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Session JA2

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8:30 - 11:30 a.m.

**Body Fluid Regulation and
Hemopoiesis in Space Flight**

BODYMASS AND FLUID DISTRIBUTION DURING LONGTERM SPACEFLIGHT WITH AND WITHOUT COUNTERMEASURES

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INTRODUCTION

Exposure to micro-g is followed by a fluid shift from the lower limbs towards the upper part of the body and simultaneously a fluid loss occurs. We therefore studied the dynamics of the fluid shift in relation to the fluid loss during short and long term spaceflights. In the latter case countermeasures were applied to prevent a fluid mobilisation from the lower limbs.

METHODS

8 male subjects took part in the study during 5 different space missions. Two subjects were on the D-2 Mission, 6 were on the Mir-Station. In the short term flights (4 subjects) no countermeasures like cuffs around the thighs were used. In the long term flights (33 - 436 days) countermeasures were applied. The tissues thickness (TT) was measured in superficial tissues by ultrasound probes attached along the tibia and in the front. Pre-, In- and postflight data were collected. During long term flights Body Mass (BM) was taken together with the TT values.

RESULTS

During all missions facial tissue swellings appeared within the first hours but tended to diminish during the flight. The shrinking of the limb tissues (- 15%) was more outspoken than the tissue swellings in the front (+ 7 %) and remained unchanged throughout the flight as observed during the short term missions. In the long term flights the application of the cuffs prevented a fluid mobilisation from the lower limbs but not the swelling of the facial tissues. In the front between the BM changes and the TT changes inflight always a strong correlation existed ($p < 0.01$).

CONCLUSIONS

Swellings of the facial tissues during space flight are dependent from the water balance of the body, they can not be prevented by countermeasures.

PLASMA VOLUME, EXTRACELLULAR FLUID VOLUME, AND REGULATORY HORMONES DURING LONG-TERM SPACE FLIGHT H.W. Lane, B.V. Morukov, I.M. Larina, S.M. Smith, A.I. Grigoriev, C.S. Leach. NASA Johnson Space Center, Houston, TX; Institute for Biomedical Problems, Moscow, Russia.

Exposure to microgravity causes headward fluid shifts, and it is hypothesized that the body perceives this as an increased circulatory volume. Within hours of entering microgravity, a 12-15% decrease in plasma volume (PV) and a 10% decrease in extracellular fluid (ECF) occur. The PV decreases through a shift of plasma out of the vascular compartment, initially to the extravascular ECF and then to the intracellular compartment. The net result is a shift of fluid from the ECF to the intracellular fluid compartment. Concurrently, erythropoiesis is downregulated resulting in a 12-15% decrease in red blood cell mass, with an overall 12-15% reduction in blood volume. These observations have been well characterized in short-term space flight. We report here data from a 115-d mission aboard the Mir space station.

Three male subjects participated in these studies (age 47 ± 12 years, mean \pm SD; body weight 77.9 ± 7.2 kg). Plasma volume was measured before flight and on landing day using the carbon monoxide rebreathing technique. Extracellular fluid volume was determined before and during flight using the bromide dilution technique. Blood and urine samples were collected, aliquoted, and frozen until postflight analysis, except for blood sodium and potassium, which were determined in "real-time" with a portable clinical blood analyzer. Plasma levels of aldosterone, antidiuretic hormone (ADH), and atrial natriuretic peptide (ANP) were determined before flight and after 110 d of flight. Results are shown below; all data are mean \pm SD.

<u>Analyte</u>	<u>Preflight</u>	<u>Inflight</u>
Plasma Volume (L)	3.16 ± 0.15	$3.01 \pm 0.08^*$
Extracellular Fluid Volume (L)	19.53 ± 2.16	15.56 ± 1.80
Aldosterone (pg/ml)	109 ± 34	73 ± 29
ADH (pg/ml)	2.6 ± 1.3	0.9 ± 0.4
ANP (pg/ml)	20.0 ± 12.7	12.6 ± 11.6

* Landing day data

The decreases in plasma volume and extracellular fluid volume are similar to changes found in 14-d Shuttle flights. After 110 days of flight, plasma ADH concentrations of all crewmembers and ANP of 2 of the 3 had decreased compared to preflight values. The initial changes in fluid volumes that occur during space flight appear to remain throughout long-term flight. This indicates that these are not transient effects, but rather reflect an adaptation to space flight which occurs within the first days to weeks of flight.

