Shuttle-Mir Science Program Phase 1A Research Postflight Science Report

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Introduction

The Shuttle-Mir Science Program, also known as the Phase 1A program, was developed as a result of a joint agreement between the United States and the Russian Federation which initiated a cooperative human space flight program. The program consisted of two long duration missions, Mir 18 and Mir 19, and one Shuttle docking mission, Spacelab-Mir (SL-M) STS-71.

The Mir 18 mission began with the launch of the Soyuz TM21 on March 14, 1995, carrying two Russian cosmonauts, Mission Commander Lieutenant Colonel Vladimir N. Dezhurov and Flight Engineer Gennady M. Strekalov, Ph.D., and U.S. Astronaut, Mission Specialist Norman E. Thagard, M.D. The Soyuz TM21 docked with the Mir on March 16, 1995. After a 116 day stay in space, most of it on the Russian Space Station Mir, the Mir 18 crew landed at Kennedy Space Center on July 7, 1995. The STS-71 crew consisted of Commander Captain Robert L. "Hoot" Gibson, Pilot Lieutenant Colonel Charles J. Precourt, Mission Specialist Ellen S. Baker, M.D., Mission Specialist Gregory J. Harbaugh and Mission Specialist Bonnie J. Dunbar, Ph.D. The SL-M mission also provided return transportation for the Mir 18 crew and transportation for the Mir 19 crew to the Mir.

The Mir 19 mission continued the joint science program and began with the launch of U.S. Space Shuttle Atlantis carrying two Russian cosmonauts, Mission Commander Colonel Anatoly Y. Solovyev and Flight Engineer Nikolai M. Budarin, to the space station Mir. Mir 19 was concluded on September 11, 1995, with the landing of Soyuz TM21 in Russia.

The Shuttle-Mir science program used the U.S. Space Shuttle and the Russian Space Station Mir capabilities to conduct joint research activities in space. Seven research areas encompassing 28 investigations were conducted on Mir and/or the Shuttle. The overall objectives of the Shuttle-Mir missions were to obtain engineering and operational experience in conducting research on an orbital space station; to conduct specific investigations in medical support, life sciences, fundamental biology, microgravity sciences, Earth observations, and life support technology; and to characterize the environment relative to microgravity and life sciences research on Mir to better understand past and future investigations. Included in this report are the final science reports from the investigations performed on Mir 18, STS-71, and/or Mir 19.

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U.S. Principal Investigator: **CLARENCE F. SAMS, Ph.D.,** NASA/Johnson Space Center

Russian Principal Investigator: **IRINA KONSTANTINOVA, Ph.D.,** Institute of Biomedical Problems

Fluid and Electrolyte Homeostasis, Dynamics of Calcium Metabolism and Bone Tissue, Red Blood Cell Mass and Survival

U.S. Principal Investigator: **HELEN W. LANE, Ph.D.,** NASA/Johnson Space Center

(Mir 18 Final Science Report)

INTRODUCTION

Objectives

Fluid and Electrolyte Homeostasis

To determine the effect of microgravity on total body water, extracellular fluid, and plasma volume

To determine the effect of microgravity on body fluid distribution (i.e.- shift between compartments)

To determine the effect of microgravity on electrolyte balance

To determine the effect of microgravity on fluid/electrolyte regulatory hormones

Dynamics of Calcium Metabolism and Bone Tissue

To determine the effect of microgravity on calcium absorption/kinetics.

To determine the effect of microgravity on total and ionized serum calcium.

To determine bone/calcium homeostasis during space flight by measuring their regulatory hormones.

To determine the effect of return to 1xg environment on calcium absorption/kinetics.

To determine changes in bone density following flight to assess the impact and recovery from flight.

To determine the accretion of bone mass following extended duration space flight.

Red Blood Cell Mass and Survival

To determine the effect of microgravity on red blood cell mass and survival.

To determine the effect of microgravity on total and ionized serum calcium.

To determine erythropoietic hormones and hematologic changes during flight.

