Red Blood Cell Mass and Plasma Volume Changes in Manned Space Flight

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Plasma volume, red blood cell mass, and erythrocyte survival determinations were performed for the Gemini astronauts before and after Gemini orbital flights IV, V, and VII. Plasma volume decreases similar to those seen after bed rest and water immersion were found in Gemini IV and V. While each of these flights was affected by different stresses and the data accumulated are not as complete or extensive as desired, the results suggest that the plasma volume changes associated with the shorter flights may have been compensated for in the longer Gemini VII flight. These preliminary studies showed decreases in the survival of erythrocytes and red blood cell mass (both studied with sodium chromate Cr 51) in Gemini V and VII. No compensation for the RBC mass decrease was found even in the longer flight. Data obtained indicate decreased RBC mass is a result of mild hemolysis of unknown cause.

Space flight has the potential of producing complex physiological changes in the human because of stresses resulting from weightlessness, acceleration, confinement, restraint, etc. Attempts have been made to predict these changes and to define their mechanisms through ground-based bed rest and water immersion studies. Bed rest and water immersion are associated with a spectrum of cardiovascular alterations; when the subject is passively tilted upright, hypotension and tachycardia tend to develop.[1-4] Decreases in plasma volume occurred during many of these simulation studies and have accompanied the tilt table intolerance[1,2,5-7] The recent Mercury, Gemini, and Russian manned orbital flights have furnished the first opportunity to evaluate the actual effects of space flight on the human. Investigations following the Mercury and early Gemini missions showed alterations in astronauts' responses to passive tilts which were qualitatively similar to the changes found after bed rest and water immersion.[8-11] In addition, radioisotope studies performed on the Gemini IV astronauts showed the expected decrease in plasma volume. Unlike bed rest studies, red blood cell masses calculated from the venous hematocrit and plasma volume data were decreased after flight. Because calculation of RBC mass from plasma volume and peripheral venous hematocrit values requires knowledge of the ratio between total body and peripheral venous hematocrit values, direct RBC mass determinations (made by tagging erythrocytes with sodium chromate Cr 51) were added to the plasma volume studies planned for Gemini V and VII.[12-14] The results of the radioisotope determinations of plasma and RBC volume changes during the Gemini flights will be discussed in this paper.

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Methods and Materials

Preflight plasma volume determinations for Gemini IV astronauts and plasma volume and RBC mass determinations for Gemini V astronauts were performed two and seven days prior to lift-off, respectively. The flight interval was 96 hours and 56 minutes for Gemini IV and 190 hours and 56 minutes for Gemini V. Postflight determinations were performed within an hour after recovery. Six days before Gemini V lift-off, blood was drawn for use as zero time for the RBC survival determination; an additional specimen was drawn two days later. In the Gemini VII flight, when the more extensive studies were performed, the RBC mass and plasma volumes were determined ten days prior to lift-off. Blood was obtained on the following day for use as zero time. Blood samples were drawn four and two days prior to lift-off for the fifth and seventh day determinations of ^{51}Cr erythrocyte survival points. The flight interval was 330 hours and 35 minutes. Upon recovery, the RBC mass, plasma volume, and survival studies were repeated. Blood was drawn on the morning following recovery. Blood for study of erythrocyte survival was drawn from the command pilot 2, 3, and 18 days after recovery, and from the pilot 2, 3, and 20 days after recovery. The RBC mass and plasma volume studies were repeated on the last day of each series.

