CR-171946

(NASA-CR-171946) BEDREST IN HEALTHY WOMEN: EFFECTS OF MENSTRUAL FUNCTION AND ORAL CONTRACEPTIVES Final Report (Johns Hopkins Univ.) 160 p CSCL 06P

N87-15681

G3/52 Unclas 40241

FINAL REPORT : CONTRACT #S: NAS9-16703, NAS9-17199

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DATES OF STUDY : JUNE 1982-DECEMBER 1985

TYPE OF CONTRACT : COST REIMBURSEMENT NON-PROFIT

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BEDREST IN HEALTHY WOMEN: EFFECTS OF MENSTRUAL FUNCTION AND ORAL CONTRACEPTIVES

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I) IDENTIFICATION OF THE TASK

This work originated as an unsolicited proposal No. JSC6-82-7994, submitted July 23, 1982, to study the physiological responses of women to bedrest. This proposal was funded during years 1 and 2 (1982-83) under contract # NAS9-16703. At this point the contract was renegotiated because of a NASA budget reallocation. The work during year 3 was performed under contract number NAS9-17199. In June 1985 an extension was granted without further funding.

II) PURPOSE AND SCOPE OF THE STUDY

With the development of the space shuttle program, space flight for the first time is available to individuals who have not been specially selected and trained to be astronauts. In addition, women are being actively recruited into the space program, both as mission specialists and as career astronauts. One purpose of this project was to examine some of the physiological responses of women to a simulated weightlessness program (12-day horizontal bedrest), to compare their responses to those reported in men during similar programs, and to test whether menstrual function might alter some of the physiological changes which occur during bedrest, specifically changes in the plasma volume, exercise tolerance, and venous compliance before and after bedrest. Specific hypotheses tested include:

1) that an elevation in blood estrogens might be associated with a retention of body fluids, and thus reduce the hypovolemia seen during bedrest. It was predicted that a smaller reduction of plasma volume would occur during bedrest when a woman is in a stage of her menstrual cycle when estrogens are elevated. Further, the use of estrogen-containing oral contraceptives may prevent or reduce the decrease in plasma volume seen during the first several days of bedrest. The body fluid-retaining effect of estrogens was postulated to occur through an increase in sodium reabsorption in the distil and collecting tubules. Therefore urine output would be predicted to be lower during bedrest when estrogens are elevated, than when estrogens are lower.

2) that the reduction in plasma volume which occurs during bedrest contributes significantly to the reduced exercise tolerance reported following bedrest. Therefore, if the loss of plasma volume during bedrest could be prevented (through an effect of elevated estrogens), then exercise tolerance following bedrest should be significantly improved over results seen when plasma volume is decreased. Specific exercise responses postulated to be influenced by the decrease in plasma volume during bedrest included exercise heart rate, stroke volume, body temperature regulation, sweat rate, and venous compliance.

Specific questions which arose <u>during</u> the study include:

1) Is there a significant danger of lower leg edema occurring in women (not previously reported in men) following bedrest .

2) Based on the changes in plasma volume seen in women with normal menstrual cycles (not on oral contraceptives) and in two women who took oral contraceptives, it appeared that elevation in estrogen concentration in the presence of high progesterone, did not consistently result in retention of plasma volume during bedrest. However when blood estrogens were elevated in the presence of low progesterone, the data suggested that there was at least a temporary maintenance of plasma volume. Therefore the original hypothesis that elevated estrogens would retain plasma volume was revised to now state that, women administered natural estrogens (premarin) during bedrest without progesterone supplement, may maintain their plasma volume during bedrest.

Physiological questions which have not been previously addressed include:

1) What specific changes occur in exercise thermoregulatory responses following bedrest? It was hypothesized that there would be a decrease in sweating sensitivity (slope of the sweat rate/core temperature (Tes) relationship), and possibly an upward shift in the Tes sweating threshold.

2) Would the exercise venoconstrictor reflex be attenuated (by a loss of sympathetic nervous system responsiveness) or potentiated (by the decrease in plasma volume) following bedrest? A loss of venoconstrictor tone could contribute significantly to the orthostatic intolerance reported in astronauts following spaceflight.

3) It has often been hypothesized that estrogens are involved in the lower sweating responses seen in women than in men. The effects of elevated estrogens to alter the sweating sensitivity (the slope of the sweat rate/core temperature relationship) and sweating core temperature threshold was examined in 7 women with and without premarin administration (1.25 mg daily) for 7-10 days. It was hypothesized that estrogen administration would reduce sweating responses, resulting in significantly higher body temperatures for a given exercise task.

111) MATERIALS AND METHODS

A) The overall protocol

The study was performed during three years, in which all data collection was performed in the summer months (late May to early September) because of the increased likelihood of recruiting subjects in these months. A total of 22 women between 21 and 39 years of age participated (see Table 1 for their physical characteristics).

i) Year 1

During the first summer (1982), six "normally cycling" women completed the protocol shown in Figure 1. The overall protocol consisted of a control month with testing at two week intervals (C1 and C2), two 12-day periods of bedrest, and a recovery month after

TABLE 1: SUBJECT CHARACTERISTICS

Subject	Age (Yrs.)	Height (cm)	Weight (kg)	VO_{2max} (ml/kg/min)	Non-Premarin	Premarin	Oral Contraceptives
Year 1							
1	39	175	57.8	33.2	X		
2	25	170	54.4	37.1	X		
3	26	170	52.5	34.7	X		
4	21	170	56.3	44.4	X		
5	33	180	73.9	28.4	X		
6	21	168	59.4	40.1	X		
-	--	---	----	----			
x	28	172	59.1	36.3			
SD	7	4	7.7	5.6			
Year 2							
1	21	173	57.3	42.5	X		
2	27	165	76.1	28.5	X		
3	23	177	66.7	36.7	X		
4	26	161	50.6	45.8	X		
5	24	166	59.6	36.8	X		
6	36	170	61.2	41.7	X		
-	--	---	----	----			
x	26	169	61.9	38.7			
SD	5	6	8.7	6.1			
Year 3							
1	26	170	72.4	30.8		X	
2	24	160	46.6	28.3		X	
3	24	180	67.0	28.4		X	
4	28	169	56.5	44.6		X	
5	23	168	56.6	44.7		X	
6	21	171	69.8	43.6		X	
7	33	174	70.6	40.1		X	
-	--	---	----	----			
x	26	170	62.7	37.2			
SD	4	6	9.8	7.7			
* A	27	170	68.6	27.2	X		
** B	25	167	64.7	26.9			X
** C	21	165	56.1	36.0			X

* the subject during year 1 who performed only a single bedrest because of leg swelling.

** the subjects during year 2 who performed only a single bedrest and who took oral contraceptives.

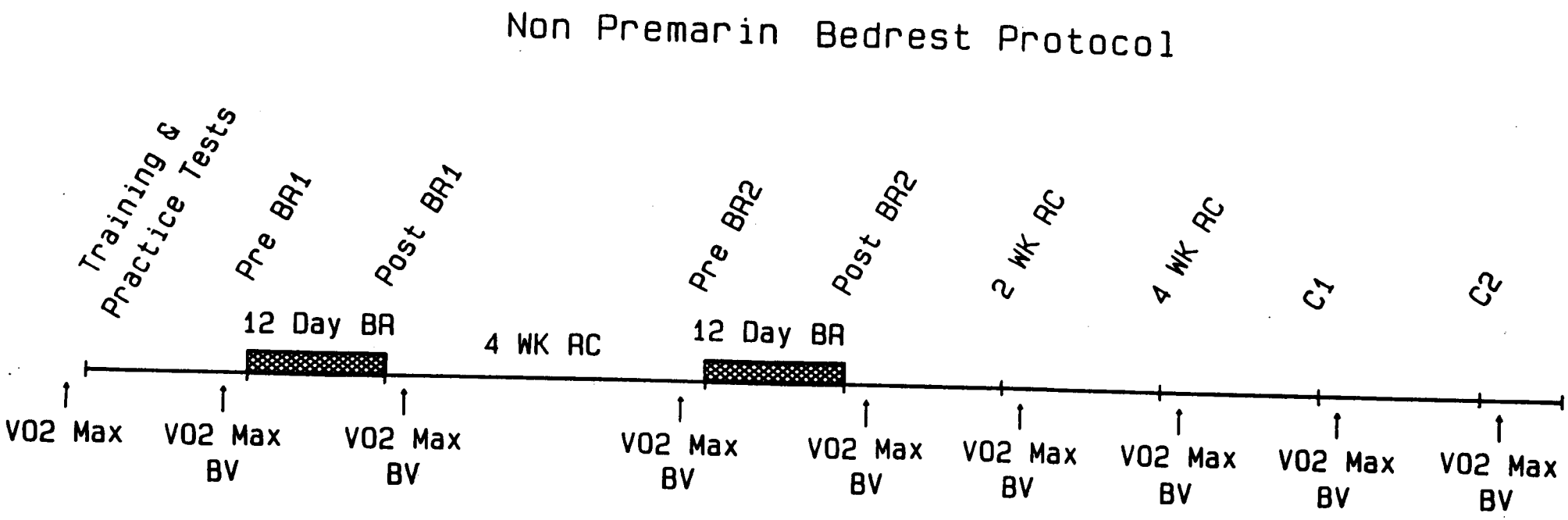

FIGURE 1: Overall protocol. Control submaximal exercise tests (C1 and C2) were performed after the recovery month (as in figure) during year 1, and after the training and practice tests during years 2 and 3. VO2 max = maximum oxygen consumption test; BV = blood volume determination with technetium labelling; PRE BR and POST BR = prebedrest and postbedrest submaximal exercise tests; and 2 and 4 WK RC = two and four week recovery submaximal exercise tests.

each bedrest, with testing performed after 2 and 4 weeks of recovery. Before beginning the study, there were several training sessions in which each woman was taught the Farhi CO2 rebreathing technique, how to position the esophageal thermocouple, and how to pedal a low-sit cycle ergometer while keeping the left arm steady enough for forearm blood flow measurements. Once these basic techniques were mastered, "practice" submaximal exercise tests were performed to further familiarize the subjects with the protocols, and to insure that they were sufficiently trained to produce reproducible data.

Two 12-day horizontal bedrest periods were performed with an ambulatory interval of from 3-4 weeks between bedrests. This timing was chosen so that each woman began the second bedrest 5-6 weeks after the start of the first bedrest. Since all of the women were expected to have menstrual cycles of from 25-32 days, the bedrest procedures were designed so that each woman would begin bedrest in different phases of the menstrual cycle, and thus should have a differing hormonal millieu. No attempt was made to begin the bedrest at a particular day or phase of the menstrual cycle. Table 2 presents the menstrual cycle stage (see methods) for each of the women on the first day of bedrest. During the recovery and control months, subjects resumed their normal lifestyle.

One additional subject began the bedrest protocol during the first year of this study. However, within 2-4 days after the end of bedrest 1, she developed severe edema in both lower legs. She was tested with the venous impedance technique for venous obstruction (blood clotting), and the results were negative. A report of this incident was immediately sent to the Committee of Human Volunteers of the School of Public Health, and all further testing was stopped until an inquest could be held to determine whether this event was likely to occur again or in other subjects. During this interval, 2 week recovery data collection was not able to be obtained. The inquest resolved that this was an unusual event, possibly provoked by the inactivity of this particular subject after bedrest, which may have delayed the recovery of venous tone in her lower legs, resulting in blood pooling and edema. Although the committee thought it unlikely that a similar incident would occur again to this subject, it was recommended that she should not undergo the second scheduled bedrest. Permission to continue the study with the other subjects was obtained in time for the 4 week recovery collections and the start of bedrest 2. (see appendix 1 for copies of correspondence with the Committee of Human Volunteers about this incident).

ii) Year 2

Six additional "normally cycling" women were recruited during the summer of 1983. Each woman performed the protocol illustrated in Figure 1 except that, 1) in order to randomize the presentation of the control tests and to evaluate possible seasonal fluctuations, the control month was perfomed before the start of bedrest 1, rather than after the end of the second recovery month, and 2) since no significant differences were seen between the duplicate maximum oxygen consumptions (VO2max) during the control month, C1 and C2 VO2 max tests were omitted.

TABLE 2: MENSTRUAL CYCLE [+]STAGE OF SUBJECTS AT THE START OF BEDREST

Subject	Bedrest 1	Bedrest 2
Non-Premarin Group		
1	1	3
2	1	2
3	3	3 (NO)
4	1	3
5	3	2
6	4	3
7	3	3
8	2	3 (LD)
9	1	3
10	1	3
11	4	1
12	2 (LD)	3 (LD)

[+] where stage 1 = early follicular (cycle days 2 - 6, prior to estimated ovulation)

stage 2 = periovular (5 days prior to estimated ovulation to 1 day after estimated ovulation)

stage 3 = early luteal (2-9 days post estimated ovulation)

stage 4 = late luteal (10 days past estimated ovulation to cycle day 1 of next cycle).

LD = luteal phase deficiency suspected from hormonal results.

NO = No ovulation suspected based on hormonal results.

Two women were recruited who were taking estrogen-containing oral contraceptives (Ovulen 21 or Orthonovum). Both of these women performed the protocols from the control month, a single bedrest, and the recovery month.

iii) Year 3

During the last year of the study, 7 women performed the protocol from the control month, a single bedrest, and the recovery month. Similar to year 2, the control month occurred before the bedrest procedure rather than after the recovery month. Each woman ingested 1.25 mg of an estrogen supplement (premarin), starting on the third cycle day of the month in which she would undergo the bedrest protocol (7-10 days before bedrest day 1). The premarin was continued during the bedrest, and for five days after bedrest. Progesterone supplements (10 mg /day Provera) were taken for 5 days, starting on the second day after bedrest in order to allow normal endometrial sloughing. A single blood volume determination (with technetium radioisotope labelling) was performed during the control month, since no significant differences were seen in any of the previous results of the duplicate measurements during the control month. This was done to prevent unnecessary exposure of these subjects to repeated radioisotope testing.

B) The Bedrest Protocol

i) The environment

Bedrests were performed at the Sheraton Johns Hopkins Inn located at 400 North Broadway. Each summer, 4 rooms were reserved for subjects (2 subjects per room), and one room was reserved for the "nurses" (persons trained and hired to look after the subjects during the bedrests), and one room was the impromptue blood chemistry laboratory. During the second and third summers, a sixth room was reserved and tranformed into a pulmonary function laboratory. The hotel provided maid service and most of the meals. Occasionally food was obtained from local restaurants chosen by the subjects. No restriction was placed on the amount or type of food eaten, although alcoholic beverages were restricted.

Each room consisted of 2 single beds and a bathroom. The beds were normal hotel beds, except that a small pressure-sensitive platform was placed under the castors at the foot of the bed. These pressure sensors were connected to automatic timers to record the time spent out-of-bed by each subject. Each morning the accumulative time for the previous 24 hours was recorded by the nurse. The installation of the platforms resulted in a 4 degree head-down tilt of the beds. However, since each bed contained one pillow, when the subject lay with her head on the pillow, her head was positioned approximately horizontal to her feet.

ii) Daily activities

On the first day of bedrest, a subject ate a light breakfast and reported to the nurse at the hotel at 9 am. She unpacked her suitcase, emptied her bladder and immediately began the bedrest. One

hour later, the first venous blood sample was obtained. Subjects maintained the horizontal position for the remainder of the bedrest, except for time allowed for bathroom activities. Subjects moved to and from the bathroom in wheelchairs, without supporting their weight on their feet. Baths, not showers were taken, and each subject was instructed to spend no more than 15-20 minutes in each 24-hour period in the sitting position, and no time standing. Sitting in bed was not permitted, although they were allowed to rest on one elbow to eat. The amount of time spent out-of-bed during each bedrest is listed in Table 3. No significant differences occured in the time out-of-bed between bedrest days (ANOVA, one-way, repeated measures design), between duplicate bedrests during years 1 and 2, (ANOVA, 2-way, repeated measures design) or between the 3 years.

For each succeeding day of bedrest, the subject was awoken at 7 am. She then took her oral temperature, emptied her bladder into a 24-hour urine container (second and third years), and ate a light breakfast. Two hours later, the morning blood sample was obtained, making sure that the subject had been horizontal during the previous 60 minutes. In this way, blood samples were controlled for posture, time since last food intake, and circadian variation.

During the second and third years of the study, pulmonary function tests were added to the bedrest protocol. Each subject performed these tests on at least 3 days before bedrest, on each day of bedrest, and on the day after bedrest. Subjects were transported to the pulmonary function room on a gurney, in order to insure that the subjects did not alter their posture from the horizontal position.

iii) Measurements obtained during bedrests

From each daily blood sample the following measurements were obtained: hematocrit (microhematocrit technique), hemoglobin concentration (cyanomethemoglobin), total solids (refractometry), and plasma osmolality (freezing point depression). Plasma estrogen and progesterone concentrations were determined from the blood samples on each day of bedrest during year 2, and on every third day of bedrest during year 3. Throughout the bedrests, urine osmolality was determined each day of bedrest. Twenty-four hour urine volumes were recorded during years 2 and 3.

Daily diaries were kept during the entire study. Each subject recorded her fluid and food intake during bedrest, her morning oral temperature, and the time at which she took estrogen medication (the oral contraceptive users and premarin subjects). Other medication and medical or menstrual symptoms also were noted.

Pulmonary function tests consisted of lung volume measurements, total lung capacity (helium dilution), forced expiratory volumes, lung diffusing capacity for carbon monoxide, the slope of phase 3 (Nitrogen washout), and maximal inspiratory and expiratory pressures.

An exploratory study was performed on one subject during the third year to determine whether brain caudate D2 dopamine receptors would be altered during the bedrest procedure (this was a special study to

TABLE 3: BEDREST TIMER DATA
(mean ± SD) No. minutes/24 hours non-horizontal

DAY OF BEDREST	1	2	3	4	5	6	7	8	9	10	11	$\bar{x}$
NON-PREMAIN BEDRESTS												
Year 1												
BR1 (n=6)												
$\bar{x}$	20.8	27.4	20.4	19.1	19.5	18.5	19.1	20.4	19.4	18.2	20.4	21.3
SD	10.9	14.0	4.4	4.5	7.0	8.0	3.0	7.0	8.31	4.2	3.8	2.5
BR2 (n=6)												
$\bar{x}$	12.7	17.4	17.9	19.6	19.8	19.1	19.8	20.5	18.5	18.6	20.7	18.6
SD	3.9	3.5	4.3	2.5	3.4	2.6	5.7	8.1	4.1	4.6	2.2	2.2
Year 2												
BR1 (n=6)												
$\bar{x}$	17.3	19.4	16.6	15.8	13.9	15.5	15.6	14.9	15.3	13.9	17.2	15.9
SD	3.1	5.8	3.5	6.0	4.9	2.7	1.9	2.8	2.6	2.5	4.9	1.6
BR2 (n=6)												
$\bar{x}$	15.6	16.9	14.7	14.8	15.6	15.1	17.3	16.7	15.4	17.8	15.1	15.9
SD	6.5	5.8	4.9	2.7	3.0	4.0	2.7	3.2	3.0	1.9	4.5	1.1
PREMARIN BEDREST												
BR1 (n=7)												
$\bar{x}$	12.6	12.4	13.4	12.3	12.4	11.2	10.5	12.7	11.7	11.2	13.1	12.1
SD	3.8	2.4	3.4	2.9	7.1	4.0	2.1	4.0	2.6	2.5	3.2	0.9
ORAL CONTRA-CEPTIVE USER BEDRESTS												
BR1 (n=2)												
$\bar{x}$	18.4	17.0	11.7	12.1	9.0	12.1	11.3	12.1	10.6	11.0	7.6	12.1
SD	1.3	12.7	0.1	3.0	4.6	6.7	2.5	5.5	0.5	7.7	2.9	3.1

test whether acute changes in fitness alters the binding of caudate dopamine receptors). Dopamine receptor binding was assessed by positron emission tomography (Wong et al, 1984), with imaging performed after intravenous injection of 11C-labelled 3-N-methylspiperone. The prebedrest imaging was performed 2 days prior to the start of bedrest in subject 19, and repeated on the last day of bedrest. During imaging the subject did not change from the horizontal position. She was transported by ambulance to the Nuclear Medicine Department in the Johns Hopkins Hospital, and immediately afterwards, performed the postbedrest submaximal exercise test.