Background/History

Fluid and Electrolyte Homeostasis

Exposure to microgravity is known to have profound effects on fluid homeostasis. The headward shift of fluids observed in either real or simulated microgravity results in increased excretion of fluids and electrolytes. Fluid homeostasis is further affected by space motion sickness which often results in increased loss of fluid and electrolytes. Apart from the issue of fluid loss (i.e.- loss of total body water) is the redistribution among the major fluid compartments: intracellular fluid, extracellular fluid, and plasma volume. The effects of prolonged exposure to microgravity on fluid/electrolyte homeostasis have not been well defined. This information is required for the development of countermeasures for future extended duration missions. This will include determining the nature and extent of fluid/electrolyte loss, as well as the physiological processes of adaptation to microgravity.

Fluid/electrolyte balance in the body is regulated by several systems. The kidneys play an important role in the regulation of fluid and electrolyte excretion/retention. There are also many endocrine and circulatory factors which act to regulate fluid homeostasis.

The studies described here are designed to investigate the possible effects of endocrine, renal and circulatory influences on fluid and electrolyte homeostasis in microgravity. The Shuttle Mir Science Program provides an opportunity to study these systems before, during, and after four months exposure to microgravity . The results may help in the assessment of the effectiveness of current countermeasures, as well as in the development of new countermeasures. The information gained from these studies will provide knowledge of basic physiological function and may also yield background information for treatment of diseases such as hypertension and kidney disease.

Dynamics of Calcium Metabolism and Bone Tissue

The effect of space flight on the skeletal system is one of the most critical issues which needs to be resolved for

extended duration missions. Due to the lack of weight bearing influence and other factors, bone mineral is lost during space flight. There is significant evidence of the negative impact of microgravity on bone homeostasis. Negative calcium balance has been noted previously in extended duration space flights (84 d Skylab) as well as following bed rest (simulated microgravity). The negative balance has been corroborated with increased excretion of calcium in the urine and feces, as well as decreased calcium absorption. The hydroxylated metabolites of vitamin D (e.g.- calcidiol, $25(0H)D_3$ and calcitriol, $1,25(0H)_2D_3$) play an important role in calcium homeostasis, primarily at the level of intestinal absorption of dietary calcium. Vitamin D intake is particularly important during extended duration space flights due to the decreased *in vivo* production of vitamin D through skin exposure to ultraviolet light.

This study was designed to provide information on the causes and possible countermeasures for microgravity induced loss of bone mass. Before, during, and after the mission calcium absorption and kinetics were determined. This will help us to understand the impact of dietary calcium on bone loss. Other related measurements will include monitoring of bone density, bone and calcium regulating hormones, and urinary indices of bone turnover. Postflight studies were designed to examine the recovery of bone mineral lost during the mission, as well as readaptation of bone regulating hormones and calcium metabolism. Potential benefits of this research include further understanding of countermeasures required for extended duration space flight as well as potential impact on treatment of skeletal disorders in the general population.

Red Blood Cell Mass and Survival

Studies in both the US and Russian space programs have demonstrated reductions in RBC mass of 20-30% after flights lasting 24-350 days. Exposure to microgravity also increases central blood volume.

Results of a recent study of RBC mass during a 9-day mission revealed a rapid decrease in total blood volume (12%) within 24 hours. The associated decrease in plasma volume resulted in an increase in packed cell volume (central body hematocrit) over that measured at 1-g. Declines in erythropoietin release and serum erythropoietin levels, probably as a consequence of increased oxyhemoglobin delivery to the kidney (assumed unchanged total renal blood flow), were also noted during this flight.