Prior to each radioisotope series, iodinated I 125 serum albumin was diluted in normal saline to concentrations of 0.5μc/ml for preflight determinations and 1μc/ml for postflight determinations. Carrier normal human serum albumin was added to inhibit radiation denaturization. Determinations of plasma volume and RBC mass were preceded by a 15 minute interval with the subject recumbent. At the end of this interval a 25 ml blood sample was obtained and 5 ml of the dilute iodinated I 125 serum albumin were injected. Plastic disposable syringes, which we have determined to deliver 5 ml ± 0.1 ml, were used for the injections. Ten milliliters of the blood drawn were used to correct for any circulating radioactivity. The remaining 15 ml were added to 3 ml of anticoagulant acid citrate dextrose (ACD) solution contained in a polyethylene mixing bag. To this

solution 100μc of sodium chromate Cr 51 were added preflight, and 200μc were added postflight. After the blood mixture had stood at room temperature for 10 to 12 minutes, 100 mg of ascorbic acid were injected into the bag to terminate the tagging process. Ten milliliters of blood treated with sodium heparin were drawn from the antecubital vein for a 15 minute plasma volume specimen, and 10 ml of the RBC tagged with sodium chromate Cr 51 were reinjected. The remaining RBC were retained for the preparation of a standard. A 10 ml sample of blood treated with heparin was drawn 15 minutes after reinjection of the RBC for a 30 minute plasma volume specimen and a 15 minute RBC mass specimen.

Duplicate microhematocrit values were determined on all blood samples (four minutes; 15,000 rpm, 12,500 × g). Duplicate 1 ml aliquots of whole blood were pipetted into counting tubes from the background blood, RBC mass standard, and RBC mass specimen. All samples were centrifuged and duplicate 1 ml aliquots of plasma were pipetted from each. With the same size needle and disposable syringe as were used for injecting the astronauts, radioactive albumin standards were prepared. The albumin was diluted with water in a liter volumetric flask. Normal human serum albumin had been added previously to the flask to prevent adsorption of the radioactive albumin to the glass. Triplicate 1 ml aliquots of this standard solution were pipetted for subsequent counting. Residual radioactivity in the injection syringes and standard syringe was removed by irrigating them with 2 ml of water.

Changes in total amount of circulating ^{51}Cr erythrocytes were used to estimate erythrocyte survival. Preflight and postflight RBC masses and the amount of ^{51}Cr per milliliter of RBC were used to calculate the total circulating ^{51}Cr erythrocytes.

The radioactivity of all samples was determined in an automatic scintillation well detector with a pulse height analyzing scaler used to separate the energy peaks of ^{125}I (0.035 and 0.0275 mev) from that of ^{51}Cr (0.323 mev). Sufficient counts were collected to reduce the average counting error to less than 0.5%. Coincident loss for the highest count rate was less than 0.1%; no correction was made. Formulas for all calculations follow:

(1) Pl vol =

$$\frac{(\text{NCPM/ml std} \times \text{DF}) + \text{NCPM std syr} - \text{NCPM spec syr}}{\text{NCPM/ml 15 minute pl spec}}$$

where pl vol=plasma volume; NCPM=net counts per minute (gross counts per minute of sample tube minus gross counts per minute of empty tube [when a previous radioisotope study had been done on a subject, a background blood specimen was drawn; the subject's own blood or plasma counts were then subtracted instead of counts per minute of an empty tube]); std=standard; DF=dilution factor=1,000 ml; syr=syringe; and spec=specimen.

(2) RBC mass $= \frac{A \times \text{volume injected}}{B} \times \text{spec hct}$

where

$$A = \text{NCPM/ml std wh bl} - \text{NCPM/ml std pl} \times (1 - \text{std hct})$$

$$B = \text{NCPM/ml spec wh bl} - \text{NCPM/ml spec pl} \times (1 - \text{spec hct})$$

hct = peripheral venous hematocrit value expressed as a decimal; wh bl = whole blood; and volume injected = 10 ml.