C) Maximum Oxygen Consumption (VO2 max) Protocol

Maximal Oxygen Consumption determination was performed approximately every two weeks during the study (C2 tests were not performed during years 2 and 3).
Prebedrest tests (PREBR) were performed within 48 hours of the start of bedrest, and postbedrest tests (POSTBR) were performed within 48 hours, but usually within 24 hours, after bedrest.

Oxygen consumption was determined at progressively increasing exercise intensities for each woman pedalling an upright cycle ergometer. Ventilation was measured in either a tissot tank (year 1) or with a dry gas meter (years 2 and 3). The oxygen concentration of the expired air was measured with a Beckman OM 11 gas analyzer, and CO2 concentration with either a Beckman LB2 (year 1) or an Applied Electrochemistry CO2 Analyzer (years 2 and 3). Each subject pedalled at a rate of 50 revolutions per minute while the exercise intensity was increased (in 25 Watt steps) every 2 minutes. For the first VO2 max determination, tests were performed at least in duplicate (on separate days) in an effort to obtain a plateau of the oxygen consumption curve during the final two exercise intensities. Control tests were repeated until this criteria was met in order to accurately establish the fitness level of each subject before bedrest. Following bedrest however, the plateau criteria could seldom be met, as most women seemed limited by leg fatigue before attaining the plateau. Non-plateau values are therefore referred to as "peak VO2" values. Heart rates were also measured during these tests with either a 12-lead EKG system (for the first test on each subject), or with a respironics heart rate monitor (for all further tests).

D Submaximal Exercise Protocol

Submaximal exercise tests were performed in approximately 2 week intervals during this study (except when the 2 week recovery data was missed during year 1). The postbedrest tests were performed immediately following the bedrest procedure. Subjects were transported in wheelchairs and by car (less than 5 minute ride) from their bed in the hotel to the Stress Physiology Laboratory in the School of Public Health. The ambient temperature for these tests was maintained at 30 ^{o}C $\pm$ 1 ^{o}C, and 50-60 % rh. Before the submaximal exercise test, subjects supported their weight only briefly, during the pre-exercise body weighing procedure. Next, they sat in the seat of the low-sit cycle ergometer for at least 40 minutes before the start of the exercise test to control posture before blood sampling,

and to allow time for attachment of measurement devices.

Each subject pedalled for 30 minutes at an exercise intensity that was 70% of her VO2 max determined just prior to the bedrest. However, exercise was stopped earlier if a subject's core temperature exceeded 39°C, or if her heart rate approached 95% of her maximal heart rate value, which was determined during the prebedrest VO2 max test. For any given subject, all exercise tests were conducted at the same time of day (± 2 hours), not more often than once a week (to avoid training or acclimation effects), at least 2 hours after a light meal, and about 1 hour after drinking 200 ml of water to assure adequate hydration.

During the first two years of the study, subjects were instructed to stop pedalling immediately at the end of the submaximal exercise test in order to obtain resting recovery data. Following the postbedrest tests (but none of the other tests), 7 out of 15 of the women felt faint and had to be moved to a horizontal position (two actually fainted). Thereafter, to avoid this traumatic experience for the subjects and investigators, subjects were instructed to free-pedal during recovery in order to assist cardiac return. During the third year of the study, all subjects free-pedalled after exercise and none experienced fainting episodes.

During each submaximal exercise test the following measurements were obtained:

- exercise time, in minutes, was recorded for each test.

- body weight, before and immediately after exercise, was measured with the subject wearing a dry scrub suit. After exercise, the subject dried herself and removed all wet clothing. Weights were obtained on a Homs scale (accuracy ± 50 gms) and were adjusted for any water drunk while placing the esophageal thermocouple.

- heart rate (HR) was measured each minute with a respironics heart rate monitor

- body core temperature (Tes) was monitored continuously with a thermocouple positioned in the esophagus at the level of the right atrium (Wenger, 1975).

- skin temperatures (Tsk) were recorded every 5 minutes with uncovered thermistors (Yellow Springs) postioned over the chest (T1), lateral upper arm (T2), lateral thigh (T3), and lateral calf (T4). Mean skin temperature (Tsk) was calculated by the formula:

$$Tsk = 0.3\ T1 + 0.3\ T2 + 0.2\ T3 + 0.2\ T4.$$

- forearm venous compliance (FVC) was measured every 2-3 minutes using the technique of venous occlusion plethysmography (Wenger, 1980). Changes in forearm circumference were measured using a Whitney mercury-in-silastic strain gauge. The forearm was suspended from the wrist with a cloth sling so that the elbow was level with the shoulder.

- cardiac output was determined after 10, 15, 20,and 25 minutes of exercise, using the Fahri CO2 rebreathing technique (Farhi, 1976). The rebreathing bag was filled with 100% O2, and the breathing rate was maintained at 60 breaths per minute during the 15-17 seconds of the rebreathing maneuver. Calculations of cardiac output were performed using the CO2 dissociation curve adjusted for the pre-rebreathing hemoglobin concentration. Heart rates were determined during the rebreathing maneuver and used to calculate stroke volume.

-local sweating responses (SR) were measured continuously before and during exercise, using a resistance hygrometry sweating system (Bullard, 1962). For determination of sweating sensitivity (slope of the SR/Tes relationship) and the Tes threshold for the onset of sweating, the local sweating data (mg/cm2/min) was paired with corresponding Tes values. A linear regression equation was used to determine the slope of the relationship, and the Tes value at which the line intersected the x axis (Tes sweating threshold).

- blood samples were obtained immediately before the start of exercise, after 2, 6, 15, 20, and 30 minutes of exercise, and 5 minutes after the end of exercise. Blood was drawn after at least 40 minutes of controlled posture, with the arm in the same position for all samples, and in a free-flowing manner (without tourniquet or vacutainer). Between sampling, the butterfly needle was kept patent with a heparin/saline lock.

From all blood samples, determinations of hematocrit (microhematocrit technique), hemoglobin concentration (cyanomethemoglobin), total solids (refractometry), and osmolality (freezing point depression) were obtained. From the resting and 30 minute exercise samples, blood lactate (Sigma enzymatic reaction), and arginine vasopressin concentration (third year only) were determined. The arginine vasopressin assay was used as an index of antidiuretic activity, and was performed using an immunonuclear radioimmunoassay kit. This is a delayed tracer technique with the plasma extraction done on octadecasilyl-silica columns. The assay is sensitive from 3-80 pg/ml. From the resting samples, plasma estrogen and progesterone concentrations were also determined with radioimmunoassay techniques (Diagnostic Products).

E) Red Cell and Plasma Volume Determinations

1) Radioisotope dilution methods

To determine Red Cell Volume (RCV), 40 microcurries of 99M technetium (Tc) pertechnitate (Brookhaven National Laboratory) was bound to a sample of red blood cells after first determining the background radiation of the sample. Exactly 5 ml of the labelled blood was then reinjected intravenously and allowed to mix in the vascular compartment for 20 and 40 minutes. Then 10 ml samples of heparinized blood were drawn to measure the 99MTc activity of the mixed blood.

Plasma volume was determined in a similar manner. Twenty microcurries of 99M Technetium pertechnitate was used to label a

sample of human serum albumin and saline. This protein solution was then injected through an arm vein and 20 and 40 minutes later, blood samples were drawn for counting. Technetium was chosen as the radioisotope in both of the above tests because of its short half-life (6 hours), and the need for multiple blood volume determinations in this study. During each RCV determination, hematocrits were measured from one of the blood samples in the exact manner that hematocrits were determined from bedrest and exercise blood samples.

2) Plasma Volume (PV) calculations during bedrest

The Absolute Plasma Volume on the first day of bedrest was calculated by multiplying the ratio of the hematocrits from the blood sample drawn during the plasma volume determination (performed on the day prior to bedrest) and the blood sample drawn during day 1 of the bedrest, by the PV determined on the day prior to bedrest (Van Beaumont, 1972). The assumptions made using this formula are that, within the 24-hour interval between the two blood samples, there was no significant change in red cell volume or red cell size.

Relative changes in plasma volume during bedrest (% change from day 1) were calculated from the changes in hematocrit and hemoglobin (Dill and Costill, 1974). The assumption with this calculation is that in the interval between blood sampling, there was no significant change in red cell volume (see later in results section). PV on each day of bedrest was calculated by multiplying the relative changes in plasma volume by the PV on day 1.

3) Relative Changes in Plasma Volume During the Submaximal Exercise Tests

Relative changes in plasma volume during exercise tests (% change between the resting and each succeeding exercise sample), were calculated (Dill and Costill, 1974) from the changes in hematocrit and hemoglobin concentration during the exercise.

F) Menstrual Cycle Determinations

Menstrual cycle data consisted of daily records of morning temperature and comments written in diaries kept by each subject. In addition, blood samples were drawn at various intervals during the study to assess hormonal function (estrogen, progesterone, LH, and FSH). Each year of the study, samples were drawn before each submaximal exercise test. Hormonal determinations were also performed during either each day of bedrest (year 2) or every third day of bedrest (year 3). From the frequency of the blood sampling (and thus hormonal determinations), it was not always possible to define the exact day of ovulation. Therefore menstrual cycle comparisons were made by comparing different stages of the cycle rather than on specific cycle days. Each woman's menstrual cycle was divided into 4 stages, in which a differing hormonal milieu would be expected (and in each case verified by the results from at least one blood sample).

Stage 1 : Early follicular stage - from cycle day 2 (day 1 = the

first day of bleeding) until 6 days prior to the day estimated as ovulation. (Only in a few subjects could the exact day of ovulation be identified by an LH peak). In subjects in whom an LH peak was not obtained, the day of ovulation was estimated by counting back 14 days from the start of the next cycle, from the morning temperature records, and from the hormonal data available. During this cycle stage low estrogen and progesterone concentrations were seen.

Stage 2: Periovular stage - from 5 days prior to the estimated day of ovulation until one day after the ovulatory day. During this stage, elevated estrogens and low progesterone concentrations occurred.

Stage 3: Early luteal phase - from 2-9 days after the estimated day of ovulation. During this stage, estrogen and progesterone concentrations were increasing.

Stage 4 : Late luteal phase - from 10 days after the estimated day of ovulation until the first day of the next cycle. During this stage estrogen and progesterone concentrations were decreasing.

IV) RESULTS AND COMMENTS

A) Body Fluid Responses During Bedrest

1) Changes in Red Cell Volume

The red cell volume data are presented in Table 4. Since there were no significant changes in body weights during the bedrest, the same patterns of change in red cell responses were found whether the data was represented as in Table 4 (absolute volumes in ml), or as the RCV corrected for body weight (ml/kg). The F value from a one-way analysis of variance test for repeated measures (ANOVA 1-W-RM) was significant ($P < 0.01$) when comparing the RCV values from the non-premarin group, but non-significant for the premarin group ($P < 0.20$).

i) Non-premarin group, Control 1 vs Control 2

There was no significant difference in RCV between the 2 Control tests. (The post hoc comparisions were performed using the Duncan Multiple Range Test, with the level of significance accepted at $P < 0.05$).

ii) Non-premarin group, Bedrest 1

Red cell volume (RCV) was measured with the technetium labelling technique (Methods) within 48 hours before bedrest 1 and within 48 hours after the end of bedrest 1. The decrease in RCV averaged only 85 ml (5.8%) after the 12 days of bedrest. This difference was not significant ($P < 0.05$).

iii) Non-premarin group, Bedrest 2

The decrease in RCV during the second bedrest averaged 63 ml, or only 4.4%. Again this change in RCV during the 12-day bedrest was not significant. However the decrease in RCV since the beginning of the study appeared to be accumulative, so that the decrease in RCV between the beginning of the first bedrest and the end of the second bedrest was significant ($p < 0.05$) and averaged 6.2%. The difference in RCV between the start of the first bedrest and the start of the second bedrest was not significant.

iv) Premarin Group

Although there was a tendency for the RCV to decrease during the bedrest (6.5% decrease), the difference between the beginning and end of bedrest was not significant. A comparison of the changes in RCV between the non-premarin and the premarin groups in response to bedrest and during recovery can be seen in Figure 2. Estrogen supplementation did not appear to alter this overall pattern of changes in RCV.

v) Changes in RCV during recovery, non-premarin and premarin groups

The significant decrease in RCV seen in the non-premarin group

TABLE 4: RED CELL VOLUMES
(ml/min)

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1	1407	1449	1435	1350	1358	1285	1418	1330
2	1303	1276	1331	1338	1170	1211	1226	1308
3	1317	1258	1304	1219	1116	1169	1153	1173
4	1489	1430	1393	1264	1272	1286	1303	1200
5	1694	1587	1506	1433	1488	1535	1407	1610
6	1305	1226	1225	1142	1177	1159	1147	1135
7	1371	1302	1445	1269	1250	1389	1445	1371
8	1531	1542	1688	1595	1440	1600	1432	1531
9	1724	1502	1512	1440	1452	1555	1550	1724
10	1469	1267	1361	1369	1269	1429	1352	1469
11	1359	1194	1432	1376	1221	1201	1459	1359
12	1719	1636	1700	1790	1571	1755	1517	1719
$\bar{x}$	1474	1389	1444	1382	1315	1381	1367	1410
SE	44.50	42.38	39.40	47.86	39.83	53.88	37.02	55.84
Premarin Group								
13	1764	1589			1271	1651		
14	924	873			866	975		
15	1423	1273			1352	1445		
16	1318	1128			1181	1293		
17	1081	1078			1295	1067		
18	1464	1549			1436	1487		
19	1305	1190			1344	1373		
$\bar{x}$	1325	1240			1249	1327		
SE	95.02	89.71			65.23	83.21		
A	1273	1412			---	1402	1440	1460
B	1290	1270			---	1275	1245	1290
C	1253	1341			1239	---	---	---

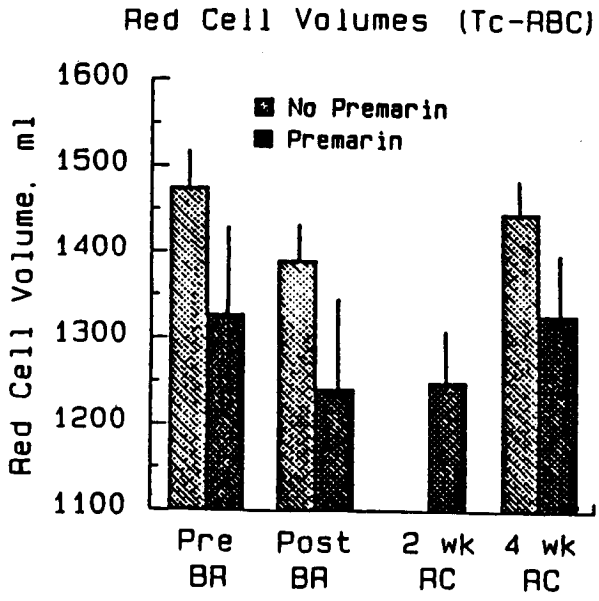

FIGURE 2: The absolute red cell volumes (mean ± SE) determined 24-48 hours before bedrest 1 (PRE BR); 24-48 hours after bedrest 1 (POST BR); and after 2 and 4 weeks of recovery from bedrest (2 wk RC and 4 wk RC) for non-premarin (n = 12) and premarin (n = 7) subjects.

over the course of the duplicate bedrests, was still continuing after 2 weeks of recovery (RCV was now 10.8% lower than at the start of bedrest 1). After 4 weeks of recovery however, the mean RCV was beginning to return toward the prebedrest value. These results suggest that there is about a 2-week delay in the effect of bedrest to alter RCV, and that only after at least 4 weeks of recovery was the RCV no longer significantly different from the prebedrest value.

Although there were were no significant changes in RCV in the premarin group between any of the measurement conditions, the pattern of response was similar to the changes seen in the non-premarin group (see Figure 2).

2) CHANGES IN PLASMA VOLUME DURING BEDREST

The absolute plasma volume values (PV) for all subjects during bedrest are presented in Table 5. These absolute values were calculated from the prebedrest technetium results and the ratio of changes in hematocrit and hemoglobin concentration (see Methods).

i) Non-premarin group, Bedrest 1.