EFFECT OF MICROGRAVITY AND ITS GROUND-BASED MODELS ON FLUID VOLUMES AND HEMOCIRCULATORY VOLUMES

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INTRODUCTION

Despite certain achievements of space exploration, many important problems of space medicine remain unresolved. There is no clear scientifically validated concept of the pathogenesis of the effect of space flight (SF) factors upon the human body; its most vulnerable functions and systems have not been identified; the compensatory reserve of the body remains undetermined. All this prevents further increase of space flight duration, prediction of the development of sub-pathological states as well as further optimisation of countermeasures and purposeful correction of the status of body functions. Among the unresolved problems of space medicine, the leading one are, in our view: the change, during SF, of the functioning of the circulatory system (CS) manifested as a decreased orthostatic tolerance of cosmonauts; disturbed cardiac rhythm, increased blood filling of parenchymatous organs during SF, the space anaemia syndrome; decreased content of fluids and hemocirculatory volumes. The subject of discussion in this work is a study of fluid and blood volumes. It is obvious that these studies require a complex approach and the use of modern measuring techniques. The most adequate are, in our view are stable and/or radioactive isotopes. Great experience has been accumulated of complex studies of fluid and blood volumes in various ground-based simulation experiments using a complex of stable and radioactive isotopes. However, scanty and fragmentary data obtained during space flight have not allowed to determine the identical nature of physiological effects seen during simulation experiments and SF. This could be resolved only by quantitative measurements of blood and fluid volumes directly during SF. After developing methods for delivery, means for investigation, and ways of returning the biomaterials to the Earth, these measurements were performed aboard the "Mir" orbital station during orbital missions (OM) 15—17 in 2 cosmonauts: the physician (OM 15—17) and commander of OM-16. The in-flight studies were performed by physician-cosmonaut.

METHODS

The following radioisotopes were used: tritium water and labelled albumin (J-131), as well as stable bromide. The following volumes were studied: total body water (TBW), intracellular water space (ICWS), extracellular fluid (ECF), and its fractions: plasma (PV) and the interstitial fluid (IFV), as well as blood and erythrocyte volumes (BV and EV). Studies were performed pre-flight, on flight days 4-5 (in physician and commander) and on day 434 (in physician) as well as during readaptation.

RESULTS

On days 4 and 5 of SF in physician and commander the TBW was lower than pre-flight by 4 and 5 % respectively. The ECF was lower than pre-flight by 9 and 10 % respectively. The ICWS within the SF duration was unchanged. BV in commander was lower than pre-flight by 8 % due to his own plasma. The erythrocyte mass volume was not decreased. Observation of physician on the SF day 434 revealed a decrease of ECF by 18 % as related to pre-flight. This was due both to plasma and to the interstitial fraction which changed more significantly. Ratios of fluid fractions changed insignificantly. The post-flight observation of commander on day 1 after completing his 158-day SF, revealed a decreased content of all fluids: TBW by 10 %, ECF by 23 %, ICWS by 5 % as related to the pre-flight value. The post-flight observation of physician on day 14 after landing demonstrated that the changes noted at the end of SF by the day of readaptation mentioned were slight. However, the changed ratio of the vascular and interstitial fractions was maintained. The work presents a comparative analysis of changes in hydrational homeostasis and hemocirculatory volume during microgravity and ground-based simulation experiments — clynostatic hypokinesia, head-down hypokinesia with a tilt angle of 5 and 15°, vertical immersion.