(3) Percent remaining ^{51}Cr per milliliter of RBC (on day X) $= \frac{C}{D}$

where

C = NCPM/ml RBC (on day X)
D = NCPM/ml RBC (on day 0)

$$\text{NCPM/ml RBC} = \frac{\text{NCPM/ml wh bl} - \text{NCPM/ml pl} \times (1 - \text{hct})}{\text{hct}}$$

(4) Percent remaining total circulating ^{51}Cr $= \frac{\text{RBC mass (on day X)} \times C}{\text{RBC mass (on day 0)} \times D}$

Table 1.—Plasma Volume Data

Gemini IV	Volume, ml: Preflight	Volume, ml: Postflight	Difference, ml
Command pilot	2,962	2,844	−118
Pilot	3,885	3,393	−492
Gemini V			
Command pilot	2,354	2,145	−209
Pilot	2,300	2,194	−106
Gemini VII			
Command pilot	2,341	2,760 (3,232)*	+419 (+891)
Pilot	2,673	2,774 (3,260)	+101 (+587)

*Values in parentheses indicate results 18 or 20 days postflight.

Table 2.—Weight and Height of the Gemini Astronauts

Gemini IV	Weight, kg (lb): Preflight	Weight, kg (lb): Postflight	Height, cm (inches)
Command pilot	70.8 (156)	68.9 (152)	180.3 (71)
Pilot	78.5 (173)	74.4 (164)	180.3 (71)
Gemini V			
Command pilot	68.9 (152)	65.8 (145)	172.7 (68)
Pilot	69.9 (154)	66.2 (146)	167.6 (66)
Gemini VII			
Command pilot	73.5 (162)	68.9 (152)	176.5 (69½)
Pilot	77.1 (170)	74.0 (163)	180.3 (71)

Results

Table 1 shows the preflight and postflight plasma volumes of the Gemini astronauts. Table 2 shows the weight and height of the astronauts. After Gemini IV, both astronauts showed a decrease in plasma volume. Similar results were obtained at the end of Gemini V. The plasma volumes obtained after the Gemini VII flight showed increased values in both astronauts. Repeat plasma volumes obtained 18 and 20 days after the flight again showed even greater increases over preflight values.

Table 3 shows the results of the RBC mass determinations obtained from the astronauts of the Gemini V and VII missions. It also shows derived RBC mass determinations for the Gemini IV astronauts calculated from the ^{125}I plasma volumes and peripheral venous hematocrit values. Direct measurements of RBC mass with ^{51}Cr showed decreases postflight ranging from 144 to 441 ml RBC.

Table 4 shows the ratio of the total body hematocrit values to the peripheral venous hematocrit values obtained for Gemini V and VII. In all four

NCPM/ml spec pl × (1—spec hct)
hct = peripheral venous hematocrit value expressed as a decimal; wh bl = whole blood; and volume injected = 10 ml.

astronauts a decrease in this ratio occurred following the flights. This postflight ratio remained the same for the two astronauts that were studied 18 to 20 days after recovery. In addition, the peripheral venous hematocrit values of Gemini astronauts are shown. Four of the six astronauts showed small decreases in their peripheral venous hematocrit values.

Table 5 shows the results of the ^{51}Cr erythrocyte survival studies. In the Gemini V flight, 72% and 73% of the ^{51}Cr remained upon recovery from an eight-day flight, which was the 14th day of the survival. When the percentages are corrected for the changes in RBC mass which occurred during flight, the values become 58% and 56%, which are significantly less than normal (65% to 78%).[15] In the Gemini VII flight, when the more extensive studies were done, preflight survival percentages on the fifth and seventh test day were close to our normal range and to the average percent remaining reported in the literature.[15,16] On recovery after their 14 day flight, which was the 23rd day of the survival, 59% and 58% of the erythrocyte ^{51}Cr remained. During the flight there was a change in the RBC mass. Correcting the percentages for the changes in RBC mass, values of 48% and 54% were obtained (normal 51% to 65%).[15] Thus the erythrocyte ^{51}Cr was lower than predicted for normals for one astronaut but not the other. The repeat RBC mass determination upon recovery was used to start a second erythrocyte survival study. On the first test day, 97% and 96% of the radioactivity remained, and 94% on the second day. For the command pilot 61% of the radioactivity remained on the 17th day. During this interval there was an increase in the RBC mass which yielded a corrected value of 74%. This was within the expected normal range of 61% to 74%.[15] The other astronaut's blood was drawn on the 19th test day. A value of 58% was obtained. When this was corrected for the change in RBC mass the corrected value of 66% was well within normal limits (58% to 70%).[15] Thus, one of the two astronauts in the Gemini VII flight showed a shortened ^{51}Cr erythrocyte survival during the period of flight but normal ^{51}Cr erythrocyte percentage before and after flight. Three of the four astronauts showed significant shortening of the erythrocyte ^{51}Cr life span during the flights. These results again show the need for correcting erythrocyte ^{51}Cr survival data for changes in RBC mass occurring during the testing period.