A new finding from this study was that newly produced RBCs stopped being released immediately as the subjects entered orbit. This conclusion was reached from the failure of labeled circulating cells to be diluted by newly produced cells, and a decline of RBC mass of 9% during the 9-day mission with concomitant normal survival of circulating red cells (loss of 0.83%/d). A change of this magnitude could only result from nearly complete cessation of release of red cells into the blood. It has been hypothesized that this decrease in release of red cells resulted from decreases in erythropoietin levels. After 22 hours of microgravity, new red cells (measured using radiolabeled iron) were being produced within the bone marrow at a rate similar to that present at 1-g, but far fewer of these cells ever appeared in the blood. Moreover, the bone marrow in these crewmembers at launch contained nearly mature cell precursors that should have been released within the next three days. Normal human bone marrow requires six days to produce an RBC. The discordance between these phenomena can be explained only by postulating that red cells that were supposed to be released into the blood were retained and perhaps destroyed within the bone marrow.

Intramedullary destruction of RBCs is a recognized phenomenon and has been termed "ineffective erythropoiesis". This process occurs in several disease states including megaloblastic anemias due to vitamin B 12 or folic acid deficiency. Studies of both ferrokinetics and heme pigment metabolism indicate that 10-20% of the hemoglobin formed in normal persons may be destroyed before appearing in circulating red blood cells. Thus, all or part of some red blood cells may be destroyed in the course of their manufacture.

Based on these observations as well as those from previous missions, we suggest that the immediate down-regulation of red-cell production in flight is accomplished through ineffective erythropoiesis resulting from decreased erythropoietin.

METHODS/RESEARCH OPERATIONS

Functional Objectives

Fluid and Electrolyte Homeostasis

This experiment was designed to collect data to assess the impact of extended-duration space flight on fluid and electrolyte homeostasis. Blood, urine, and saliva samples were collected for determination of biochemical and endocrine indices, as well as measurements of body mass and dietary intake. Tracers were used to estimate fluid compartments and water turnover.

Dynamics of Calcium Metabolism and Bone Tissue

This experiment was designed to collect data to assess the impact of extended-duration space flight on calcium kinetics and bone homeostasis. Blood, urine, saliva, and fecal (ground-based only) samples were collected for determination of biochemical and endocrine indices, as well as measurements of body mass and dietary intake.

Tracers were used to estimate calcium absorption and kinetics.

Red Blood Cell Mass and Survival

This experiment was designed to collect data to assess the impact of extended-duration space flight on erythropoiesis. Blood and urine samples were collected for determination of biochemical and endocrine indices. Tracers were used to estimate red blood cell mass and survival.

Hardware Items

Preflight & Postflight

-70° C freezer

Refrigerator

Refrigerated centrifuge

PCBA

Body weight scale

Inflight

Blood Collection Kits & Accessories

Urine Collection Kits & Accessories

Saliva Collection Kits

Tracer Kits

EuroMir Freezer

Mir Centrifuge

Bar Code Reader

PCBA Kit

Thermoelectric Freezer (TEF)

Thermoelectric Holding Facility (TEHOF)

TEHOF

Rack-mounted Centrifuge

PVPD & Accessories

LSLE Refrigerator

LSLE Freezer

BMMD

Method/Protocol

Fluid and Electrolyte Homeostasis

This experiment was designed to collect data to assess the impact of extended-duration space flight on fluid and electrolyte homeostasis. Blood, urine, and saliva samples were collected for determination of biochemical and endocrine indices, as well as measurements of body mass and dietary intake. Tracers were used to estimate fluid compartments and water turnover.

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RESULTS

List of Pre-, In-, and Postflight Anomalies

Pre-, Postflight

None

Inflight

Mir 18. The failure of the ESA freezer compromised the urine and saliva analyses. Postflight debriefs with the crew indicated that following the shutdown of the ESA freezer, urine samples were transferred to the Mir refrigerator. While this apparently protected some of the analytes, it will be impossible to recreate the sample history as the Automatic Temperature Recorder (ATR) was never activated prior to flight.

STS-71. None.

Completeness/Quality of Data

Completeness of Data

Only two of the four inflight integrated metabolic sessions were completed by all subjects, a third session was conducted by Subject 3 only (obtained 58% of inflight science). A total of 30 blood tubes were collected on board Mir, and 25 aboard STS-71 .

