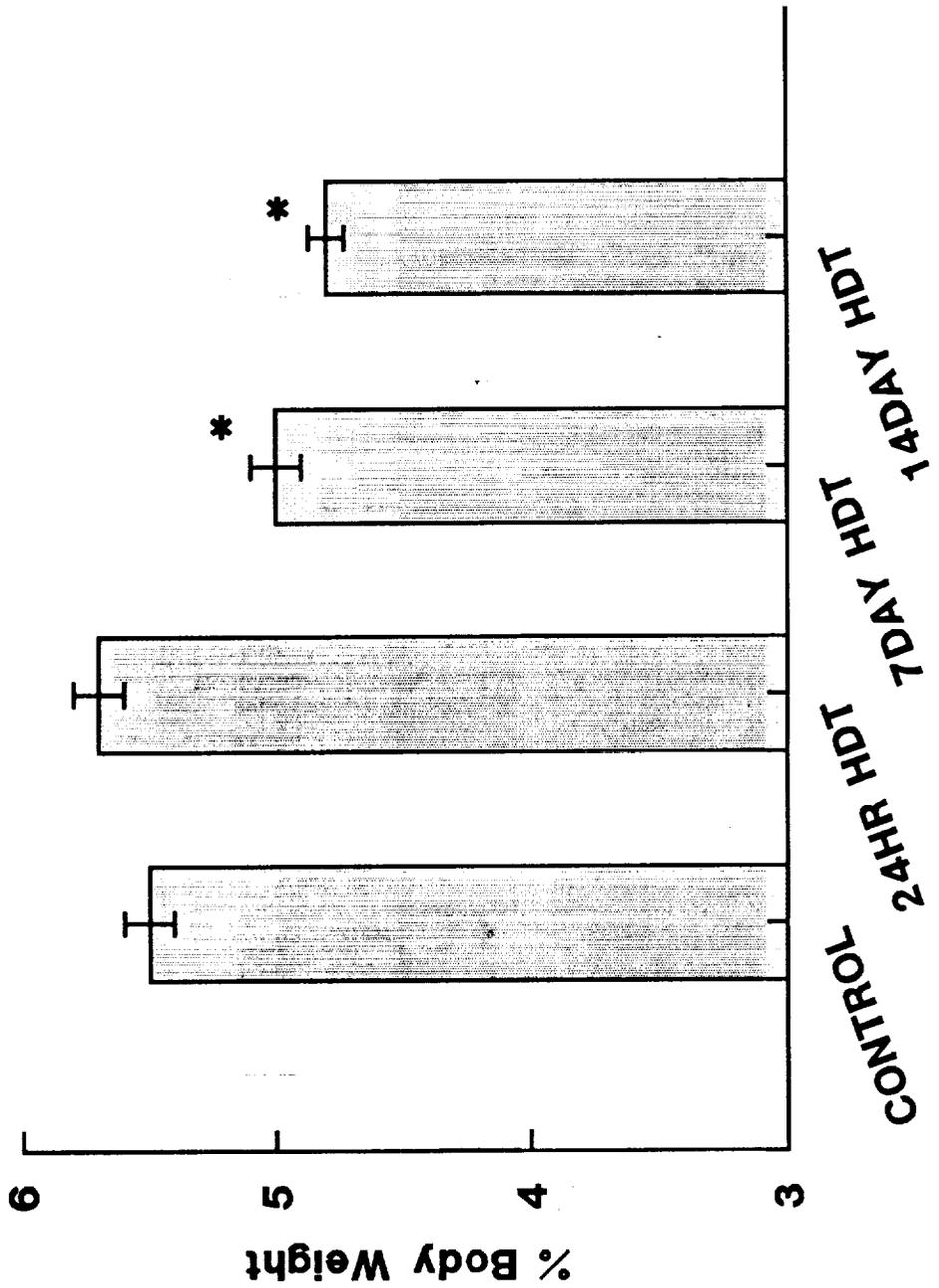


Figure 3

EFFECT OF HDT ON EXTRACELLULAR FLUID VOLUME

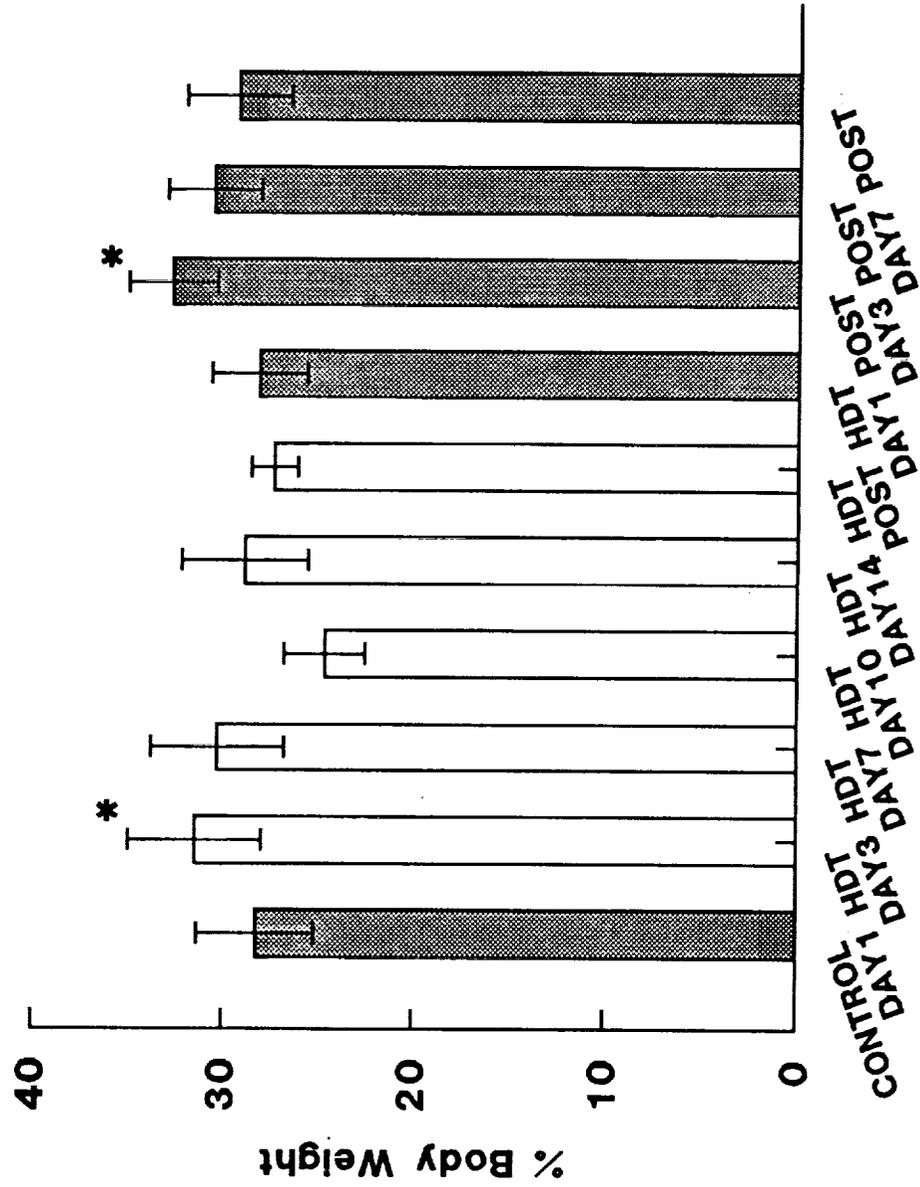


Figure 4

EFFECT OF HDT ON GLOMERULAR FILTRATION RATE

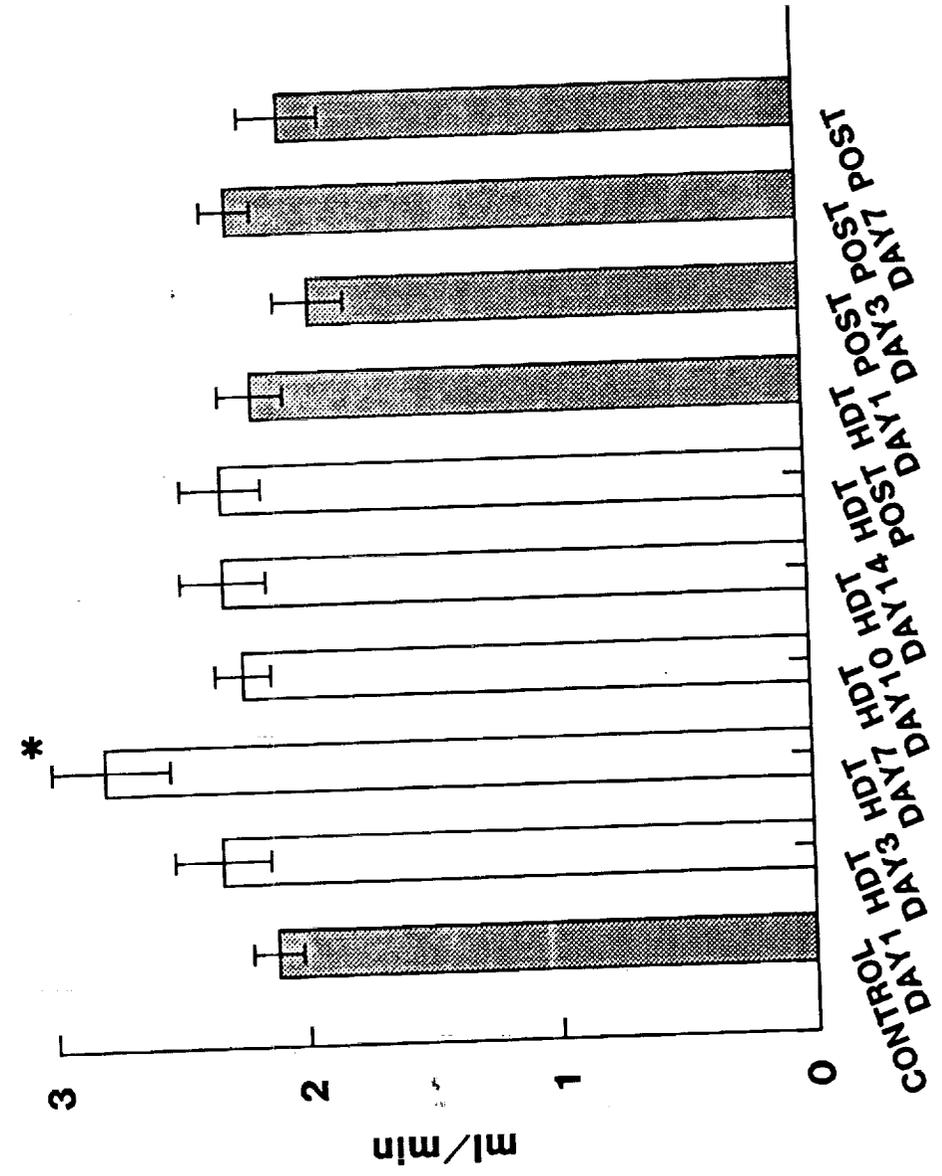


Figure 5

EFFECT OF HEAD DOWN TILT ON RENAL PLASMA FLOW

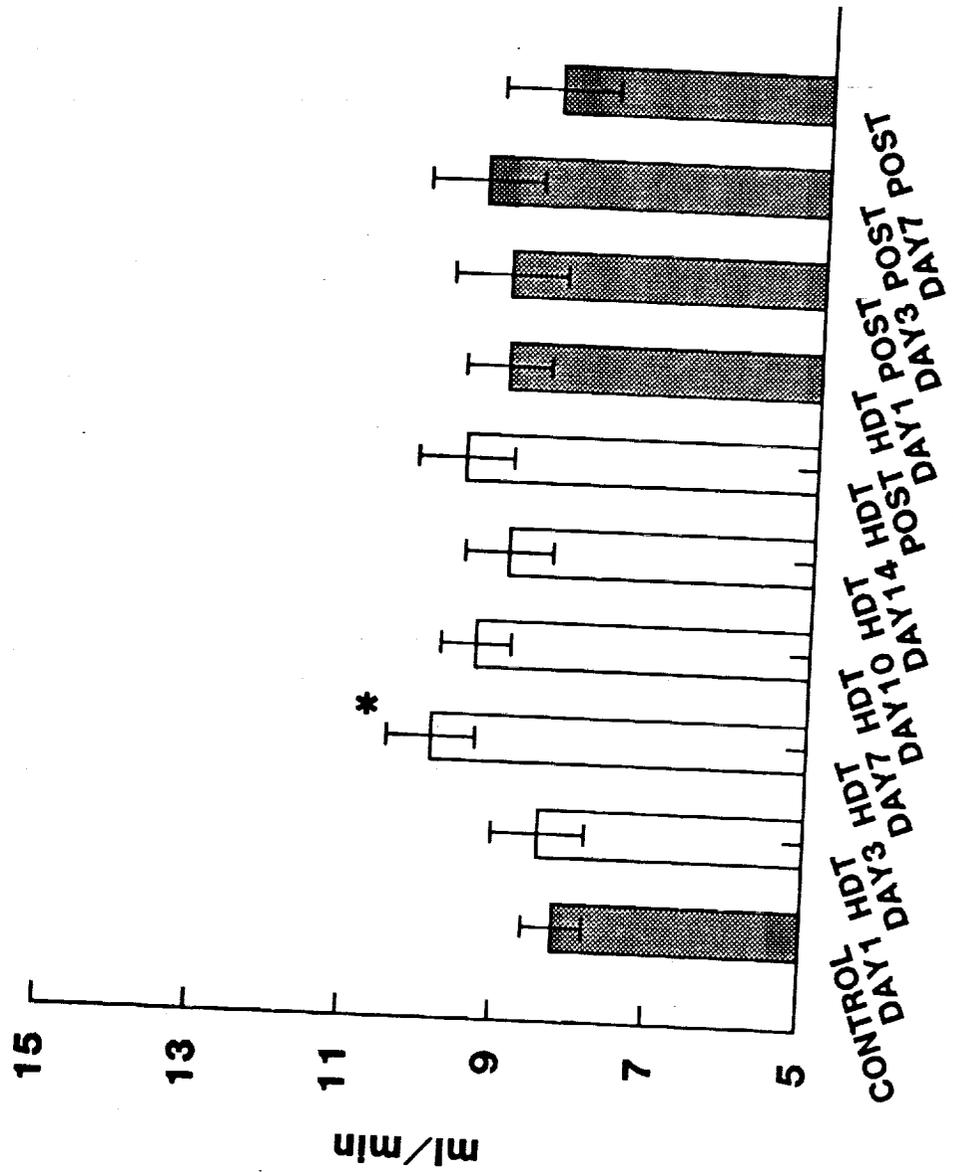


Figure 6

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LOCAL FLUID SHIFTS
AND EDEMA IN HUMANS
DURING SIMULATED MICROGRAVITY

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A. Mechanisms of Headward Edema Formation during Head-Down Tilt

Co-Investigators: S.E. Parazynski, M. Aratow, B. Tucker, J. Styf, and A. Crenshaw

Recent Results:

To understand the mechanism, magnitude and time course of facial puffiness that occurs in microgravity, seven male subjects were tilted 6° head-down for 8 hours, and all four Starling transcapillary pressures were directly measured before, during, and after tilt (1-4). Head-down tilt (HDT) caused facial edema and a significant elevation of microvascular pressures measured in the lower lip: capillary pressure increased from 27.7 ± 1.5 mm Hg pre-HDT to 33.9 ± 1.7 mm Hg by the end of tilt (Fig. 1). Subcutaneous and intramuscular interstitial fluid pressures in the neck also increased as a result of HDT, while interstitial fluid colloid osmotic pressures in these tissues remained unchanged. Plasma colloid osmotic pressure dropped significantly by 4 hours of HDT (21.5 ± 1.5 mm Hg pre-HDT to 18.2 ± 1.9 mm Hg at 4 hours HDT), suggesting a transition from fluid filtration to absorption in capillary beds between the heart and feet during HDT (Fig. 2). After 4 hours of seated recovery from HDT, microvascular pressures (capillary and venule pressures) remained significantly elevated from baseline values, despite a significant HDT diuresis and the orthostatic challenge of an upright, seated posture. These results suggest that facial edema resulting from HDT is primarily caused by elevated capillary pressure in the head and decreased plasma colloid osmotic pressure. Post-tilt maintenance of elevated cephalic capillary pressure may suggest a compensatory vasodilation to maintain microvascular perfusion.

Significance and Future Plans:

This study represents the first direct measurement of all four Starling pressures in humans and the first time that micropuncture was applied to the human microcirculation above heart level (5). These results have elucidated the mechanism of facial puffiness during microgravity. Our results also indicate the need for measurement of intracranial pressure (ICP) during head-down tilt and actual microgravity. These results have important implications to long-duration missions because some cosmonauts had facial edema for up to one year and intracranial edema may limit performance. Future plans will: 1) investigate the post-tilt recovery period for longer times, 2) hopefully investigate ICP in rhesus monkeys during a future Cosmos mission, and 3) develop a noninvasive ICP technique for application to studies of crew during actual microgravity.

B. Postural Responses of Head and Foot Microcirculations and their Sensitivity to Bed Rest

Co-Investigators: M. Aratow, J.-U. Meyer, and S.B. Arnaud

Recent Results:

To explore further the mechanism of facial puffiness, headache, and nasal congestion associated with microgravity, the postural responses of the cutaneous microcirculation in the forehead and dorsum of the foot of 8 healthy men were studied by changing body position on a tilt table and measuring blood flows with a laser-Doppler flowmeter (6-8). Increasing arterial pressure in the feet by moving from a 6° head-down tilt to a 60° head-up posture significantly decreased foot cutaneous flow by $46.5 \pm 12.0\%$ (Fig. 3). Raising arterial pressure in the head by tilting from the 60° head-up to 6° head-down posture significantly increased forehead cutaneous flow by $25.5 \pm 7.2\%$. To investigate the possibility that these opposite responses could be modified by simulated microgravity, tilt tests were repeated after 7 days of 6° head-down tilt bed-rest. On the 1st and 2nd days after bed-rest, flows in the foot were decreased by $69.4 \pm 8.8\%$ and $45.8 \pm 18.7\%$, respectively, and increased in the head by $39.3 \pm 8.6\%$ and $15.5 \pm 5.9\%$, respectively. These responses were not significantly different from those recorded before bed-rest.

Significance and Future Plans:

Cutaneous microcirculatory flow in the feet is well regulated to prevent edema when shifting to an upright position, whereas there is little regulation in the head microcirculation with head-down tilt. The lack of regulation in the forehead cutaneous microcirculation increases capillary flow, and consequently increases fluid filtration. This phenomenon helps explain the facial edema associated with the simulated or actual microgravity environment. Future plans include longer-term bed-rest experiments and studies of intracranial blood flow by transcranial Doppler and correlation of blood flow alterations with performance indices in human subjects. The development of arterial and microvascular adaptations to gravitational blood pressure gradients is well documented in tall species such as humans and giraffes. It is expected that some or all of this vascular adaptation will be lost during long-duration flight.

C. Transcapillary Fluid Transport Associated with LBNP with and without Saline Ingestion

Co-Investigators: S. Fortney, M. Aratow, D.E. Watenpaugh,
and A. Crenshaw

Recent Results:

Lower body negative pressure (LBNP) may enhance fluid replacement during spaceflight by sequestering fluids in the lower body to help maintain plasma volume and post-flight orthostasis. We hypothesized that saline ingestion during LBNP would further increase transcapillary fluid filtration into leg interstitium and further improve postflight orthostatic tolerance. Six subjects underwent 4 h of 30 mm Hg LBNP and 50 min of recovery on two separate days with and without drinking one liter of isotonic saline during LBNP (9-11). Interstitial fluid pressures (IFP), venous pressure (VP), and change in circumference (LC) were continuously measured in the leg. Whole-body transcapillary fluid transport rate (TFT, net filtration if $TFT < 0$) was determined by subtracting urine production and insensible fluid loss from changes in plasma volume. Leg IFPs decreased in parallel with LBNP (3.0 ± 2.6 mm Hg to -26.5 ± 2.9 mm Hg, $p < 0.05$), yet VP remained constant (Fig. 4). Although IFPs returned to baseline after LBNP alone, LC remained $4.1 \pm 1.3\%$ above baseline at 50 min of recovery ($p < 0.05$) (Fig. 5). Saline ingestion increased post-LBNP IFP and LC relative to LBNP alone. TFT was 145 ± 10 ml/h (723 ± 43 ml) during LBNP with saline ingestion, compared to -7 ± 12 ml/h (-40 ± 64 ml) during LBNP alone.

Significance and Future Plans:

Increased vascular transmural pressure during LBNP led to venous pooling and filtration into lower body interstitium, yet reabsorption from upper-body interstitium compensated for this filtration during LBNP alone. Saline ingestion with LBNP supplemented lower-body interstitial volume. Post-LBNP reabsorption of fluid from lower-body interstitium was similar with and without saline ingestion, which indicates about half of the fluid load remained in the interstitial space at 50 min of recovery. Future plans may include studies of other types of fluid ingestion and LBNP as well as evaluation of the effect on post bed-rest orthostatic intolerance. These results provide objective data on possible use of LBNP and saline ingestion to improve orthostatic tolerance following short-duration as well as long-duration flight.