Prior to the launch of Gemini VII, the percentages of reticulocytes in the peripheral blood were determined on four occasions (ten, nine, four, and two days prior to launch). All reticulocyte percentages during this interval were between 0.7% and 1.1%. The reticulocyte counts of both astronauts showed no change on recovery or for two days postflight. By the third day postflight the reticulocyte percentage of the command pilot had risen to 1.4% and finally to 3.4% by the 18th day. The pilot's reticulocyte 20 days after recovery was 1.3%.

Table 3.—Red Blood Cell Mass Data

	RBC Mass, ml		Difference, ml
Gemini IV	Preflight	Postflight	
Command pilot	1,894*	1,670*	−224
Pilot	2,590*	2,262*	−328
Gemini V			
Command pilot	1,913	1,530	−383
Pilot	2,006	1,565	−441
Gemini VII			
Command pilot	2,077	1,682 (2,045)†	−395 (−32)
Pilot	1,969	1,825 (2,046)	−144 (+77)

*Derived from plasma volumes.
†Values in parentheses indicate results 18 or 20 days postflight.

Table 4.—Peripheral Venous Hematocrit Values and Total Body/Peripheral Hematocrit Ratio

	Preflight		Postflight	
Gemini IV	Peripheral Hematocrit Value, %	Ratio*	Peripheral Hematocrit Value, %	Ratio*
Command pilot	0.43	...	0.41	...
Pilot	0.44	...	0.44	...
Gemini V				
Command pilot	0.46	0.97	0.47	0.88
Pilot	0.48	0.97	0.46	0.90
Gemini VII				
Command pilot	0.46	1.02	0.45 (0.46)†	0.84 (0.84)
Pilot	0.49	0.86	0.47 (0.46)	0.84 (0.84)

*Ratios are calculated by dividing total body hematocrit value by peripheral venous hematocrit value, where total body hematocrit = $\frac{\text{RBC mass}}{\text{RBC mass} + \text{plasma volume}}$.
†Values in parentheses indicate results 18 or 20 days postflight.

Table 5.—^{51}Cr Erythrocyte Survival

	Mean Predicted Normal, %	Gemini V, % Remaining		Gemini VII, % Remaining	
Test Day	Remaining	CP*	P†	CP	P
Preflight					
2	95	(91)‡	(93)	...	...
5	84	...	...	(88)	(87)
7	81	...	...	(81)	(82)
Flight Interval					
14	65-78	58(73)	56(72)	...	...
23	51-65	...	...	48(59)	54(58)
Postflight					
1	98	...	...	(97)	(96)
2	85	...	...	(94)	(94)
17	61-74	...	...	74(61)	...
19	58-70	...	...	...	66(58)

*CP signifies command pilot.
†P signifies pilot.
‡Values in parentheses are not corrected for changes in RBC mass.