CONCLUSIONS

Due to the inadequate number of observations during SF, the conclusions are preliminary. On days 4 and 5 of adaptation to SF, a new level was formed of hydrational homeostasis and hemocirculatory volumes at a lower quantitative level most marked was the decrease of the extracellular fluid volume and its fractions. The intracellular fluid volume was unchanged, which disturbed their ratios. During a prolonged space flight in physician, the changes progressed. The most marked were also changes in the extracellular water space, mainly due to the interstitial fraction. During readaptation for 14 days, the changes noted in-flight, practically returned to pre-flight values. A comparative analysis of changes in fluid and blood volumes during microgravity and ground-based simulation experiments demonstrated that, preliminary, they have a common direction of changes. However, each of the above models has its peculiarities and differences.

SEVENTEEN WEEKS OF HORIZONTAL BED REST, LOWER BODY NEGATIVE PRESSURE TESTING, AND THE ASSOCIATED PLASMA VOLUME RESPONSE

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INTRODUCTION

Both space flight and BR are associated with a cephalad shift of body fluids, diuresis, a decrease in plasma volume (PV) and orthostatic intolerance. The loss of orthostatic tolerance can be documented during bed rest (BR) using lower body negative pressure (LBNP).

METHODS

This study was conducted in Methodist Hospital, Baylor College of Medicine, as an adjunct investigation to a primary study designed to document hypokinesia-induced Ca^{++} loss. We examined PV in 4 healthy male subjects before, during, and after 17 weeks of horizontal BR. LBNP was performed weekly to document orthostatic tolerance. The LBNP protocol consisted of a 10-min control period at ambient pressure; 5 mins each at 5, 10, and 20 mm Hg, but it increased at 30, 40, and 50 mm Hg LBNP. Pre-BR, peak HR was 97 ± 10 bpm, occurring at 50 mm Hg. After 3 days of BR, all HR responses, including values after release of LBNP, were only slightly elevated (ns) above pre-BR level. Peak HR was 118 ± 21 bpm at 50 mm Hg decompression (ns). After 3 weeks of BR, peak HR was 110 ± 16 bpm at 50 mm Hg decompression (ns). The slight increase (ns) in HR persisted throughout the 17 weeks of BR. A decrease in the duration of tolerance to LBNP occurred in 3 subjects. Mean PV was decreased 5% to 4% (sig different from almost all other days) on day 36 and 42 of BR, respectively. All other PV values did not vary much, ranging from -1.5% to 1% of control.

CONCLUSIONS

The data indicate that the HR changes associated with orthostatic instability develop early, after as few as 3 days of BR, and persist throughout the entire 17 weeks of horizontal BR. Sandler (NASA 1988 Technical Memorandum 88314) summarized data from many BR studies and reported that PV exhibited a rapid 8-10% loss over the first few days of BR. PV values were then stabilized at -15 to 20% between 14 to 28 days and exhibited decreases up to 30% when the duration of BR was from 100 to 200 days. Udden et al (Space Physiology and Medicine, Lea & Febiger, p 350, 1994) reported a 23% decrease in PV after 24 hours of space flight; values 9 days later, at landing, were only decreased by 10%. PV values returned to control six days after landing. In the 17 week BR study the peak magnitude of the PV decrease, (-5%) detected on day 36 of BR, was one-half that reported after 9 days of space flight. On day 15 of BR, PV values were no different from those at day 0. In conclusion, the data show a decrease in PV like other BR and space flight studies, but the magnitude of the decrease and the time frame in which the decrease occurred were different. In general, PV was maintained during the 17 weeks of horizontal BR. The data suggest that the slight decrease in PV did not, by itself, alter the HR changes associated with the orthostatic stress induced by LBNP.

EVAPORATIVE WATERLOSS IN SPACE THEORETICAL AND EXPERIMENTAL STUDIES.

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INTRODUCTION

During space flight often water loss occurs in man but it is unknown whether a reduced intake or an increased output is responsible for the fluid loss. In a theoretical study evaporative water loss (EVA) was estimated and compared with results obtained during head down tilt (HDT) studies.

METHODS

In the theoretical study besides the usual climate factors prevailing in a space craft micro-g conditions were assumed which would exclude thermal convection.