Plasma volume decreased significantly ($P < 0.01$) during the first 5-7 days of bedrest and then became relatively stable for the remainder of the bedrest (see Figure 3). The average decrease in PV was 505 ml (19.9%) between the first and the last day of bedrest.

ii) Non-premarin group, Bedrest 2

The PV at the start of the second bedrest did not differ significantly from the PV at the start of the first bedrest (Table 5). There was a tendency towards a smaller decrease in PV during the second bedrest (averaged 12.3% between day 1 to the last day of bedrest 2) than during the first bedrest (19.9%). However, the difference in plasma volumes between the duplicate bedrests was not significant ($P < 0.05$, determined using a 2-way ANOVA, repeated measures, split plot design, ANOVA-2W-RM-SP).

iii) Effect of menstrual cycle stage on the loss of PV during bedrest

For the non-premarin group, the change in PV was examined in each woman as a function of the stage of the menstrual cycle (see Methods) during the first 5 days of bedrest. There were no significant differences between the decreases in PV during cycle stages 1, 3, and 4. However, if a woman began bedrest in stage 2 of her menstrual cycle, the periovular stage, the decrease in PV was postponed. There was also a tendency for women in the late luteal phase of the cycle (stage 4) to maintain or expand PV during the first 5 days of bedrest, however this was a less consistent finding and was not present in every subject. Shown in Figure 4 are the changes in PV for the six women who began bedrest during year 1. The results shown illustrate PV changes in 3 women who began bedrest in the second menstrual stage (dotted lines), and 3 women who began bedrest in one of the other stages (1,3, or 4). The women who began bedrest in stage 2 showed no significant drop in PV during the first 4 days of

TABLE 5: PLASMA VOLUMES DURING BEDREST

Subject	Bedrest Days 1	2	3	4	5	6	7	8	9	10	11	12
Non-Premarin Group												
Bedrest 1												
1	2625	2547	2339	2266	2078	1924	1646	1706	1999	1661	1948	1981
2	2058	1603	1480	1548	1367	1559	1506	2045	1449	1541	1623	1613
3	2458	2492	1992	1896	2142	1970	1946	2455	1741	1959	2041	2226
4	3011	2614	2326	2049	2017	2074	2212	2027	2007	2022	2203	2418
5	3248	3174	3241	3092	2537	2781	2580	2488	2613	2707	2632	2771
6	2498	2727	2467	2281	1993	2100	2100	1934	1921	2014	2161	2130
7	2112	1542	1770	1748	1939	1681	1437	1596	1570	1635	1675	
8	2999	2888	2786	2843	3079	2611	2457	2373	2730	2672	2484	
9	2670	2672	2762	2940	2898	2376	2485	2567	2382	2757	2367	
10	1892	1789	1596	1415	1330	1370	1548	1497	1466	1403	1409	
11	2297	2217	2101	1675	1643	1698	1758	1670	1710	1680	1734	
12	2511	2415	1770	1660	1660	1856	1875	2010	1872	2053	2052	
$\bar{x}$	2531	2390	2219	2117	2056	2000	1962	2030	1955	2008	2027	
SE	113.68	141.21	147.93	158.43	152.37	116.43	111.38	102.51	117.20	130.34	102.11	
Bedrest 2												
1	2073	2030	1750	1657	1897	2089	1966	1913	2007	1749	2222	2028
2	2015	1862	1608	1672	1751	1690	1748	1740	1965	1739	1779	1824
3	2066	2048	1896	1706	1787	2063	1941	1846	1916	1962	2062	1875
4	2376	2133	1942	2064	1999	2089	2050	2161	2061	2057	2071	2120
5	3283	2930	2992	3480	2977	3012	2999	3034	3146	3014	2922	3029
6	2378	2068	1990	2192	1940	1751	2037	2108	1955	2157	2262	1989
7	2414	1763	2022	1997	2217	1922	1640	1826	1788	1869	1916	
8	2929	2823	2722	2779	3008	2551	2400	2319	2666	2612	2538	
9	2681	2685	2773	2953	2910	2388	2496	2581	2392	2769	2377	
10	2041	1929	1723	1526	1434	1478	1670	1613	1582	1512	1519	
11	2186	2020	2053	1637	1608	1658	1718	1632	1671	1643	1695	
12	2898	2788	2043	1917	1910	2143	2165	2321	2161	2368	2369	
$\bar{x}$	2445	2256	2126	2131	2119	2069	2069	2091	2109	2120	2144	
SE	115.01	116.33	124.28	171.05	150.86	118.27	110.68	116.78	121.78	131.69	107.85	

TABLE 5 (continued)

Subject	Bedrest Days 1	2	3	4	5	6	7	8	9	10	11	12
Premarin Group												
13	2941	2738	2860	2571	2659	3000	2833	3019	2849	2903	2696	3044
14	1708	1634	1501	1569	1545	1498	1523	1653	1695	1674	1563	1576
15	2851	2442	2419	2476	2582	2560	2662	2464	2651	2806	2499	2645
16	2524	2339	2258	2269	2308	2427	2399	2597	2483	2479	2500	2610
17	2253	2164	2242	2234	2328	2281	2149	2361	2451	2406	2374	2395
18	2636	2446	2280	2274	2195	2187	2621	2307	2408	2479	2445	2547
19	2768	2659	2729	2665	2472	2763	2832	2607	2593	2656	2514	2818
$\bar{x}$	2525	2346	2327	2294	2298	2388	2431	2429	2447	2486	2370	2519
SE	149.30	128.65	153.24	125.99	129.35	168.44	163.94	145.05	127.20	140.77	129.16	162.54
A	2599	2775	1869	1721	1768	1760	2742	2056	1894	1988	1932	1950
B	2632	2129	2442	2256	2216	1945	2206	2069	2161	2398	2303	
C	2152	2122	1654	1529	1546	1735	1791	1943	1740	1827	1705	

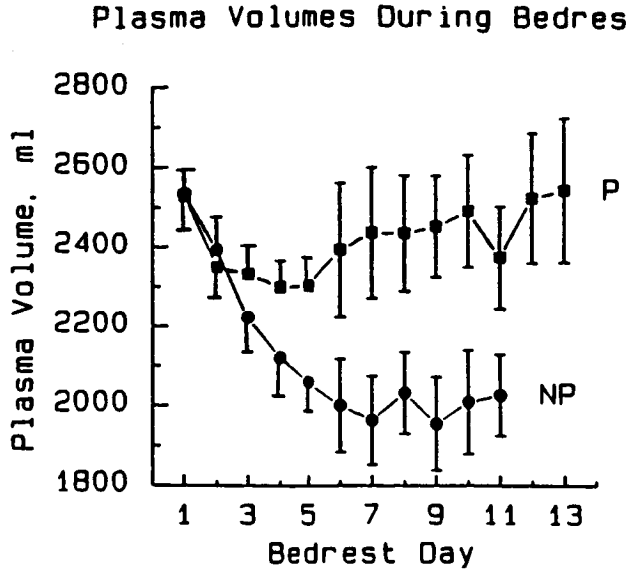

FIGURE 3: Absolute plasma volumes (mean ± SE) during bedrest for the non-premarin group (NP) during bedrest 1 and the premarin group (P).

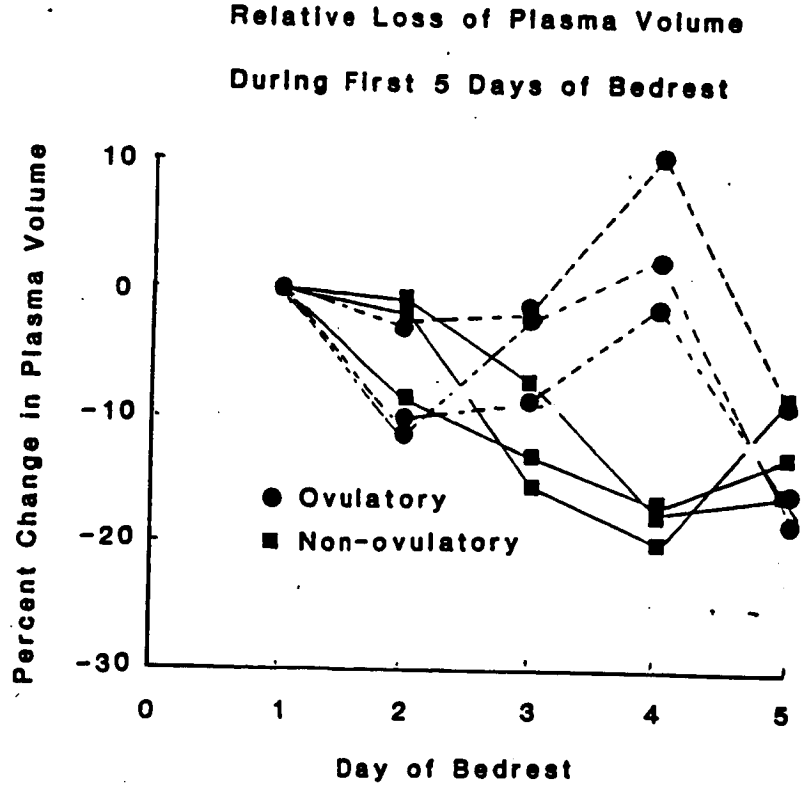

FIGURE 4: Relative changes in plasma volume during the first 5 days of bedrest for 6 subjects (non-premarin) who began bedrest in either the perivular stage (stage 2) of the menstrual cycle, or in a non-ovulatory stage (1,3, or 4).

the bedrest, and in 2 cases, PV even increased above the day 1 PV level. These results led us to revise our initial hypothesis that elevated estrogen levels would be associated with a retention of PV during bedrest. (Blood estrogens would be elevated during stages 3 and 4 as well as during stage 2). Our new hypothesis now stated that, when blood estrogens are elevated in the presence of low progesterone concentrations, the water-retaining effects of the estrogens may, at least temporarily, prevent the hypovolemia which occurs at the beginning of bedrest.

iv) Effect of estrogen-containing oral contraceptives on the PV changes during bedrest.

During the second year of the study, 2 women who were taking oral contraceptives containing synthetic estrogen (mestranol, 80 and 100 mcg/tab) and a progestin (norethindrone or ethynodiol diacetate), performed a single bedrest procedure. The decreases in PV seen in these 2 women (Table 5, subjects B and C), did not differ significantly from the responses seen in the non-premarin group (years 1 and 2). The decrease in PV between the first and last day of bedrest was 20.8% and 12.5% for these two women respectively, with a significant decrease in PV during the first 4-5 days of bedrest. These data suggest that elevations of blood estrogens in the presence of elevated progesterone, may not be associated with a maintenance of PV during bedrest.

v) Effect of Premarin on the change in PV during bedrest

Figure 3 illustrates the mean change in PV from the 12 non-premarin subjects (bedrest 1 data) and the mean change in PV from 7 women who performed an identical bedrest protocol, except that they ingested 1.25 mg/per day of premarin for 7-10 days before bedrest and throughout the bedrest protocol. During the first 2 days of bedrest, the PV decreased in the premarin group in a pattern similar to that seen in the non-premarin group. During the 3rd to 5th day of bedrest, PV remained relatively stable. Then between bedrest days 7-13 (except for day 11), the PV recovered and was not significantly different from the PV of each woman on the first day of bedrest ($P < 0.05$, ANOVA-1W-RM, with the Duncan Multiple Range test to compare for differences between bedrest days).

vi) Changes in PV during recovery from bedrest

Plasma volume recovered to prebedrest levels within 24-48 hours in most subjects. Figure 5 illustrates the mean PV $\pm$ SE, measured with the technetium-labelling technique. Plasma volumes were measured within 48 hours before and 48 hours after bedrest (PREBR and POSTBR) and after 2 and 4 weeks recovery from bedrest. Results are shown for the 12 non-premarin subjects and the 7 premarin subjects.

For the non-premarin group, the F ratio determined from an ANOVA-1W-RM was non-significant ($P< 0.20$), suggesting that the decrease in PV which occurred during bedrest was completely restored within 24-48 hours.

In the premarin group, the F ratio was significant ($P <0.02$).

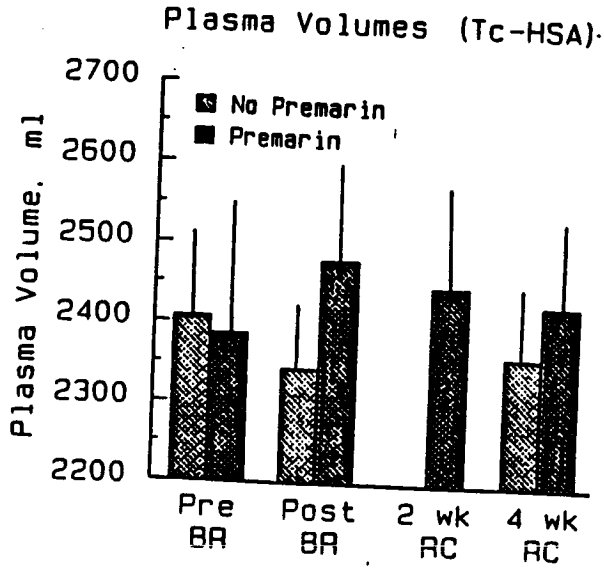

FIGURE 5: Absolute plasma volumes (mean ± SE) determined with the technetium labelling technique 24-48 hours before bedrest 1 (PRE BR); 24-48 hours after bedrest 1 (POST BR); and two and four weeks after the end of bedrest (2 wk RC and 4 wk RC, respectively) for subjects in the non-premarin group (n = 12) and in the premarin group (n = 7).

Further tests (Duncan Multiple Range), concluded that the PV 24-48 hours after bedrest and 2 weeks after bedrest, were significantly greater than the PV before bedrest ($P < 0.05$).

3) CHANGES IN BLOOD PROTEINS AND ELECTROLYTES DURING BEDREST

i) Non-premarin group, bedrest 1

Plasma osmolality increased significantly ($P < 0.01$) during bedrest (see Figure 6) from an average bedrest day 1 value of 279 mosmol/kg, to a highest average value of 287 mosmol/kg, which was measured on the 7th day of bedrest. This increase in plasma osmolality occurred in the presence of an average 18% net loss of total circulating osmotically active particles (TCO) from the plasma in this same interval (see Figure 7). TCO values were significantly lower ($P < 0.05$) than the first day of bedrest from the 3rd to the last day of bedrest.

The plasma total protein concentration increased significantly ($P < 0.01$) during bedrest (Figure 8). At the same time, there was an average 13% net loss of total circulating protein content (TCP), as seen in Figure 9. The above results suggest that during bedrest there was a net loss of hypotonic, protein-poor fluid from the vascular compartment.

ii) Non-premarin group, bedrest 2

A similar increase in plasma osmolality ($P < 0.01$) occurred during the second bedrest (Figure 6) and this increase was accompanied by a significant ($P < 0.01$) decrease in TCO, as seen in Figure 7. The TCO were significantly reduced (Duncan Multiple Range Test) below the values obtained on the first day of bedrest from the second to the last bedrest day.

The plasma total protein concentration did not increase significantly ($P < 0.50$) during the second bedrest (Figure 8), and TCP decreased (average 11.1% decrease between day 1 and the last day of bedrest) in a manner similar to that seen during the first bedrest (Figure 9).

iii) Premarin Group

The mean plasma osmolality increased during bedrest in the premarin group (Figure 10), but the difference was not significant ($P < 0.20$). During bedrest days 2-5, there was a significant ($P < 0.01$) decrease in TCO, but by the end of the bedrest, the TCO value did not differ significantly from the day 1 value (Figure 7).

The increase in plasma protein concentration during bedrest was not significant ($P < 0.50$) in the premarin group (Figure 10), and a transient decrease in the TCP occurred, with average values significantly lower than the first day of bedrest on only the 4th and 5th days of bedrest (Figure 9). Thereafter, the TCP values recovered to eventually exceed the day 1 mean value on the last bedrest day.

4) FLUID INTAKE AND OUTPUT DURING BEDREST

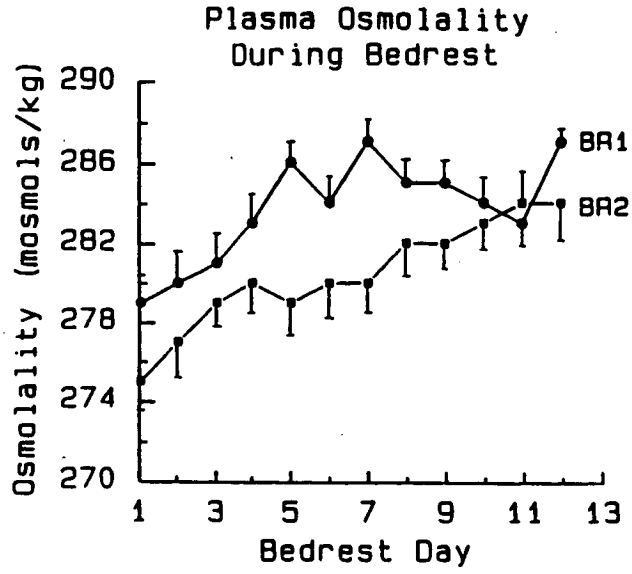

FIGURE 6: Plasma osmolality (mean ± SE) on each day of bedrest for the non-premarin group (n = 12) during bedrest 1 (BR1) and bedrest 2 (BR2).

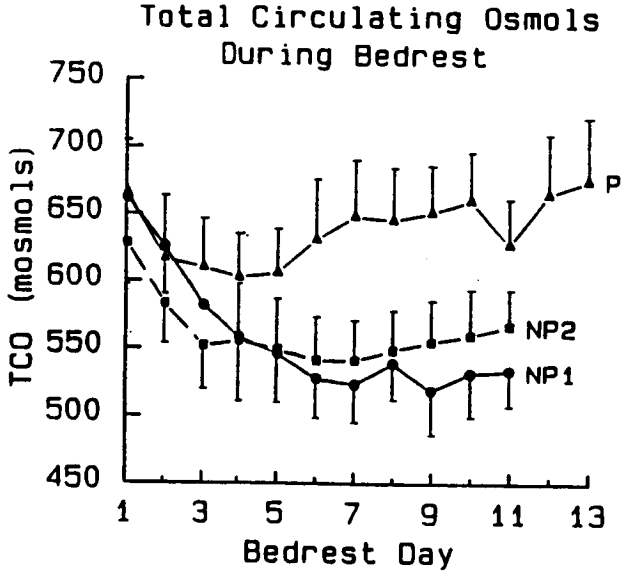

FIGURE 7: Total Circulating Osmols (plasma water x osmolality) mean ± SE, for the non-premarin group (n = 12) during bedrest 1 (NP1) and bedrest 2 (NP2), and in the premarin group (n = 7) during bedrest.

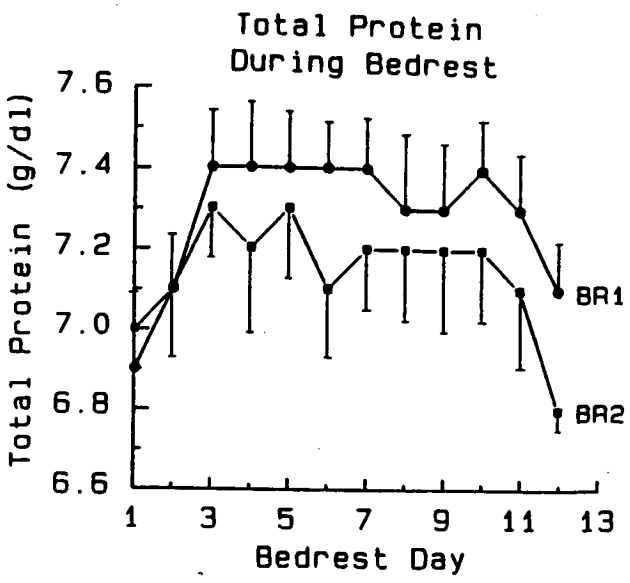

FIGURE 8: Total protein concentration (mean ± SE) during bedrest for the non-premarin group (n = 12) during bedrest 1 (BR1) and bedrest 2 (BR2).

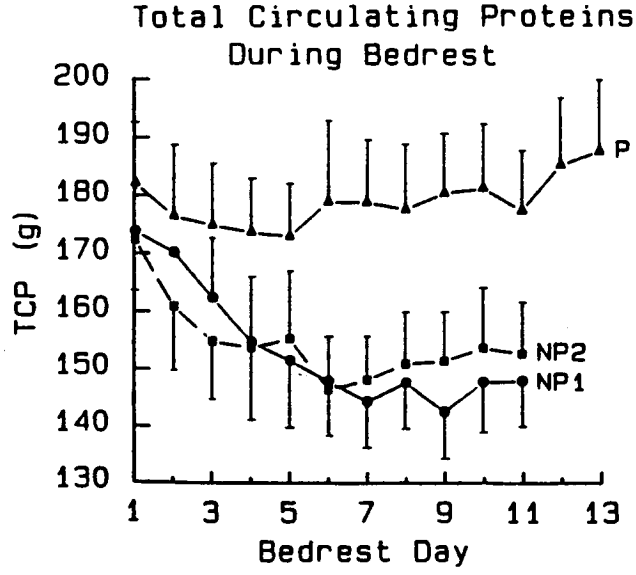

FIGURE 9: Total circulating proteins (plasma volume x total protein concentration), mean ± SE, for the non-premarin group (n = 12) during bedrest 1 (BR1) and bedrest 2 (BR2), and for the premarin group (n = 7) during bedrest.