References:

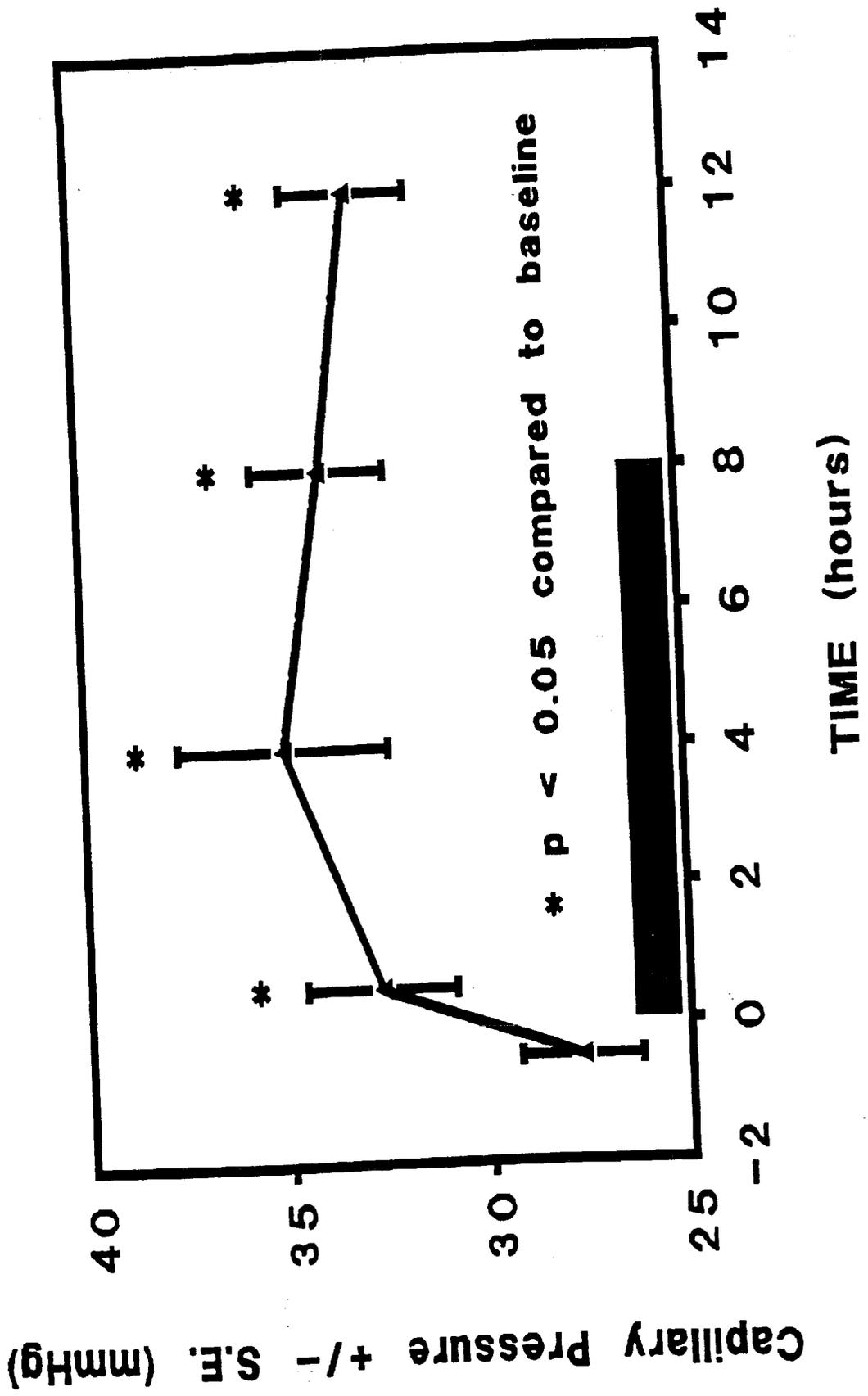
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Figure Legends:

- Figure 1: Capillary blood pressure increased significantly in the lip within the first half hour of HDT and remained elevated throughout HDT and in the recovery period. Lower bar indicates period of HDT.
- Figure 2: Plasma colloid osmotic pressure decreased significantly after 4 hours HDT. Lower bar indicates period of HDT.
- Figure 3: Responses of the forehead and dorsal foot cutaneous microcirculations to an arterial pressure increase before and after a one week period of bedrest. Forehead microcirculatory flow increases significantly whereas that in the foot decreases significantly with increased local blood pressure. The clear bars represent the percentage change in forehead cutaneous flow caused by a tilt to the head-down position, and the response of the foot cutaneous flow caused by a tilt to the head-up position is represented by the shaded bars. The magnitudes of these changes due to 7 days of bed rest were not significantly different from each other.
- Figure 4: Tissue fluid and foot venous pressures during LBNP with and without saline ingestion. The lower rectangle labelled "LBNP" in each graph represents the time period during which LBNP was applied to each subject. The subdivisions at the beginning and end of the rectangle represent the ramp up and ramp down of the chamber pressure. The rectangle in each graph labelled "saline" represents the time period over which the subject was required to drink 1 liter of isotonic saline.
- Figure 5: Calf circumference change, calculated plasma volume, and serum colloid oncotic pressure during LBNP with and without saline ingestion. The lower rectangle labelled "LBNP" in each graph represents the time period during which LBNP was applied to each subject. The subdivisions at the beginning and end of the rectangle represent the ramp up and ramp down of the chamber pressure. The rectangle in each graph labelled "saline" represents the time period over which the subject was required to drink 1 liter of isotonic saline.

FIGURE 1

Capillary Blood Pressure



Plasma Colloid Osmotic Pressure

Colloid Osmotic Pressure +/- S.F. (mmHg)

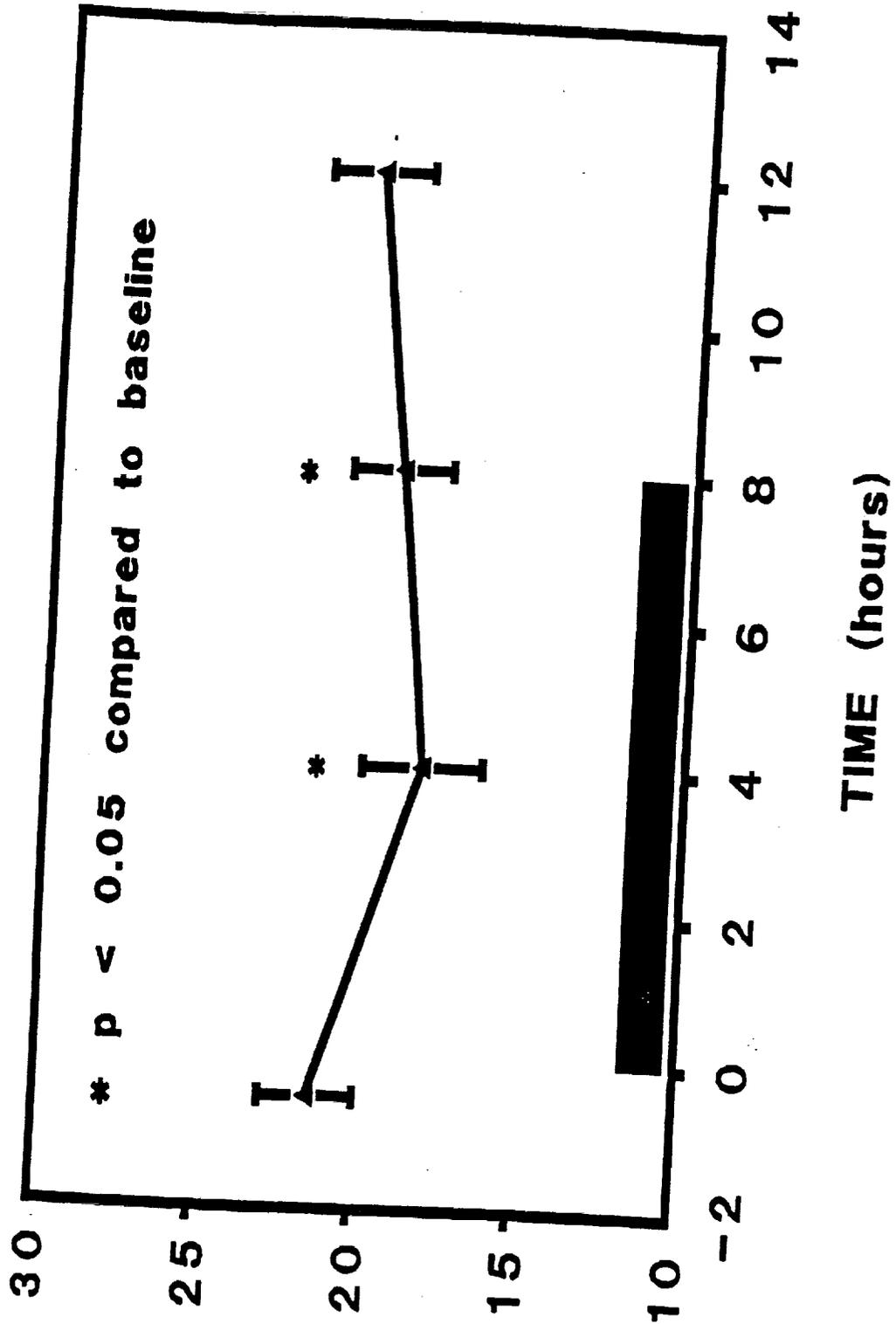
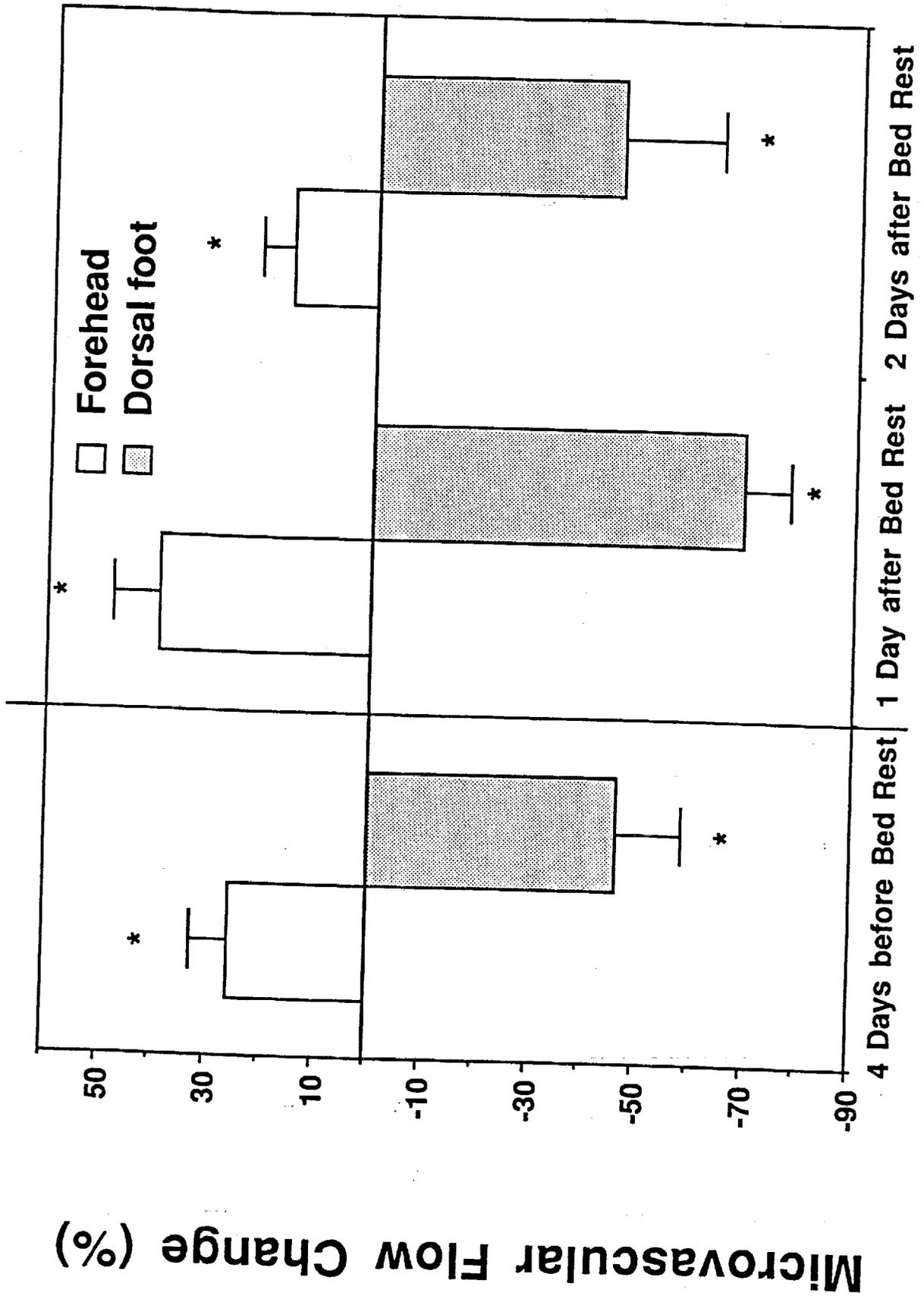


FIGURE 2



*p < 0.05 compared to pre-tilt microvascular flow

FIGURE 4

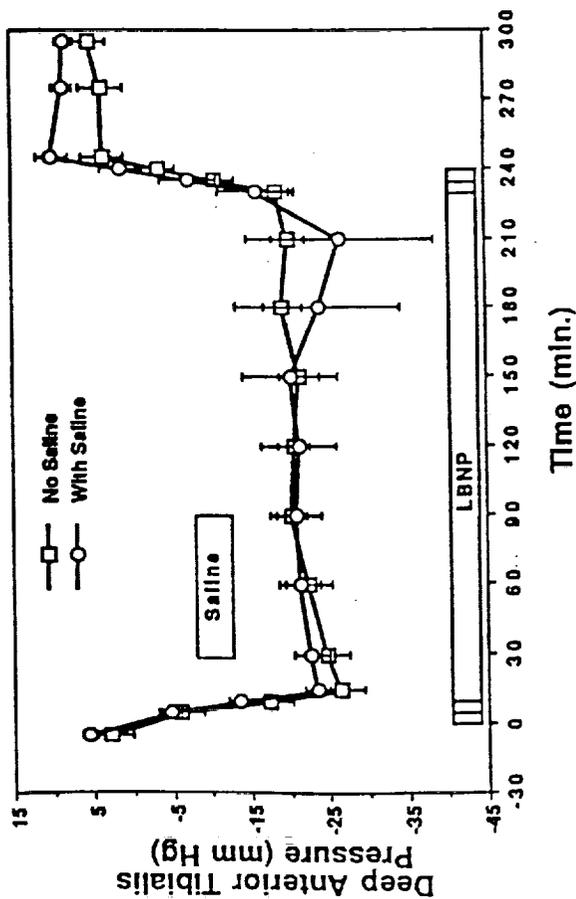
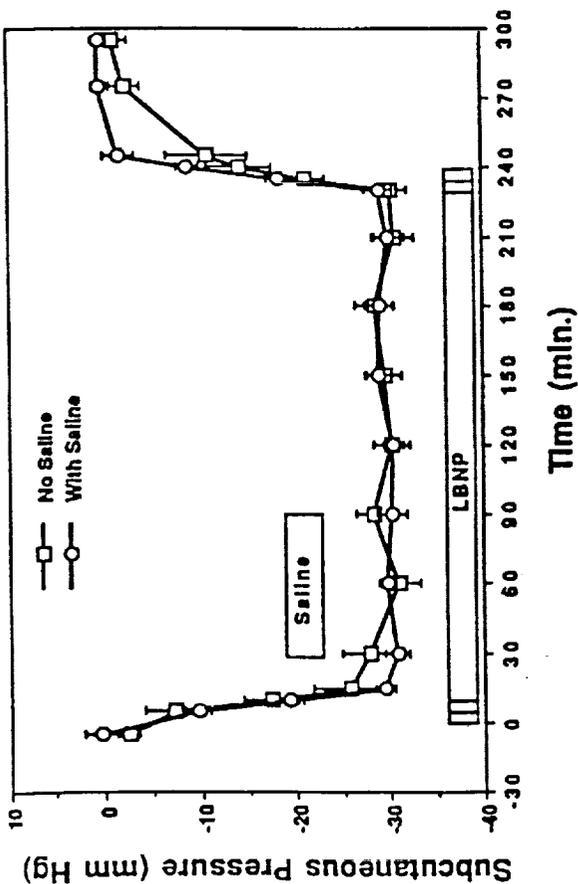
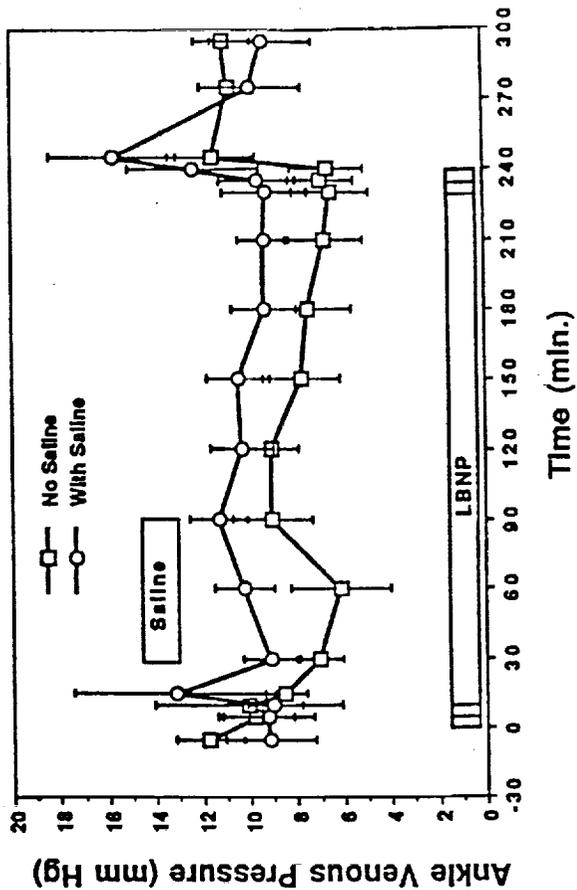
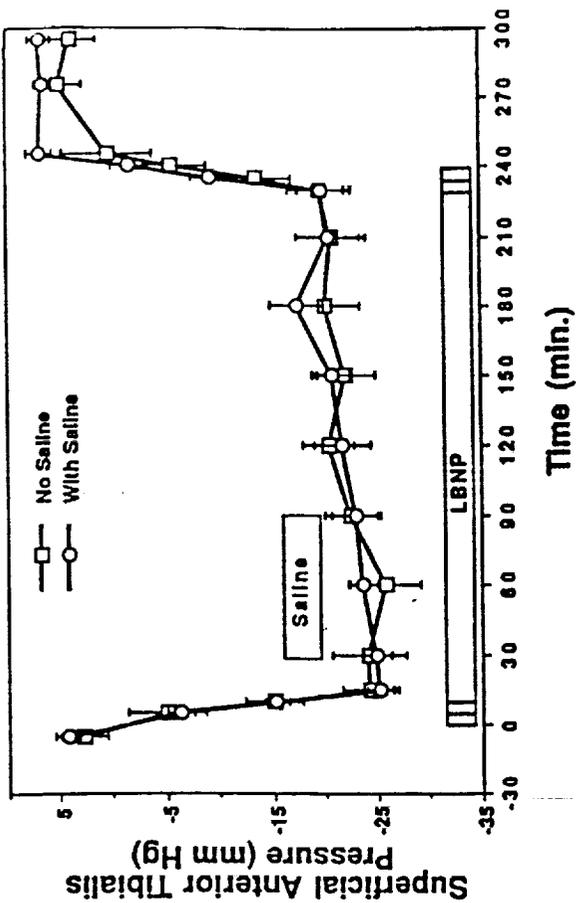
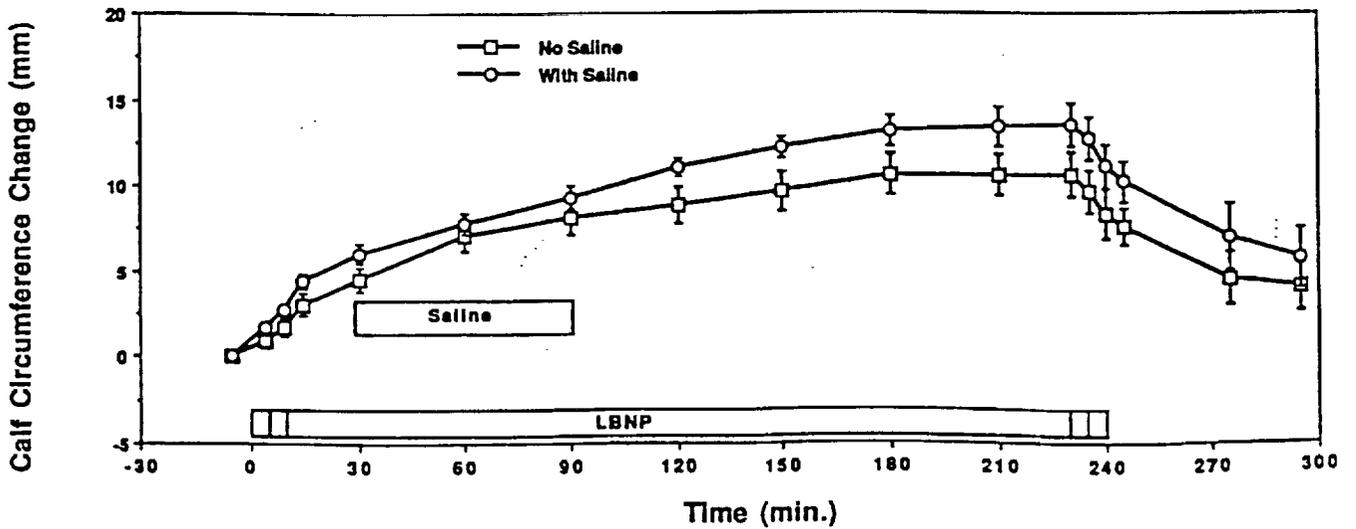
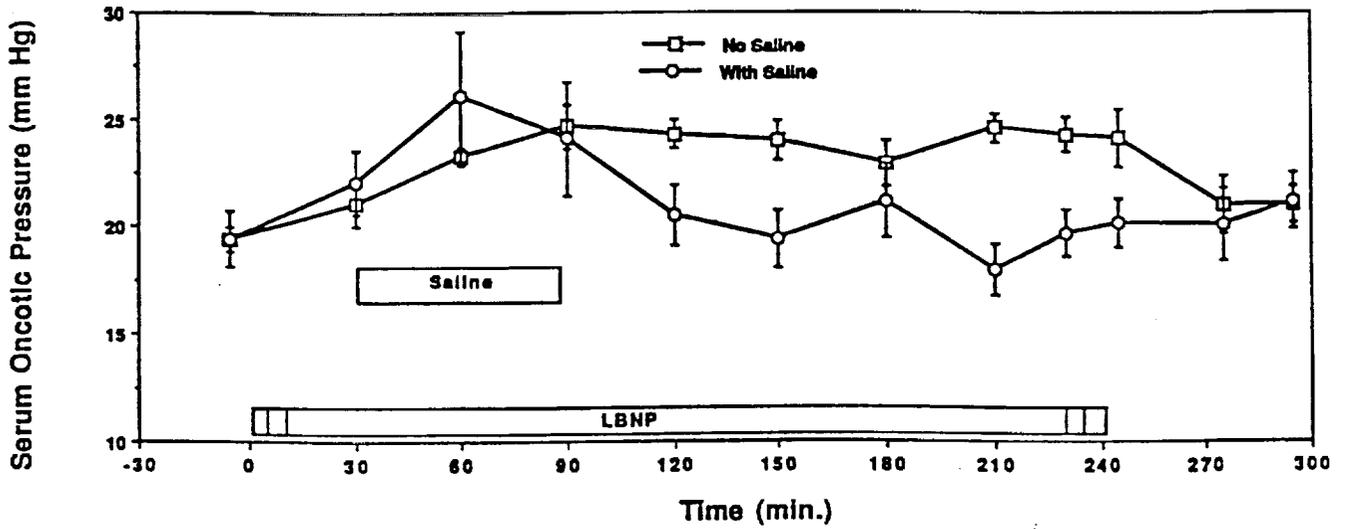
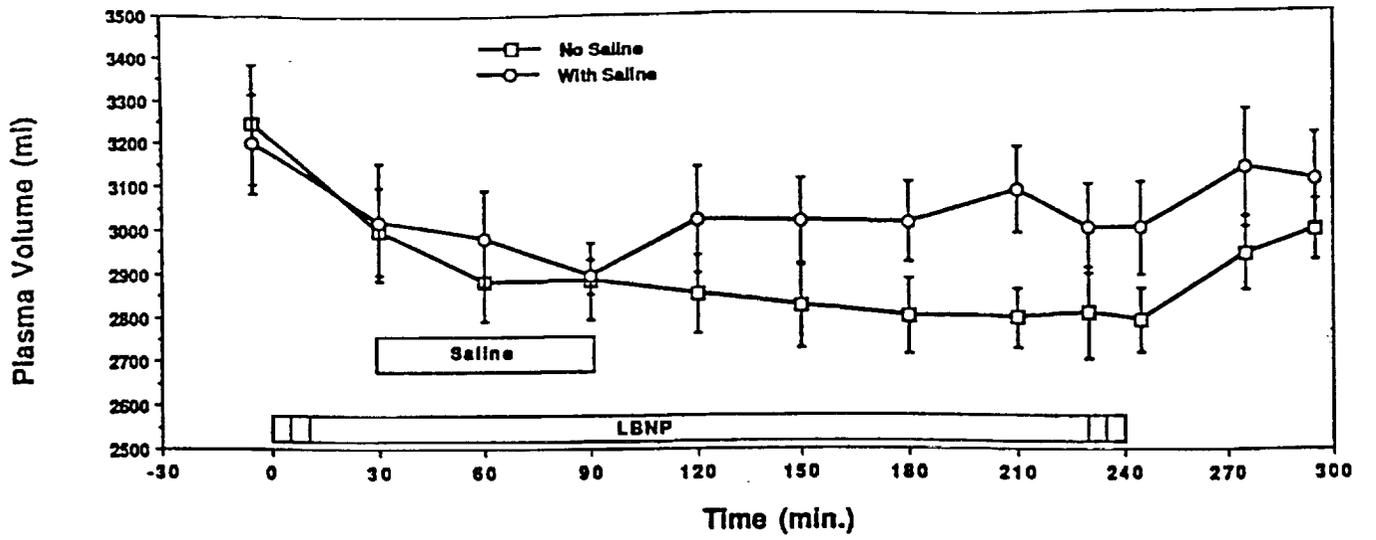