Comment

These preliminary radioisotope studies of the astronauts who participated in the Gemini IV, V, and VII flights show decreases in plasma volume during two of these flights. In all four astronauts in whom RBC masses were determined before and after flight a decreased RBC mass was found. Erythrocyte ^{51}Cr survivals determined during Gemini V and VII showed evidence of shortened survival times in three astronauts which is presumptive of a hemolytic state. Four of the six astronauts showed a minimal change in peripheral

venous hematocrit value following flight. Four of the astronauts showed a decrease in the ratio of total body hematocrit to peripheral venous hematocrit values following flight. These must be considered preliminary studies of the effect of space flight on astronauts. The radioisotope studies for the flights cannot be considered ideal nor up to the level ordinarily expected of studies designed to investigate environmental effects on RBC mass, plasma volume, and RBC survival. Since there is no previous experience with space flight reported in the medical literature, it seems worthwhile to report these preliminary results. Because of the problems of scheduling, and the safety requirement that no blood be drawn from the astronauts for three days prior to lift-off, all venipunctures were necessarily kept to a minimum. The blood studies on recovery were accomplished with makeshift facilities on the recovery aircraft carriers. The radioisotope studies were only a small part of the demands on the astronauts' time. This precluded the use of more refined techniques and drawing more frequent blood specimens to obtain die-away plots of injected radioactivity for estimation of erythrocyte survival.

Each space flight was different not only in the total time involved, but in the environmental factors influencing the astronauts' blood volumes, etc. As an example, postflight plasma volumes should have been measured with the astronauts fasting after an overnight rest, as in the control studies. Instead, the studies were done after the astronauts had experienced a high thermal load in the warm weather of the Atlantic. No restriction of water intake was possible just prior to reentry or immediately following reentry. Thus, ad lib water probably influenced these results and may even have caused the increased plasma volumes seen after Gemini VII. In spite of the preliminary nature of the study and the variabilities inherent in the experimental design, certain, trends are evident in the data.

The plasma volume following the Gemini missions were more variable than were the RBC mass changes. Poor injection techniques were probably not the cause of differences seen because the volumes injected were large enough to make extravasation obvious. Temporary sequestration in the arm vein probably did not occur because the specimens taken at 15 and 30 minutes produced nearly identical plasma volume values. Simulation experiments such as bed rest and water immersion studies predicted decreases in plasma volume over the flight interval, and in fact changes were noted after Gemini IV and V.[1,2,5-7] However, for Gemini VII the plasma volume of at least one of the astronauts had risen significantly immediately postflight and of both the astronauts by 18 to 20 days after recovery. The reasons for these changes can only be speculative. During the Gemini VII mission the pilots were not only in space for a longer period of time but also spent many days out of their space suits, thereby reducing their thermal load. The plasma volume increases noted during the Gemini VII mission corrected for the decreased RBC masses sufficiently to bring the total blood volumes back to preflight values. Therefore one could speculate that the plasma volume increase was of a compensatory nature effective in reconstituting the blood volume, and that Gemini VII was the only flight long enough for this compensatory mechanism to become effective. There are other evidences that physiological adaptation to the situation may have occurred by the 14th day. The Gemini VII flight studies showed less roentgenographic evidence of demineralization of the os calcis, weight loss, and lower heart rate responses to tilt than were predicted from a projection of the progressive difference between the four and eight day missions.[11,17,18] However, since these represent only three flights and six individuals, bilogical uniqueness may have played a decisive role in the failure of these changes to progress during the longer flight. The final 18 to 20 day determinations for Gemini VII were done with the astronauts performing normal duties and in the postprandial state. Therefore, it is probable that the increases were influenced by the time of day, activity state, and recent ingestion of liquid.

As in bed rest and water immersion studies, the plasma volume changes noted after the Gemini missions were not great enough to be a major cause of postflight orthostatic intolerance to passive tilts. Because plasma volume increases during the Gemini VII mission resulted in essentially normal blood volumes, hypovolemia prior to tilt could not have contributed to orthostatic intolerance noted in these crewmen.[11]

Both the derived RBC masses obtained after the Gemini IV mission and the directly measured RBC masses obtained from the Gemini V and VII missions were decreased postflight. Quantitatively a 20% RBC mass decrease was found after the eight day Gemini V mission. One pilot of Gemini VII showed a 19% loss in RBC mass, while the other crew member's RBC mass decreased 7%. The RBC masses of the two Gemini VII astronauts returned to preflight values within three weeks after the flight. Unpublished hematological studies from our laboratories performed on Gemini VII crew members showed that the mean RBC volume increased during the flight interval. This increase in erythrocyte mean cell volume might have obscured the extent of RBC mass reduction.