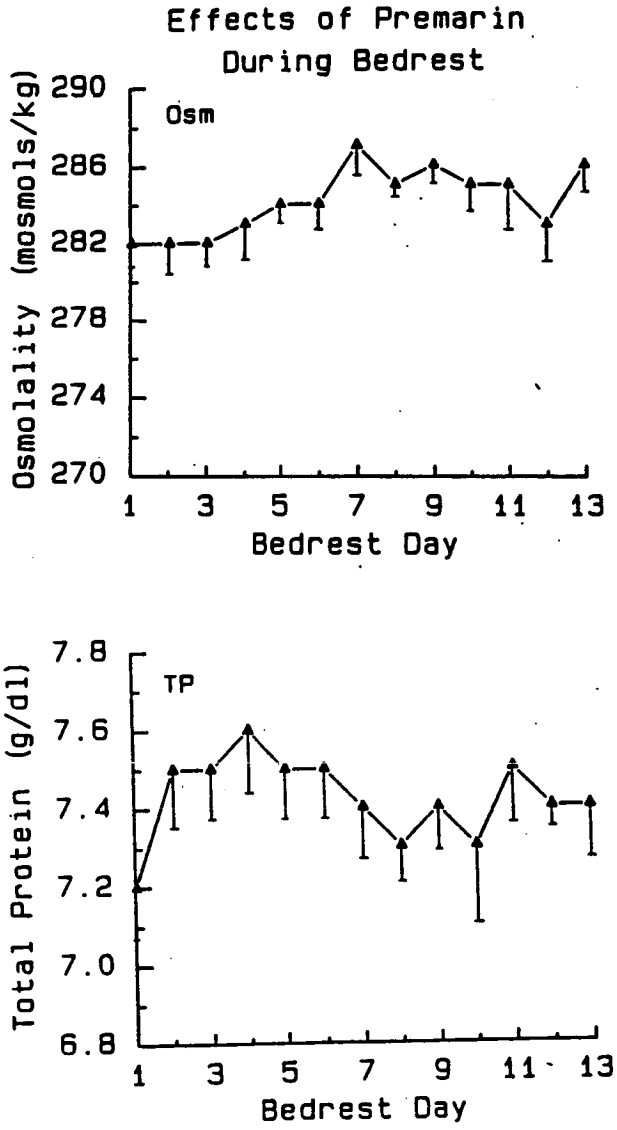

FIGURE 10: Plasma osmolality (OSM, mean ± SE) and total protein concentration (TP, mean ± SE) for the premarin group (n=7) during bedrest.

i) intake

Fluid intake during bedrest was crudely calculated based on the information recorded in each subject's diary. The amount of fluid drunk each day was measured and the water content in the food was estimated. When an ANOVA-1W-RM was performed on the data from each of the bedrests, the differences across bedrest days were not significant during either bedrest 1 of the non-premarin group ($P < 0.10$) or during bedrest in the premarin group ($P < 0.20$). There was a significant difference between fluid intake on various days of bedrest for the non-premarin group during the second bedrest ($P < 0.05$). There was no consistent trend however (Figure 11), with the largest difference seen between bedrest days 6 and 9.

Although there may appear to be a greater fluid intake in the non-premarin group during the second bedrest than during the first bedrest, when an ANOVA-2W-RM-SP was performed to test whether these differences were significant, the differences between bedrest 1 and bedrest 2 were not significant ($P < 0.50$).

ii) urine output

Figure 12 illustrates the changes in 24 hour urine volume during bedrests (the first value does not represent a full 24-hour sample since the early morning urine collection was not included). None of the differences in urine output between bedrest days were significant; for the non-premarin group, bedrest 1 ($P < 0.30$) or bedrest 2 ($P < 0.20$), or for the premarin group ($P < 0.70$). These results represent the data only from years 2 and 3 of this study, since 24-hour urine volumes were not recorded during year 1.

iii) fluid intake - fluid output

The difference between the fluid intake and fluid output was calculated for each woman during bedrest (only data from the second year were used in the non-premarin calculations). This is not a true water-balance calculation, since the output is not corrected for insensible water losses or fluid loss in the stool (both would have to be estimated, and large errors would occur). As seen in Figure 13, during the first 4-5 days of a bedrest, a negative fluid balance was seen in each bedrest condition, with the difference between fluid in and urine out closer to zero during the later days of the bedrests. Differences between bedrest conditions were not significant.

4) URINE OSMOLALITY DURING BEDREST

The osmolalities (mean value $\pm$ SE) determined from the 24-hour urine collections are shown in Table 6. The urine osmolality decreased, especially during the first few days of the bedrests. This difference was significant during bedrest 1 in the non-premarin group ($P < 0.05$), but not significant during the second bedrest ($P < 0.20$). The changes in urine osmolality during bedrest in the premarin group were not significant ($P < 0.70$).

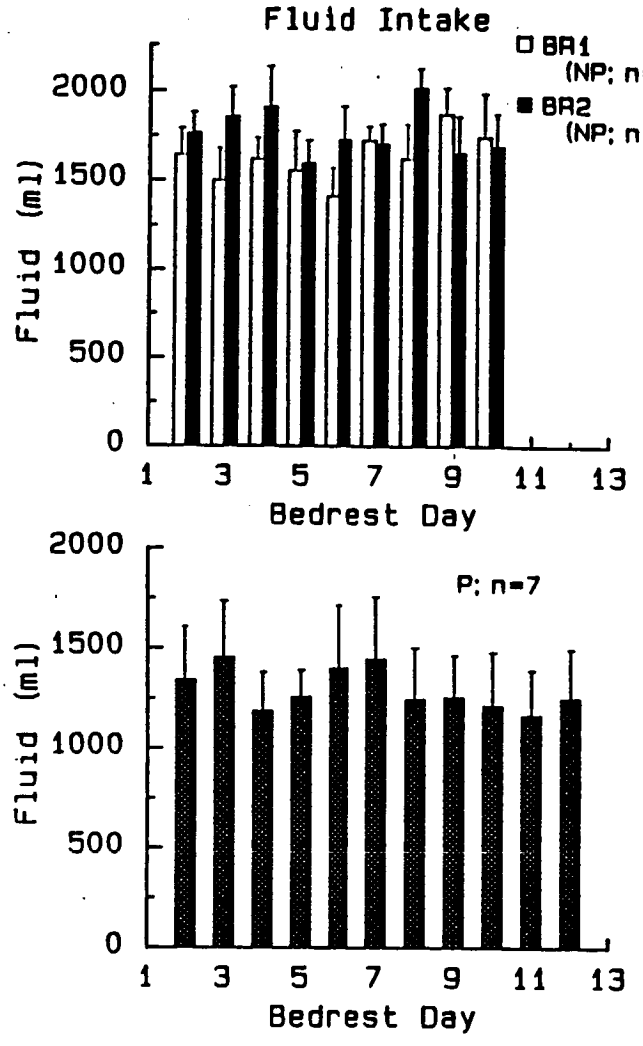

FIGURE 11: Fluid intake (mean ± SE) during bedrest for the non-premarin group (NP) during bedrest 1 (BR1) and bedrest 2 (BR2), and for the premarin group (P). Fluid intake was estimated from the fluid and food entries in each subject's diary.

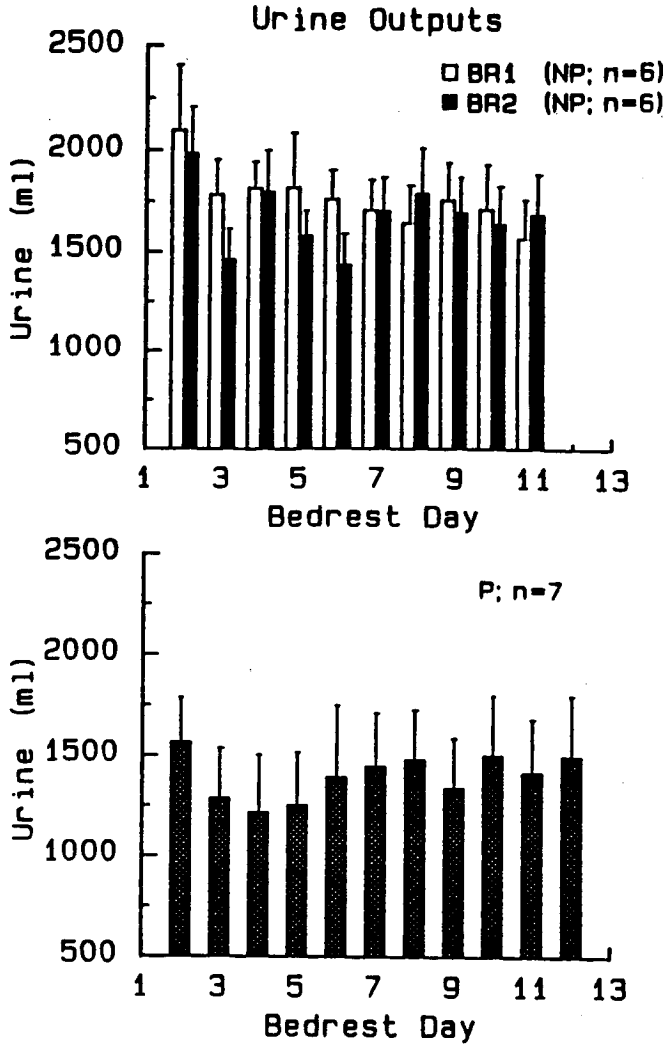

FIGURE 12: Urine output (mean ± SE) during bedrest for the non-premarin group (NP) during bedrest 1 (NP1) and bedrest 2 (NP2), and for the premarin group (P) during bedrest.

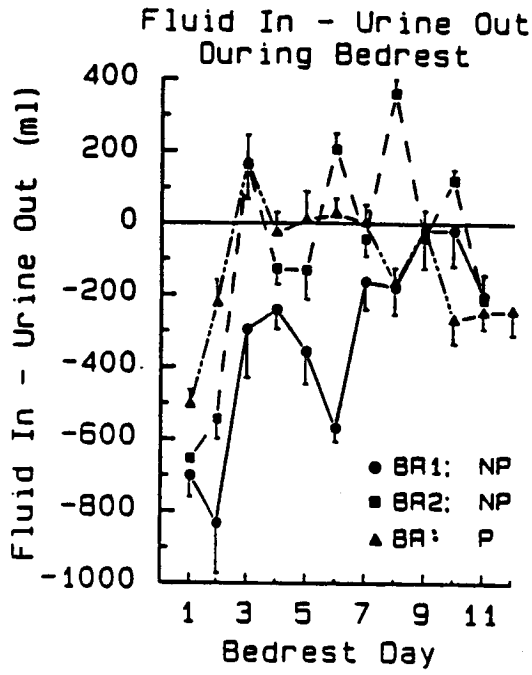

FIGURE 13: Fluid in - fluid out (mean ± SE) for the non-premarin group (NP, n = 6) and the premarin group (P, n = 7) during bedrest.

TABLE 6: URINE OSMOLALTIES DURING BEDREST (mean values ± SE)

Day of Bedrest	1	2	3	4	5	6	7	8	9	10	11	12
Non Premarin												
Bedrest No. 1												
Mean	594	439	386	411	335	431	405	390	435	386	440	412
SE	80	50	54	73	43	57	68	46	57	55	41	56
Bedrest No. 2												
Mean	439	365	411	452	402	452	539	451	509	408	474	507
SE	69	50	73	69	67	55	63	55	60	75	81	72
Premarin												
Mean	475	403	494	470	505	523	525	436	542	395	515	500
SE	51	69	43	98	60	107	80	86	76	77	103	90

B) MAXIMAL EXERCISE RESPONSES

i) Effect of menstrual cycle

For the non-premarin subjects, there were at least 5 determinations of maximal oxygen consumption (VO2 max) which were performed during varying stages of each woman's menstrual cycle, and which would not have been affected by bedrest. These tests included control months (C1 and C2), prebedrest tests (PREBR1 and PREBR2), and the 4 wk recovery from bedrest. The data from these tests were compared for each woman, averaging the VO2 max data from tests done in the luteal and follicular phases. The results are shown in Table 7. There was no significant difference in VO2 max in these women between these 2 stages of the menstrual cycle ($P < 0.70$).

ii) Non-premarin group, Bedrest 1

The VO2 peak value obtained following the first bedrest was significantly reduced from the prebedrest value, whether the results were expressed as liters of O2 consumed per minute (average decrease of 11.2%), or corrected for body mass by dividing the peak O2 consumption by body weight (10.4%), as shown in Table 8.

iii) Non-premarin group, Bedrest 2

Following the second bedrest however, the reduction in VO2 peak was not significant either when expressed as l/min (average decrease of 4.1%) or as ml/min/kg body weight (average decrease of 4.3%).

iv) Premarin group

The decrease in VO2 peak following bedrest in the premarin group was significant ($P < 0.01$) and averaged 21.6% (l/min) and 24.5% (ml/min/kg body weight). There was considerable variability in this decrease in VO2 peak however between subjects, and thus the decrease in VO2 peak between the premarin group and the decrease seen in the non-premarin group after the first bedrest was not significant (t-test comparison).

v) Recovery Data

VO2 max was almost completely recovered to the prebedrest level by 2 weeks of recovery from bedrest (see Table 8) and this difference was not significant ($P < 0.01$) for either the non-premarin or the premarin groups. Also no significant differences were seen between 2 and 4 week recovery comparisons, prebedrest and 4 wk recovery comparisions, or control and recovery tests.

vi) Correlation between the Pre-Bedrest VO2 max and the % decrease in VO2 peak following bedrest 1.

Linear regression analysis was performed to determine the slope and correlation for the relationship between the prebedrest fitness level of each subject (prebedrest VO2 max), and the reduction in VO2 peak. The calculations were performed on the non-premarin group for both the first and the second bedrests. The regression equations and

TABLE 7:

MENSTRUAL CYCLE COMPARISON OF VO_2MAX: COMBINED DATA FOR ALL PRE-BEDREST, AND 4, 6, AND 8 WEEKS AFTER BEDREST DATA.

SUBJECT	FOLLICULAR STAGE (VO_{2MAX})	LUTEAL STAGE VO_2MAX
1	37.8 (N=2)	36.6 (N=3)
2	44.6 (N=4)	47.0 (N=1)
3	39.8 (N=4)	44.0 (N=1)
4	43.7 (N=2)	42.0 (N=2)
5	31.3 (N=3)	31.6 (N=2)
6	40.2 (N=3)	39.9 (N=2)
7	26.4 (N=1)	27.4 (N=2)
8	40.8 (N=1)	42.9 (N=2)
9	36.4 (N=2)	35.2 (N=1)
10	45.8 (N=1)	41.2 (N=2)
11	38.9 (N=2)	33.5 (N=1)
12	35.7 (N=1)	35.0 (N=2)
$\bar{X}$	38.5	38.0
STANDARD DEVIATION	5.5	5.7
STANDARD ERROR	1.5	1.6

NS ($P < 0.70$) PAIRING DESIGN TEST

MENSTRUAL CYCLE STAGE WAS VERIFIED FOR EACH WOMAN FROM RECORDS OF MORNING TEMPERATURE, FROM PERSONAL DIARIES, AND FROM BLOOD ESTROGEN/PROGESTERONE CONCENTRATIONS

TABLE 8: VO_{2max} and VO_2 PEAK RESULTS

Subject	Pre BR1	Post BR2	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1	33.2	33.5	34.3	34.6	35.8	36.8	42.2	38.7
2	37.1	38.7	40.3	39.7	41.0	47.2	47.0	51.9
3	34.7	31.1	35.5	31.7	38.3	44.0	46.9	42.0
4	44.4	41.1	42.9	46.2	42.7	40.8	43.1	47.0
5	28.4	26.2	32.1	31.4	28.8	32.1	33.4	31.0
6	40.1	38.0	42.0	37.9	38.8	39.1	38.4	40.7
7	28.5	24.4	26.3	26.0	26.3	26.4		
8	42.5	36.7	43.2	36.8	41.2	40.8		
9	36.8	32.1	36.0	32.3	35.4	35.2		
10	45.8	37.6	44.9	37.4	39.5	37.4		
11	41.7	28.9	33.5	34.9	33.6	36.1		
12	36.7	34.7	33.2	35.4	33.9	35.7		
$\bar{x}$	37.4	33.5	37.0	35.3	36.2	37.6	41.8	41.8
SD	5.46	4.99	5.39	4.79	4.81	5.19	4.79	6.53
Premarin Group								
13	30.8	26.3						
14	28.3	22.2						
15	28.4	16.3						
16	44.6	35.5						
17	44.7	36.4						
18	43.6	31.0						
19	40.1	28.7						
x	37.2	28.0						
SD	7.15	6.65						
A	27.2	27.3			26.4	30.2	29.3	27.2
B	26.9	27.3			28.4	27.3	26.8	26.9
C	36.0	29.0			39.3	40.5	39.4	36.0

correlations are shown below:

Bedrest 1, VO2 values expressed as l/minute.

$y = -17.8x + 29.1$. $r = -0.48$.

Bedrest 1, VO2 values expressed as ml/min/kg

$y = -4.6x + 6.0$ $r = -0.12$

Bedrest 2, VO2 expressed as l/minute

$y = -0.49 + 8.3$ $r = -0.31$

Bedrest 2, VO2 expressed as ml/min/kg

$y = -0.20 = 2.9$ $r = -0.27$

C) SUBMAXIMAL EXERCISE RESULTS

i) Exercise duration

The total exercise times during the submaximal tests are listed in Table 9. During control or prebedrest tests, the exercise duration was about 30 minutes. Occasionally, there was difficulty obtaining the final 30 minute blood sample, and the exercise time was prolonged by one or two minutes. For tests in which the exercise was stopped earlier, the subject's heart rate exceeded 95% of her prebedrest maximal heart rate, which was measured during VO2 max determination. The only exception was subject 17, who was stopped during her postbedrest and recovery tests because of the core temperature limitation. (An exercise test is immediately terminated if core temperature exceeds 39 degrees C).

The average exercise times in the prebedrest and control tests were all between 28 and 30 minutes. Following bedrest however most women could not finish the entire protocol without reaching the heart rate or core temperature criteria. The average exercise duration for the non-premarin group was 21 minutes for both the postbedrest 1 and postbedrest 2 tests. A similar decrease in exercise duration occurred following bedrest in the premarin group (the postbedrest duration averaged 16.9 minutes).

Most of the women in the non-premarin group completed the 30-minute exercise test after both 2 and 4 weeks of recovery from bedrest. For the premarin group, 4 of the women were told to stop exercise early during the 2 week recovery tests, and 3 stopped early during the 4 week recovery test.

ii) Changes in plasma volume during exercise tests

Plasma volume decreased significantly ($P < 0.01$) in all tests during exercise. Figure 14 illustrates the PV changes which occurred in the non-premarin group during the pre and postbedrest tests. Plasma volume decreased rapidly with the onset of exercise, with most

TABLE 9: EXERCISE ENDURANCE TIMES

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK RC	4-WK RC	C1	C2
Non-Premarin Groups								
1	30	30	30.5	30	29.5	30	30	31
2	30	13	30.5	14.3	29	27	29.5	31
3	30	12	30	12.3	29.7	16.5	20	30
4	30	20.5	30	14	15	13	16.7	25.5
5	30	22	30	14	31.3	30	30	30
6	30	20.5	33.3	22	29.5	30	30	29.7
7	30	19	29.5	16	30	30	30.5	30
8	30	20	30	30	30	30	30	30.7
9	30	21.5	30	25.5	30	30	31	30
10	30	26	30	25.5	30	30	30.5	30
11	30	28	30	17.3	30	30	32	30
12	30	21	30	30	30	30	30.5	30
$\bar{x}$	30	21.1	30.3	20.9	28.3	27.2	28.3	29.8
SD	0	5.0	0.9	6.7	4.1	5.6	4.5	1.3
Premarin Group								
13	30	16			30.5	30	30.5	30
14	30	11.5			23.5	16	30	30
15	30	26.5			31	30	30	30
16	29.5	10			13.5	24	30	29.5
17	30	17.5			20.5	22	30	30
18	30	25			25	31	30	30
19	30	12			30	30	30.5	30
$\bar{x}$	29.9	16.9			24.8	26.1	30.1	29.9
SD	0.1	6.0			5.9	5.2	0.2	0.1
A	32.5	22.5			--	32.5	30.1	30
B	30	21.7			30	34.5	30	34
C	30	18			30	30	30	--

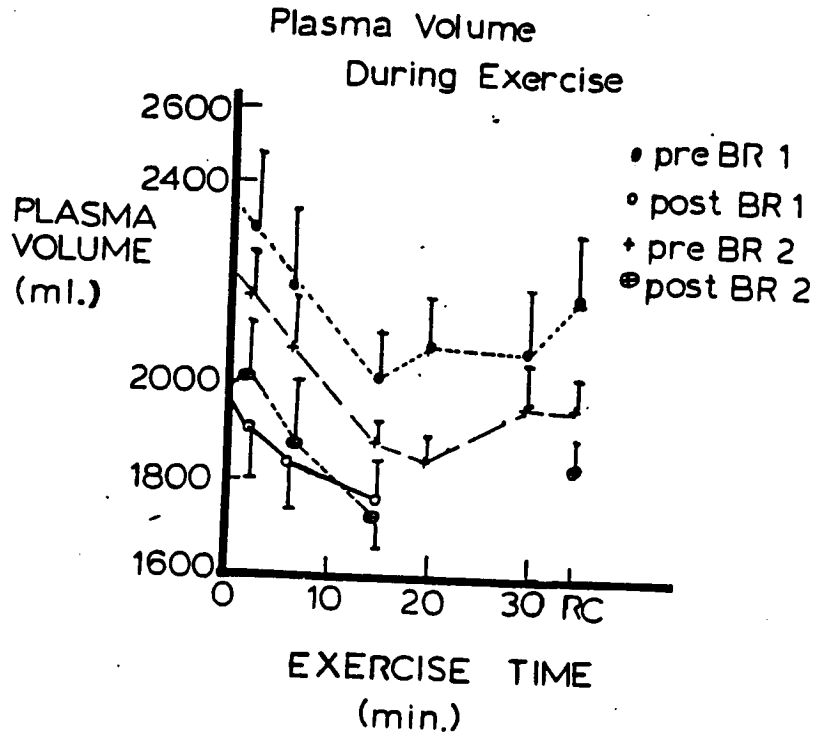

FIGURE 14: Absolute plasma volume (mean ± SE) during the submaximal exercise tests for the non-premarin group (n = 12) during the pre and postbedrest tests before or after bedrest 1 and bedrest 2.

of the changes occurring within the first 10-15 minutes. Thereafter, the decrease in PV was attenuated, and even in some subjects partially recovered. Significantly smaller PV were seen during postbedrest tests than during prebedrest tests in the non-premarin group ($P < 0.01$). Absolute PV did not differ significantly ($P < 0.50$) in the premarin group between the pre an postbedrest tests (Figure 15).