FIGURE 5





The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that every entry should be supported by a valid receipt or invoice. This ensures transparency and allows for easy verification of the data.

In the second section, the author details the various methods used to collect and analyze the data. This includes both primary and secondary data collection techniques. The analysis focuses on identifying trends and patterns within the dataset, which are crucial for making informed decisions.

The third section provides a comprehensive overview of the results obtained from the study. It includes a detailed breakdown of the findings, supported by statistical analysis. The results indicate a significant correlation between the variables being studied, which has important implications for the field.

Finally, the document concludes with a series of recommendations based on the findings. These suggestions are aimed at improving the efficiency and accuracy of the processes being analyzed. The author also acknowledges the limitations of the study and suggests areas for future research.



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P.19

HORMONAL REGULATION OF FLUID AND ELECTROLYTE METABOLISM IN ZERO-G AND BEDREST

NOX

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Supported by NASA Grant 199-14-12-03

INTRODUCTION:

The study of man in spaceflight has consistently indicated changes in fluid and electrolyte balance. Sodium (Na), Potassium (K) and Calcium (Ca) excretion are increased, accompanied by changes in the levels and responsiveness of adrenal hormones and the sympathetic nervous system (SNS). These hormones and neurohumors are critical to the regulation of blood pressure, blood flow and blood volume. The primary objectives of the research conducted under this task have been to use -6° head down bedrest (BR) as the analog to spaceflight, to determine the long term changes in these systems, their relationship to orthostatic tolerance and to develop and test suitable countermeasures.

Over the course of this work we conducted a series of BR studies designed to:

- (1) Determine the physiological response to postural change and to 7 days BR in males;
- (2) Compare the effects of 7 days BR in male and female subjects;
- (3) Determine the mechanisms underlying these responses during (a) short duration BR (7 days), (b) more prolonged BR (30 days);
- (4) Investigate the relationship between the mechanisms regulating fluids and electrolytes during BR and the development of orthostatic intolerance post BR;
- (5) Use the information derived to develop and test pharmacological, dietary and other counteractive options.

SIGNIFICANCE:

The importance of the proposed work lies in its ability to provide practical, effective solutions to the problems of post-flight orthostatic tolerance and readaptation to 1G after missions of short or prolonged duration, based on knowledge of the mechanisms underlying the problem. It is obvious that post-flight orthostatic hypotension involves multiple systems which seem to be affected to varying degrees in different individuals. Furthermore, the vasomotor regulatory deficits after relatively short exposures may be more readily compensated for by techniques (such as volume expansion) than those occurring after prolonged missions, when a new state of physiological adaptation to weightlessness has been achieved; nor might a single countermeasure be effective in all individuals.

The importance of postural cues to the regulation of aldosterone secretion and the importance of the secretions of the adrenal gland as a whole and the autonomic nervous system in the homeostatic maintenance of fluid and electrolyte balance have long been recognized. The experiments in this task should contribute to better understanding of the mechanisms that regulate the effective levels of circulating aldosterone, and, in particular, the ways in which other metabolic and neuroendocrine

changes occurring in weightlessness affect the responsiveness of the adrenal to its regulatory influences.

There are few data on these regulatory systems beyond seven days of -6° BR and on fluid volume regulation in general beyond 14 days of horizontal BR (Greenleaf and Kozlowski, 1982; Greenleaf, 1984). Two 56 day horizontal BR studies suggesting reduced sensitivity of endocrine and metabolic target organ responsiveness were conducted almost 20 years ago (Vernikos-Danellis *et al.*, 1974). Indirect evidence from animals and man have also indicated this is probably the case with more prolonged exposures. Antiorthostatic BR (-6°) has proven its usefulness as a simulation for the initial response to weightlessness and physiological changes occur earlier and are more pronounced than they are with horizontal BR. With the advent of the space station era, the understanding of physiological changes occurring in both male and female subjects in weightlessness should form the rational basis for the development of procedures to prevent or control these changes on extended space missions.

PROGRESS:

We use a subject population of healthy volunteers, 30-50 years of age, to best approximate the astronaut corps. Diet is strictly regulated and contains 120 mEq/day Na and 70-80 mEq/day K; three days are allowed at the beginning of each study for equilibration.

The first two studies in the series were identical in design and their primary purpose was to determine the immediate effects of assuming the -6° head down posture and to compare these responses in male and female subjects. Such early responses have not been measured either in flight or in ground studies. In flight, understandably, it has been impossible to do so without interfering with the heavy schedule of the first day. Nor is it likely that such measurements will be possible within the foreseeable future. Furthermore, data on fluid and electrolytes would be inevitably affected by the malaise and/or vomiting of the early phases of the space adaptation syndrome or by medications taken for this. In contrast to investigations using immersion for simulation of space flight, BR studies had not used sufficiently frequent sampling to document the early changes. Yet, the immediate and dramatic responses to simply assuming upright posture, in those systems that regulate blood volume and blood flow, are well known and it could well have been expected that assuming the head down posture would produce equally immediate and marked effects in those systems.

Eight males and eight females were selected from groups of 14-16 after preliminary screening tests which included a PV determination, cardiovascular and endocrine responses to a Standard Posture Test (SPT, one hour supine, one hour standing) and taking into consideration the phase of the menstrual cycles of the females. No significant correlation between menstrual phase and response was evident. Subjects of both sexes were selected to cover the widest possible range of "normal" blood pressures and plasma volumes, so that a fair assessment of the contribution of the initial physiological status to the responses to BR and post BR orthostatic intolerance could be made.

In the SPT, blood samples were drawn before and at 2.5, 5, 15, 30 and 60 minutes after standing for the determination of PRA, A-II, ACTH, AVP, cortisol, aldosterone, Na, K, hematocrit and hemoglobin. The last two parameters were used to obtain a rough index of posture-associated changes in PV using the method of Greenleaf *et al.*, (1977). The data from this test were compared with that of Day 1 of BR and of the first day of recovery (R+1) when upright posture was assumed again.

RESPONSES TO 6° HEAD DOWN BEDREST:

Figures 1 and 2 show the immediate responses to the posture test and to the assumption of the -6° head down position in one group of males. It is quite apparent that the responses to these two postures are mirror images of each other, both qualitatively and temporally.

Similarly, Figure 3 shows that within five minutes of assuming the -6° head down position, there was a significant decline in heart rate ($p < 0.05$) that was sustained for the next two hours before gradually increasing toward normal during the next six hours. There were no changes in indirect systolic or diastolic arterial blood pressure or plasma ACTH during the first 24 hours after assuming the head down position. However, there were prompt and sustained decreases in plasma vasopressin (AVP), plasma renin activity (PRA) and plasma aldosterone concentration (PAC) over the first eight hours (all $p < 0.01$ by ANOVA). Of note is the finding that PRA reaches a nadir by two hours that is sustained at four and eight hours, but that it increases by 24 hours to values similar to those at 0 time. By contrast, the nadir in plasma aldosterone concentration is achieved at four hours and, although the values increase gradually during the next 20 hours, aldosterone levels are still depressed at 24 hours compared to the 0 time value.

The rapid inhibition in levels of hormones that regulate salt and water metabolism after assumption of the head down position is reflected by the changes in renal fluid and Na excretion during the first days of head down BR in both sexes (Fig. 4 and 5) and an increase in K excretion by the end of the seven day BR period. Fluid and especially Na retention was apparent on becoming ambulatory again. There were no significant sex differences in the parameters measured over a 7 day BR period. With continued bedrest an uncoupling between PRA and aldosterone has been consistently observed. PRA increased and PAC decreased or remained unchanged (see Figure 6).

Measurements of plasma A-II changes did not justify the explanation that the apparent dissociation between PRA and aldosterone could have involved inhibition of lung converting enzyme due to the hemodynamic changes associated with this position, during 7 days of BR. On the other hand in a subsequent 30 day BR study, the data suggested that under resting conditions, both the conversion of angiotensin-I to A-II and the stimulation of aldosterone by endogenous A-II are progressively diminished after 15 days of head down bedrest, (DeCherney *et al.*, 1989).

In addition, BR exceeding 7 days showed the following results. Plasma volume measured using Evans Blue, continued to decline slowly until on d25 it had decreased by 12%. The volume responsive hormones, plasma AVP and PRA remained elevated, but PAC remained at control values throughout the 30d BR period. The response of adrenal aldosterone to graded doses of ACTH or A-II were significantly greater as BR progressed whereas the cortisol response was unaltered by 30d BR. In contrast both the systolic and diastolic blood pressure (BP) responses to A-II (Figure 7 and 8) were greatly reduced by the 16th day of BR. We believe these changes are related to the overall Na deficiency induced by BR. Such enhanced adrenal sensitivity to infused A-II and reduced vascular smooth muscle responses to this peptide have been reported in experimental animals and humans after drastic dietary manipulation of Na. Similarly, the BP response to NE has been reported to be reduced by Na deficiency. In our study the rise in diastolic BP to graded doses of infused NE appeared reduced but the dose of NE was too small to induce significant increases under control conditions. To our knowledge, such observations have only been reported in response to dietary Na manipulations or pathological conditions but not to physiological environmental change (i.e. BR) and are worthy of further pursuit.

Accompanying the changes in the vasomotor hormones involved in fluid and electrolyte changes was a significant reduction in the responsiveness of the carotid sinus cardiac baroreflex response measured using an Eckberg cuff (Figure 9). This effect was evident at d12 of BR and persisted through at least 5 days of ambulatory recovery (Convertino et al, 1990). Furthermore, the buffer capacity of the reflex was reduced as indicated by the decrease in the R-R range. Consequently, not only was the BP response to A-II reduced but the capacity to respond and compensate for moment to moment changes in blood pressure was also reduced by prolonged BR.

POST BEDREST ORTHOSTATIC INTOLERANCE:

During the course of these studies a physiological pattern emerged characteristic of individuals in their normal ambulatory state who are most likely to become syncopal after a period of BR (F). These were subjects showing the lowest resting initial BP's, the highest resting plasma volume (PV); the lowest resting PRA and the smallest decrease in plasma volume on standing. This preservation of an expanded PV becomes a very critical mechanism for the maintenance of BP in these individuals under normal ambulatory conditions (Bannister, 1979) and would therefore be expected to gain importance during any perturbation. There was no correlation between the decrease in PV during BR and post BR orthostatic intolerance but there was a good correlation between the reduced sensitivity of the high pressure baroreflex during BR and post BR orthostatic syncope (Convertino et al, 1990), (Figure 10).

The most significant endocrine differences between these individuals (F) and those who did not become syncopal (NF) became apparent during the effort of individuals to maintain orthostatic control on standing after 7d BR. In NF's there was potentiation of NE, Dopamine and Epinephrine responses to standing after 7d BR as compared to ambulatory controls, suggesting that NF's probably maintain their BP, supported by a large and sustained increase in sympathetic activity. On the other hand F's were

unable either to increase or sustain increased circulating NE and PRA levels (Figures 11 and 12) on standing.

COUNTERMEASURES:

Based on the data from these studies a variety of approaches designed to expand PV and restore baroreflex sensitivity have been and continue to be tested. The results to date from our studies may be summarized as follows:

PV expansion (16%) may be achieved with acute (2 day) administration of fludrocortisone after 7d BR, (Vernikos et al. In Press). It may also be prevented by daily bouts of 30 minutes isotonic exercise (at 50% max VO₂) twice a day during 30d of BR, (Greenleaf et al. In Press).

Increased dietary carbohydrate throughout bedrest was ineffective in increasing the NE response to standing. On the other hand, a combination of dextro amphetamine and atropine together with expanded PV after fludrocortisone resulted in greatly enhanced and sustained HR, NE and PRA responses. Four of 7 previously documented F's were protected by this treatment.

PLANS:

As a result of these and other findings, we decided to split the work in this task into 2 tasks this year. One task will focus on the PV and progressive baroreflex sensitivity changes during BR periods longer than 30d. The contribution of the low pressure baroreflex and changes in compliance to the development of orthostatic intolerance during BR will be addressed. The countermeasure effectiveness of fludrocortisone will be compared to that of NaCl and water ingestion. On the one hand, the dosage regimes will be refined for maximum effectiveness, and on the other, the mechanism by which fludrocortisone exerts its protective effects in orthostatic intolerance will be investigated. Although it is possible that all of its BP regulating properties may be mediated by its Na retaining activity, it is also likely that it may possess other independent actions on the autonomic or central control of BP, and provides an interesting investigative tool.

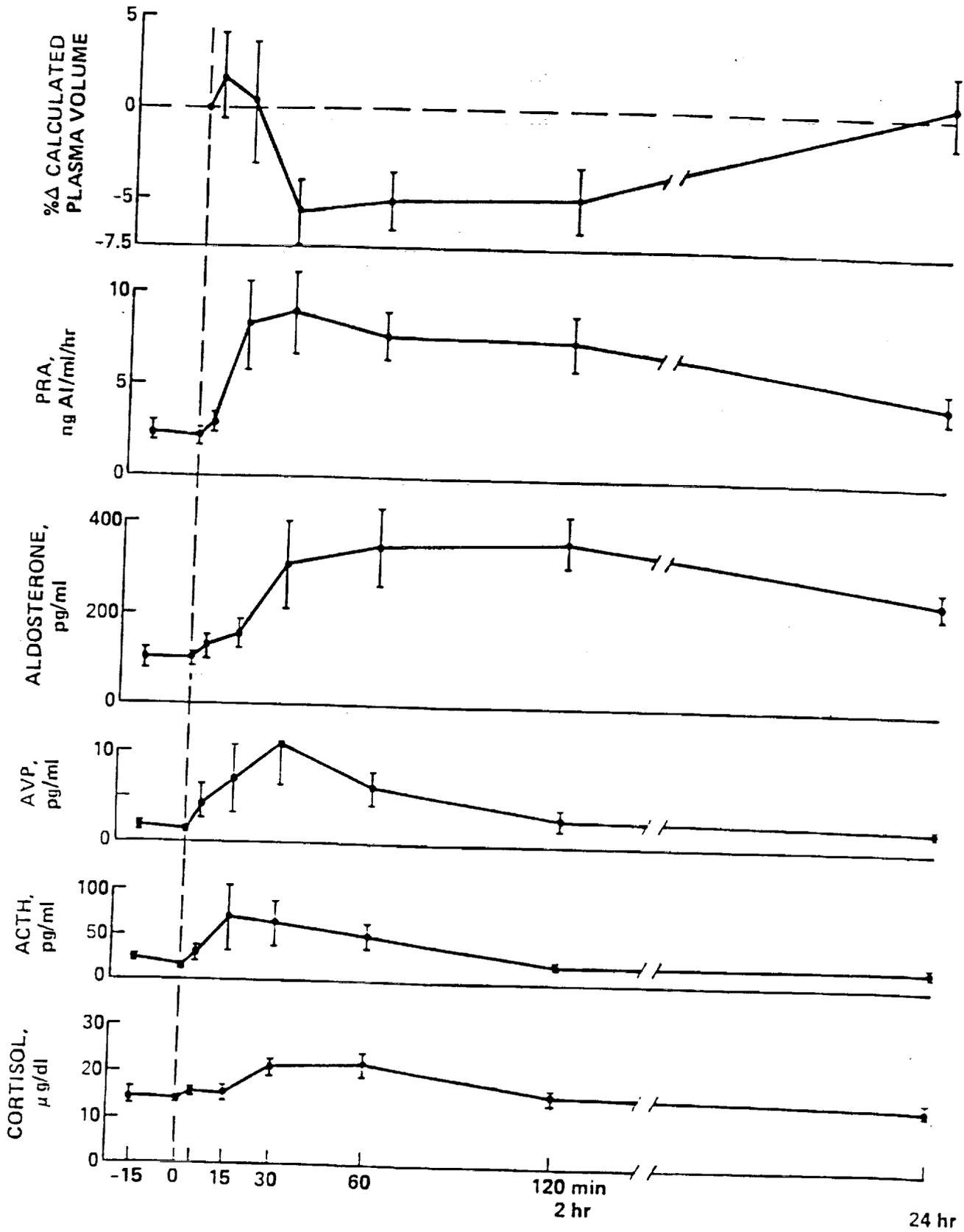
The other task, will focus on the endocrine and neurohumoral regulation of fluids and electrolytes, the uncoupling of endocrine regulating mechanisms, sympathetic nervous system and target organ systems observed in flight and in BR studies, the progression of these changes with more prolonged exposures and the renal consequences of these changes. The role of Na and K in the development of these changes and the relationship of these to the cardiovascular system will continue to be addressed.

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Plasma Volume and Hormone Responses to Standing in Males.

FIGURE 1



Plasma Volume and Hormone Responses in Males on assuming the 60° Headdown Posture.