Experimental studies were performed in 12 male subjects measuring EVA in supine and HDT conditions. EVA was measured with an evaporimeter (Servo-Med Sweden) in 8 points along body axis.

RESULTS

The theoretical study revealed an evaporative loss of $6.1 \text{ g m}^{-2} \cdot \text{h}^{-1}$, which is a very low rate compared to data seen on ground.

Subjects with high ($n = 4$) and low ($n = 6$) EVA rates during rest in supine position were seen. During HDT the subjects with high resting EVA rates responded with significantly reduced EVA values ($p < 0.01$). The individual type of subject seen in supine position determined the EVA rate rather than the HDT manoeuvre.

CONCLUSIONS

Theoretically low EVA rates in micro-g can be expected. Simulated micro-g can affect EVA depending on individual. Whether this plays a role under stress conditions like in space remains to be determined. Only direct measurements in space can solve the problem.

ERYTHROPOIETIN UNDER REAL AND SIMULATED MICRO-G CONDITIONS IN HUMANS

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INTRODUCTION

It was the aim of this study 1) to analyze the time course of erythropoietin during earth-bound micro-g simulations such as bed-rest, isolation and confinement, head-down tilt (-6°), and immersion so as to evaluate 2) which factors could contribute to alterations found in erythropoietin under real micro-g conditions during and after short- (<10 days) and long-term (>6 months) space-flights.

METHODS

Serum and plasma samples were taken and analysed for erythropoietin by radioimmunoassay and enzyme linked immunoassays before, during and after the following test settings: bed-rest (N=10, male, 24 hrs); isolation and confinement (N = 4; 1 female, 3 male, 8 weeks); head-down tilt (-6°) (N = 8, male, 42 days); immersion (N = 8, male, 1 hr); short- (N = 4, male, 10 days) and long-term (N = 1, male, 135 days) space-flight.

RESULTS

During bed-rest (24 hrs) no significant changes in erythropoietin could be observed. The subjects confined in a diving chamber facility for 8 weeks showed, after 3 weeks inside the chamber, an erythropoietin decrease until the last week inside the chamber. In the recovery period a slight increase was observed, but erythropoietin concentrations did not reach the pre-isolation control level. In the control period before head-down tilt (-6°) the subjects showed normal resting values for erythropoietin, but already on the 2nd day of head-down tilt the erythropoietin concentrations were decreased ($P < 0.01$). During the following weeks the erythropoietin levels remained below the control value and were increased during the 1st week post-head-down tilt ($P < 0.05$). After immersion (1 hr) the erythropoietin values were unchanged, whereas 24 hrs later a significant increase could be determined ($P < 0.05$). During the German *D-2* mission, a short-term space-flight (10 days), the astronauts showed pre-flight normal resting erythropoietin levels (9.3 ± 2.2 mU . ml⁻¹). In-flight (4th day) the erythropoietin concentrations were decreased (6.0 ± 5.1 mU . ml⁻¹): two astronauts had very low erythropoietin levels (subject A 0.3 mU . ml⁻¹; subject D 3.3 mU . ml⁻¹) while the other ones showed nearly unchanged concentrations. On the recovery day the erythropoietin concentrations were slightly further decreased (5.6 ± 3.3 mU . ml⁻¹) and increased slowly towards control level in the post-flight phase (7th day 7.4 ± 3.4 mU . ml⁻¹; 15th day 10.9 ± 2.1 mU . ml⁻¹). During the *EUROMIR'94-E* mission, a long-term space-flight (135 days), the cosmonaut showed pre-flight normal resting erythropoietin levels (14.4 mU . ml⁻¹). One day after the recovery the erythropoietin concentration was slightly elevated, but in the normal range (19.4 mU . ml⁻¹). In the following post-flight phase the erythropoietin values increased markedly (2nd day 46.3 mU . ml⁻¹) and remained elevated (5th day 43.1 mU . ml⁻¹).