There were 365 urine samples collected during the three preflight data collection sessions including back-up crewmembers). There were 51 inflight urine collections aboard Mir (14 Subject 1, 11 Subject 2, and 26 Subject 3) and 22 aboard the STS-71 (6 Subject 1, 6 Subject 2, and 10 Subject 3). Of the preserved samples (thymol and thimerosal), seven syringes contain less than 5 mL urine (maximum volume is 7 mL). The frozen samples have not been aliquoted as of this point. There were 225 postflight urines collected during the three sessions.

Three postsleep saliva samples were not collected during STS-71. This will affect the accuracy of calcium kinetic determinations on these subjects.

Bone densitometry data was not collected on Subject 1 and Subject 2 (obtained 33% of science). Remaining DEXA testing will be scheduled on Subject 3.

Extracellular fluid volume (ECFV) data was not collected on Subject 1 postflight (obtained 93% of science).

Plasma volume data was only collected once (Subject 2) or twice (Subject 1, Subject 3) preflight due to change to cardiac output (CO) rebreath methods. CO gas was not available for the January BDC session (obtained 92% of science).

The third postflight RBC mass and calcium absorption data collection session has not been completed (scheduled for R+14). This is scheduled for September. This is not included in the above calculations of percent of obtained science.

Additional body mass data (both inflight and postflight) may be available from the flight data files or surgeon records.

Quality of Data

The full impact of the freezer failure and samples thawing is not quantifiable, however, it is known that the ^{15}N-urobilinoid measurements are lost as a result of this. Postflight debriefs with the crew indicated that following the shutdown of the ESA freezer, urine samples were transferred to the Mir refrigerator. While this apparently protected some of the analytes, it will be impossible to recreate the sample history as the Automatic Temperature Recorder (ATR) was never activated prior to flight.

The dietary intake data quality is compromised by the fact that subjects did not barcode all consumed food items. Preliminary data support this with extremely low intakes of food in some crewmembers. Postflight food consumption is compromised due to failure to record non-provided food items.

The fluid and electrolyte data may be compromised by constraint violations by some of the subjects (e.g., no alcohol consumption, must be fasting). Incomplete urine collections will compromise the quality of data for all relevant experiments.

There are concerns regarding the size of the UCD, in that the large internal volume may not have allowed for adequate mixing of the LiCI marker with the urine, especially with small voids (< 100 cc).

Postflight urine collection data quality is compromised by the fact that many voids were not labeled with time of collection (particularly during R+0 and R+1).

Additional Data Collections

There appear to be additional days of food/fluid logs during Mir 18, however, this may represent requirements for other investigators.

Tables, Graphs, and Figures Index

Table 1. Data Collection Sessions/Functional Objectives

DISCUSSION

Research Findings

Fluid and Electrolyte Homeostasis

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 + 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 ± SD.

Analyte	Preflight	Inflight
Plasma Volume (L)	3.16+0.15	3.01+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.

Dynamics of Calcium Metabolism and Bone Tissue

The effect of near-weightlessness on the human skeletal system is one of the most critical concerns in safely extending space missions. Minerals are lost from bones during flight as a result of skeletal unloading, thereby increasing calcium excretion in the urine. Bone loss contributes to the increased risk of renal-stone formation associated with high concentrations of solutes in the urine during and after flight. This study was designed to examine calcium and bone homeostasis during a 115-day mission on board the Mir Space Station.

Three male subjects participated, and data were collected before, during and after the mission. Blood and urine samples were collected, aliquoted, and frozen until postflight analysis, except for blood ionized calcium and pH, which were determined in "real-time" with a portable clinical blood analyzer. Biochemical and endocrine indices of bone metabolism were determined. Calcium absorption and kinetics were studied using a dual isotope technique. Oral (^{43}Ca, 125 mg) and intravenous (^{46}Ca, 8 mg) tracers were administered (oral tracer followed 1 hr later with I.V. tracer), with timed blood, urine, and saliva samples being collected over 3-5 days. Fecal samples were also collected during pre- and postflight sessions. Calcium isotopic enrichments in biological samples were determined using thermal ionization mass spectrometry. Absorption data were determined using the ratio of the two isotopes in samples obtained >24 hours post dosing.

