Influence of Spaceflight on Erythrokinetics in Man

Abstract. *A significant postflight reduction in the circulating red cell mass has been observed in both the American and Soviet manned programs. The mechanism and etiology of this loss were studied in blood samples from the four payload crewmen of Spacelab 1 taken before, during, and after flight. These samples and samples from control groups on the ground were analyzed for selected hematological and biochemical parameters, which were chosen on the basis of data previously collected, the restraints imposed by the use of human subjects, and the guidelines established for the first Spacelab mission. Twenty-two hours after weightless exposure, there was an increase in hemoglobin and hematocrit. On day 7 in flight, the hemoglobin and hematocrit remained high and there was a slight decrease in reticulocyte number. On landing, red cell mass, plasma volume, hematocrit, and reticulocyte number were decreased. Throughout the 2-week postflight sampling period, hemoglobin, hematocrit, and reticulocyte number remained below the preflight value. Since this crew was not exposed to 100 percent oxygen these results are viewed as evidence that other spaceflight factors cause the measured red cell mass reduction.*

A consistent influence of spaceflight on the human hematological system has been a reduction in the circulating red blood cell mass (RCM). This phenomenon has been observed in both the American (Gemini, Apollo, Skylab, and ASTP) and Soviet (Soyuz-Salyut) crews (*1*). It has not been possible to delineate the cause of the RCM reduction from previous spaceflights. The most generally accepted theory of causation has been inhibition of bone marrow function through decreased erythropoietin. This phenomenon could cause at most a 1 percent decrease per day in the RCM. This was assumed to be augmented by exposure of the American crews to hyperoxia resulting in enhanced red blood cell destruction, which could account for the greater than 1 percent per day decrease found in the shorter missions. The experiment conducted during the 10-day Spacelab 1 mission in November 1983 was designed to measure factors involved in the control of erythrokinetics which might be altered after exposure to microgravity. Several of the hematological and biochemical parameters were not previously investigated in blood specimens collected during spaceflight. Only selected hematological factors are reported here.

The two mission specialists (MS1 and MS2) and the two payload specialists (PS1 and PS2) aboard Spacelab 1 were the subjects of this experiment. A group of six subjects from a human subject pool served as ground-based controls in a bed rest study, a technique used to simulate microgravity and as a simulation of Spacelab 1 protocols (*2*). Control subjects were selected on the basis of similar age, weight, sex (male), physical condition, and overall health status. The crew members' inflight period was simulated in the control subjects by placing them in bed rest at −6° head-down for a number of hours equal to the flight period. Each crew member and control subject acted as his own control. Inflight and postflight results were compared to preflight baseline data. Similarly, the baseline data for the ground controls before bed rest were compared to the results during and after bed rest. Both studies followed guidelines for appropriate institutional human experimentation and radiation safety.

Blood samples were obtained three or four times before flight (before bed rest), twice during flight (during bed rest), and four times after flight (after bed rest), as noted in Table 1. During the 88 days of each study about 540 ml of blood were withdrawn from each individual. Biomedical laboratory staff members collected preflight and postflight blood samples and all samples from the ground control subjects by venipuncture, using standard clinical materials and procedures (*2*).

Inflight blood samples were collected by trained mission and payload specialists with NASA's inflight blood collection system (IBCS), an assemblage of standard blood collection equipment and supplies similar to those of the ground-based study. The IBCS included three trays, each containing the equipment required for a single day's blood collection. Each tray contained evacuated Corvac blood collection tubes with disodium ethylenediaminetetraacetate (EDTA), heparin, or no anticoagulant, materials for preparation of dried blood smears (including reticulocyte stain, new methylene blue N), and other blood collection supplies. The Corvac tubes were treated to withstand liquid nitrogen temperature. They contain a gel to keep the cellular and fluid phases separated after centrifugation. The IBCS included a minicentrifuge for hematocrit determinations.

All samples were stabilized or processed by centrifugation within minutes of collection. After processing, inflight samples were frozen at −195°C and stored in a cryogenic freezer until landing. Hematocrits were determined and slides for reticulocyte and white cell differential classifications were prepared in flight.

Radionuclide measurements (*3*) of red cell mass and plasma volume were made 65 days before flight, on landing day, and 7 days after flight. Erythropoietin was measured with fetal mouse liver cell cultures (*4*). At this date measurement of erythropoietin levels is not complete for the control subjects, although in previous bed rest studies no change in serum erythropoietin titers was evident (*4*).