The peripheral venous hematocrit values of four of the six crew members of the Gemini missions decreased postflight, from which it may be inferred that RBC mass decreases were proportionately greater than plasma volume decreases. These results are contrary to results found with bed rest when plasma volume decreases have been noted with associated rises in peripheral venous hematocrit values.[2,5,8] Significant changes in the ratio of total body hematocrit to peripheral venous hematocrit values were found to occur during the flight inter-

vals of Gemini V and VII. The causes of this drop is unknown. This shows again the potential error of calculating the RBC mass by the indirect method.

There are four mechanisms which could explain the decrease in RBC mass observed in these studies: (1) increased intravascular destruction, (2) decreased production rate, (3) external or interstitial bleeding, or (4) incomplete mixing of the radioactive cells used in the RBC mass determination.

There is no clinical evidence to suggest that part of the intravascular RBC were sequestered from the 15 minute distribution space of the reinjected radioactive RBC. However, the evidence against sequestration is twofold: (1) surface counting immediately following the injection of radioactive RBC into the Gemini VII astronauts, with a scintillation detector placed over the heart, showed an early equilibrium value which remained unchanged for a prolonged period, and (2) the ^{51}Cr radioactivity per milliliter of RBC decreased only the amount expected from studies of normals between the 15 minute and the 24 hour sample. This indicated that adequate mixing had occurred prior to the 15 minute sample. Bleeding internally is neither plausible nor supported by the clinical findings. Guaiac tests of fecal specimens saved throughout the Gemini V mission were negative and amounts of ^{51}Cr found in them showed no evidence of blood loss.

Red blood cell survival data would indicate that increased RBC destruction over the flight occurred in at least three of the four astronauts tested. No direct in flight measurements were made that would provide information about changes in the production rate of erythrocytes. An increased erythrocyte production rate would ordinarily follow a decrease in erythrocyte survival. We have evidence that this did not happen since a RBC mass decrease occurred and since the ^{51}Cr percentage remaining per milliliter of RBC was within normal limits postflight. If erythrocyte production rate had increased, the percentages before correction with the RBC mass to total circulating ^{51}Cr remaining would have been abnormally low because of dilution of the ^{51}Cr RBC with newly released RBC. In addition, the reticulocyte data indicated that the RBC production rate at the end of the flight was probably close to what it had been preflight.

In the command pilot of Gemini VII whose RBC mass decreased, an increase in reticulocytes occurred by 3 days postflight and a slight increase occurred in the pilot of this mission by 20 days. These data would indicate that the RBC production rate increased postflight to compensate for a decrease in RBC mass. Additional support to this theory is given by the RBC masses and survival studies performed 18 to 20 days postflight. By this time the RBC masses of the Gemini VII astronauts had returned to their preflight values. In addition, the ^{51}Cr percentages remaining per milliliter of RBC gave falsely low values because of dilution with newly released RBC. When these percentages were corrected to total circulating percent remaining ^{51}Cr, normal survivals were obtained. These results indicate hemolysis during flight probably associated with a normal RBC production rate in at least three of the four astronauts studied. In the two astronauts that were studied 18 to 20 days postflight, the production rate had increased and the RBC masses and survivals had returned to normal.

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Generic and Trade Names of Drugs

Sodium chromate Cr 51—*Chromitope Sodium, Rachromate-51.*
Iodinated I.125 serum albumin—*Albumotope I-125, Risa 125.*

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