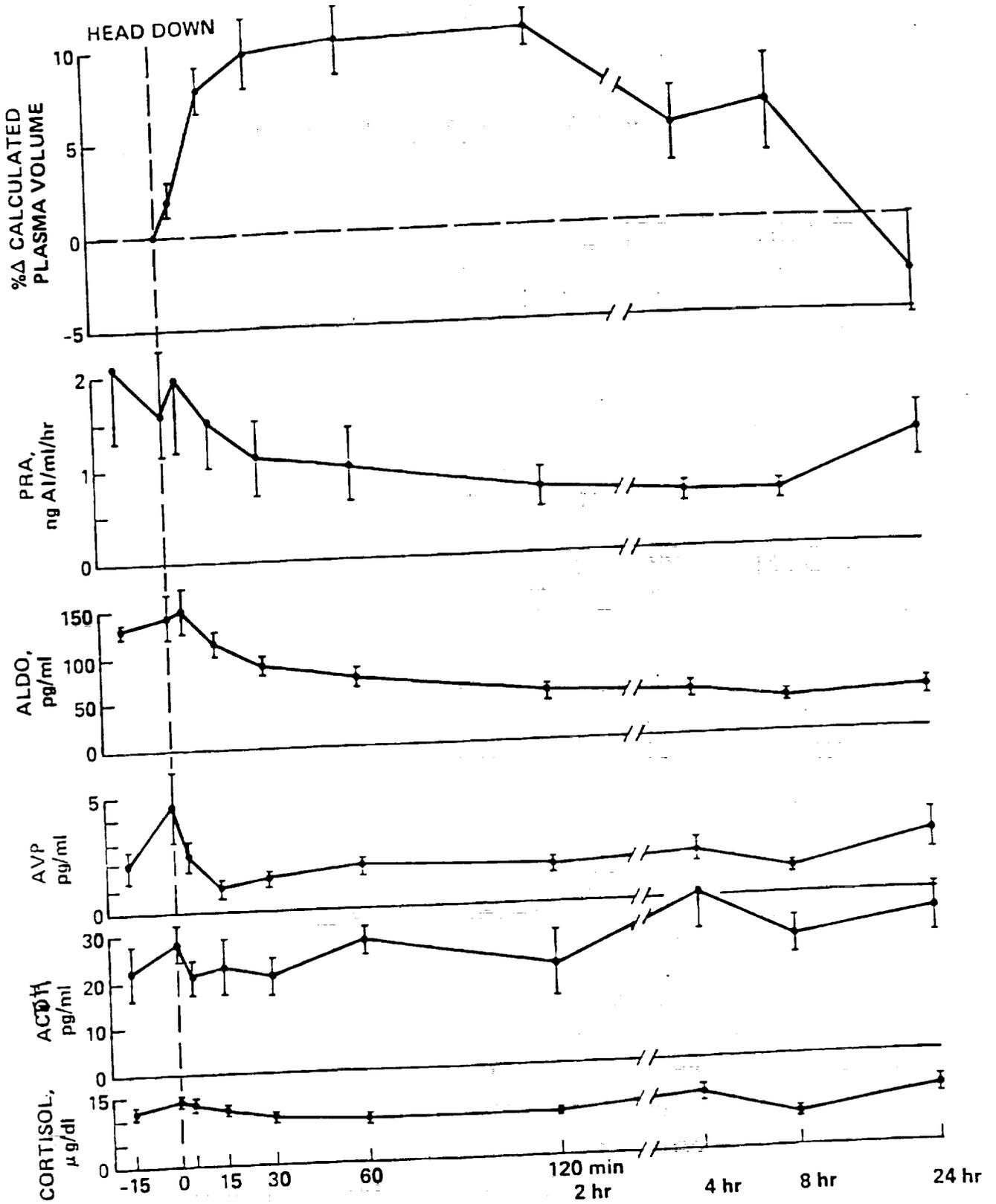
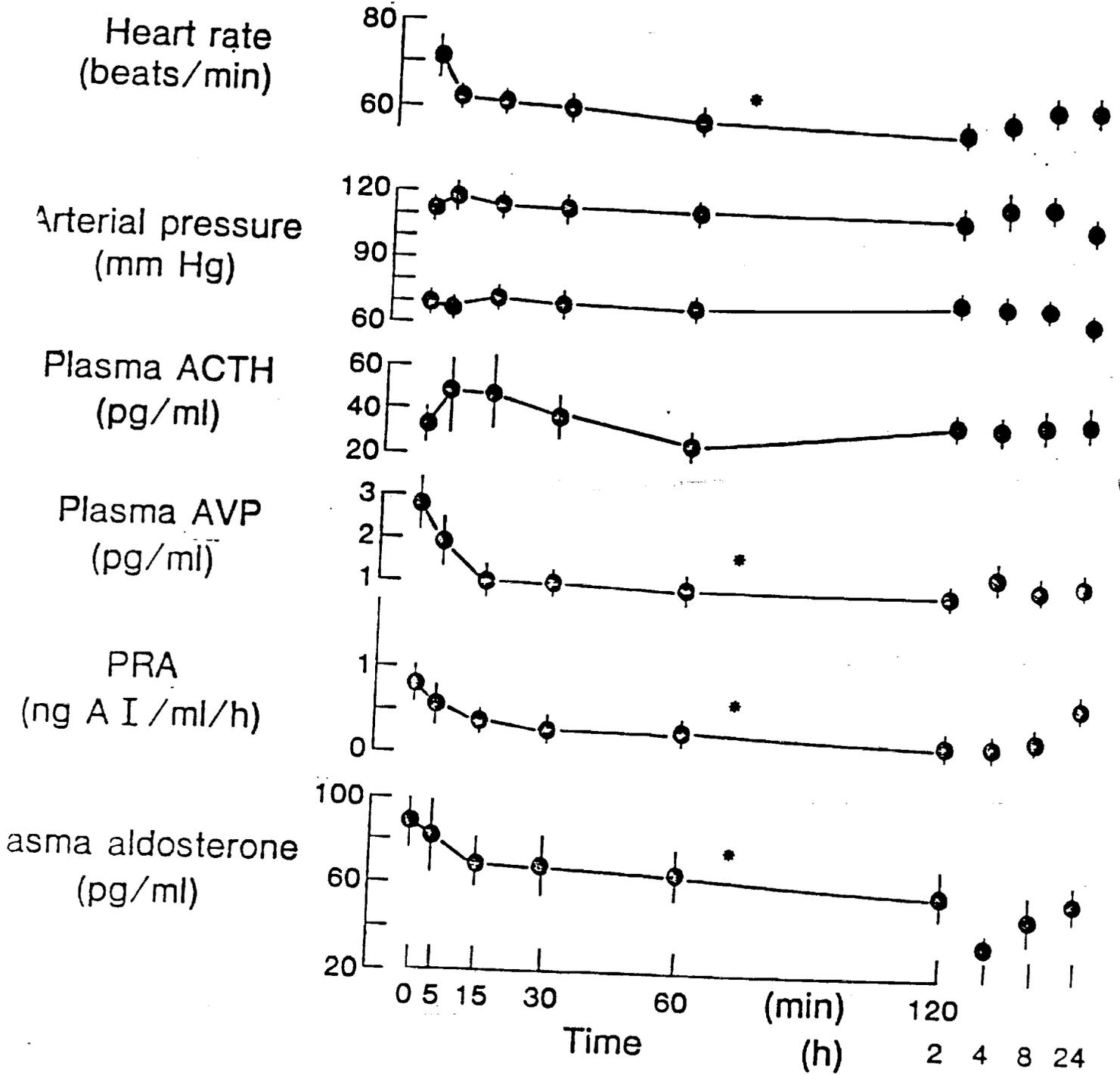


FIGURE 2

FIGURE 3

EARLY RESPONSES TO 6° HEADDOWN TILT



* Decreases significant by ANOVA

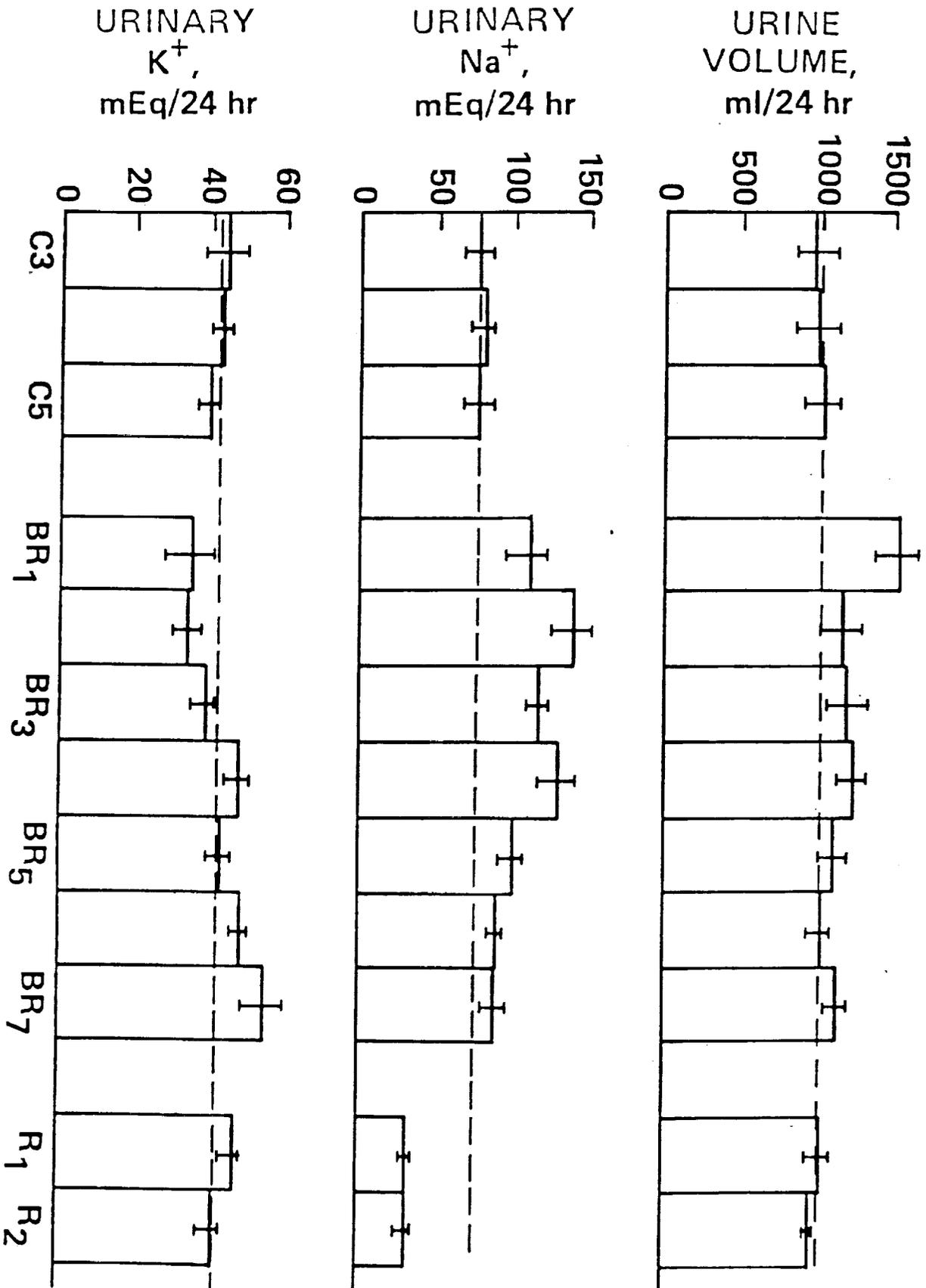


FIGURE 4

FIGURE 5. Fluid and electrolyte excretion in cynomolgus during -6h head-down bedrest

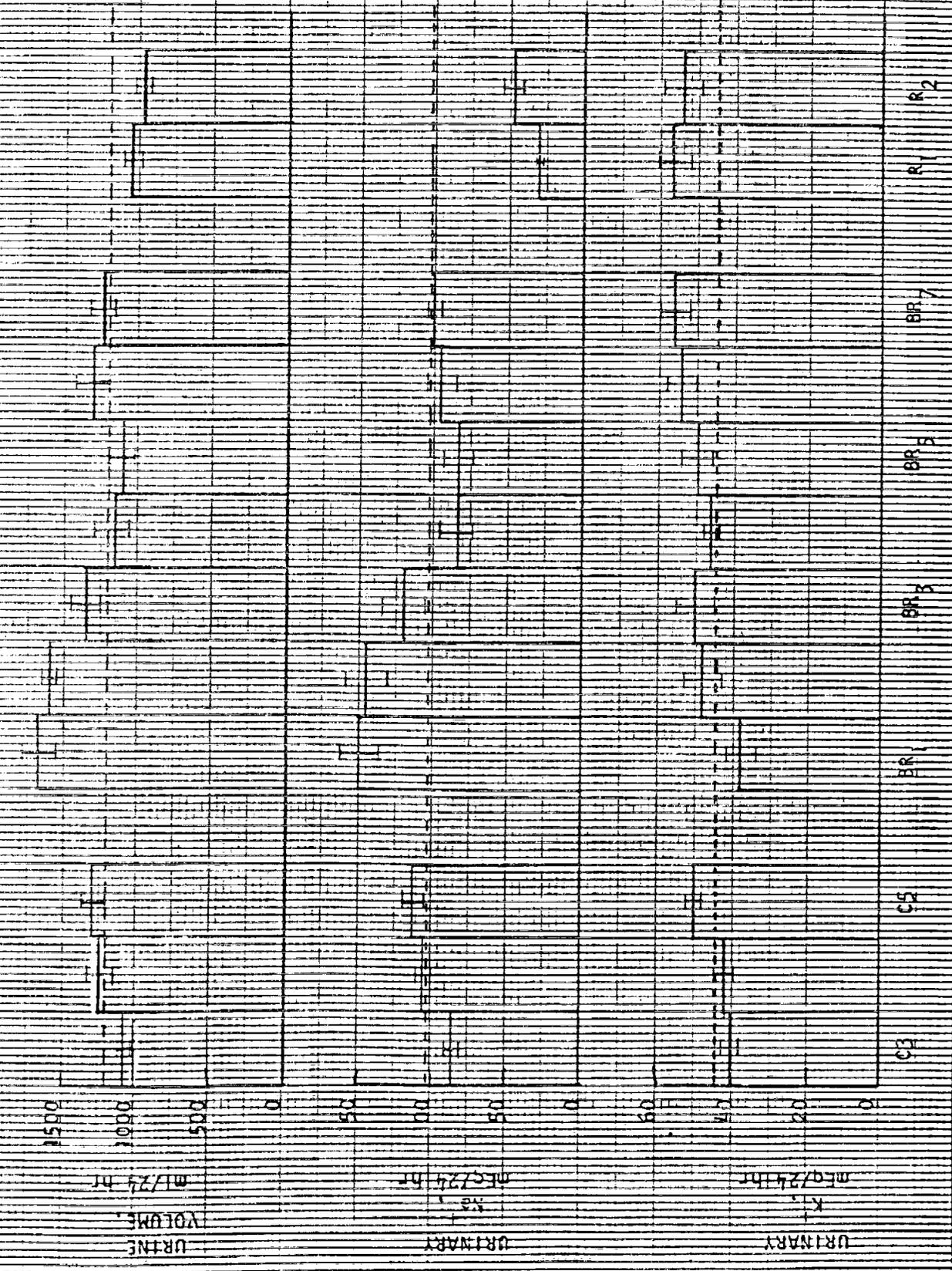


FIGURE 6

PLASMA RENIN ACTIVITY INCREASES AND ALDOSTERONE DECREASES DURING HEADDOWN BEDREST

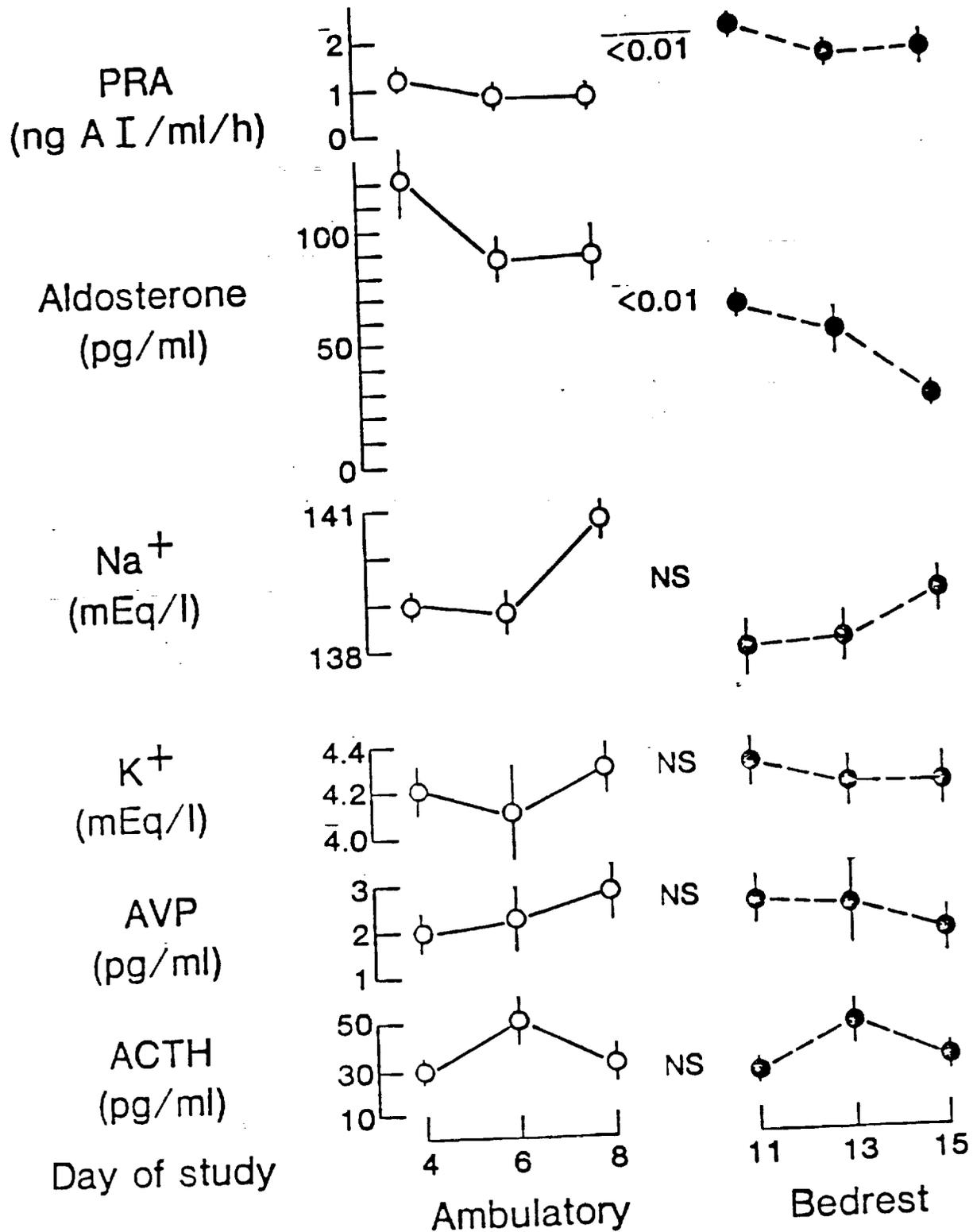


FIGURE 7

Subject descriptions and changes in plasma and blood volumes during head down bedrest (Males).

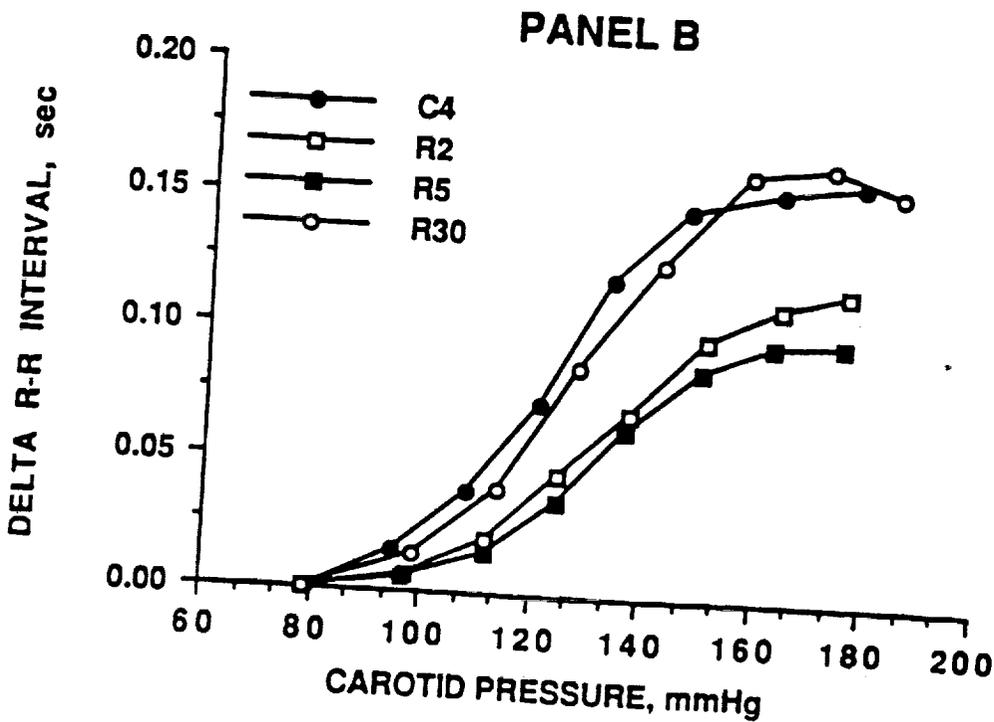
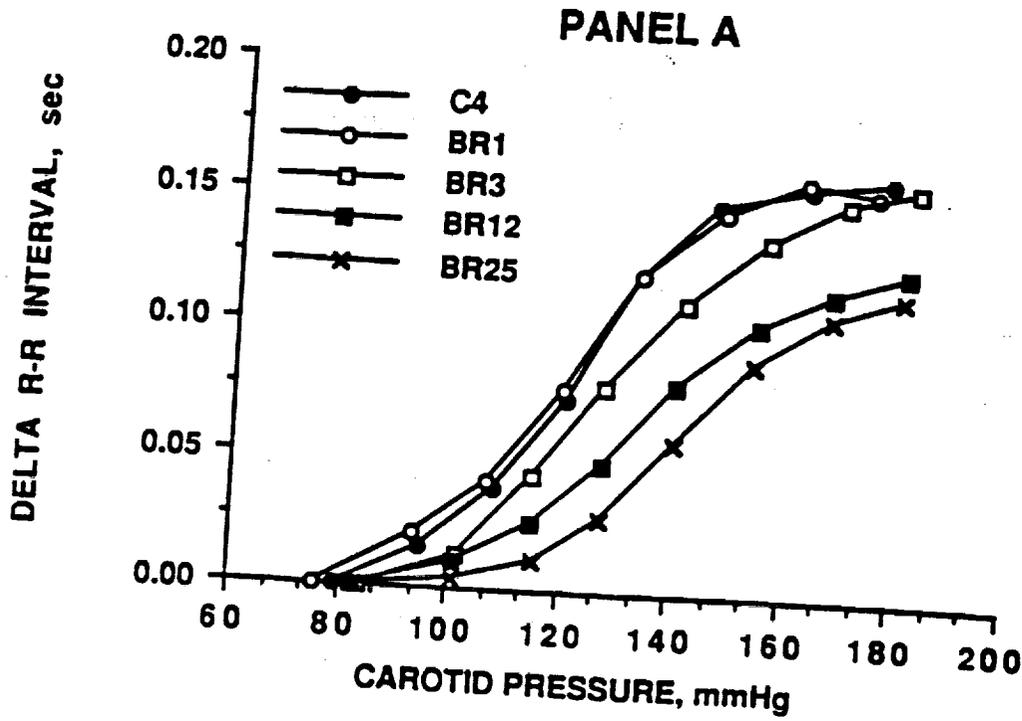
Subject #	Age (Yrs)	Height (Cm)	Weight (Kg)	Decrease in Plasma Volume		Decrease in Blood Volume	
				(ml)	%	(ml)	%
72	49	165	68.2	66	2.9	195	5.0
160	45	188	94.0	177	5.5	342	6.3
161	38	178	75.5	143	5.6	360	8.3
162	38	188	83.2	146	3.8	168	2.7
163	50	180	56.4	423	15.2	440	9.8
164	42	185	84.0	460	13.0	539	9.5
165	38	188	85.0	719	18.2	1138	17.5
166	38	170	68.2	190	6.8	381	8.2
\bar{X}	42	180	76.7	290.5	8.9	445	8.4
- SEM	2	3	4.2	73.6	2.0	108	1.6

FIGURE 8

Subject descriptions and changes in plasma and blood volumes during head down bedrest (Females).