There was no preflight or postflight diet control. A shuttle diet was consumed in flight. The ground control subjects ate a standard hospital diet throughout. All of the crewmen ingested an antimotion sickness drug either before or just after the beginning of the flight. These drugs decreased their hunger and thirst. This could have affected the initial inflight specimen by accelerating any dehydration resulting from adaptation to microgravity. Because the STS-9 Spacelab 1 mission was in continuous operation, the crew members worked two different shifts: MS2 and PS2 slept from about 10:30 p.m. to about 6:30 a.m. and MS1 and PS1 slept from about 10:30 a.m. to about 6:30 p.m., central standard time. Two weeks before launch, the sleep-wake cycle of MS1 and PS1 was shifted by 12 hours. The cycle of half of the ground control subjects approximately matched that of the "second-shift" crew members. This may have confounded the data obtained 1 day before flight (day F − 1) and on mission day 1 (MD1).

A multi-way analysis of variance for repeated measures was used. No data were disregarded and there was only one missing flight sample. The Ryan-Einot-Gabriel-Welsch multiple comparison test was used to compare days of the experiment (*5*).

The results for selected hematology parameters are given in Table 1. Statistically significant inflight differences were found for hemoglobin (increase) and reticulocyte number (decrease on MD7). Postflight results showed that 2 hours after landing there were statistically significant differences in reticulocytes, red cell mass, and blood volumes, all of which decreased. Hemoglobin increased. When these measurements were repeated 8 days after the mission, the RCM remained decreased. Other pa-

rameters that showed changes consistent with the RCM decrease had not returned to preflight values by the end of the postflight sampling period (12 days after landing: day L + 12). The changes in the subjects in bed rest were different in that the RCM was not significantly lower on day L + 0 but the plasma volume decrease was statistically significant.

Circulating blood volume was found to have decreased after space missions when it was measured (*6*). It has been postulated that this is a result of bone marrow inhibition since red blood cell survival (estimated by using [^{14}C]glycine and ^{51}Cr during Skylab) was unchanged, ruling out shortened life-span, and reticulocyte numbers were depressed after flight. However, iron turnover was unchanged. In this experiment a decrement in RCM approximately equal to that observed in crewmen returning from Apollo flights of similar duration (*7*) was measured. Because the American spacecraft before the space shuttle had a 5-psi atmosphere with elevated oxygen partial pressures, oxygen inhibition of bone marrow function or even peroxidation of red blood cell membranes resulting in a shortened red blood cell life-span would have been possible (*8*). The question of whether hyperoxia was a cause of this decrease in red cell mass and plasma volume has been answered in this experiment, since Spacelab 1 crewmen were not exposed to 100 percent oxygen or hyperoxia at any time during this flight.

The very early inflight and bed rest increases in hematocrit and hemoglobin are believed to be related to an early decrease in plasma volume, which we and others have measured in other head-down bed rest studies (*2*). This is presumed to be a result of the cephalad extracellular fluid shifts in both situations.

A statistically significant mean decrease in reticulocyte numbers was noted in the specimens taken on MD7 and immediately after landing. This was not found in the control subjects. A similar decrease was found in reticulocyte numbers after the longer Skylab missions (*9*), and six of the eight crew members who participated in the first four shuttle missions showed decreases in reticulocyte numbers (*10*). Thus, spaceflight conditions generally appear to cause a decrease in the number of circulating reticulocytes.

The failure to find a significant decrease in serum erythropoietin in flight suggests that inhibition did not occur. However, there is a large inherent variation in these determinations. Use of a

Table 1. Spacelab hematology results. The mean of two preflight values (measured in samples taken 65 and 7 or 8 days before flight) for each of four crew members (Spacelab 1) or six subjects (simulation) is listed for each parameter. Percent change was calculated for each subject for other days of the flight or simulation, and the mean percent change is shown. On day F − 1 (1 day before launch) several parameters were significantly different from their levels on the other two preflight days, probably because of such factors as stress and previous blood withdrawals. Therefore day F − 1 was not included with the other preflight days in percent change calculations. MD1 and MD7 are mission days 1 and 7, and L + 0 is landing day.