A similar pattern of plasma volume decrease during exercise occurred during all exercise conditions despite the significant differences in absolute PV. Figure 16 illustrates the changes in plasma volume during the pre and postbedrest exercise tests, where the data are presented as the % change in PV (% difference from the resting sample). The decrease in PV during bedrest was significant ($P < 0.01$) for each exercise test condition (PREBR, POSTBR, C1, C2, 2wk RC, 4wk RC). However a comparision of the % changes in PV between the pre and postbedrest results (ANOVA-2W-RM-SP) was non-significant ($P < 0.10$) for non-premarin bedrests 1 and 2 as well as for the premarin results ($P < 0.10$).

iii) Changes in blood electrolytes and proteins during exercise tests

Plasma osmolality increased during all exercise tests ($P < 0.01$). Figure 17 (upper panel) illustrates the increase in plasma osmolality during exercise for the non-premarin group, comparing pre and postbedrest results. The bottom panel of this same figure illustrates the changes for the premarin group. An ANOVA-2W-RM-SP was used to compare the differences in osmolalities between pre and postbedrest conditions. Non-significant differences between the pre and postbedrest tests occurred in the non-premarin group during both the first ($P < 0.80$) and second ($P < 0.90$) bedrests, and also between pre and postbedrest tests in the premarin group ($P < 0.70$).

Total protein concentration increased significantly ($P < 0.01$) during each exercise test. Figure 18 (upper panel) illustrates these changes in total protein concentration for the non-premarin group during the pre and postbedrest tests (bedrests 1 and 2). During the first bedrest, the total protein concentrations were significantly higher ($P <0.05$) during the postbedrest test than during the prebedrest test. During the second bedrest, though the average total protein concentration was higher at each exercise interval, this difference was not significant ($P < 0.30$).

In the premarin group, an increase in total protein concentration occurred during the exercise tests. There were no significant ($P < 0.10$) differences in these protein values between the pre and postbedrest tests.

iv) Cardiovascular responses during exercise

Exercise heart rates

Figure 19 illustrates the exercise heart rates during the pre and postbedrest exercise. The exercise heart rate following bedrest was significantly higher than the prebedrest value for the non-premarin group following bedrest 1 ($P < 0.05$), but not quite significant following bedrest 2 ($P < 0.10$). During the 2 and 4 week recovery

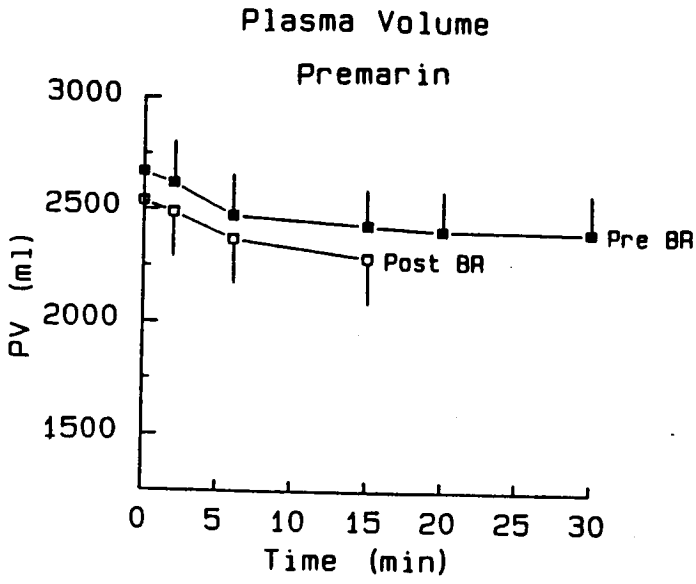

FIGURE 15: Absolute plasma volume (mean ± SE) during the submaximal exercise tests for the premarin group (n = 7) during the pre and postbedrest tests.

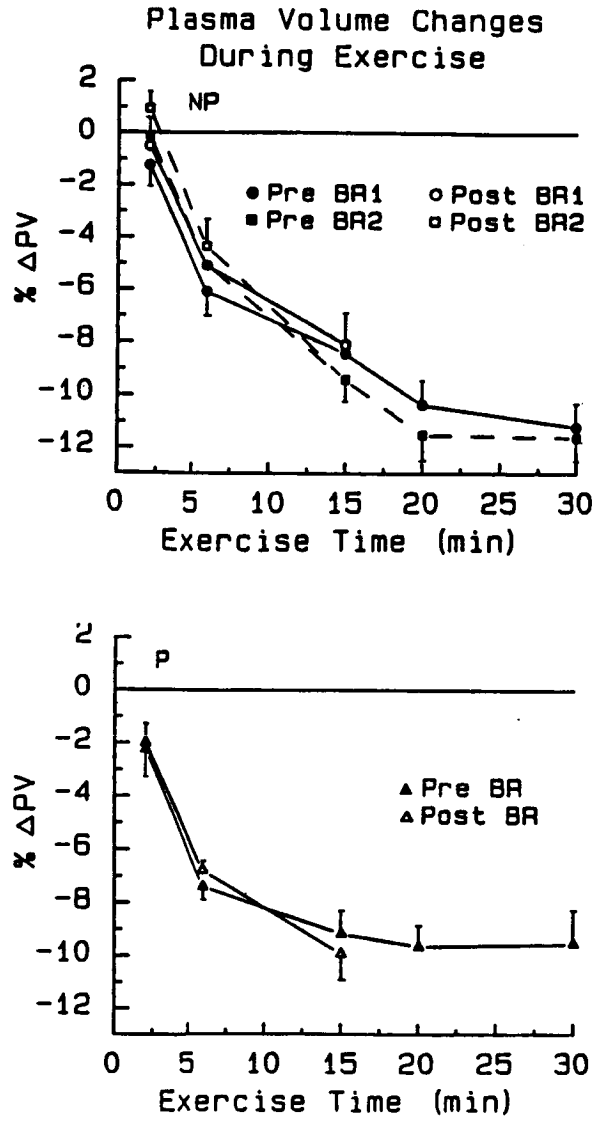

FIGURE 16: The percent changes in plasma volume (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and for the premarin group (P, n = 7) before and after bedrest.

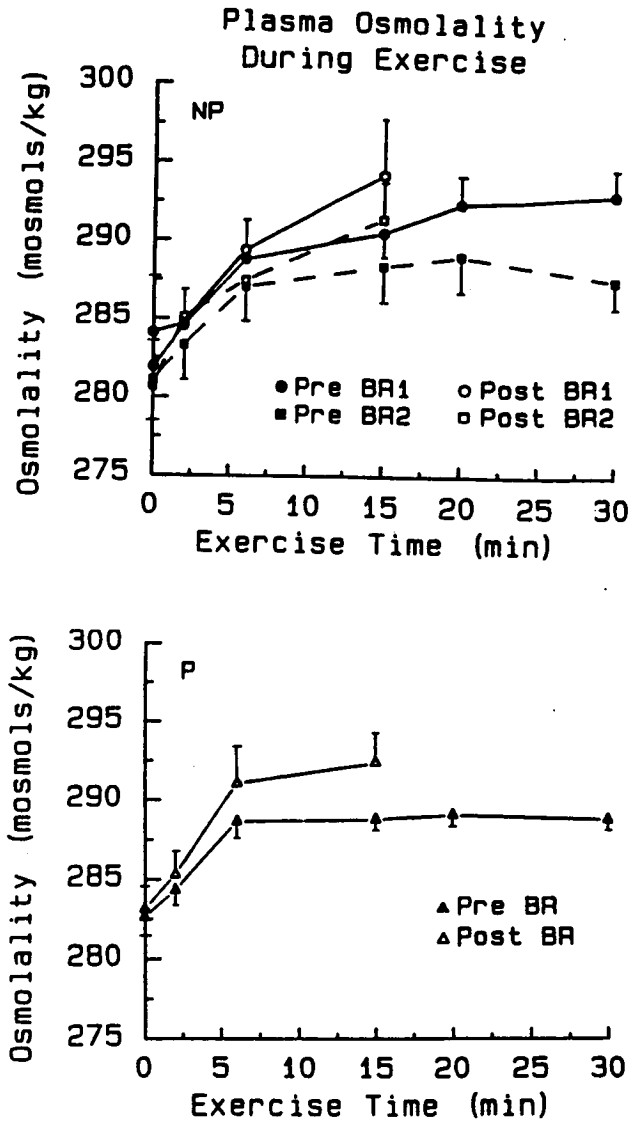

FIGURE 17: Plasma osmolality (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and in the premarin group (P, n = 7) before and after bedrest.

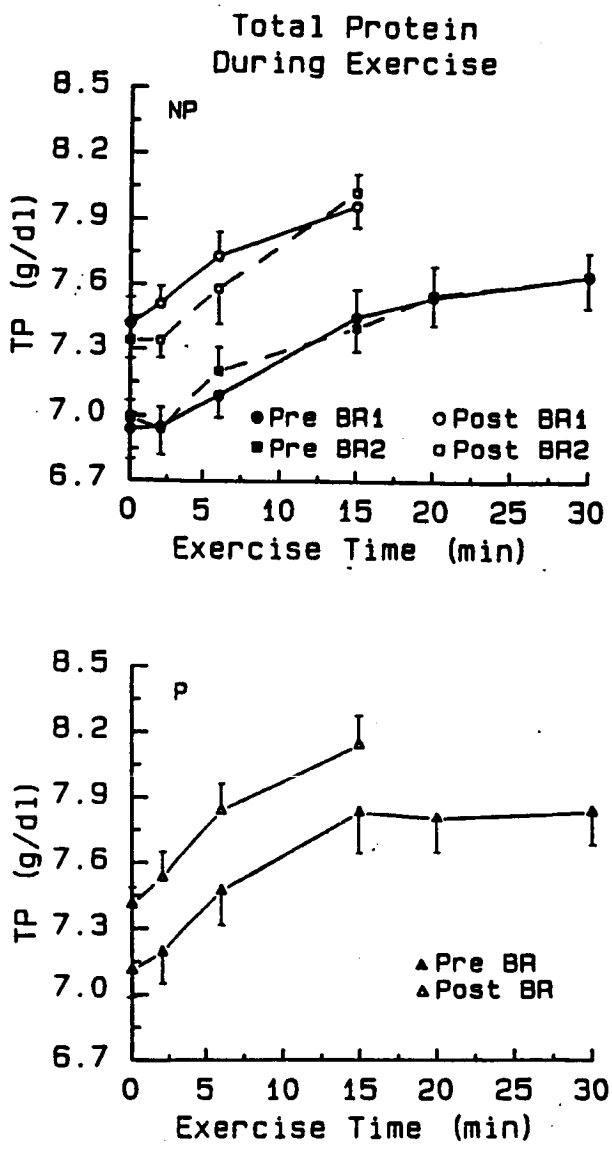

FIGURE 18: Total protein concentration (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and for the premarin group (P, n = 7) before and after bedrest.

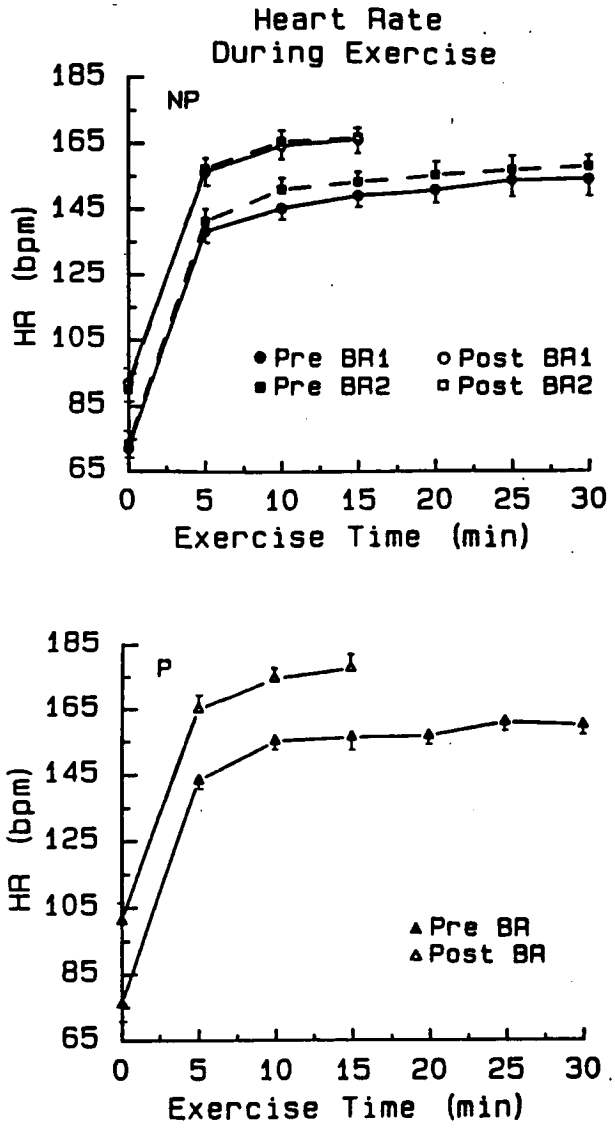

FIGURE 19: Heart rate (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and for the premarin group (P, n = 7) before and after bedrest.

exercise tests, the exercise heart rates were not significantly different from the prebedrest tests ($P < 0.10$) for the 2 week recovery test, and $P < 0.50$ for the 4 week recovery comparison. The heart rate responses between the two prebedrest tests did not differ significantly ($P < 0.50$).

For the premarin group, heart rate changes similar to those seen in the non-premarin group occurred. Following bedrest, exercise heart rates were significantly higher than during the prebedrest test ($P < 0.05$). The exercise responses seen during the 2 and 4 week recovery tests did not differ significantly from the prebedrest test ($P < 0.30$ for the 2 week recovery test, and $P < 0.80$ for the 4 week recovery test).

In both the non-premarin and the premarin groups, the postbedrest heart rate was higher (paired t-test comparision, $P < 0.05$) than the prebedrest value even before the start of the exercise.

Exercise Cardiac Outputs

Cardiac outputs were performed at 4 exercise intervals; after 10, 15, 20, and 25 minutes of exercise. As there were no significant differences between the sampling times ($P < 0.05$), all cardiac outputs from a given test were averaged and these mean values are presented for each subject in Table 10.

No significant differences occurred for either the non-premarin, or the premarin group between experimental conditions. An ANOVA-1W-RM was performed on each set of data, where the F ratio for the non-premarin group was 1.83 ($P < 0.10$, $n = 77$), and for the premarin group was 1.75 ($P < 0.20$, $n = 30$). Thus cardiac output did not differ significantly during exercise after bedrest or during any of the recovery tests.

Exercise stroke volumes

Stroke volumes were calculated by dividing the cardiac output by the heart rate during the rebreathing technique. The values shown in Table 11 are the average stroke volumes, calculated from the cardiac outputs performed during the submaximal exercise tests.

Significant differences in exercise stroke volumes occured in the non-premarin group (ANOVA-1W-RM), where the F ratio was 3.05, significant at the $P < 0.02$ level. Post hoc analysis (Duncan Multiple Range Test) found that the stroke volumes during the postbedrest 2 test were significantly lower than stroke volumes during either prebedrest 1 or 2 tests. Stroke volumes were lower during postbedrest 1 tests than during the prebedrest 1 condition for 10 out of 12 subjects. However this difference was not significant at the $P < 0.05$ level.