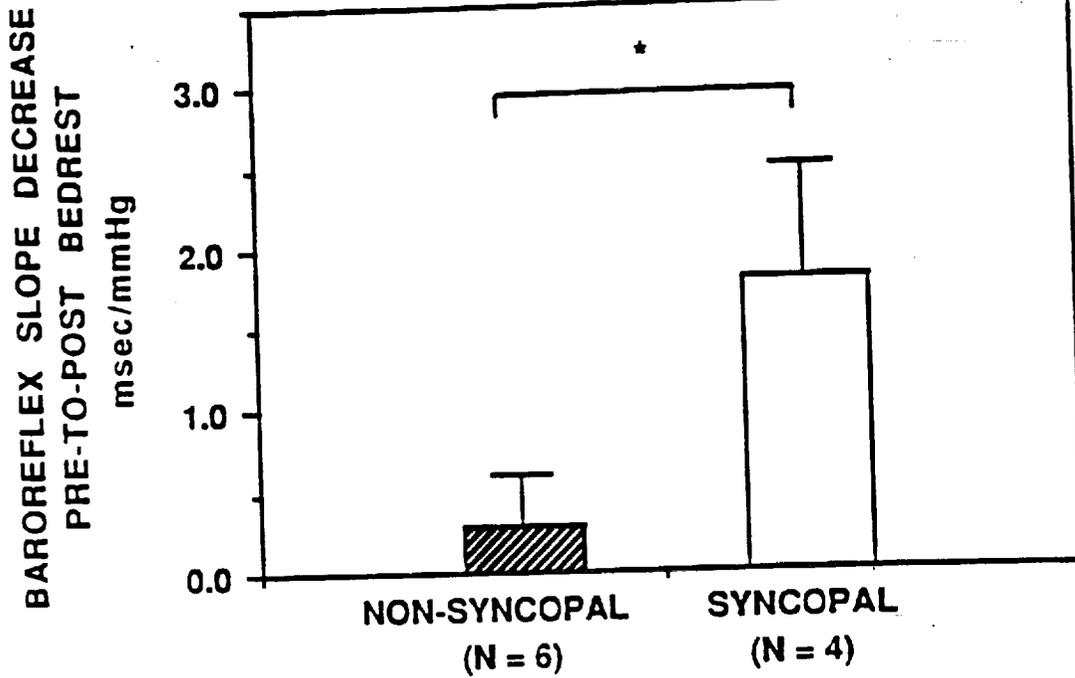
Subject #	Age (Yrs)	Height (Cm)	Weight (Kg)	Decrease In Plasma Volume		Decrease In Blood Volume	
				(ml)	%	(ml)	%
198	41	157	49.6	270	10.5	476	12.0
200	36	173	76.6	170	7.3	240	6.5
201	30	138	58.9	163	5.7	306	6.9
202	35	173	84.8	259	8.7	402	8.8
204	37	158	63.9	553	18.6	693	15.3
205	44	161	63.9	255	10.4	515	13.5
207	34	166	50.5	119	4.7	81	2.1
209	40	157	63.6	304	12.0	290	7.7
- M	37	160	64.0	262	9.7	375	9.2
- SEM	1.6	4.0	4.2	47.3	1.55	66.6	1.6

FIGURE 9

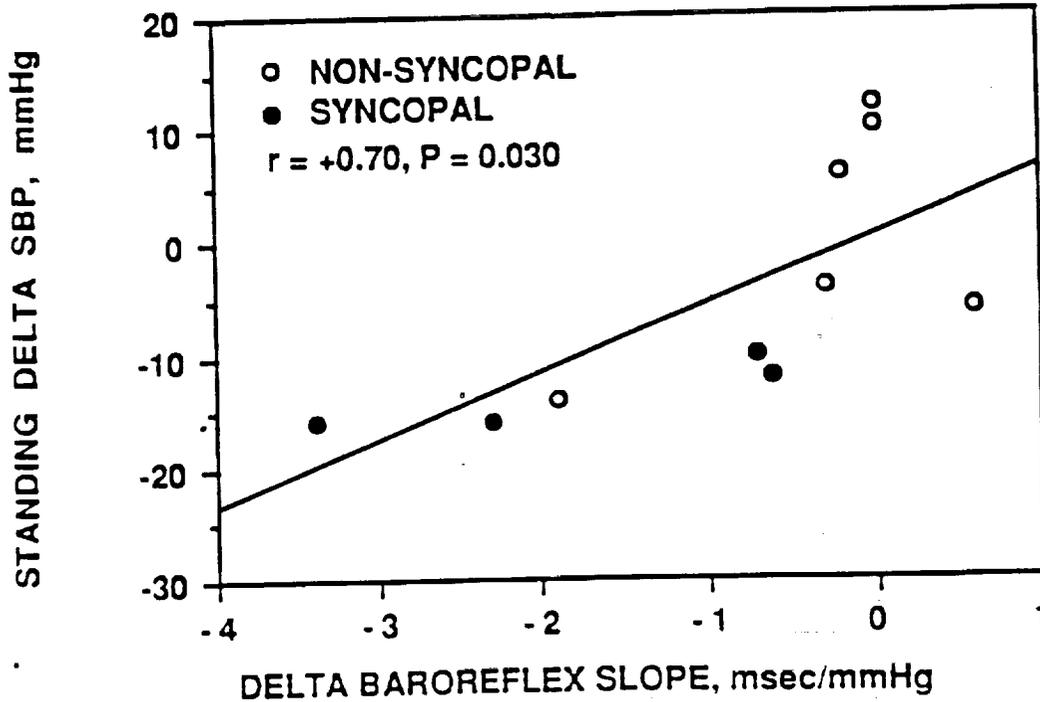


Carotid baroreceptor-cardiac reflex response relationships. Panel A depicts relations generated on days 1, 3, 12, and 25 of bedrest (BR) and the pre-bedrest control day (C4). Panel B depicts relations generated on days 2, 5 and 30 of post-bedrest ambulatory recovery (R) and C4.

PANEL A



PANEL B



Reduction in the maximum slope of the carotid baroreceptor-cardiac relationship after bedrest in non-syncopal and syncopal subjects (Panel A) and the relationship between the change in maximum slope and the change in systolic blood pressure (SBP) during the post-bedrest stand test (Panel B). Asterisk indicates differences at $P < 0.05$.

FIGURE 11

Plasma Renin Activity Responses to Standing in Female F and MF Subjects before and after a 64 Bed Rest

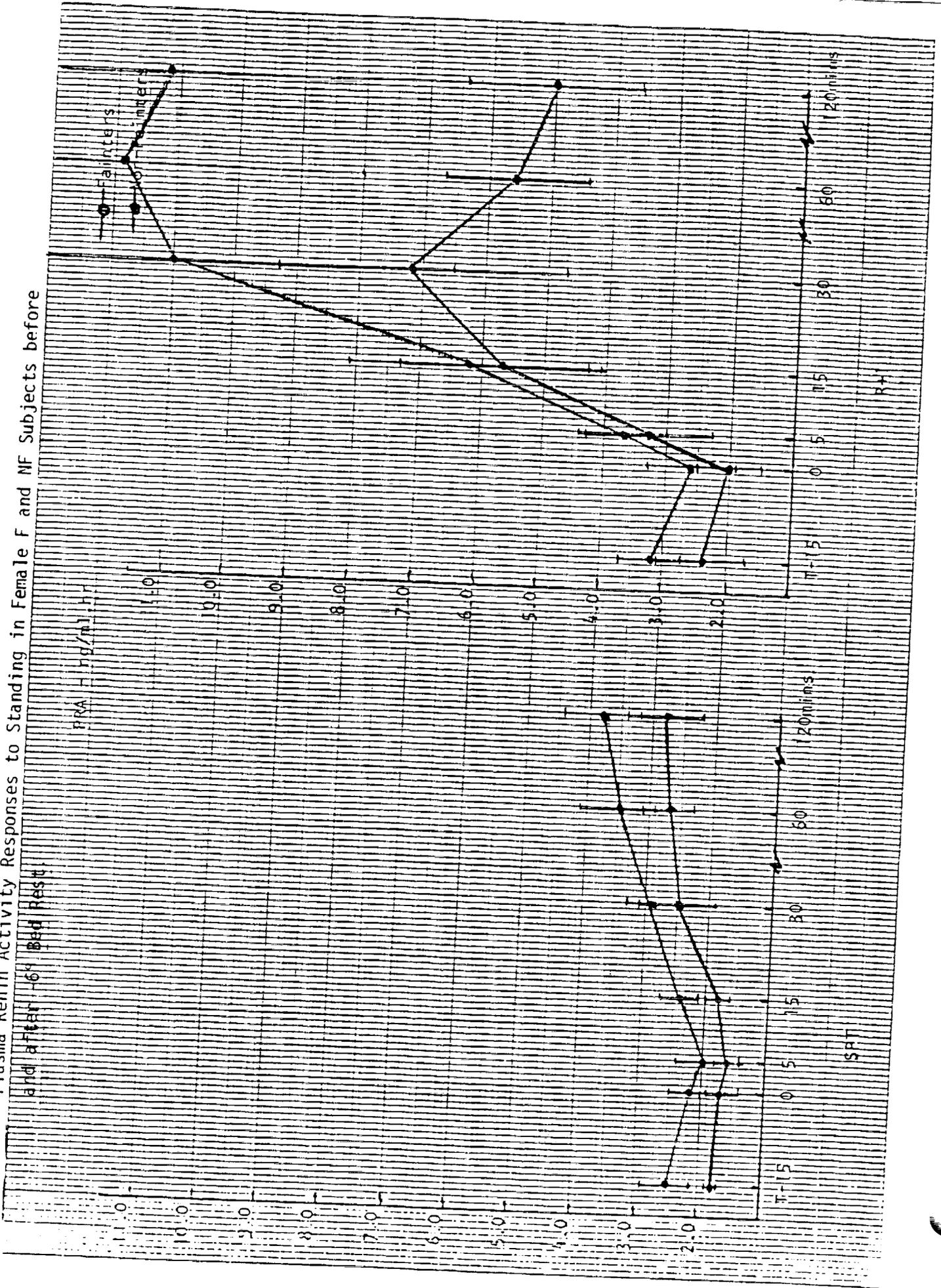
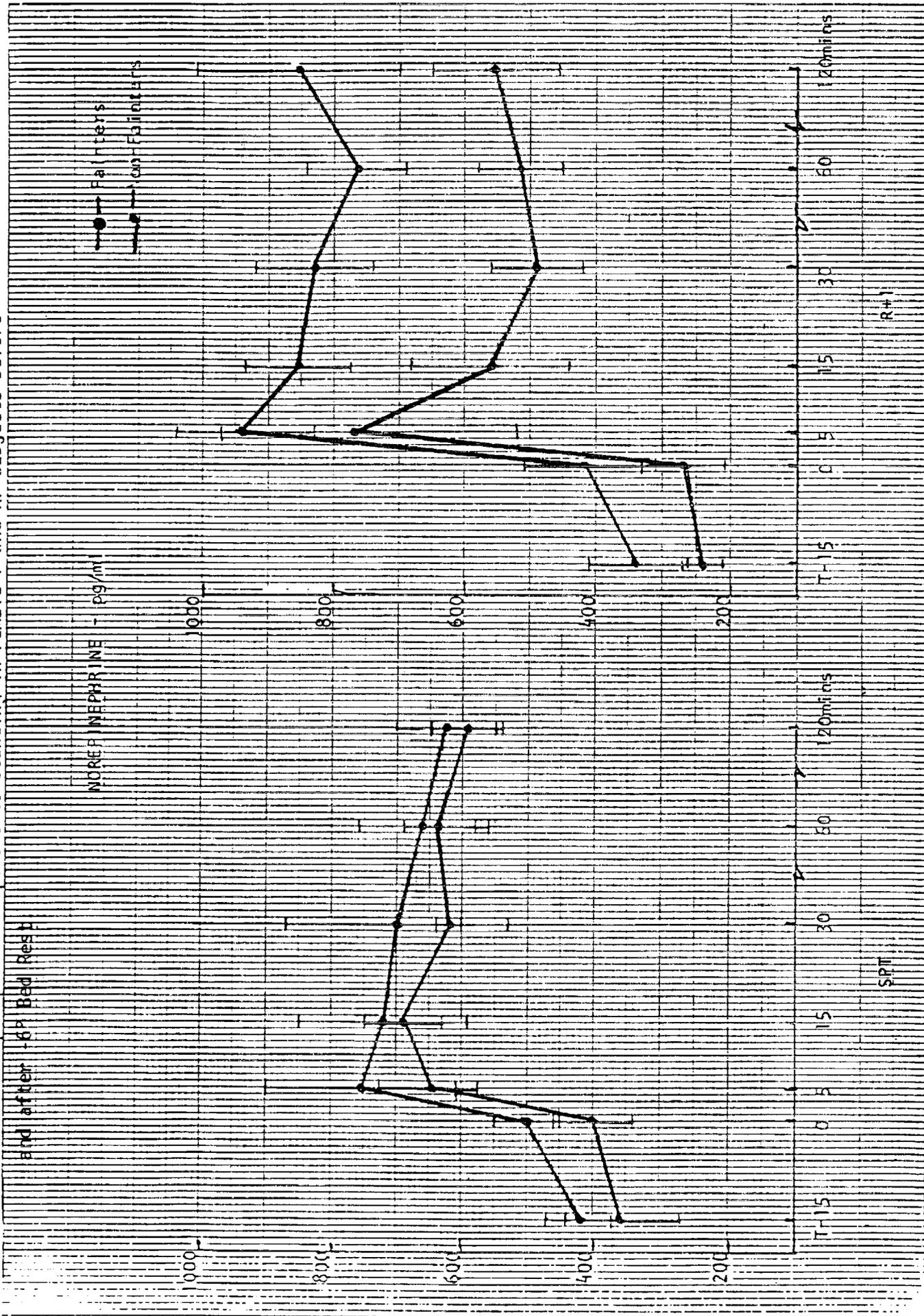


FIGURE 12
 Plasma Norepinephrine Responses to Standing in Female F and MF Subjects before and after 16h Bed Rest





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TITLE:

Hormonal Regulation of Fluid and Electrolyte Metabolism
during Periods of Headward Fluid Shifts

Principal Investigator:

Dr. L. C. Keil, Nasa Ames Research Center

Co-Principal Investigators:

W.B. Severs, Pennsylvania State University

T. Thrasher, University of California at San Francisco

D.J. Ramsay, University of California at San Francisco

INTRODUCTION:

In the broadest sense, this project evaluates how spaceflight induced shifts of blood and interstitial fluids into the thorax affect regulation by the central nervous system (CNS) of fluid-electrolyte hormone secretion. Specifically, it focuses on the role of hormones related to salt/water balance, and their potential function in the control of intracranial pressure and cerebrospinal fluid (CSF) composition. Fluid-electrolyte status during spaceflight gradually equilibrates, with a reduction in all body fluid compartments. Related to this is the cardiovascular deconditioning of spaceflight which is manifested upon return to earth as orthostatic intolerance.

END

PROJECTS WITHIN THIS WORK UNIT

GROUND-BASED STUDIES

Small Animal Studies

The objective of this task was to determine the role of intracranial pressure (ICP) on the CNS regulation of fluids and electrolytes. To do this it was necessary to measure ICP in conscious unrestrained rats. With some difficulty this was accomplished. Our initial studies showed that an intraventricular (IVT) infusion of angiotensin II increased ICP, and this increase could be blocked with prior IVT administration of vasopressin. Since both of these hormones are endogenous to CSF it is possible that they are involved in ICP regulation either by affecting CSF formation and/or drainage. Recent results indicate that the ICP increase following angiotensin II administration is due to a stimulation of CSF secretion.

As these ICP studies continued we found that prolonged, low volume infusions (0.5 μ l/min) of artificial CSF into a lateral cerebroventricle more than doubled ICP. If this same volume was infused bilaterally into each lateral cerebroventricle, the rise in pressure was even more pronounced. One explanation for the rise in ICP may be a dilution of the neurochemical control system(s) with artificial CSF that disrupts the pressure autoregulation since artificial CSF does not contain any hormonal or neurochemical factors.

Primate Studies

When nonhuman primates are water immersed to the neck they show patterns of diuresis and natriuresis similar to humans. Anesthetised animals showed an increase in 1) left ventricular end-diastolic pressure urine flow, sodium/potassium clearance and atrial natriuretic peptide. Experiments by Gilmore, et al. showed that water immersion diuresis in monkeys could not be abolished by removal of neural afferent input to the CNS or with administration of large doses of vasopressin. Perhaps changes in ICP provide an important redundant signal that can trigger renal and hormonal responses to the "hypervolemia" associated with headward fluid shifts in the absence of peripheral pressure/volume sensors. Intracranial pressure measurements have not been made in animals or humans exposed to water immersion or head-down tilt.

To determine the ICP effects of headward fluid displacement we exposed anesthetised rhesus to a short period of -6° head-down tilt followed by a 30 min period of water immersion. The increase in ICP was greater with water immersion. ICP remained elevated throughout the 30 minutes of immersion. A sustained increase in ICP has been observed for immersion periods up to 60 minutes.

Headward fluid shifts and increased atrial pressure are known to stimulate release of ANP and a fall in plasma vasopressin (see above). The role of afferent neural input from the heart has been determined by use of the surgical denervation. Another procedure for acute and reversible cardiac "denervation" is being used to determine the relationship between cardiac afferent input and plasma fluid/electrolyte hormone levels in response to changes in left and right atrial pressure in conscious animals. These studies are in progress.

FLIGHT STUDIES

Objective

Although fluid-electrolyte balance in rats has not been determined during flight, post-flight hormone measurements and salt-water loading experiments indicate that rats respond to

microgravity by readjustment of their fluid-electrolyte metabolism. The purpose of this investigation was to make post-flight determinations of pituitary oxytocin (OT) and vasopressin (VP) content as possible indicators of changes in hormonal regulation of fluid-electrolyte balance during flight.

Two Cosmos experiments (U.S./U.S.S.R.) have been completed over the past three years. Cosmos 1887 which flew in the Fall of 1987 for 12.5 days and Cosmos 2044 which was a 14 day flight in 1989. In Cosmos 1887, pituitary levels of oxytocin (OT) and vasopressin (VP) were measured in the flight rats and their ground based controls. A significant reduction in both posterior lobe hormones were found in the flight animals when compared to either set of ground-based controls. Difficulties were encountered in landing which cast some doubt on whether the results reflected the effects of spaceflight or simply the conditions associated with the delayed recovery. We had another opportunity to repeat the pituitary measurements as well as determine natriuretic peptide content of atria in Cosmos 2044. The results of this 14 day flight were similar to those from Cosmos 1887. Pituitary OT and VP levels in the flight animals were lower than all the controls including a third control group of tail suspended animals for a direct comparison of results from this model with those from flight. Atrial natriuretic peptide (ANP) content was also reduced in the atria of flight rats.

The reason(s) for the reductions in the tissue contents of these fluid-electrolyte hormones of flight animals are unclear. A simultaneous reduction in pituitary OT and VP occurs with water deprivation that is also accompanied by a loss of body weight. Body weight was not significantly decreased in the flight rats, and postflight measurements of water and food consumption indicated that an appropriate amounts had been consumed. It has yet to be determined if this reduction reflects increased secretion or decreased hormone synthesis and storage. The lack of significant changes in the tail suspended group make this model questionable for use in at least some aspects fluid-electrolyte hormone studies.

FUTURE PLANS:

Determine if head-down rats exhibit changes in pituitary and cardiac hormones similar to those observed in animals exposed to 14 days of spaceflight. Study the effects of continuous intraventricular infusions of neuropeptides (8 to 24 hr) on CSF pressure and possible changes in CSF outflow from ependymal and arachnoid surfaces.

PUBLICATIONS:

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**AUTOGENIC-FEEDBACK TRAINING: A
COUNTERMEASURE FOR ORTHOSTATIC INTOLERANCE**

ADS

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NASA has identified cardiovascular deconditioning as a serious biomedical problem associated with long-duration exposure to microgravity in space. High priority has been given to the development of countermeasures for this disorder and the resulting orthostatic intolerance experienced by crewmembers upon their return to the 1-g norm of Earth. The present study was designed to examine the feasibility of training human subjects to control their own cardiovascular responses to gravitational stimulation (i.e., a tilt table). Using an operant conditioning procedure, Autogenic-Feedback Training (AFT), we would determine if subjects could learn to increase their own blood pressure voluntarily.