Parameter and units	Preflight	Percent change (mean ± standard error)															
		F − 1			MD1			MD7			L + 0			L + 1			L + 8			L + 12 or L + 13		
Spacelab 1																						
Erythrocytes, $\times 10^{12}$ per liter	4.96	−2.35	±	2.16	1.41	±	1.10	4.30	±	0.94	−5.83	±	1.03	−8.83*	±	1.04	−11.43*	±	1.10	−12.90*	±	3.43
Hemoglobin, g/dl	14.6	−2.2	±	0.4	3.7*	±	1.6	8.4*	±	1.1	3.4*	±	0.3	−1.0	±	0.6	−10.3*	±	0.7	−8.8*	±	1.3
Hematocrit, liter/liter	0.43	−4.9	±	0.5	3.5	±	1.6	1.9	±	2.0	−3.2	±	0.8	−4.9*	±	1.0	−7.9*	±	1.1	−6.1*	±	1.2
Reticulocytes, percent of red blood cells	1.3	−50.4*	±	11.8	−17.4	±	31.8	−53.8	±	10.1	−58.6*	±	7.8	−6.0	±	10.7	−14.0	±	9.1	10.2	±	19.9
Reticulocytes, $\times 10^9$ per liter	64.2	−51.2*	±	12.5	−17.0	±	31.4	−54.7*	±	14.8	−60.9*	±	7.7	−14.9	±	9.0	−23.9	±	8.6	−1.8	±	17.1
Red cell mass, mg/kg	27.54										−9.30*	±	1.60				−6.04*	±	0.72			
Plasma volume, ml/kg	44.82										−5.98	±	4.30				3.39	±	1.86			
Blood volume, ml/kg	72.36										−10.50*	±	0.87				−1.34	±	0.34			
Erythropoietin, U/ml	0.32	14	±	16	−50	±	27	−73	±	21	−72	±	10	−33	±	12	−33	±	14	−73*	±	23
Simulation																						
Erythrocytes, $\times 10^{12}$ per liter	4.93	0.54	±	1.65	2.72	±	2.03	4.65	±	3.36	4.56	±	3.30	−1.09	±	2.63	−5.32*	±	2.48	−5.76*	±	1.90
Hemoglobin, g/dl	14.5	2.9	±	1.5	5.8*	±	2.0	5.2	±	3.1	5.3	±	3.5	0.7	±	2.7	−3.4	±	2.3	−4.1	±	2.0
Hematocrit, liter/liter	0.44	0.72	±	1.9	3.1	±	2.5	4.9	±	3.4	4.8	±	3.9	−0.6	±	3.3	−4.4	±	2.6	−4.9*	±	2.1
Reticulocytes, percent of red blood cells	0.7	25.8	±	24.9	7.6	±	18.2	9.3	±	7.0	2.3	±	16.3	−0.72	±	11.2	9.7	±	33.5	17.9	±	22.7
Reticulocytes, $\times 10^9$ per liter	35.0	28.7	±	24.9	12.7	±	17.0	16.9	±	8.3	7.4	±	14.2	−1.2	±	8.5	2.0	±	27.6	13.9	±	22.6
Red cell mass, ml/kg	27.69										−3.31	±	1.59				−6.30*	±	2.59			
Plasma volume, mg/kg	41.97										−6.29*	±	3.67				2.85	±	2.22			
Blood volume, ml/kg	69.65							−5.60	±	2.52	−5.36	±	2.30				−1.00	±	1.91			

*Significantly different from preflight value ($P < 0.05$).

larger number of subjects might have resulted in a difference of statistical significance. Erythropoietin decreased in flight in all crew members. The method used should have been able to measure as significant a 50 percent decrease if it had occurred consistently (coefficient of variation, 25 percent).

The lack of significant change in erythropoietin with a significant decrease in reticulocyte number and a decrease of about 1 percent per day in mean RCM suggests that inhibition of erythropoiesis is not the primary or only cause of the inflight RCM reduction. The decrease in RCM seems not to be a result of the increased hematocrit and hemoglobin, since it was not found in the bed rest subjects, who showed a statistically significant mean decrease in plasma volume.

The findings reported are preliminary. Many factors remain to be analyzed, including the effects of salt and water ingestion before landing, the influence of antimotion sickness drugs, and circadian shift effects; additional data will be forthcoming.