For the premarin group, the F ratio was 7.63, significant at the $P < 0.01$ level. A post hoc analysis (Duncan Multiple Range Comparison) determined that stroke volumes were significantly lower during postbedrest tests than during prebedrest tests ($P < 0.05$). No significant differences occured between prebedrest and recovery or

TABLE 10: MEAN CARDIAC OUTPUT VALUES
(ml/min)

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1	13548	13041	10592	10157	12583	10512	8517	11083
2	11254	8965	10021	10367	11852	12647	11684	9160
3	9804	11517	10663	11126	10171	9211	13985	12081
4	9017	12459	10380	12023	12448	9023	8953	9305
5	11840	12145	14644	8738	12506	14023	12112	7573
6	14261	15305	13110	16982	14955	13681	13195	13392
7	10314	11005	11791	10345	12475	11833	12120	10314
8	12374	12799	9838	9194	11673	10630	12988	12374
9	15803	14207	14630	11630	14124	14165	15289	15803
10	10298	10730	11726	9130	12223	10519	11709	10298
11	11050	12239	9539	8699	12771	10527	10671	11050
12	13205	12322	10457	11360	12154	9302	13595	13205
$\bar{x}$	11897	12227	11449	10812	12494	11339	12068	11303
SE	555	451	490	621	327	521	546	615
Premarin Group								
13	10521	9571			9077	8360	9219	10521
14	8997	7673			7142	7386	5934	8997
15	9438	9771			9662	9426	10235	9438
16	11673	11902			11354	7156	11495	11673
17	12437	11728			11335	12003	11891	12437
18	13920	12327			13634	12903	14793	13920
19	9970	7584			10420	10934	10951	9970
$\bar{x}$	10993	10079			10374	9738	10645	10993
SE	470	297			547	605	723	470
A	11866	11456			13082	6316	11093	11866
B	9340	8841			13082	10560	10696	10911
C	11171	7951			10365	9570	9570	--

TABLE 11: STROKE VOLUMES DURING EXERCISE
(ml)

Subject	Pre BR1	Post BR2	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1	96	85	78	68	81	76	56	81
2	85	63	70	65	72	78	71	59
3	58	64	63	64	59	51	78	67
4	55	75	71	68	73	53	52	53
5	75	69	79	49	70	82	74	46
6	97	96	95	101	93	88	85	91
7	70	69	75	64	84	83	82	70
8	74	70	65	55	67	65	74	74
9	109	89	106	72	99	97	106	109
10	73	63	75	55	76	66	76	73
11	76	74	61	50	78	64	74	76
12	91	77	90	74	78	63	88	91
$\bar{x}$	80	74	77	*65	78	79	76	74
SE	4	4	4	4	3	4	4	5
Premarin Group								
13	69	55			59	56	59	69
14	53	42			41	45	35	53
15	62	59			60	60	65	62
16	70	65			64	43	70	70
17	72	64			65	69	65	72
18	90	69			79	84	80	90
19	67	44			69	75	74	67
$\bar{x}$	69	*57			73	62	64	69
SE	4	4			4	5	5	4
A	69	60			80	102	68	78
B	59	51			83	83	67	66
C	78	48			65	73	65	78

* Significantly different from pre-bedrest value.

control tests.

v) Thermoregulatory responses

a) Thermoregulatory responses as a function of menstrual cycle phase

Data from the control and prebedrest tests from this study were combined with other data collected in a separate study to analyze the effect of menstrual cycle phase on thermoregulatory responses. Using each woman as her own control, 8 normally cycling women were studied in the follicular and luteal phases of their menstrual cycles. We reported no significant differences in body temperature responses during exercise (except for the expected increase in body core temperature in the luteal phase), and no differences in either total body sweat losses or local sweating responses (see abstract entitled " Thermoregulatory response to exercise at different phases of the menstrual cycle" in Appendix 3.

b) Effect of Premarin on thermoregulatory responses

The control and prebedrest data from the women in this study were used to test the effect of premarin on thermoregulatory responses. Five women in this study performed the control exercise tests without taking either oral contraceptives or premarin. Each woman also performed premarin exercise tests, after ingesting 1.25 mg premarin for 7-10 days. We reported no significant alteration in body temperatures, skin conductances, total body sweat loss, sweating sensitivity or sweating threshold with the use of premarin (see abstract entitled "The lack of an affect of elevated estrogens on exercise thermoregulation" in Appendix 3).

c) The effect of bedrest on esophageal temperature during exercise - non-premarin group

The esophageal temperatures (Tes, mean $\pm$ SE) during the submaximal exercise tests are illustrated in Figure 20. During each submaximal test there was a significant increase in the Tes during exercise. During the first bedrest, the Tes values during the postbedrest exercise were significantly higher ($P < 0.05$) than the temperatures during the prebedrest condition (ANOVA-2W-RM-SP). No significant differences were seen between the prebedrest and the 2 week ($P < 0.70$) or the 4 week ($P < 0.90$) recovery tests. Even before the start of exercise, the resting Tes in the postbedrest test was significantly higher (paired t comparison, $P < 0.05$) than the comparable prebedrest value.

Although Tes values were consistently higher during all postbedrest tests, these differences were not significant ($P < 0.90$ for the pre to postbedrest 1 comparison, and $P < 0.20$ for the pre to postbedrest 2 comparison). The difference between the pre and postbedrest Tes values after 15 minutes of exercise (the last value obtained in most postbedrest tests) was significantly higher than the prebedrest Tes at the same time interval (paired T comparision, $P < 0.01$). Thus during the postbedrest tests, Tes values were not significantly

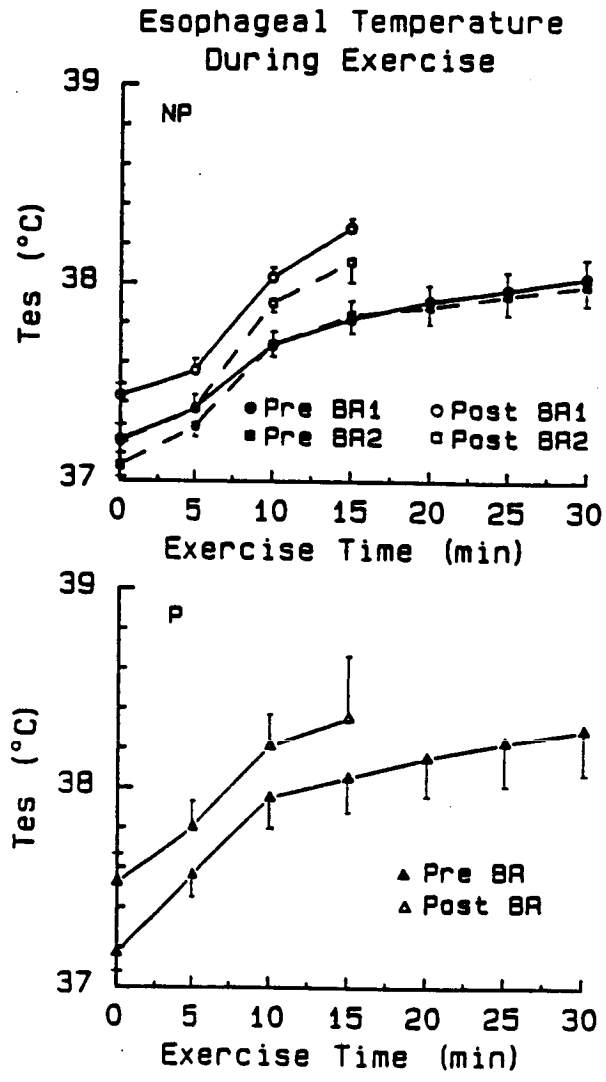

FIGURE 20: Esophageal temperatures (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and for the premarin group (P, n = 7) before and after bedrest.

higher than the prebedrest values during the beginning minutes of the exercise test, but by the end of the test they were significantly higher.

Esophageal temperatures during submaximal exercise, premarin group

No significant differences occurred between the Tes responses of the prebedrest and the 2 or 4 week recovery tests. Although the resting postbedrest Tes was significantly higher than the prebedrest resting value ($P < 0.05$), as the exercise continued the differences between the pre and postbedrest values were no longer significant ($P < 0.09$, ANOVA-2W-RM-SP). Although the mean Tes at each exercise interval was consistently higher in the postbedrest tests (Figure 20), even a comparision of the 15 minute values (paired t comparison, $P < 0.09$) showed a non-significant difference between the pre and postbedrest Tes values.

d) Mean Skin Temperatures During the Submaximal exercise tests, non-premarin group

The mean skin temperature was calculated from 4 skin sites (Methods) and are illustrated in Figure 21. Although the mean skin temperatures during the prebedrest tests (both first and second bedrest) decreased during the exercise tests, while the postbedrest values either did not change or increased slightly, there was considerable variability among the individual responses. For any given exercise condition, the changes in mean skin temperature during exercise were not significant; prebedrest 1, $P < 0.80$; prebedrest 2, $P < 0.50$; postbedrest 1, $P < 0.70$; postbedrest 2, $P < 0.70$. No significant differences occurred in mean skin temperature responses between any of the exercise conditions (ANOVA-2W-RM-SP), $P < 0.20$).

Mean Skin Temperatures during Submaximal Exercise Tests, premarin group

The pattern of change in mean skin temperature during the exercise tests appeared different from the pattern seen for the non-premarin group. Again, there was considerable variability among subjects, and the increase in mean skin temperature during exercise (Figure 21, bottom panel) was not significant during either the prebedrest ($P < 0.20$) or the postbedrest ($P < 0.50$) condition. No significant differences occurred in mean skin temperature response between any of the exercise conditions (ANOVA-2W-RM-SP), $P < 0.50$).

e) Total body sweat losses during submaximal exercise tests

Total body weight loss was used as an estimate of the total sweat loss during the submaximal exercise tests. The change in body weight (in grams) during exercise was divided by the number of minutes of exercise and by the surface area of each woman (from Dubois nomogram based on height and weight). The results presented in Table 12 are the sweat rate results (g/min/m2 body surface area) obtained during each exercise test.

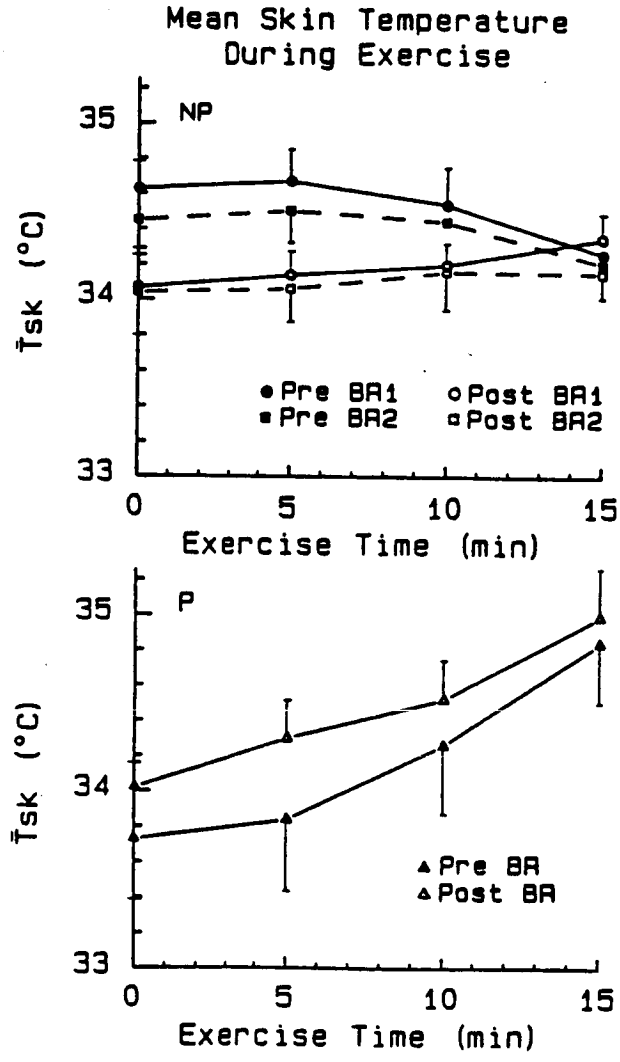

FIGURE 21: Mean skin temperature (mean ± SE) during the submaximal exercise tests for the non-premarin group (NP, n = 12) before and after bedrest 1 and bedrest 2, and for the premarin group (P, n = 7) before and after bedrest.

TABLE 12: TOTAL BODY SWEAT LOSS

($g/min/m^2$)

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1	11.33	8.97	11.63	9.92	11.68	10.00	9.56	11.33
2	12.66	17.79	13.28	17.92	12.24	10.97	11.31	12.66
3	9.79	19.22	11.46	14.99	11.15	14.47	15.22	9.79
4	13.35	14.72	16.28	16.65	16.89	19.54	17.08	13.35
5	8.58	8.48	7.74	12.14	16.62	9.36	8.65	8.58
6	14.94	13.71	7.82	5.22	8.99	8.50	11.87	14.94
7	10.36	13.24	15.93	16.09	15.17	13.05	12.17	10.36
8	7.57	10.19	8.99	9.54	9.78	8.77	8.82	7.57
9	10.31	12.59	9.58	14.30	9.80	8.73	10.52	10.31
10	9.44	12.79	10.67	10.98	12.00	11.78	8.74	9.44
11	9.18	11.50	9.38	13.50	10.40	11.18	6.74	9.18
12	10.33	14.48	17.54	13.45	10.33	12.28	14.51	10.33
$\bar{x}$	10.65	*13.14	11.69	*12.89	12.09	11.55	11.27	10.65
SE	0.58	0.89	0.93	0.98	0.75	0.87	0.85	0.58
Premarin Group								
1	10.45	19.12			10.58	10.39	11.63	10.45
2	7.48	18.72			8.92	10.68	7.41	7.48
3	8.06	9.04			8.24	7.37	6.59	8.06
4	11.71	18.79			13.02	11.36	11.45	11.71
5	10.37	16.38			12.20	8.87	11.59	10.37
6	8.85	11.50			9.70	8.81	8.52	8.85
7	8.88	10.81			9.80	9.30	8.47	8.60
$\bar{x}$	9.40	14.91			10.35	9.54	9.38	9.36
SE	0.52	1.51			0.60	0.47	0.75	0.53
A	7.36	10.20			9.20	11.84	9.20	10.05
B	10.23	12.57			7.58	6.71	6.82	10.23
C	11.90	15.53			9.46	12.42	--	11.90

* Significantly different from pre-bedrest 1.

There were no significant differences in the total sweat losses between the non-premarin and the premarin group, which averaged 10.65 g/min/m2 for the non-premarin group and 9.40 g/min/m2 for the premarin group.

For the non-premarin group, significant differences ($P < 0.05$) occurred in the total sweating results between exercise conditions (ANOVA-1W-RM). The total sweat loss was significantly greater ($P < 0.05$) than the prebedrest condition during postbedrest 1 and postbedrest 2 (Duncan Multiple Range Comparisions). No significant differences occurred between other exercise conditions.

For the premarin group, the F test ratio comparing all conditions was not significant ($P < 0.10$). However for every subject, the total body sweat losses were greater during the postbedrest test than during the prebedrest test (see Table 12).

f) Sweat sensitivity and Tes threshold determinations

Local sweat rates (SR) were obtained from sweat capsules placed over a skin site on the chest and plotted as a function of the corresponding Tes (see Methods), and the slopes of these SR/Tes relationships are shown in Table 13.
During the first year of the study, the sweat system was not yet built, and so local sweat records for subjects 1-6 could not be obtained. Also any subject in whom the data was "missing" from more than one exercise test was not included in any of the data analysis. (This included subjects 7, 9, and A). Data became "missing" if the sweat capsule leaked during the test.

The statistical analysis was affected by the small number of subjects in each group (4 non-premarin, 7 premarin, and 2 oral contraceptive users) and by the fact that, since sweating slopes and threshold values are not normally distributed, non-parametric statistical analysis were required. In order to obtain the largest number of comparisions, all pre and postbedrest data (from the non-premarin, the premarin, and the oral contraceptive users) were combined to test whether bedrest reduces the slope of the sweating response, and the significance of this comparison was tested using a Mann-Whitney U test. The Z statistic was 1.79, which is significant for a one-tailed design at $P < 0.04$. Decreases in the sweating slope following bedrest occurred in 6 out of the 8 bedrests in the non-premarin group, in 6 out of 7 of the premarin group, and in both of the oral contraceptive users.

g) Sweating thresholds

The same limitations as above applied to the calculations of the sweating thresholds. These results are presented in Table 14, and the pre and postbedrest data were also analysed by combining the results from all groups and performing a Mann-Whitney U test. The Z value was 0.82, which was non- significant for either a one-tailed ($P < 0.21$) or a two-tailed ($P < 0.41$) analysis.

vi) Venous lactate values during exercise

TABLE 13: LOCAL SWEAT SLOPES (SR/Tes)
$mg/min/cm^2/^oC$

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
8	0.83	0.88	0.86	0.28	0.26	0.4	0.94	0.83
10	0.88	0.72	1.14	2.5	1.13	1.6	0.69	0.88
11	0.69	0.66	0.74	0.39	0.76	0.47	0.55	0.69
12	0.9	0.62	1.35	1.05	0.79	0.81	0.82	0.90
$\bar{x}$	0.82	0.72	1.02	1.05	0.73	0.82	0.75	0.83
SE	0.04	0.05	0.04	0.44	0.15	0.23	0.07	0.04
Premarin Group								
13	3.88	0.56			2.81	1.74	4.49	3.88
14	0.19	0.29			0.3	0.35	0.21	0.19
15	1.07	0.49			0.84	0.75	0.93	1.07
16	0.44	0.37			0.47	0.67	0.98	0.44
17	0.5	0.3			0.31	0.54	0.53	0.50
18	1.87	0.61			0.68	2.23	1.43	1.87
19	0.9	0.62			1.32	1.28	0.99	0.90
$\bar{x}$	1.26	0.46			0.96	1.08	1.36	1.26
SE	0.45	0.17			0.31	0.24	0.45	0.45
B	0.98	0.51			0.86	0.56	0.78	
C	0.46	0.29			0.67	0.6	0.59	

TABLE 14: LOCAL SWEAT RESPONSE = TRS THRESHOLDS

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
8	37.43	37.49	37.43	37.15	37.32	37.43	37.59	37.35
10	37.15	37.46	37.25	37.47	37.18	37.15	37.11	37.37
11	37.1	37.41	37.44	37.58	37.62	37.1	37.44	37.48
12	37.15	37.43	37.46	37.59	37.36	37.15	37.24	37.33
$\bar{x}$	37.21	37.44	37.39	37.44	37.37	37.20	37.34	37.38
SE	0.07	0.01	0.04	0.02	0.08	0.04	0.09	0.03
Premarin Group								
13	37.02	36.84			36.9	37.14	37.2	37.03
14	36.78	37.19			37.07	37.01	36.75	36.78
15	37.28	37.47			37.17	37.05	37.4	37.28
16	37.54	37.02			37.45	37.19	37.49	37.54
17	38.21	38.11			37.81	38.26	37.73	38.21
18	37.9	37.77			37.06	37.76	37.35	37.90
19	37.45	38.26			37.4	37.73	37.37	37.45
$\bar{x}$	37.45	37.52			37.26	37.44	37.32	37.45
SE	0.17	0.19			0.11	0.16	0.11	0.17
B	37.59	37.76			37.66	37.29	37.25	37.47
C	36.56	36.72			37.41	37.56	37.00	36.56

The individual blood lactate values obtained from each resting and final exercise sample are shown in Table 15. Blood lactate increased significantly during each exercise condition ($P < 0.01$). For the non-premarin group, venous lactate increased by an average 29.4 and 29.0 mg % during the prebedrest 1 and prebedrest 2 exercise respectively. Following bedrest, the increase in venous lactate was significantly greater ($P < 0.01$); 47.4 and 45.7 mg% during the postbedrest 1 and 2 tests, respectively. Although not as high as the postbedrest tests, venous lactate values were still significantly higher than the prebedrest tests during the 2 week (34.8 mg%) and the 4 week recovery (34.0 mg %) tests.

For the premarin group, venous lactates also increased significantly more ($P < 0.01$) during the postbedrest test than during the prebedrest condition (Table 15). However the rise in venous lactate was not significantly different ($P < 0.05$) from the prebedrest condition during the 2 and the 4 week recovery tests.

vii) Change in forearm venous compliance during exercise

The change in forearm venous compliance (FVV) which occured during the pre and post bedrest 1 tests in the non-premarin group is illustrated in the upper panel of Figure 22. During exercise there was an increase in venous tone (decreased FVV), which persisted throughout the exercise test, despite the marked increases in body temperatures. This venoconstriction during exercise was also seen during the postbedrest tests. Although all mean postbedrest FVV values were smaller than the prebedrest values, thus suggesting a potentiated venoconstriction, the differences were not significant (ANOVA-2W-RM-SP, $P < 0.20$). No significant differences occurred between the prebedrest 2 and postbedrest 2 tests ($P < 0.20$), the prebedrest 1 vs 2 week recovery ($P < 0.70$) tests, or the 4 week recovery tests ($P < 0.02$). Figure 23 illustrates that the apparent differences in the FVV response between pre and postbedrest tests were due to a shift in the resting values and not the result of a change in the rate of venoconstriction during the exercise. This is evident from the fact that the shape of the relative changes in the venoconstrictor response in the pre and postbedrest tests was almost identical.

Similar FVV responses occurred in the premarin group (see the lower panels of Figures 22 and 23). The change in FVV during pre and postbedrest exercise was not significantly different ($P < 0.10$). There also were no significant differences between prebedrest and 2 week ($P < 0.10$) or 4 week ($P < 0.10$) recovery tests.