When operant conditioning is used to train voluntary control of an autonomic response, the process is called "biofeedback". The question that dominated biofeedback research in its earliest years and excited the interest of the scientific community concerned the rules of plasticity for visceral and central nervous system (CNS) function. It was Miller's contention (1969) that visceral and CNS events may be modified by contingent reinforcement (i.e., operant conditioning) in the same way overt behaviors or skeletal responses may be conditioned. Hence, the "same rules" apply for describing the process by which a pilot learns to control eye-hand coordination when learning to fly an aircraft as in the situation where an individual learns voluntary control of his own heart rate or the vasomotor activity of his hands.

The question as to the specific mechanism by which control of an autonomic response may be learned has spawned considerable basic research. When either classical or operant conditioning is used to modify a visceral response, there are a number of different ways that the effect can be produced (Miller & Brucker, 1979). Skeletal responses may produce *mechanical artifact* in the measurement of the visceral response. For instance, contractions of the abdominal muscle may produce pressure changes in the intestine that can be mistaken for intestinal contractions, (Miller, 1977). Skeletal muscles may produce purely *mechanical effects* on visceral processes. Yogis who claim the ability to stop their hearts actually perform valsalva maneuvers, building sufficient thoracic pressure to collapse the veins returning blood to the heart. Although heart sounds and pulse cannot be detected, the electrocardiogram shows that the heart still beats (Anand & Chhina, 1961). Skeletal responses may stimulate a *visceral reflex* such as heart rate and blood pressure increased by isometric contractions (Lynch, Schuri & D'Anna, 1976). Any of these skeletally influenced responses may be learned but they do not indicate learning by the autonomic nervous system.

A series of clinical investigations was initiated on patients with generalized bodily paralysis who suffered from episodic orthostatic intolerance, (Brucker & Ince, 1977; Pickering, et al., 1977). It was hypothesized that if learned control of blood pressure could be demonstrated in these individuals where skeletal influence was not a factor, then the basic research question of visceral plasticity could be examined and the therapeutic benefits of such training could be explored. The results of these studies showed that patients could learn to produce increases in blood pressure ranging from 20 to 70 mm Hg, with the consequence of eliminating their orthostatic intolerance. These studies succeeded in establishing that control of blood pressure can be learned independent of skeletal musculature or changes

in respiration. They demonstrated also that training increases specificity of control, eventually eliminating accompanying pulse rate increases. And performance of these patients conformed to the cardinal "rule" of operant conditioning: skill increases with practice.

The implications of these results for developing a potential countermeasure for orthostatic intolerance in cardiovascularly deconditioned crewmembers, are apparent. Paralyzed patients show much greater spontaneous variability in blood pressure than do normotensives, but bedrest studies indicated that normal subjects also tend to exhibit weaker homeostatic control over cardiovascular responses after prolonged inactivity (Sandler & Vernikos, 1986). Rather than attempting to remove the influence of skeletal musculature (as was the goal of the above authors), contraction of muscles by non-paralyzed subjects would be expected to enhance the desired effect of increasing blood pressure. The presence of sympathetic vasomotor innervation in normals should further facilitate peripheral vasoconstriction.

The hypotheses of this study were:

1. Normotensive individuals could learn to increase blood pressure under supine conditions.
2. Control of blood pressure could be produced under conditions of gravitational stimulation.

METHODS

Subjects. Six men and women between the ages of 32 and 42 participated in this study. Subjects were physically fit as determined by medical examination and their participation was voluntary.

Apparatus. A primary criterion for this type of training, is that the individual must be presented with on-going information about his own physiological responses in real-time (e.g., displaying heart rate on a digital panel meter). For the present study, a computer-controlled blood pressure monitoring system was developed, which provided continuous "feedback" of both systolic and diastolic blood pressure on every beat of the heart (Tursky, Shapiro & Schwartz, 1972). This non-invasive system used two blood pressure cuffs, mounted over the brachial arteries of the left and right arms.

The cuff measuring systolic blood pressure was initially inflated to just above systoli. Using the R wave of an electrocardiogram to initiate a timing window, cuff pressure automatically deflated or inflated, in 3 mm Hg increments, as the system "searched" for the presence of Karotkoff sounds detected by a crystal microphone beneath the cuff. If the K-sound was present, cuff pressure was increased on the subsequent heart beat; if absent, cuff pressure was decreased. In this manner, it was possible to track blood pressure on each heart beat. The tracking cuff was inflated for a period of one-minute at a time, alternating with deflation during 30-second "rest periods" to allow normal circulation to resume. The measurement of diastolic blood pressure (on the other arm) reversed this process.

Procedure. Each subject was given 4 to 9 training sessions (15-30 minutes in duration). Baseline recordings were taken of resting supine heart rate and blood pressure and changes in these variables resulting from passive head-up tilt of 45 degrees. Subjects were then provided with information on their own blood pressure in the form of a computer screen numerical display which updated on each heart beat and/or two mercury columns showing systolic and diastolic pressure, respectively. Under supine conditions, subjects were instructed to increase their own blood pressure, and given an opportunity to practice control. When blood pressure increases were demonstrated under supine conditions, subjects were again tilted to 45 degrees (head up) and asked to increase their blood pressure.

RESULTS

Under baseline supine and passive tilt conditions, the blood pressure tracking system was able to reliably measure blood pressure and heart rate on a beat-to-beat basis. All subjects showed, in response to passive tilt, an initial drop in systolic pressure, increase in diastolic pressure and a corresponding rise in pulse rate (Figure 1).

During supine training sessions, all subjects demonstrated learned increases in blood pressure ranging from 20 to 50 mm Hg (Figures 2-3). In all of these subjects, this same degree of blood pressure control was also possible under subsequent head-up tilt conditions. Figure 4 shows the data of one of these subjects. The left side of this graph shows one minute of resting blood pressure and heart rate, followed by a voluntary increase of blood pressure during tilt of maximally 50 mm Hg. Heart rate showed an initial increase from 64 to 96 beats per minute, with a subsequent fall in pulse rate without changing blood pressure levels.

CONCLUSIONS

This study demonstrates that learned control of blood pressure by normotensive individuals is possible. This skill could be a valuable adjunct to other counter-measures (e.g., inflight fluid loading and exposure to Lower Body Negative Pressure, LBNP). A bed-rest study could be conducted which would best evaluate the effectiveness of this procedure, alone and in combination with other treatments, as a countermeasure for orthostatic intolerance in cardiovascularly deconditioned people. The results of that study would determine the value of developing AFT for preflight and in-flight procedures for treatment of orthostatic intolerance in aerospace crews. For example, blood pressure conditioning sessions could be incorporated into the spacelab exercise facility.

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FIGURE CAPTIONS:

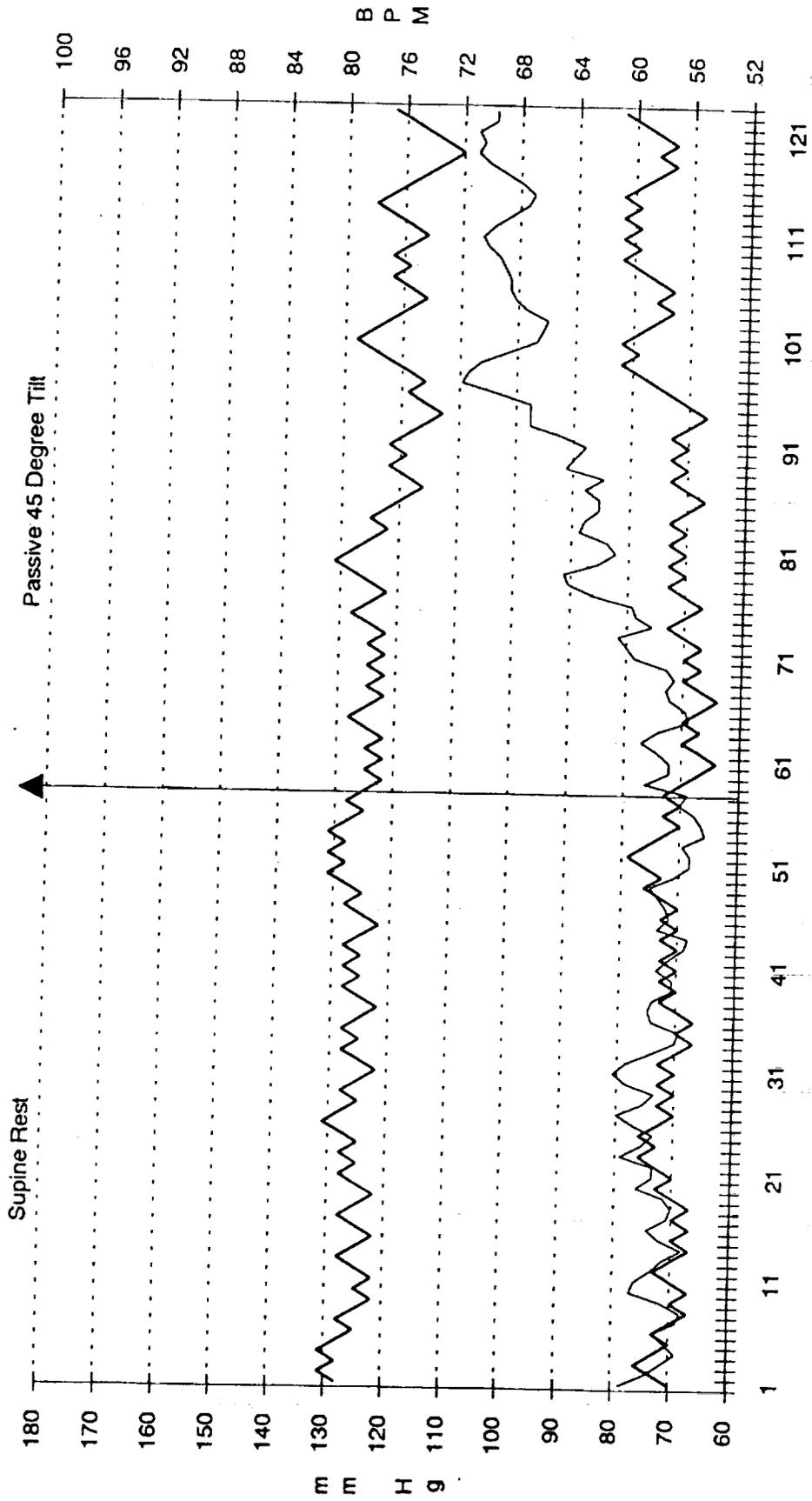
Figure 1: The data of a representative subject during supine baseline and passive tilt conditions. The upper dark line represents systolic blood pressure, the lower dark line is diastolic blood pressure (read axis on left, mm Hg). The thin line is heart rate (read axis on right, BPM). Note: all subsequent graphs are read similarly.

Figure 2: A two minute sample of one subject's data while practicing blood pressure increases under supine conditions.

Figure 3: A two minute sample of one subject's data while practicing blood pressure increases under supine conditions.

Figure 4: A two minute sample of one subject's data while practicing blood pressure increases under head-up tilt of 45 degrees.

Subject 6, Session 1, File OI06111, Minutes 5, 6



Subject 11, Session 2, File OI11211, Minutes 6, 7

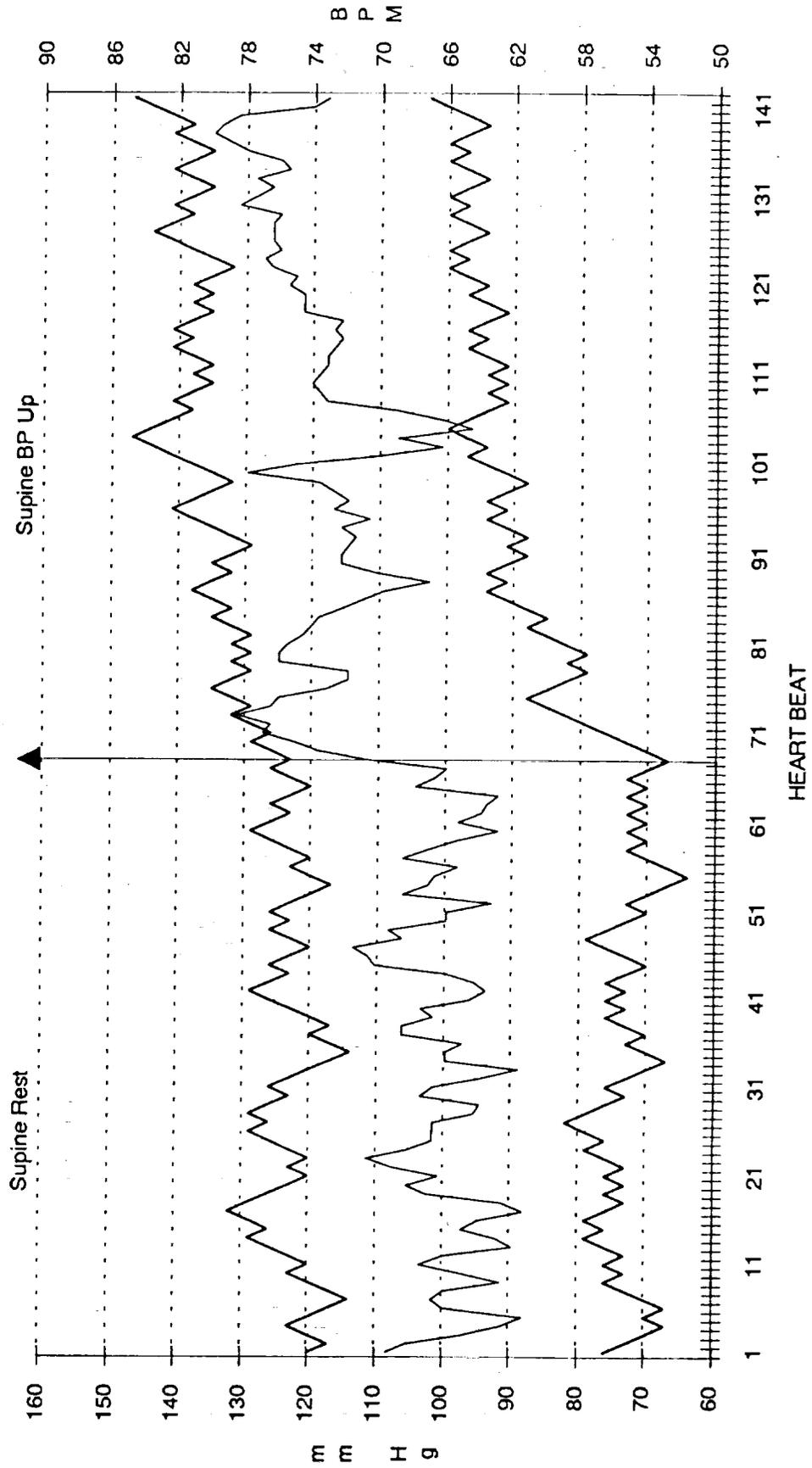
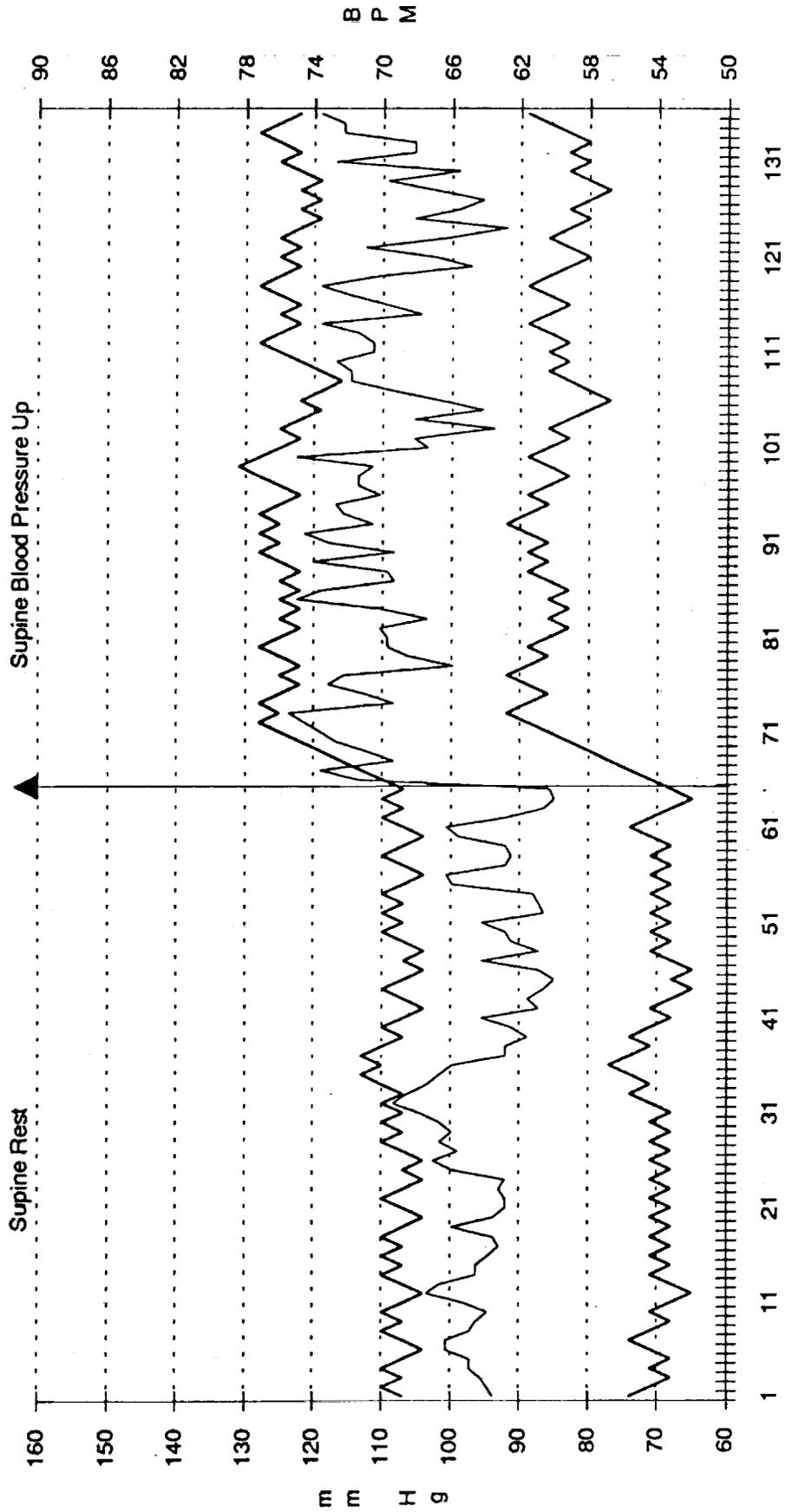


FIG. 2

Subject 10, Session 5, File OI10511, Minutes 6 & 7



HEART BEAT

FIG. 3

Subject 6, Session 6, File OI06611, Minutes 11, 12

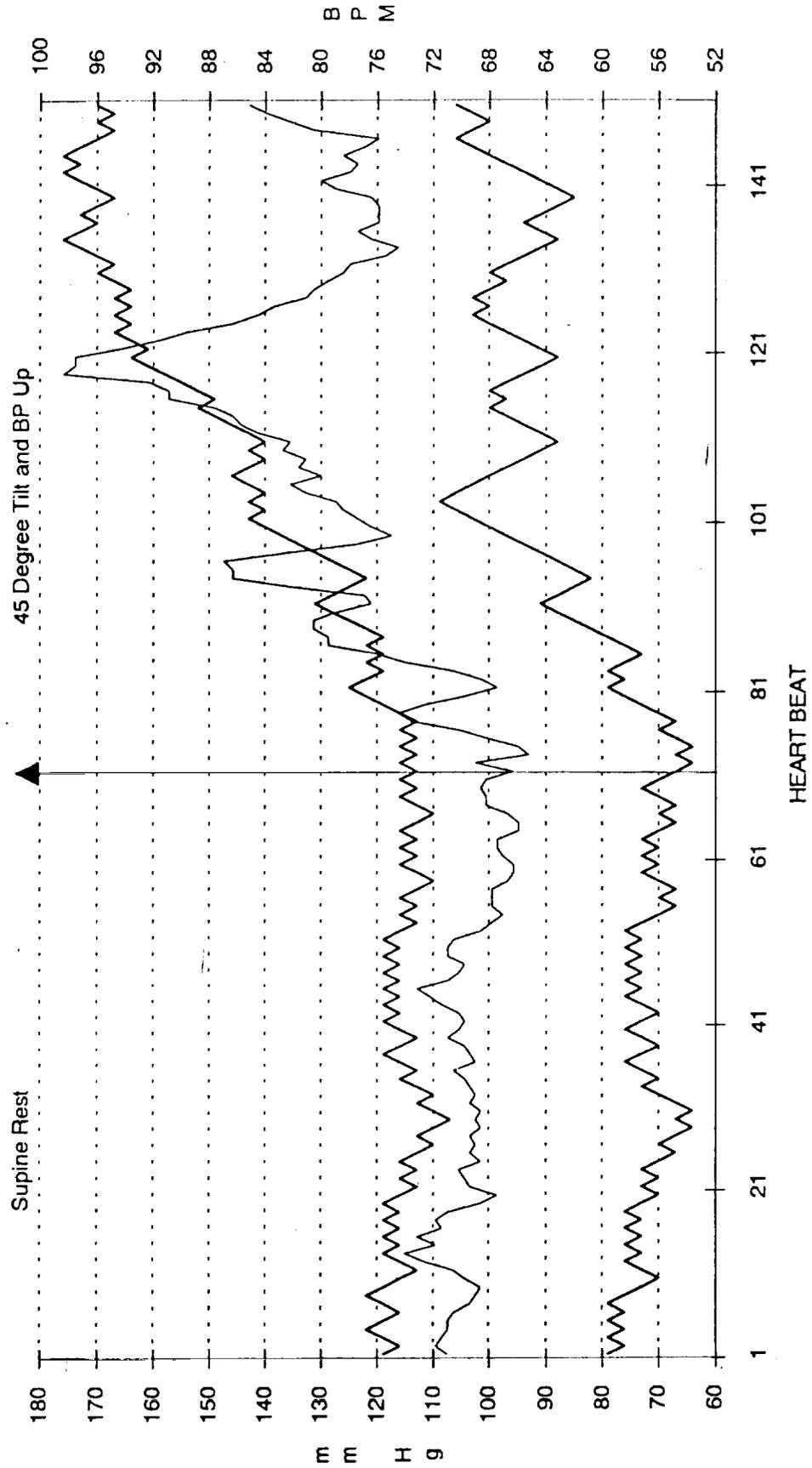


FIG. 4



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RESEARCH REPORT

Title: Cardiovascular Dynamics During Space Sickness and Deconditioning
(NAG 2-514)

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I. INTRODUCTION

We are currently funded by NASA for the project, "Cardiovascular Dynamics During Space Sickness and Deconditioning" (#NAG2-514). NASA has given priority to the investigation of two problems encountered in the long-term space flights currently being planned: 1) space motion sickness and, 2) cardiovascular deconditioning. We have proposed to use spectral and nonlinear dynamical analysis of heart rate data to quantify the presence of these problems and to evaluate countermeasures against them.