CAROLYN S. LEACH
PHILIP C. JOHNSON
NASA Johnson Space Center, Medical Sciences Division, Houston, Texas 77058

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11. Coinvestigators for this experiment were J. P. Chen (University of Tennessee Memorial Research Center, Knoxville), W. Crosby (Walter Reed Army Medical Center, Washington, D.C.), C. D. R. Dunn (Johnson Space Center and Baylor College of Medicine, Houston, Texas), R. D. Lange (University of Tennessee Memorial Research Center), E. Larkin (Veterans Administration Hospital, Martinez, Calif.), and M. Tavassoli (University of Mississippi Medical Center, Jackson). We thank the Spacelab 1 payload crewmen who provided the samples.

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Venous Pressure in Man During Weightlessness

Abstract. *To determine whether the body fluid shift from the lower limbs toward the head that occurs during spaceflight leads to lasting increases of venous pressure in the upper body, venous pressure and hematocrit measurements were made on four astronauts before flight and 1 and 12 hours after recovery and compared with measurements in space. During the mission the hematocrit was elevated and the venous pressure lowered by 1 to 8 centimeters of water as compared with the preflight data. One hour after landing the hematocrit decreased, indicating a hemodilution, venous pressures were unexpectedly high, and a body weight loss of 4 to 5 percent was observed. Twelve hours later the venous pressures were the lowest recorded during the study. The fluid shift apparently takes place during the first several hours of spaceflight. Thereafter, the pressure in the peripheral veins and the central circulation is lower than that measured before flight.*

Reports from American and Russian astronauts indicated that during spaceflight appreciable amounts of body fluids are translocated from the lower to the upper parts of the body (*1*). An increase in central venous pressure should accompany this and should have a similar effect on the pressure in an arm vein. As a consequence a negative water balance should ensue, as proposed by Gauer and Henry (*2*).

Before Spacelab, no direct venous pressure measurements were available to test this hypothesis. We conducted experiments (1ES026 and 1ES032) on Spacelab 1 to clarify this point by measuring the pressure in an antecubital vein and comparing the results with data obtained on the ground.

Methods. The equipment consisted of a small conventional strain gauge connected with a 19-gauge needle, a preamplifer, a small oscilloscope, and a tape recorder to store the signals. Pulse-cod-

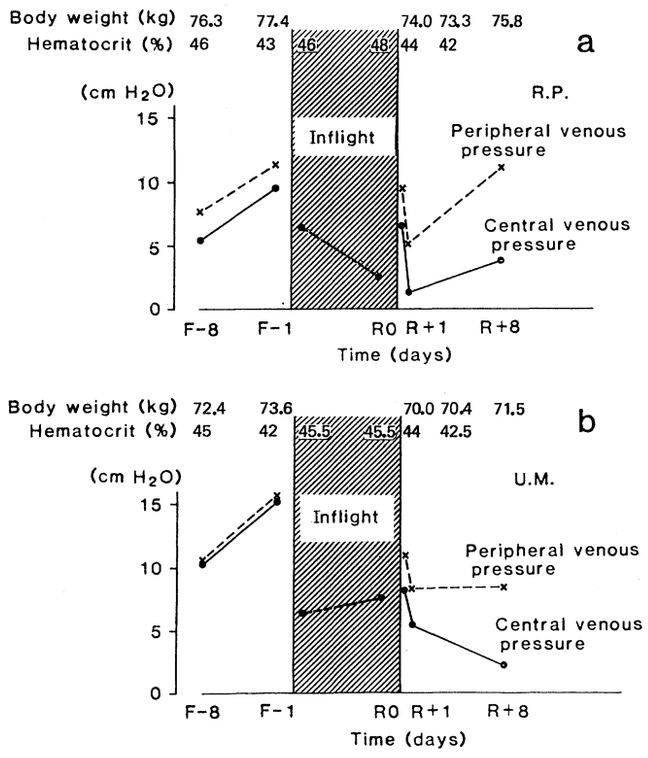

Fig. 1. Time course of body weight, hematocrit, and peripheral, and central venous pressure in two astronauts before, during, and after the Spacelab 1 mission. The data are characteristic for all four subjects. Times were: F − 8, 8 days before flight; F − 1, 1 day before flight; R + 0, 1 to 2 hours after recovery; and R + 1, 12 hours after recovery.