D) 17-beta Estradiol and Progesterone Results

1) During Bedrest

The 17-beta estradiol and progesterone values obtained from blood samples drawn at the same time of day from each woman during bedrest is shown in Tables 16 and 17. Normal cyclic fluctuations in blood estrogens occurred in the non-premarin group, with peak 17-beta estradiol concentrations of about 200-400 pg/ml near ovulation. The

TABLE 15: VENOUS LACTATE DATA (mg%)

	Pre-BR1		Post-BR1		Pre-BR2		Post-BR2		Two Week Recovery		Four Week Recovery	
Subject	R	EX	R	EX	R	EX	R	EX	R	EX	R	EX
Non-Premarin Group												
1	4.57	10.59	8.37	25.19	6.70	10.90	9.83	27.76	19.34	32.82	5.73	15.76
2	16.68	48.93	15.58	57.99	3.55	52.27	12.44	69.76	12.53	48.06	6.83	74.04
3	9.41	43.46	15.68	107.52	5.10	35.34	16.85	63.01	11.64	54.00	8.46	60.12
4	23.81	90.45	17.05	93.20	12.68	89.35	8.72	96.96	8.29	107.18	6.58	105.38
5	9.00	19.86	9.31	48.13	15.27	23.50	8.05	57.54	12.68	50.13	4.50	13.21
6	9.97	41.94	9.31	60.78	4.20	11.93	---	---	14.27	42.81	4.27	23.38
7	7.07	21.79	3.14	47.81	7.48	61.48	7.32	71.20	11.27	50.20	11.14	38.86
8	7.57	27.21	7.56	38.47	5.69	23.33	8.11	27.79	8.12	27.71	10.48	21.25
9	10.36	35.00	8.55	57.42	8.44	23.70	7.32	45.85	11.55	34.01	11.69	44.63
10	9.66	15.42	7.76	36.05	10.09	30.53	9.41	34.54	11.34	31.44	8.56	28.95
11	11.38	34.10	10.20	47.04	11.53	49.02	9.34	70.81	15.33	54.90	12.87	47.75
12	6.44	28.05	8.18	59.27	9.61	36.57	9.12	43.84	10.34	30.66	10.48	35.72
$\bar{x}$	10.49	34.73	10.06	*56.57	8.36	37.33	9.68	*55.37	12.23	*46.99	8.47	*42.42
SE	1.43	5.82	1.12	6.42	1.00	6.25	0.80	6.21	0.85	5.91	0.80	7.42
Premarin Group												
13	5.30	29.24	8.44	49.66	---	---	---	---	7.34	29.52	5.08	6.68
14	6.62	70.62	9.54	88.99	---	---	---	---	6.07	88.36	9.93	59.83
15	11.05	27.16	9.21	40.43	---	---	---	---	1.25	37.81	0.85	9.69
16	5.46	49.88	7.17	58.46	---	---	---	---	3.92	39.79	9.59	17.20
17	6.79	27.59	11.15	62.40	---	---	---	---	12.58	59.59	3.03	14.46
18	10.12	37.83	10.65	47.40	---	---	---	---	11.46	22.45	9.32	18.11
19	11.92	20.95	7.79	48.10	---	---	---	---	7.74	25.81	6.25	18.63
$\bar{x}$	8.18	37.61	9.14	*56.49	---	---	---	---	7.19	48.26	6.29	20.66
SE	0.97	6.06	0.51	5.63	---	---	---	---	1.39	8.17	1.24	6.25
A	16.19	71.76	15.00	76.44	---	---	---	---	5.55	62.16	18.82	39.89
B	14.34	26.93	13.50	52.41	---	---	---	---	10.58	31.21	14.55	41.43
C	---	---	10.37	63.21	---	---	---	---	10.02	31.84	6.03	37.13

* Significantly different from PreBR1 Exercise Value

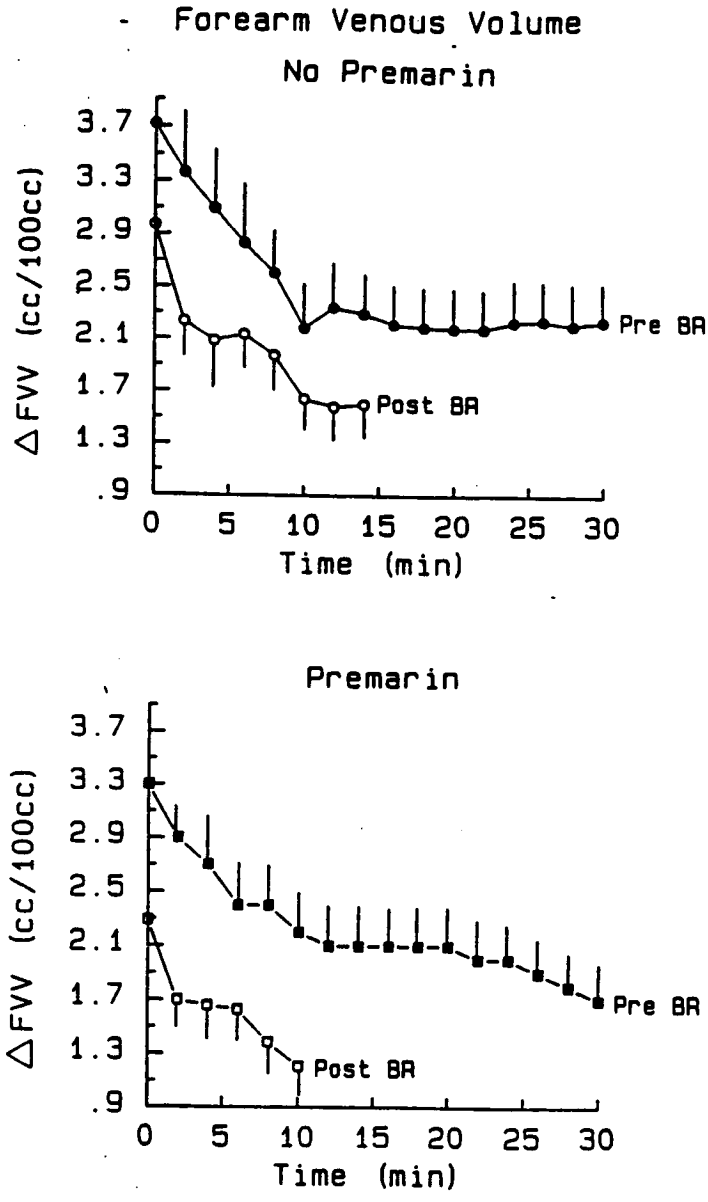

FIGURE 22: The change in forearm venous volume (compliance) between 0 and 30 Torr arm cuff congesting pressures (mean $\pm$ SE) during the submaximal exercise tests for the non-premarin group (n = 12) before and after bedrest 1, and for the premarin group (n = 7) before and after bedrest.

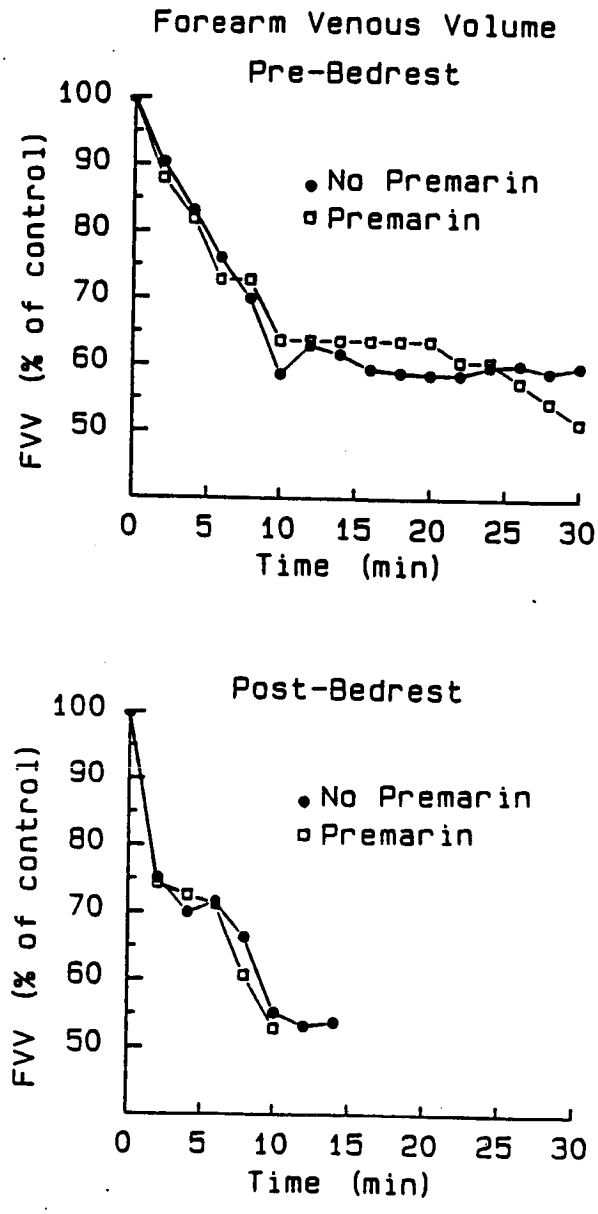

FIGURE 23: The relative change in forearm venous volume between the resting value and sucessive exercise time intervals during the submaximal prebedrest and postbedrest exercise tests for the non-premarin (n = 12) and the premarin (n = 7) groups.

TABLE 16: ESTROGEN RESULTS DURING BEDREST
(pg/ml)

Subject	Bedrest Days 1	2	3	4	5	6	7	8	9	10	11	12	13
Non-Premarin Group													
Bedrest 1													
7	35.8	146.2	23.8	218.1	196.0	334.5	323.2	247.3	139.7	99.5	106.0		
8	37.2	37.6	32.0			56.4	85.6	40.0	49.2	50.4			
9	59.6		73.6	87.1	156.7	157.3	212.3	122.8	31.0	57.3	68.5		
10	88.9	94.6	136.8	102.9	258.5	480.5	472.6	201.0	162.2	140.3	154.1		
11	80.8	81.9	93.8	134.0	106.9	123.2	97.6	177.3	150.8	160.1	184.4		
12	150.1	132.6	260.7	282.9	133.9	168.3	239.5	209.9	249.0	170.6	155.7		
Bedrest 2													
7	118.4	260.3	259.4	369.6	204.4	68.3	49.4	43.1	25.2	31.2	29.3	34.7	
8	59.4	41.1	UD	UD	35.9	--	101.9	82.5	UD	26.5	UD	UD	
9	74.7	56.0	75.1	34.1	35.6	61.2	73.4	UD	UD	UD	UD	--	
10	306.4	228.3	336.4	398.7	292.2	157.7	214.6	176.2	200.9	119.7	126.1	--	
11	110.8	215.4	145.3	126.0	146.2	92.6	140.7	137.9	159.0	125.1	124.5	121.8	
12	115.7	106.6	102.4	UD	42.2	51.4	70.7	53.5	UD	73.3	54.9	--	
$\bar{x}$	75.4	98.6	103.5	165.0	170.4	220.0	238.5	166.4	130.3	113.0	133.7		
SD	38.9	38.6	79.9	74.3	52.9	143.6	132.9	67.9	73.1	47.4	41.2		
Premarin Group													
13				437.4			355.8			363.0			461.9
14				220.9			341.1			324.0			326.3
15			233.9			131.8			185.7			314.6	307.2
16			194.6			266.4			296.3			286.4	
17			186.1			156.1			61.1			194.4	
18		156.3			232.9			166.5			225.7		
19		334.6			449.0			234.2	387.4		279.1		
$\bar{x}$		245.5	204.9	329.2	341.0	184.8	348.5	200.4	232.6	343.5	252.4	265.1	365.1
SD		89.1	20.8	108.3	108.1	58.6	7.3	33.9	122.1	19.5	26.7	51.3	68.9
C		76.6	24.8	64.0	87.6	153.6	98.0	78.0	70.4	111.2	97.2	127.2	

* UD = Undectable

TABLE 17: PROGESTERONE RESULTS DURING BEDREST
(ng/ml)

Subject	Bedrest Days 1	2	3	4	5	6	7	8	9	10	11	12	13
Non-Premarin Group													
Bedrest 1													
7	11.2	12.0	8.9	14.3	8.7	9.2	8.8	8.0	8.1	4.2	2.7		
8	0.9	0.8	2.7	6.7	5.4	4.1	4.6	3.8	3.3	3.7			
9	0.5		0.8	0.6	0.6	0.9	1.1	1.5	2.4	3.8	2.8		
10	0.9	0.5	0.6	0.6			0.8	1.8			7.0		
11	0.8	0.8	0.6	0.7	0.6	0.5	0.5	0.8	0.4	0.5	0.7		
*12	0.5	1.0	0.8	0.9	1.0	3.7	2.1	3.8	2.7	1.5	2.1	5.4	
Bedrest 2													
7	5.9	4.5	6.5	11.7	6.3	6.3	1.9	0.9	0.6	0.7	0.6	0.5	
*8	2.8	4.9	2.5	3.1	4.2	5.2	5.6	4.4	3.3	2.1	1.1	--	
9	7.7	9.1	9.3	6.9	10.7	12.8	7.5	4.0	1.5	0.9	0.7	--	
10	5.2	>10	>10	>10	--	>10	>10	>10	7.7	3.0	2.0	--	
11	0.5	0.4	0.5	0.6	0.5	0.5	0.5	0.7	0.5	0.4	0.6	0.5	
*12	2.8	3.3	2.0	2.2	0.8	0.3	0.7	0.2	0.2	0.0	0.2	--	
$\bar{x}$	2.5	3.0	2.4	4.0	3.3	3.7	3.0	3.3	3.4	2.7	3.1	5.4	
SD	3.9	4.5	3.0	5.1	3.3	3.1	2.9	2.4	2.6	1.5	2.1		
Premarin Group													
13				1.7			7.7			18.4			
14				0.1			0.1			0.1			0.1
15			0.1			0.1			0.1			0.1	
16			0.1			0.1			0.1				
17			0.1			0.1			0.1			0.1	
18		0.1			0.1			0.1			0.2		
19		0.1			0.2			2.4			5.3		
$\bar{x}$		0.1	0.1	0.9	0.2	0.1	3.9	1.3	0.1	9.3	2.8	0.1	0.1
SD		0.0		0.8	0.0		3.8	1.2		9.1	2.6		0.0

* Luteal Phase Deficiency

progesterone levels in the non-premarin group also showed cyclic fluctuations as would be expected from normally cycling women. However in two of the subjects, subject 8 during bedrest 2 and subject 12 during both bedrests 1 and 2, the progesterone concentrations during the luteal phase were abnormally low, and the cycles were defined as a luteal phase deficiency using the definition of Abraham et al (1974). See Figure 24 for an illustration of the hormonal responses from one of these subjects. Also during the first year of the study, subject 3 had an extremely short (18-day) cycle during the first bedrest, and blood hormonal values obtained during the post bedrest exercise test and morning temperature data suggest that this subject did not ovulate during this menstrual cycle.

The 17-beta estradiol and progesterone values obtained from blood samples in the premarin group are also presented in Tables 16 and 17. The 17-beta estradiol values averaged from 184 to 365 pg/ml during bedrest, with consistent elevations seen throughout the bedrest protocol - except for subject 17 who forgot to take her pill on the morning of bedrest day 9. Progesterone levels for 5 of the subjects remained less than 0.1 ng/ml, suggesting that ovulation had been inhibited for most subjects. Subjects 13 and 19 appeared to have ovulated despite the premarin. Subject 19 reported "breakthrough bleeding" and increased the dosage of premarin to 2 mg/day

2) Before the submaximal exercise tests

The 17-beta estradiol and progesterone values obtained from the resting blood sample drawn immediately before the start of the submaximal exercise tests are shown in Tables 18 and 19, respectively. The 17-beta estradiol concentration ranged from 35.5 to 336.7 in the non-premarin group during the prebedrest tests, and from 105.4 to 337.9 pg/ml in the premarin group. Again, the progesterone data are representative of either a preovulatory stage or a non-ovulatory cycle for all premarin subjects except subjects 13 and 19 in the postbedrest test.

E) Arginine Vasopressin Concentrations during the Submaximal Exercise Tests

To test our hypothesis that plasma ADH (arginine vasopressin) may be involved in the alteration of thermoregulatory function, plasma arginine vasopressin concentrations were measured from the resting and final exercise blood sample during submaximal exercise tests. Samples were obtained only during the last year of the study (premarin group), and the resting and final exercise values (pg/ml) are shown in Table 20. No significant differences ($P < 0.30$) were found (ANOVA-1W-RM) between any of the arginine vasopressin values, including rest and exercise, and pre and postbedrest values.

F) Pulmonary Function Test Results

Forced vital capacity (FVC) increased in each subject (n=13) during bedrest. Total lung capacity increased in each subject, while residual volume and resting volume of the lung did not change. No change in FVC was found in an ambulatory control group using identical measurement techniques. (see the manuscript in Appendix 2

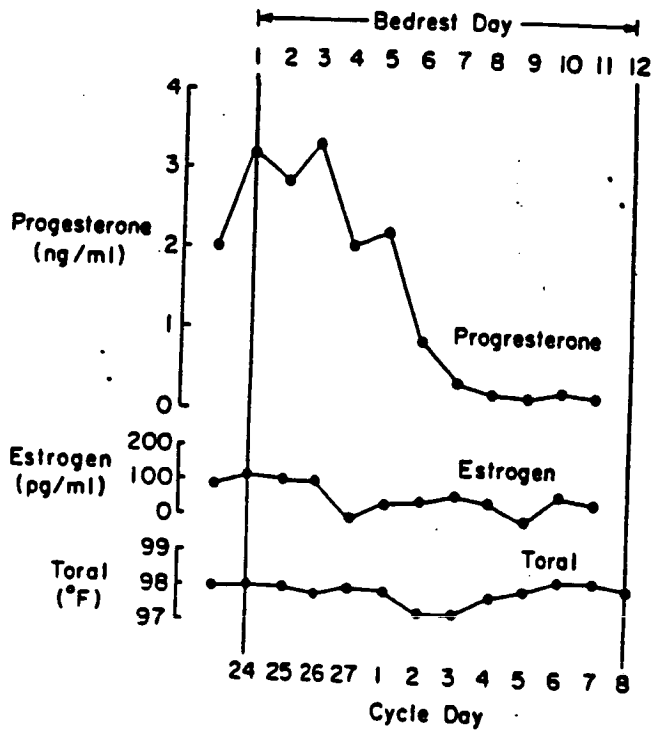

FIGURE 24: Endocrine measurements of one subject during bedrest. An insufficiency of progesterone secretion was documented according to the method of Abraham.