CONCLUSION

It is concluded that 1) head-down tilt (-6°) causes a rapid erythropoietin decrease in man; 2) isolation and confinement *per se* lead to diminished erythropoietin concentrations; 3) during a short-duration spaceflight (<10 days) extremely low erythropoietin concentrations were observed in-flight in two out of four astronauts, whereas in the other ones unchanged erythropoietin concentrations were determined. After two weeks post-flight all subjects showed normal erythropoietin concentration; 4) increased erythropoietin concentrations above control range were found immediately after long-term space flights; 5) changes in central blood volume, i.e. central venous pressure, might be involved in the modulation of erythropoietin production and release under simulated and real micro-g conditions; and 6) the head-down tilt (-6°) earth-bound simulation reflects most likely the changes in erythropoietin production and release observed under micro-g conditions in man.

VERTEBRAL BONE MARROW CHANGES FOLLOWING SPACE FLIGHT

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INTRODUCTION

It is known from bone biopsies that marrow fat increases 100% during the first 20 weeks of paralysis. The exact function of marrow adipose cells and their relation to bone metabolism and hematopoiesis is unknown, however, it is known that bone marrow adipose cells have a reciprocal relationship to hematopoietic tissue. As the hematopoietic tissue expands the lipid fraction of the adipose cells decreases while the opposite occurs during decreases in hematopoiesis. A number of studies suggest linkage between the bone marrow microenvironment and osteoblastic activity. With magnetic resonance spectroscopy (MRS), the possibility exists to examine these changes in vivo. One objective of our Life and Microgravity Spacelab (LMS) experiment, flown in July of 1996, was to document this expected change in the marrow composition using a noninvasive MRS technique developed in our laboratory.