We recently reported the first evidence that space motion sickness may be associated with very low frequency oscillations in heart rate which can be easily detected using frequency analysis of Holter monitor data (Fig. 1). These oscillations were not appreciated in earlier studies, which confined their analysis to alterations of mean heart rate and not to dynamic beat-to-beat fluctuations. These heart rate oscillations probably reflect altered autonomic nervous function and are of potential practical importance because they may 1) serve as the first objective non-invasive way of assessing susceptibility to space motion sickness in flight, 2) help monitor the efficacy of preventive and therapeutic measures and, 3) permit comparison with the dynamics of conventional terrestrial motion sickness.

We also reported the use of spectral analysis in detecting a loss of normal heart rate variability in healthy athletic men subjected to 7-10 days of head-down bed rest, a model for cardiovascular deconditioning during space flight (Goldberger AL, et al. Atropine unmasks bed rest deconditioning effect in healthy men: a spectral analysis of cardiac interbeat intervals. J. Appl. Physiol. 61:1843-1848, 1986). Similar analysis may be of practical use in assessing the efficacy of countermeasures, such as intermittent centrifugal acceleration or time-varying lower body negative pressure.

The goals of this project, in concert with colleagues at NASA-Ames and JSC are:

- 1) To compile digitized databases of continuous ECG recordings a) from crew members of previous and future flights and b) from previous studies of induced motion sickness in ground-based simulations.
- 2) To correlate the low frequency ($\leq .01$ Hz) heart rate oscillations observed during space flight with a) subjective motion sickness symptoms, b) activity level, and c) a respiratory signal derived from the Holter ECG.
- 3) To determine whether heart rate dynamics during terrestrial motion sickness (rotating chair test) are equivalent to those observed in space flight.
- 4) To develop a physiological model of heart rate variability that explicitly includes gravitational forces and that can be used to simulate the oscillations observed in space and to test the role of autonomic perturbations in their pathogenesis.

5) To quantitate the loss of heart rate variability associated with bedrest deconditioning; to determine whether countermeasures (e.g. intermittent acceleration) prevent this deconditioning effect; and to determine whether bedrest deconditioning induces changes in heart rate dynamics comparable to those actually observed during space flight.

II. RECENT ACCOMPLISHMENTS

A. Analysis of Ground-Based Motion Sickness Tests

In collaboration with Pat Cowings, Ph.D. and her associates at NASA-Ames, we have performed detailed spectral and time series analysis of data from 20 healthy volunteers studied during a rotating chair protocol designed to simulate ground-based motion sickness. Analysis of the relatively short (<5 min) data segments obtained at successive stages of the protocol did not reveal heart rate patterns or changes that were predictive of susceptibility to terrestrial motion sickness. However, the short data segments available from the study preclude any conclusions about lower frequency fluctuations (e.g., $\leq .05$ Hz) that may be of importance. For example, in our preliminary analyses of space flight data, the oscillations we detected were $\leq .01$ Hz. Similarly, pathologic heart rate oscillations we have observed in other settings (e.g., heart failure) were also usually $\leq .04$ Hz.

B. Analysis of In-Flight Data

Apart from the Holter records that we have analyzed previously (Fig. 1 from: Goldberger AL et al. Low frequency heart rate oscillations in space shuttle astronauts: a potential new marker of susceptibility to space motion sickness. Space Life Science Symposium. Three Decades of Life Science Research in Space. Washington, D.C. 1987:78-80), the only existing records of in-flight heart rate variability are found in the records acquired by Dr. Cowings and on echocardiograms given to us by Dr. Charles of NASA Johnson. Release of in-flight data from Dr. Cowing's laboratory is still pending administrative clarification from NASA Headquarters and NASA-Ames. We have developed image processing software to help extract the heart-rate data from Dr. Charles' video tapes. However, preliminary analysis of these data show that they do not provide a consistent recording of continuous heartbeat cycles since the echocardiographic transducer is not in one locus for sustained periods. Also, the recordings contain frequent interruptions due to change from M-mode to 2D images. Therefore, analysis of continuous in-flight data remains of critical importance.

C. Analysis of Other Heart Rate Data

In collaboration with Lewis Lipsitz, M.D. of the Gerontology Division at Beth Israel Hospital and Harvard Medical School, we analyzed spectral characteristics of heart rate variability before and during postural tilt in young and old subjects. We found that young, healthy subjects with syncope had a significant increase in low frequency heart rate variability during tilt compared to those without vasovagal syncope. On the other hand, elderly subjects did not develop syncope and showed reduced supine heart rate

variability, as well as absent or attenuated low frequency activation during tilt. Our findings may provide a marker for susceptibility to vasovagal syncope and may provide a physiologic explanation for resistance to vasovagal syncope in old age.

D. Mathematical Modeling and Nonlinear Analysis

Interpretation of the observed heart rate variability is being made with the aid of mathematical models of the cardiovascular system. We have devised a preliminary nonlinear model of heart rate control that under different parameter values yields erratic fluctuations, sustained oscillations and abrupt changes of the type we have observed under a variety of physiologic and pathologic conditions (Fig. 2).

We have also analyzed the nonlinear dynamics of normal heart rate variability in healthy subjects. To test the hypothesis that physiologic beat-to-beat variability in sinus rhythm represents nonlinear "chaos" -- a non-random type of erratic behavior generated by deterministic processes -- we computed Lyapunov exponents for heart rate time series (10,240 consecutive data points over 1 1/2 hours) of subjects under basal conditions, after filtering with singular value decomposition. All data sets had a positive Lyapunov exponent (.02-.04) consistent with an underlying nonlinear chaotic mechanism. This novel finding will be presented at the 1990 National American Heart Association Meeting.

A flow chart of our ECG data analysis protocol is given in Fig. 3.

III. FUTURE PLANS

A. In-Flight Data Analysis

Analysis of in-flight data (with suitable pre- and post-flight controls) remains a high priority. We have arranged with Dr. M. Bungo and Dr. J. Charles of JSC to collaborate in the analysis of Holter monitor data to be provided by the Soviets from ongoing and future flights. We have participated extensively in discussion and briefings with Dr. Bungo and colleagues by telephone and in person during a May 1990 invited visit to JSC, to review the technical aspects of data collection and data analysis. During that visit Dr. Goldberger and Dr. Rigney presented a seminar on Cardiac Dynamics and met with members of the JSC cardiovascular research team.

Based on conversations with Dr. J. Stoklosa of NASA Headquarters, we anticipate the imminent release of data from Dr. Cowings' laboratory with recordings of in-flight and post-flight data from several U.S. astronauts.

B. Bedrest Studies

During our May 1990 visit to JSC we met with Suzanne Fortney, Ph.D. and made plans to collaborate in the analysis of heart rate data obtained from healthy subjects during a bedrest protocol. We have begun to perform analysis on the first subjects in this session to test the hypothesis that bedrest

deconditioning alters heart rate variability, particularly with an attenuation of higher frequency components due to vagal tone (Fig. 4).

C. Management Distribution and Archiving of Physiological Signals

We have been informed that essentially all the computer tapes with heart rate data from earlier missions (Mercury, Gemini, Apollo and Skylab) have already been discarded because of lack of storage space at NASA/Johnson and incompatibility of the tapes with current equipment. Given the great expense of these missions and the uniqueness of the data, a centralized, accessible and comprehensive library of these kinds of records is of critical importance. It should be emphasized that these heart rate data are not only of value to groups such as ours interested specifically in space sickness and cardiovascular deconditioning. They are also an invaluable resource for investigators in other areas, such as studies of circadian rhythms.

Details related to archiving and distribution of the ECG data needs to be decided in collaboration with NASA. In particular, the possibility of distributing these data after de-identification in the form of compact discs should be explored. We have practical experience with this novel form of inexpensive (\$3.00/disc) data archiving and distribution. Other important issues relating to the contents of the database, authorization for its use, and so forth, will also require collaboration with NASA during the definition phase of the project. This new archiving and retrieval system using compact discs would greatly simplify information and storage by Life Science Investigators.

Discussion with NASA is also required concerning the protocol for recording and archiving of heart rate data from future flights. Careful analysis of existing data will help guide the formulation of protocols for data acquisition on future missions. Should heart rate data be acquired throughout the flights or just at selected times? What control data should be acquired pre-flight and post-flight? What equipment should be used to record these data?

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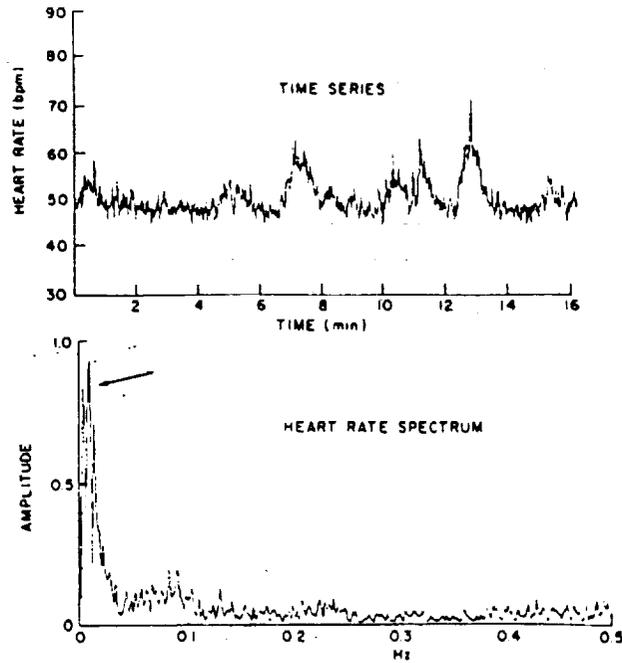


Figure 1. Heart rate time series and corresponding frequency spectrum from an astronaut with space motion sickness (SMS). Upper panel: During SMS, the astronaut's heart rate is seen to exhibit a series of large amplitude oscillations, not seen under normal conditions, that might be used as a marker of the syndrome's presence. Lower panel: This is the Fourier spectrum of the above heart rate time series, showing the range of frequencies over which the oscillations occur. They are found in the band centered around 0.01 Hz that is indicated by the arrow.

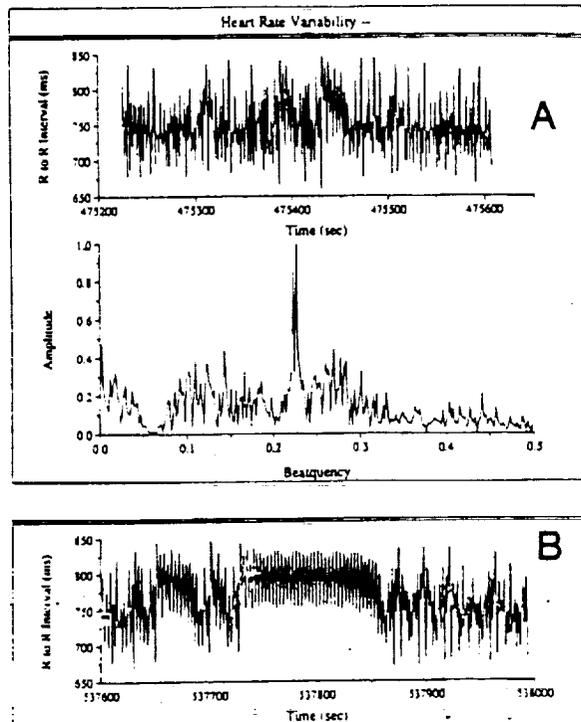
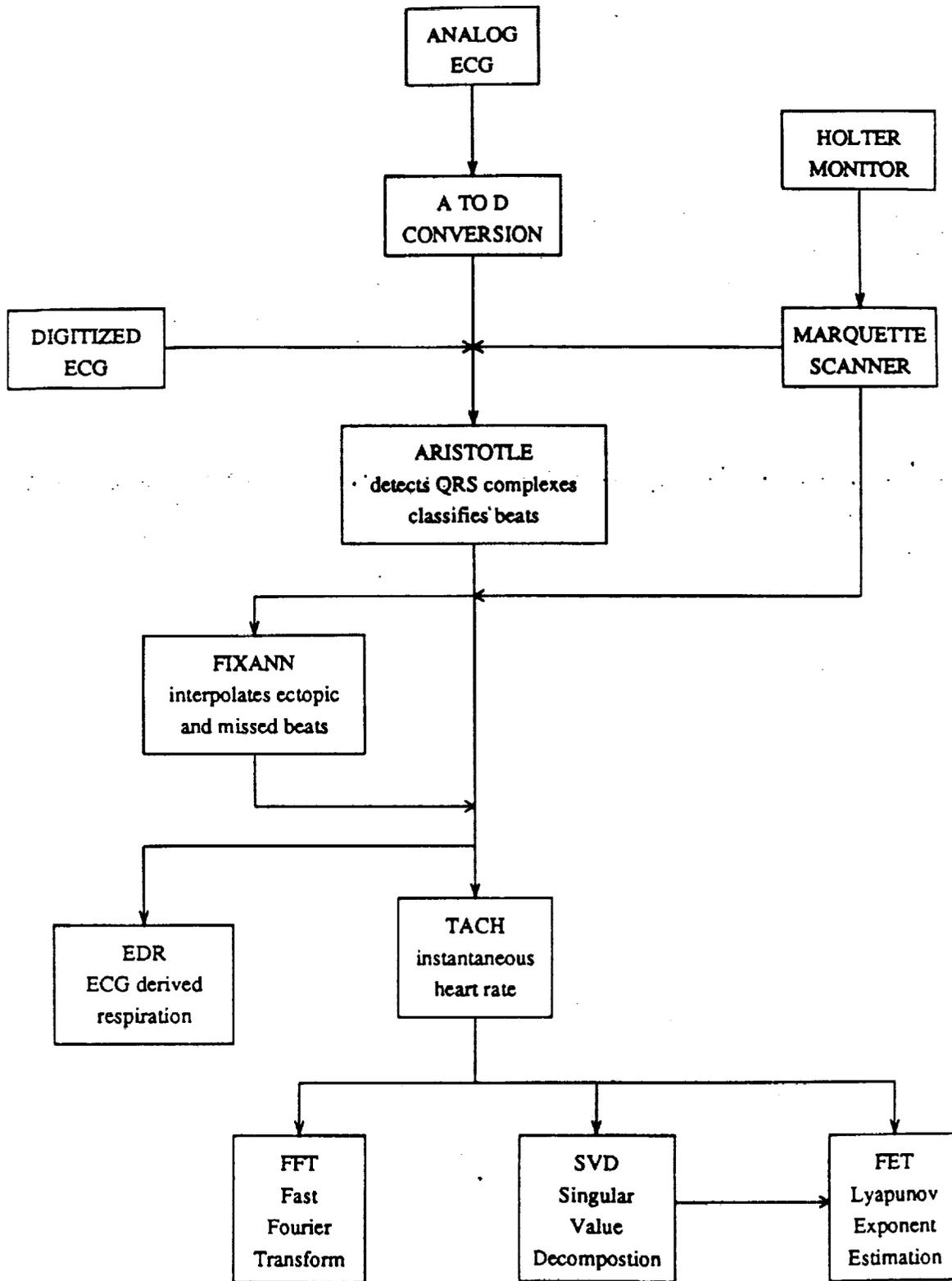


Figure 2. Erratic and periodic heart rate data in a totally deterministic, nonlinear model of cardiovascular control. A. For certain parameter values, the heart rate fluctuates deterministically for thousands of beats. The peak at 0.25 beat^{-1} is due to baroreflex. B. The continuation of the simulation in (A) demonstrating intermittency that starts and stops abruptly.

Figure 3. Flow chart for electrocardiographic data analysis in our laboratory.



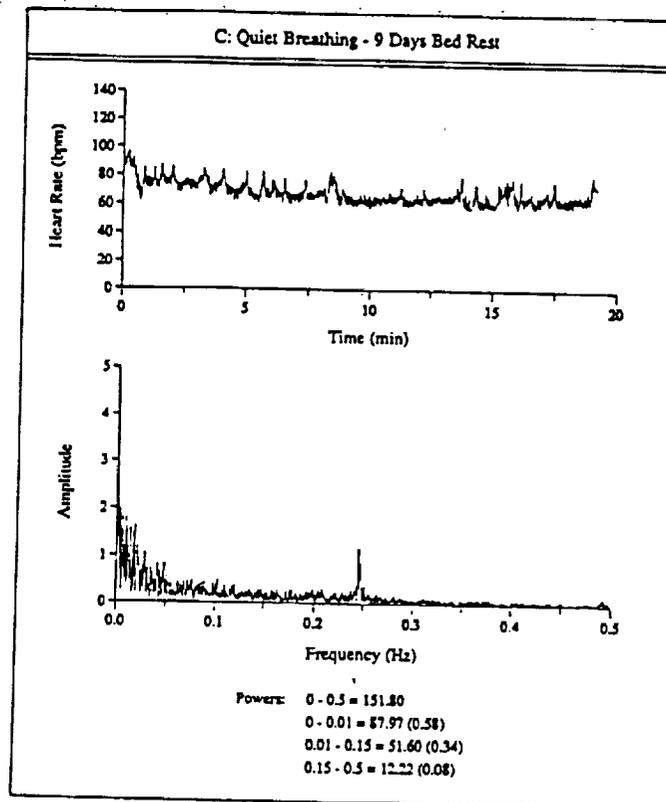
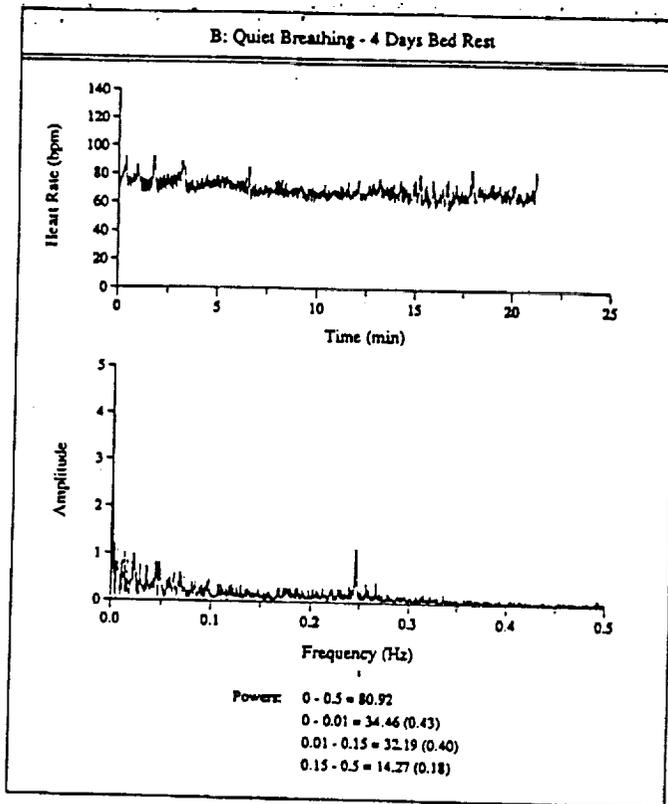
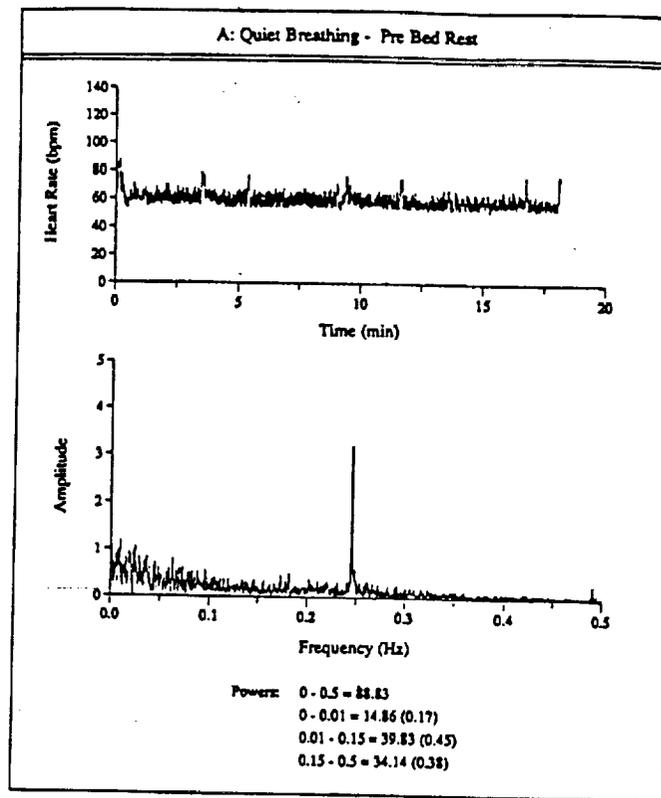
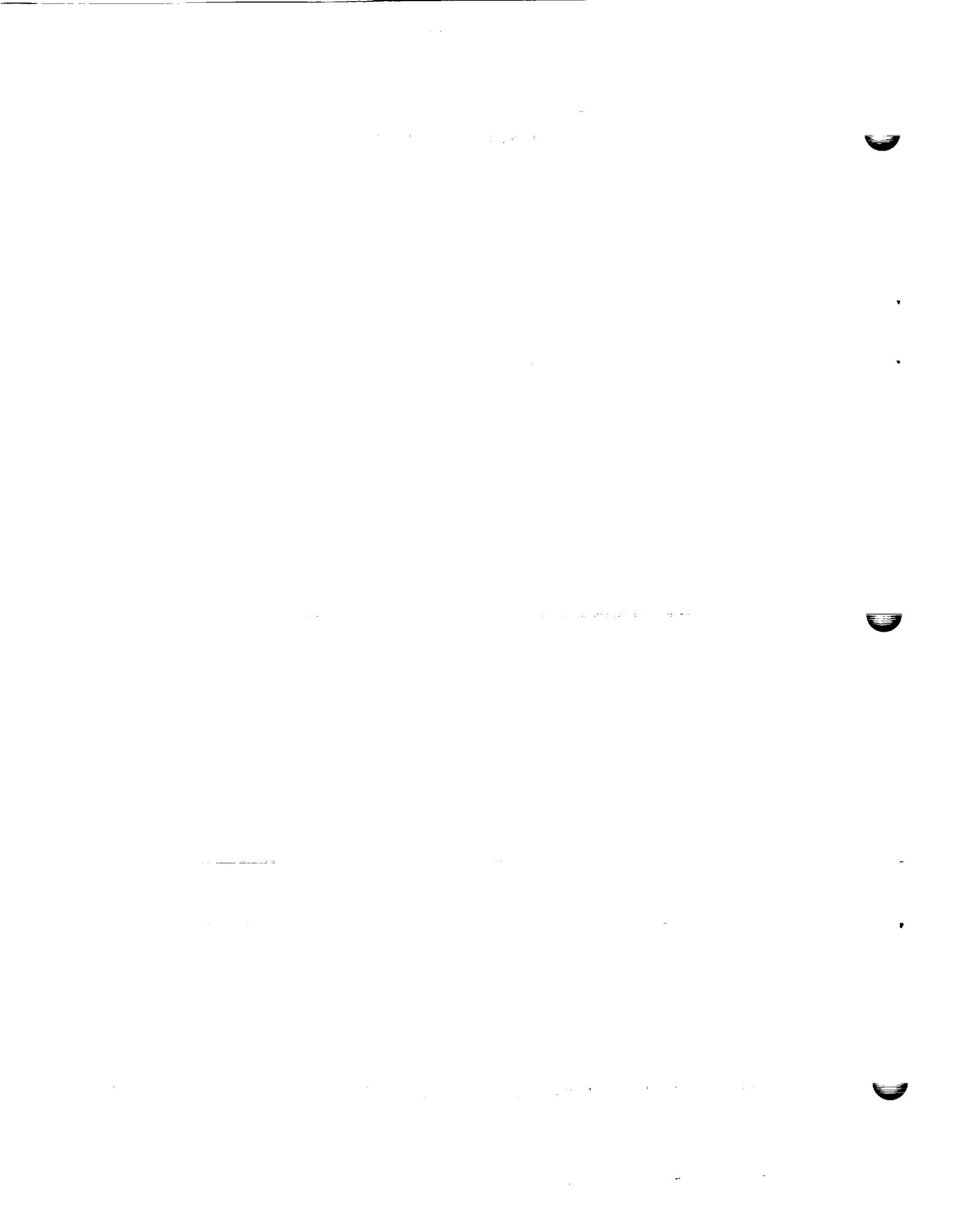