Serum concentrations of intact parathyroid hormone were reduced almost 30% during flight compared to preflight. Serum 25-0H Vitamin D (calcidiol) decreased during winter training in Russia (compared to autumn in Houston), and decreased further during flight. Serum 1,25(0H)$_2$ Vitamin D (calcitriol) concentrations were also reduced almost 30% during flight. Serum osteocalcin tended to decrease during winter, and was increased or unchanged during flight. Bone-specific alkaline phosphatase concentrations were an average of 39% lower on flight day 14 and 11% lower on flight day 110 than preflight values. Serum total calcium was unchanged, the ionized fraction increased slightly, and venous whole blood pH did not change. Urinary calcium excretion was higher during flight than before. Urinary collagen metabolite excretion (n-telopeptide and pyridinium crosslinks) was almost 40% greater than the preflight level. Calcium absorption decreased during (38±18% below preflight values on flight day 110) and after flight (56±9% below preflight on landing day, n=2; and 29±28% below preflight on return +6 days). By 3 months postflight, calcium absorption had returned to 4±20% below preflight values. These data showed that inflight bone loss is associated with increased resorption and decreased formation. Calcium balance is further altered by decreased PTH activation of calcidiol, with subsequent decreased calcium absorption. These data will be critical for assessing the efficacy of countermeasures to the weightlessness-induced bone loss. Further studies are needed to develop techniques to maintain bone and calcium homeostasis during extended-duration space flight.

Red Blood Cell Mass and Survival

Decreases in red blood cell mass (RBCM) and hematocrit have been reported after U.S. space missions (Skylab and Shuttle). The role of erythropoietin (EPO) in relationship to the rate of change in RBCM was investigated in 3 male crewmembers who were in space for 115 days. Blood samples were collected before, during, and after flight to assess erythropoiesis. RBCM was determined with stable isotopes (^{50}Cr). The inflight diet contained an average of 13.5 mg iron per day. In-flight serum EPO concentrations were decreased compared to preflight levels. Hematocrit was also lower during and after flight. Indices of iron storage and availability, however, were increased. Serum ferritin was greater during flight (average > 100 ng/mL) than before flight. Serum iron was increased in two subjects (≈20% greater than preflight) and unchanged in the third. Total iron binding capacity was ≈10% lower during flight, and was still below preflight levels 9 days after landing (R+9). At landing, RBCM was 17% lower than preflight values, while serum ferritin concentrations were elevated. Serum EPO at landing was decreased in 2 of 3 crewmembers, and elevated (80% greater than preflight) in all 3 crewmembers 9 days later. All other indicators of iron status were unchanged. Serum ferritin concentrations were below preflight levels when assessed at R+3 months. In-flight anemia represents an adaptation to weightlessness and can be used as a model for understanding the mechanisms of erythropoiesis.

TABLE 1. DATA COLLECTION SESSIONS/FUNCTIONAL OBJECTIVES

	Calcium Metabolism			RBC Mass & Survival			Fluid & Electrolyte		
	Preflight	Inflight	Postflight	Preflight	Inflight	Postflight	Preflight	Inflight	Postflight
Blood									
Requested	18	12	18	21	9	30	30	24	36
Received	18	7	18	21	9	30	28	14	22
Urine (days x crewmember)									
Requested	54	12	66				54	72	66
Received	45	7	60				45	38	42
Saliva									
Requested	54	12	66				27	36	27
Received	53	9	56				27	21	18
Feces (days x crewmember)									
Requested	54		66						
Received	45		60						
Bone Densitometry									
Requested	3		6*						
Received	1		2						
Food/Fluid/Drug/Exercise									
Requested							54	177	45
Received							45	no interpretable data	42
Body Mass									
Requested				3		6	54	75	45
Received				3		6	45	60	45
Potable Water									
Requested								15	
Received								11	

* Bone densitometry to be performed every 6 months until recovery or 2 years postflight.