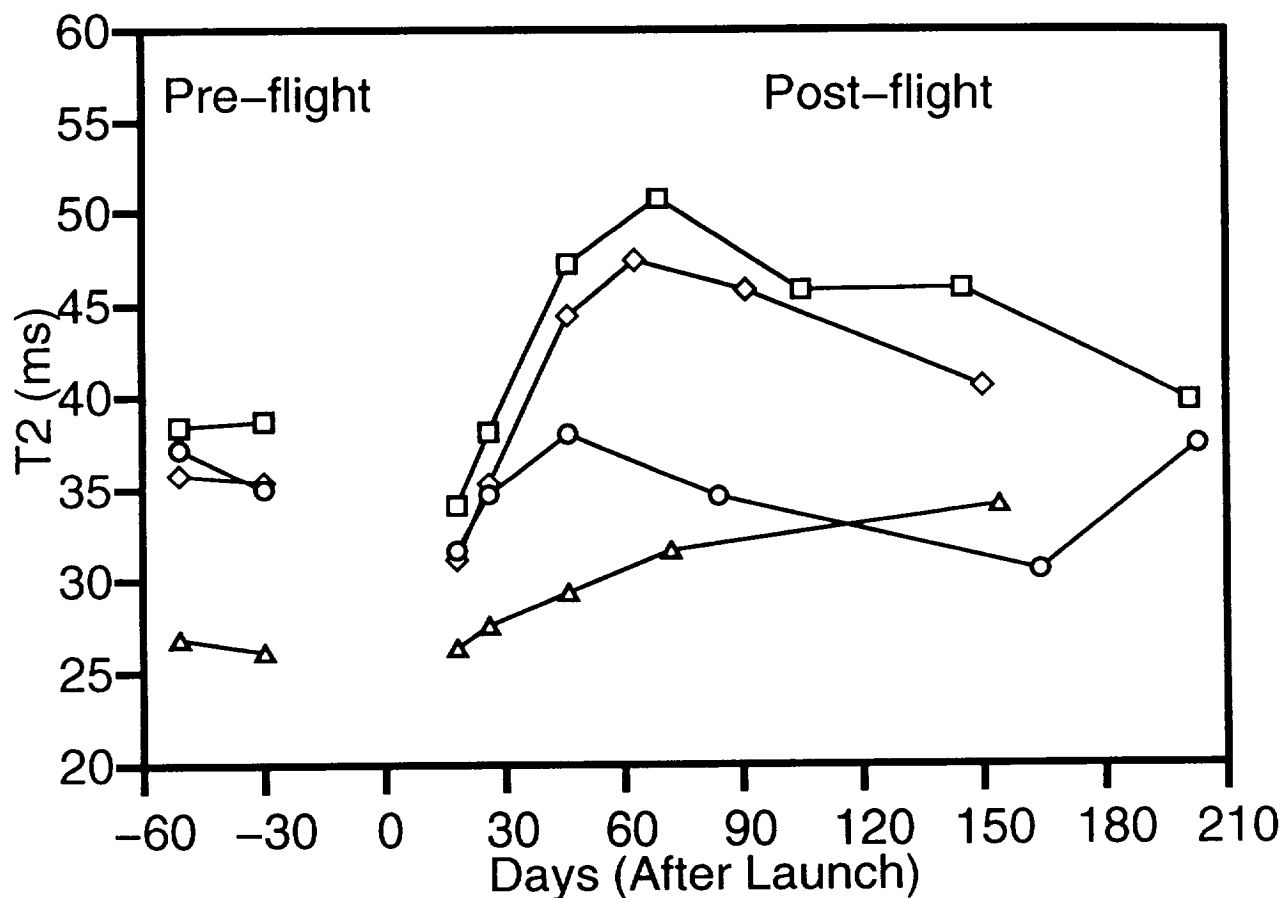
METHODS

LMS was a 17 day Spacelab mission dedicated to life and microgravity research. The 4 payload crewmembers participated in the magnetic resonance experiment which involved MRS scanning at L-60, L-30, R+2, R+14 and R+30 days. To measure the fat to water ratio in vertebral bone marrow, volume selective proton spectra were obtained using a surface receive coil. A cubic volume of interest of 15mm x 15mm x 15mm located in the center the L3 vertebral body was selected based on the initial scan of the spine region. A Gradient Inversion Spectroscopy technique was used to acquire spectra at TE = 12, 18, 24, and 30 ms with TR = 2s. The images were corrected for T2 weighting by exponential extrapolation of the spectra obtained at various TE. The intensities of fat and water were calculated by integrating the areas under the fat and water peaks after baseline correction. Bone marrow cellularity was determined from the fat to water ratio.

RESULTS

Immediately post-flight no significant change in the fraction of the water (cellular) component was found although subsequent post-flight measurements may indicate some change. There appeared to be a small decrease in the T2 of the cellular component post-flight, but what was surprising was the increase in T2 in all crewmembers that was clearly evident by the final data collection point at 30 days post-flight. We obtained IRB and astronaut permission to obtain additional measurements when the crewmember's time and schedule permitted. The data collected to date are shown in figure 1. For 3 of the 4 crewmembers, the T2 remains elevated above baseline 130 days after landing. There was no change in the T2 of the fat component. The T2 of the fat and water components for three volunteers measured over a one year interval overlapping the time when the flight data was collected showed no significant change.

Figure 1



DISCUSSION

Since the fraction of the cellular portion of the marrow is changing only slightly if at all, implies that the observed T2 change in the cellular component represents a change in the cellular composition of the marrow. One explanation is increased hematopoiesis to replace lost red cells following flight since the loss of red cell mass during short duration weightlessness is documented. However, the time frame of the T2 response is much longer than needed to replace lost red cells which should be completed in about one month after flight. Another explanation for the post-flight T2 response might be increased osteoblastic activity which might be expected to have a longer time frame. Our 17 week bed rest studies demonstrated an increase in bone formation markers compared to pre-bed rest after reambulation; alkaline phosphatase by 50% and osteocalcin by 33%.

CONCLUSION

There are significant T2 changes in the vertebral bone marrow observed with MRS after short duration flight (17 days). These changes demonstrate a time course lasting several months suggesting accelerated osteoblastic activity after return to earth's gravity. These findings have significant implications for medical research on earth as well as microgravity.