Figure 4. Heart rate time series and spectra from a young healthy adult female before and during bedrest study. Note the prominent, vagally-mediated high frequency peak in panel A associated with metronomic breathing at .25 Hz. During bedrest (B, C) there is attenuation of this peak, consistent with a loss of vagal tone associated with deconditioning. Average heart rate is also increased. Data are from the study being conducted by Dr. Suzanne Fortney, JSC. Spectral power for different bands is shown below each data set. Numbers in parentheses indicate percentage of total power in each band.



omit

SUMMARY:

Cardiovascular Measurements in Chronically Instrumented Conscious Monkeys

November 21, 1990

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SUMMARY: Cardiovascular Measurements in Chronically Instrumented Conscious Monkeys

Flow Measurement Comparison Studies

These studies are being conducted to compare the ability to measure blood flow in chronically instrumented animals using four different techniques, the electromagnetic, ultrasonic transit-time, ultrasonic pulse-Doppler, and ultrasonic directional-Doppler. The studies are conducted in phases, with phase 1, bench comparisons completed, and phase 2, animal studies in progress.

The bench studies demonstrate that all flowmeters possess good linearity of output with volume flow calibrations, in excess of the maximum physiologic range of flow velocities.

To date, 5 animals have been studied after chronic implantation of pairs of flow probes on the left and right iliac arteries. The studies indicate that the EMF and transit-time probes both compare well as volume flow measuring devices, and linearity of calibrations compare favorably in all three techniques. The EMF probes are less stable relative to zero flow, and require an occlusive flow reference for meaningful measurements. The transit-time device seems to be much more stable at zero, since electrical contact with electrodes is not necessary, as with the EMF system. The transit-time technique may well require an occlusive zero reference for best accuracy, since this parameter depends partially upon the actual alignment of the vessel and probe after the full development of connective tissue around the probe.

Long Term Implants in Small Monkey

This project examines the long-term viability for measurement of aortic pressure, aortic blood flow, and left ventricular pressure in primates. Eight animals have been studied after chronic implantation of left ventricular pressure gauges (Konigsberg), indwelling catheters for calibration of the Konigsberg, and either EMF or Transonic ultrasonic flow probes around the aorta. The Konigsberg transducers measured LV pressure reliably for four to six months. The indwelling catheters remained patent for various times, from three to seven months. All flow transducers worked well for the duration of the implant.

Attached is a figure (Figure 1) showing signals obtained from two animals. The left hand panel shows the signals from the Konigsberg LV transducer, LV dP/dt , and the Transonic flowprobe around the aorta, at four months post-implantation. The right panel shows similar signals from the other animal at six months, with an electromagnetic flow probe around the aorta.

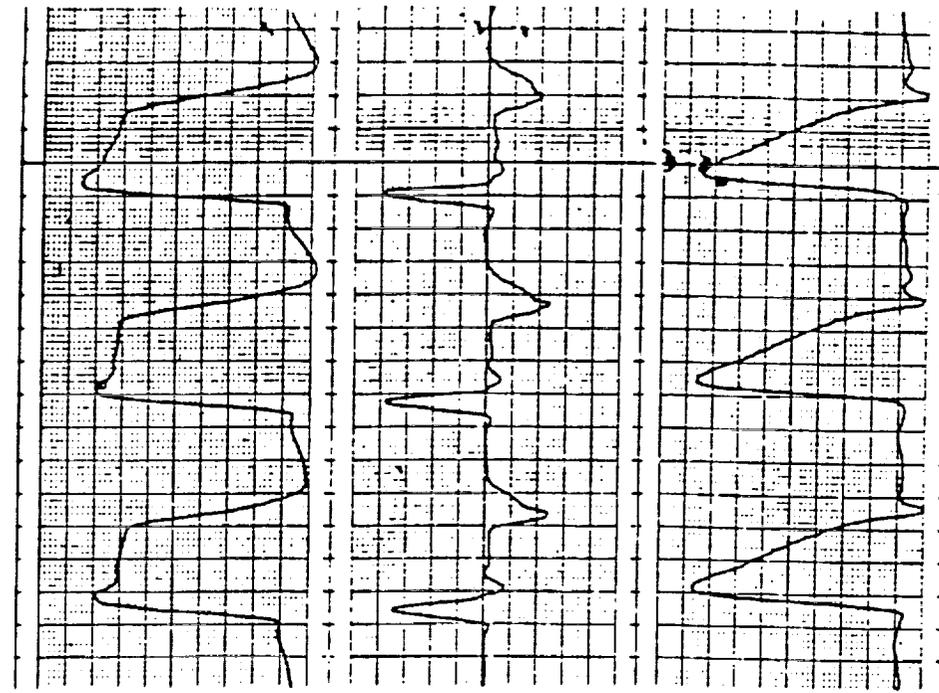
We have also utilized the instrumentation for the two studies referenced at the beginning of this Progress Report. Examples of the phasic data in chronically-instrumented primates are shown in Figures 1 and 2.

Future Plans and Rationale for Chronically Instrumented Monkeys for Understanding Cardiovascular function in Long Duration Missions

The problems with cardiovascular deconditioning will become much more intense with the projected long-duration missions planned by NASA. In order to study the problems and hope to gain any insight into the mechanisms which may ameliorate the deleterious effects of long-term space flight in microgravity, a non-human primate model to assess chronic cardiovascular function in a conscious state will be required.

Prolonged spaceflight and microgravity induce body fluid shifts, which increase cardiac dimensions and pressures, which in turn, alter cardiac output, the distribution of blood flow to vital organs and adrenergic control and reflex control of the cardiovascular system. It is important to determine the mechanisms for these cardiovascular alterations during microgravity and spaceflight in order to design countermeasures for future prolonged spaceflight.

To accomplish this, a Rhesus monkey model will be utilized to measure cardiac output, cardiac function, and regional blood flows during prolonged spaceflight and microgravity. A second major goal will be to determine whether prolonged spaceflight and microgravity alter reflex and adrenergic control of cardiac function and regional blood flow in the Rhesus monkey. This will be achieved by examining the effects of 1) baroreflex perturbation with inferior vena caval occlusion (IVCO) and bilateral carotid occlusion (BCO), 2) low pressure cardiac receptors perturbation with volume loading, lower body negative pressure (LBNP) and lower body positive pressure (LBPP), 3) stimulation and blockade of autonomic receptors with α , β , and cholinergic subtype selective agonists and antagonists. However, before all of these goals can be accomplished, the appropriate instrumentation must be calibrated and verified to be useful for cardiovascular experimentation in spaceflight. A third major goal is to examine the above interventions on coronary and cerebral blood flows in the Rhesus monkey. The fourth major goal is to determine whether prolonged spaceflight and microgravity induce catecholamine desensitization in the Rhesus monkey; which could be the underlying biochemical mechanism responsible for alterations in adrenergic control.



LEFT VENTRICULAR
PRESSURE

LV DP/dt

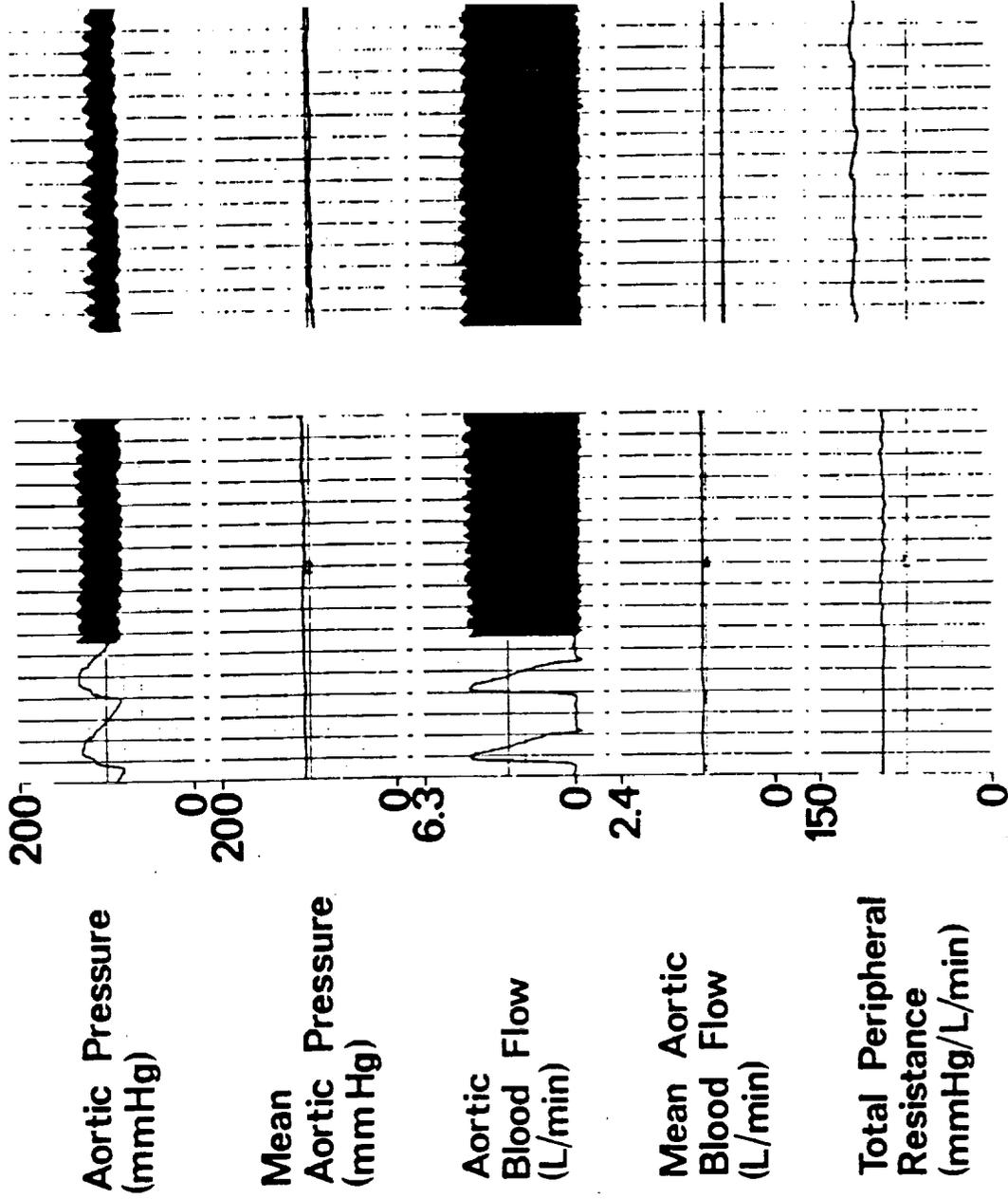
AORTIC BLOOD
FLOW

TRANSONIC FLOW PROBE,
FOUR MONTHS

ELECTROMAGNETIC FLOW PROBE,
SIX MONTHS

FIGURE 1.

Monkey



Control

ANF

0.3 µg/kg/min

FIGURE 2. The effects of ANF, 0.3 µg/kg/min, on phasic and mean measurements of aortic pressure and aortic blood flow with computed total peripheral resistance at the bottom in a conscious monkey before (left panel) and 30 min after infusion of ANF (right panel). Note that ANF reduced mean

INSIGHTS INTO CONTROL OF HUMAN SYMPATHETIC NERVE ACTIVITY DERIVED FROM THE VALSALVA MANEUVER

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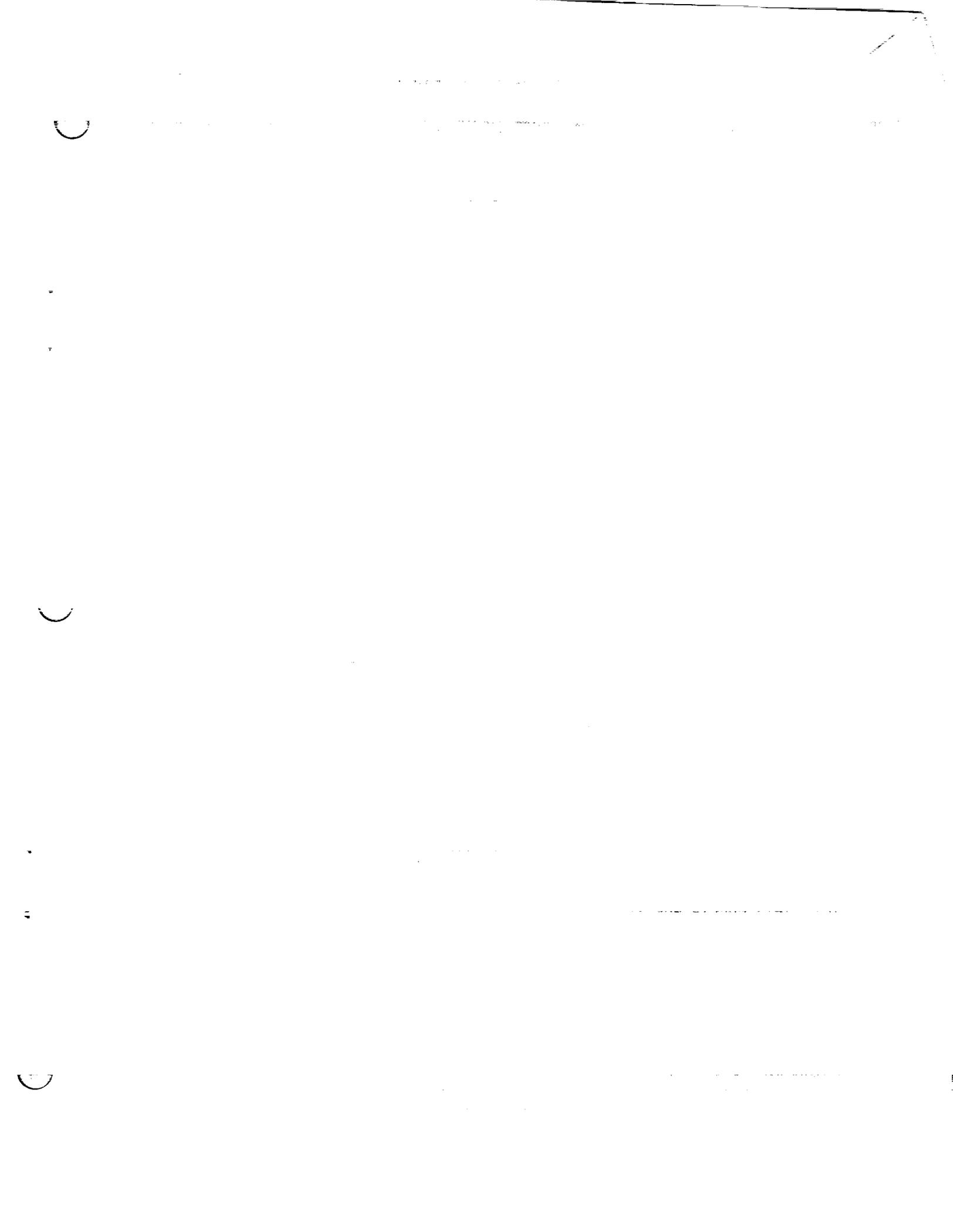
The Valsalva maneuver, straining against a closed glottis, is a time-honored method for perturbing human arterial pressure and autonomic cardiovascular neural outflow. We studied nine healthy young adults who were trained to perform graded, carefully controlled Valsalva maneuvers. These subjects strained at intensities of 10, 20, and 30 mmHg for 15 seconds, and controlled their breathing frequencies and tidal volumes before and after straining. We recorded the electrocardiogram, non-invasive blood pressure (Finapres), and peroneal muscle sympathetic nerve activity. An additional six subjects performed Valsalva maneuvers during measurement of right atrial and intraarterial pressures.

Valsalva straining provoked alternating, reciprocal changes of arterial pressure and muscle sympathetic nerve activity. At the beginning of straining (phase 1), arterial pressure rose and sympathetic activity disappeared. During the next several seconds of straining (early phase 2), arterial pressure fell and sympathetic activity increased; during the final seconds of straining (late phase 2), arterial pressure rose and sympathetic traffic declined. After release of straining (phase 4) arterial pressure rose, and sympathetic neurons fell silent. Sympathetic silence substantially outlasted the elevation of atrial and arterial pressure that occurred after release of straining.

As expected, the reduction of arterial pressure during straining was proportional to the intensity of straining. Increases of muscle sympathetic nerve activity also were proportional to the intensity of straining and to the reduction of arterial pressure. The elevation of pressure after straining was also directly proportional to the intensity of straining. Moreover, there was a highly significant relation between the increase of muscle sympathetic nerve activity during straining and the subsequent elevation of pressure after straining. This relation provides some justification for use of pressure elevation after Valsalva straining as a noninvasive index of preceding sympathetic activity.

These results provide insights into baroreflex modulation of human muscle sympathetic nerve activity. It is likely that increased intrathoracic pressure during Valsalva straining reduces aortic distending pressure and thereby, the degree of stretch placed upon aortic baroreceptors. Several conclusions issue from this assumption. First, during the earliest seconds of straining, peripheral arterial distending pressure increases at a time when absolute aortic distending pressure is reduced. Sympathetic silence during this period attests to the importance of carotid baroreceptors in modulation of muscle sympathetic nerve activity. Second, the decline of sympathetic activity as arterial pressure is rising during the late straining phase suggests that sympathetic motoneurons are more influenced by arterial pressure trends than absolute levels; reductions of sympathetic traffic began at a time when absolute levels of both peripheral arterial and aortic distending pressures were below baseline levels. Third, sympathetic silence after release of straining and return of right atrial and arterial pressures to normal indicates that the preceding pressure transients in some way rest the usual relation that exists between arterial pressure and muscle sympathetic nerve activity.







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16. Abstract On 5-7 December 1990, a workshop was held at the Johnson Space Center to promote communication and cross fertilization of ideas among NASA cardiopulmonary principal investigators. This was the first such meeting of cardiopulmonary investigators sponsored by the Johnson Space Center, Kennedy Space Center, and the Ames Research Center. Each principal investigator gave a 20-minute summary of recent progress in his or her laboratory. Topics covered included flight echocardiography (J. Charles), pulmonary function (H. Guy), central hemodynamics (R. Latham), glycerol hyperhydration (M. Riedesel), spectral analysis (C. Knapp and A. Goldberger), lower body negative pressure countermeasures (S. Fortney), orthostatic tolerancy (J. Buckey), autonomic function (V. Convertino, M. Smith, D. Eckberg), cardiac deconditioning (C. Tipton), fluid and renal responses to head-down tilt (B. Tucker), local fluid regulation (A. Hargens), endocrine regulation during bedrest (J. Vernikos, C. Wade), autogenic feedback (P. Cowings), and chronic cardiovascular measurements (S. Vatner). The program ended with a general discussion of weightless models and countermeasures.			
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