TABLE 18: ESTROGEN RESULTS FROM EXERCISE TESTS
(pg/min)

Subject	Pre BR1	Post BR1	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1		220.9	442.8	129.7	197.8	278.5		
2		76.9	49.8	355.0	64.0	219.7	272.7	38.9
3	93.6	101.2	222.1	101.8	127.7	112.5	94.4	309.5
4		336.7	433.6	57.8	535.4	39.8		56.2
5	77.4	47.9	91.2	271.3	62.6	189.1		114.9
6		60.1	114.9	179.8	43.3	202.4	109.6	254.6
7	128.1	29.6	313.6	34.7				
8	70.0	50.4						70.0
9		68.5	46.1				32.3	
10	88.9	162.8	121.4	121.1			81.2	88.9
11	35.5	184.4	66.2	124.5			56.1	35.5
12	150.1	74.6	90.4	54.9			126.8	150.1
$\bar{x}$	91.9	117.8	181.1	141.1	171.8	173.7	110.4	124.3
SE	35.00	87.5	142.8	91.7	170.7	77.3	72.5	91.9
Premarin Group								
13	196.4	505.7			40.2	20.0	20.0	196.4
14	337.9	216.3			242.9	66.2	138.5	337.9
15	220.3	234.3				172.3	322.0	220.3
16	125.0	143.1			120.8	20.0	20.0	125.0
17	129.7	297.4			20.0	20.0	20.0	129.7
18	105.4	134.8			76.1	121.2		105.4
19	340.4	205.7			225.8	93.6	33.2	340.4
$\bar{x}$	207.9	248.2			121.0	73.3	92.3	207.9
SE	91.2	116.9			86.2	54.9	111.1	91.2
A	281.5	440.4	105.6	71.2	643.7	119.8	210.7	267.1
B	9340	8841			13082	10560	10696	10911
C	11171	7951			10365	9570	9570	--

TABLE 19: PROGESTERONE RESULTS FROM EXERCISE TESTS
(ng/ml)

Subject	Pre BR1	Post BR2	Pre BR2	Post BR2	2-WK	4-WK	C1	C2
Non-Premarin Group								
1		0.3	6.4	0.4	7.2	0.3		
2		5.3	0.5	8.4	0.4	9.4	48.6	0.2
3	0.3	0.4	0.5	0.4	0.4	0.5	0.3	0.5
4		0.3	0.3	2.0	0.3	0.3		0.2
5	11.8	0.4	0.2	14.2	0.3	6.8		7.1
6		0.3	0.3	4.8	0.2	4.8	0.3	7.8
7	7.2	0.6	6.0	0.6				
8	0.4	3.7	3.4	1.1			0.6	0.4
9	0.9	2.8	5.4	0.7			3.6	0.9
10	2.3	---	0.6	2.0			1.9	0.9
11	2.3	0.7	0.6	0.6			1.0	2.3
12	0.5	0.8	2.2	0.2			1.5	0.5
$\bar{x}$	3.0	1.4	2.4	3.0	1.5	3.7	7.2	2.1
SD	3.9	1.6	2.3	4.1	2.6	3.6	15.7	2.8
Premarin Group								
13	0.1	24.8			2.5	0.2	0.1	0.1
14	0.1	0.1			0.1	3.2	5.8	0.1
15	0.2	0.1				0.2		0.2
16	0.1	0.1			5.5	0.1	0.1	0.1
17	0.1	0.3			0.1	0.1	0.1	0.1
18	0.1	0.1			0.1	10.9		0.1
19	0.1	7.2			0.1	9.1	1.6	0.1
$\bar{x}$	0.1	4.7			1.4	3.4	1.5	0.1
SD	.0	8.6			2.0	4.3	2.2	.0
A	10.5	8.9	28.8	0.4	3.0	7.7	16.8	1.6
B	26.9	27.3			28.4	27.3	26.8	26.9
C	36.0	29.0			39.3	40.5	39.4	36.0

TABLE 20: ARGININE VASOPRESSIN RESULTS
(pg/ml)

	Pre-Bedrest			Post-Bedrest		
Subject	R	EX	D	R	EX	D
13	4.49	7.20	2.71	4.40	10.48	6.08
14	3.84	3.97	0.13	2.92	6.45	3.53
15	4.68	4.03	-0.65	5.82	2.92	-2.90
16	3.35	6.52	3.17	4.94	5.49	0.55
17	4.92	7.40	2.48	16.45	9.29	-7.16
18	4.75	6.08	1.33	5.02	4.36	-0.66
19	3.22	4.18	0.96	5.28	6.97	1.69
$\bar{x}$	4.18	5.63	1.45	6.40	6.57	0.16
SE	0.25	0.53	0.50	1.58	0.93	1.52

D = (exercise - rest)

for a more complete description of these results).

G) Positron Emmision Tomography Result

No change was found in the D2 receptor binding of the caudate nucleus following bedrest. See Figure 25 for the slopes of the caudate/cerebellum binding ratios obtained during the prebedrest (7/11/84) and postbedrest (7/25/84) tests.

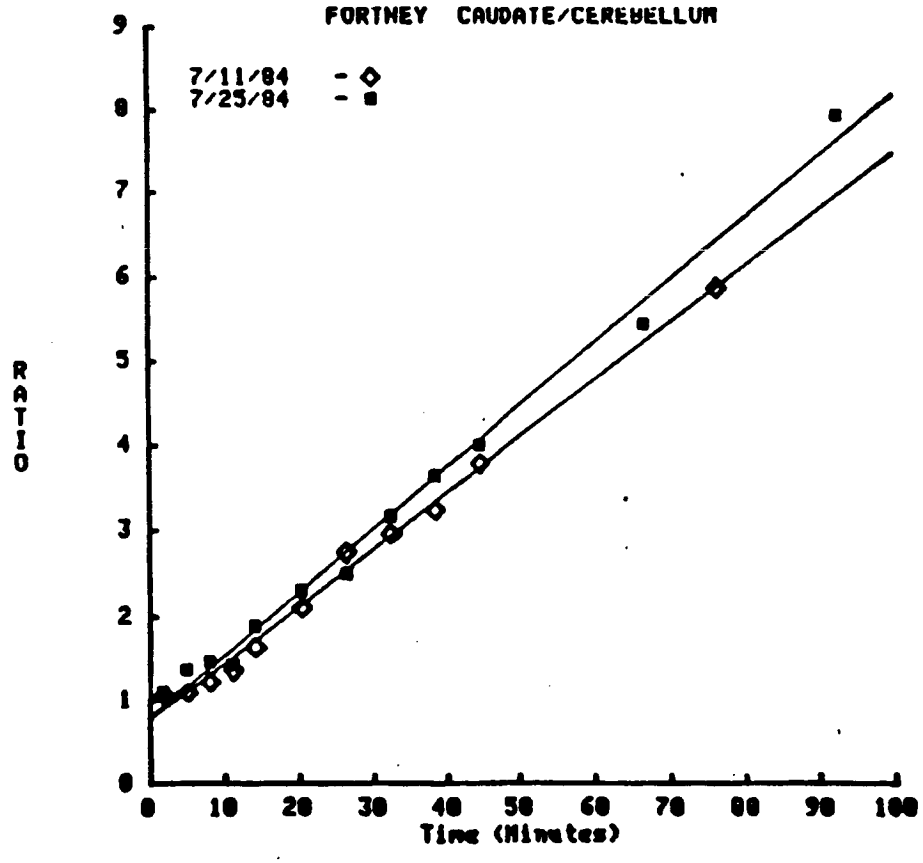

FIGURE 25: The ratio of 11C-labelled 3-N-methlyspiperone binding in the caudate/ cerebellum as an index of dopamine D2 receptor binding in one subject before (7/11/84) and after (7/25/84) bedrest. The similarity of the two relationships suggest no change in the number of central dopamine D2 receptors in the caudate nucleus during bedrest.

V) DISCUSSION OF RESULTS

A) Body Fluid Responses During Bedrest

1) Comparison to previous studies

A fairly consistent finding is that plasma volume decreases during spaceflight (Johnson, 1979) and during programs of bedrest. Greenleaf and coworkers (1977) utilized the data from several bedrest studies to characterize a hyperbolic relationship between the decrease in plasma volume as a function of the number of days of bedrest. According to their calculations, plasma volume decreases to an asymptote of about 22.5% below prebedrest level after about 30 days of horizontal bedrest. After 11 days of bedrest, a 13% decrease in plasma volume would be expected. Most of the data used in these calculations were obtained from studies of the responses of male subjects. In the present study, the hypothesis was tested that women may have a smaller reduction in plasma volume during bedrest, especially during the pre-ovulatory and the luteal phases of the menstrual cycle, through a direct or indirect action of estrogens to retain body water. This hypothesis was based on early observations of hemodilution during estrogen therapy (Whitten et al, 1951: Preedy et al 1956), possibly through a sodium conserving action in the kidneys (Dignam, 1956). In addition, Gaebelein and Senay (1982) observed that the decrease in plasma volume during exercise was less during the luteal phase, when estrogens would be higher, than during the early follicular phase. Our results however did not strickly support this hypothesis. The decrease in plasma volume seen in the women without estrogen supplementation was similar to that predicted by Greenleaf's formula; it averaged 19.9% following bedrest 1 and 12.3% following bedrest 2 (Table 5). If anything, the women in our study lost more plasma volume than that reported for men under similar conditions.

No attempt was made in this study to control either fluid or food intake. Therefore some of the day-to-day variations in blood and urine constituents were undoubtedly influenced by changes in the diet. Nevertheless, while there was no consistent change in the amount of fluid or food intake, as assessed from the diary records, consistent changes in plasma volume, electrolytes and proteins occured during bedrest. The blood and urine responses seen in this study were similar to those found in a previous study (Greenleaf et al, 1977) which studied the body fluid responses of 7 men during a similar bedrest protocol (non-exercise condition). In both studies plasma osmolality and protein concentration increased significantly during bedrest, although there was a net loss in the plasma content of total protein (TCP) and osmotically active particles (TCO). The mechanism responsible for this loss of a hypotonic fluid from the vascular compartment during bedrest is most likely multifactorial. In another paper by Greenleaf and Kozlowski, the body fluid shifts during bedrest were divided into 3 separate stages. During the first day of bedrest, fluid moves from the lower regions of the body into the thoracic region, stimulating volume receptors, and producing a diuresis. Then during the next 2 weeks of bedrest, plasma volume reduction continues, and the extracellular volume is restored and possibly even exceeds the prebedrest level. After 2 weeks of bedrest,

the plasma volume is still below the prebedrest level, but it remains fairly stable; extracellular water is normal, and intracellular water is reduced. Thus during the early hours of bedrest, the initial reduction in plasma volume may be due to either a Henry-Gauer type reflex (Gauer, 1963) or to the stimulation of selective natriuretic peptides (Greenleaf, 1985). Later reductions in plasma volume could result from a redistribution of water between various body fluid compartments, or from potential alterations in protein, electrolyte or hormonal regulations. The data in this study support a multifactorial mechanism rather than a simple Henry Gauer reflex. The diuresis in this study occurred during only the first 1 or 2 days of bedrest (Figure 12), yet plasma volume continued to decrease significantly for another 4-5 days before the plasma volume remained relatively stable (Figure 4). This lack of correlation between the changes in plasma volume and urine output under conditions of a stable fluid intake, suggest that the later decreases in plasma volume may have occurred at the expense of some other fluid compartment. The higher urine osmolality on the first day of bedrest supports the suggeston of the stimulation of a natriuretic factor during the first days of a bedrest.

Whatever the mechanism by which plasma volume is gradually reduced during bedrest, it is very rapidly recovered following bedrest. Within 24-48 hours after the end of the bedrest protocol, the plasma volume of the non-premarin subjects averaged only about 3% less than their prebedrest plasma volume (Figure 5). Thus studies in which post-flight plasma volume was estimated from blood samples drawn several hours after return to normogravic conditions, may have underestimated the plasma volume changes during weightlessness.

2) Effect of menstrual cycle on plasma volume changes during bedrest

The effect of menstrual cycle stage on plasma volume changes during bedrest was minimal. As seen in Figure 3, if a woman began bedrest in the pre-ovulatory stage (stage 2) of her menstrual cycle, the decrease in plasma volume at the onset of bedrest was postponed for one or two days. Thereafter, plasma volume decreased rapidly to the level of plasma volume seen in the women who began bedrest in other stages of the menstrual cycle. If a woman reached the pre-ovulatory stage of her cycle in the latter stages (days 7-12) of a bedrest protocol, a temporary hemodilution occured, which again disappeared within one or two days (see abstract entitled "Plasma volume responses during bedrest in healthy women" Appendix 3). The predicted retention of plasma volume in the luteal phase of the cycle was sometimes, but not consistently seen in these subjects. The plasma volume responses of the two subjects who took estrogen-containing oral contraceptives were not different from the plasma volume responses of the non-premarin group. Thus only in conditions in which blood estrogens were elevated in the presence of low concentrations of progesterone did consistant plasma volume retention occur.

3) Effect of bedrest on menstrual function

Bedrest presents both a physiological as well as a psychological

stress to a woman, and stress is a well-known modifier of menstrual function. Therefore it might be expected that menstrual cycles would be altered during bedrest. The potential consequences of disruption of normal menstrual function during weightless conditions are poorly understood. Indeed, the consequences and the choice whether to treat menstrual dysfunction during other stressful conditions (athlete's ammenorrhea) are currently under debate (Loucks and Horvath, 1985). During exposure to long-term weightlessnss, a cessation of menstrual function potentially could have serious consequences. A decrease in blood estrogen levels could potentially accelerate the bone mineral loss in women astronauts. Although this study did not directly address the problem of menstrual function regulation, it was noted that for the 6 "normally cycling women" in whom daily hormonal samples were obtained during bedrest, two of these women had evidence of luteal phase deficiency. However, the conclusion that the bedrest protocol specifically produced this menstrual irregularity cannot be drawn, since control endocrinological data were not obtained from these two women during non-bedrest conditions.

4) The potential for lower leg edema following bedrest

The potential for lower leg edema following exposure to weightlessness was emphasized in a review article by A.R. Hargens (1982). He demonstrated that the interstitial fluid pressure in the lower legs of male subjects decreased during head-down tilt as interstitial fluid was shifted from lower body to upper body regions. Hargens suggested that "countermeasures may be necessary to maintain precapillary-muscle tone during long space flight in order to prevent swelling of lower leg tissues upon readjustment to Earth's gravity". To date however, there have been no published accounts of severe lower leg edema following bedrest or spaceflight. In this study, subject "A" developed edema in both lower legs which probably was a consequence of her participation in the bedrest study. Upon finishing the bedrest protocol and the postbedrest exercise tests, this subject remained in the sitting position for a prolonged interval (typing a term paper all night). It is possible that this period of inactivity prevented the restoration of a normal venous tone in her lower legs, resulting in blood pooling and excessive fluid extravascularization. Similar conditions of inactivity may need to be avoided following spaceflight to prevent this painful and disabilitating experience.

5) Effect of premarin to restore plasma volume during bedrest

In the original hypothesis, elevated blood estrogens were proposed to be associated with body fluid retention. However from the results of the two oral contraceptive users (who took pills containing synthetic estrogens and progestins), and because of the greater hemodilution seen during cycle stage 2 (pre-ovulatory) rather than during cycle stage 3 (early luteal), this initial hypothesis was modified to now predict fluid retention in conditions of elevated blood estrogens only in the presence of low blood progesterone. The estrogen supplement used to test the hypothesis was premarin, a natural estrogen supplement which has been used for estrogen replacement therapy. Premarin tablets administer about 48% estrone sulfate, 26% equilin sulfate, and 26% other hormones. One hour after

ingestion of a 1.25 mg tablet, total estrogen concentrations should be elevated in the following proportions, 87% equilin, 8% estrone, and 5% 17-beta estradiol (Whittaker, 1980). One disadvantage of premarin administration is that, although total estrogens are significantly elevated, the most biologically active human estrogen (17-beta estradiol) is only moderately elevated (in our study, 17-beta estradiol was elevated in the plasma to 200-400 pg/ml). However this moderate elevation in 17-beta estradiol is also an advantage, since moderate levels may prevent many of the estrogenic side effects, such as blood clotting and migrane headaches, reported with estrogen treatment. In future studies however, a better estrogen supplement may be low doses of estrace, which is pure 17-beta estradiol.

It is clear from the results shown in Figure 4, that the premarin administration was effective in restoring plasma volume during bedrest. During the first 2 days of bedrest, the plasma volume response of the premarin group was similar to that of the non-premarin subjects. Thereafter, the loss of plasma volume was attenuated and then reversed. The mechanism by which premarin restored plasma volume during bedrest is uncertain. Although the urine losses in the premarin group tended to be less than in the non-premarin group, there was much variability in subject responses and no significant differences were seen between the two groups for urine loss, fluid intake, or the difference between fluid in and fluid out. The concentration of blood electrolytes and total protein in the two groups during bedrest were similar, thus not only was water retained by the premarin action, but also electrolytes and proteins.

6) Changes in red cell volume during and after bedrest

A decrease in red cell mass has been reported following both US and Soviet space flights. The Skylab data indicated that once a loss of red cell volume is triggered, it may continue for as long as two weeks after the cessation of the flight (Nicogossian, 1982). The precise mechanism for the decrease in red blood cells has been variously postulated to involve an inhibition of new red cell production through decreased erythropoietin release and new red cell formation, increased intravascular hemolysis, or sequestration of the red blood cells (Nicogossian, 1982). Red cell mass was determined in this study with a Technetium radioisotope labelling technique. One advantage of this method is that the half-life of the label is short enough that eight repeated measurements could be obtained at 2-week intervals during this study. During a single bedrest, the red cell mass decreased 4-7% in these women although this difference was not significant (Table 4). Prior to the start of the second bedrest (with about a 4-week recovery), the red cell mass was not completely restored to the prebedrest 1 level. A further 4.4% decrease in red cell mass occured during bedrest 2, resulting in significant accumulative reduction from the prebedrest 1 value. This reduction in red cell mass persisted and increased during the next 2 weeks of ambulatory recovery. Although these results shed no new light into the possible mechanism of the decrease in red cell loss, it is clear that this response is not rapidly reversible (as the plasma volume response), and that accumulative effects are seen with repeated

bedrests, which are separated by 4 weeks of recovery.

7) The effect of repeated bedrest

One unique aspect of this study was that repeated identical bedrests were performed, with the duplicate bedrests separated by a 3-4 week period of ambulatory recovery. (In previous studies in which repeated bedrests were performed, some alteration in the bedrest protocol, ie. exercise intervention, precluded direct comparision of the results from the two bedrests). Several small differences between responses measured during the first and second bedrest were seen in this study. First the decrease in plasma volume during the second bedrest was only about 60% of the decrease in plasma volume seen during the first bedrest. Although the starting plasma volume was slightly smaller during the second bedrest, the average plasma volume remained higher than the bedrest 1 values througout the last 8 days of bedrest (Table 5). Also, smaller increases in plasma osmolality and total protein concentration occurred during the second bedrest (Figures 6 and 8). These results suggest the interesting possiblility that there is an adaptation of the body fluid responses with repeated bedrest. Possibly, during the initial bedrest exposure, a redistribution of fluid or proteins occurred between body fluid compartments, such that there was an increase in the volume or capacity of the interstitial compartment even in the presence of a reduction in the plasma compartment (Greenleaf, 1982). The mechanism which altered the distribution of fluid between the interstitial, plasma and possibly intracellular compartments, might involve alteration in the local tissue metabolism of these fluid compartments, or an alteration in the protein composition or content (reminesent of Senay's theory (1972) of how heat acclimation alters the regulation of plasma volume). Following the first bedrest, these body fluid alterations may have been retained until the start of a second bedrest and been responsible for the smaller disturbance of body fluid balance during the second bedrest, ie an increase in prebedrest interstitial volume could function to maintain plasma volume. Thus a peripheral tissue body fluid "adaptation" may occur with repeated weightless exposures. Alternately, a "central" modification may occur with repeated bedrests. The redistribution of blood volume into the thoracic regions during the first bedrest could somehow result in a decrease in the sensitivity of blood volume receptors, resulting in an attenuation of the bedrest-induced diuresis during the second bedrest.

B) MAXIMAL EXERCISE RESPONSES FOLLOWING BEDREST

1) Difficulty in obtaining VO2 max following bedrest

Measurements of maximum oxygen consumption (VO2 max) are often interpreted as a measure of aerobic capacity, and when corrected for body mass, is an indication of aerobic fitness. In order to accurately determine an individual's VO2 max however, conditions must exist in which the subject is able to exercise to an intensity at which oxygen transport is the limiting factor. If the active muscle mass is too small, local muscle fatigue occurs before the maximal aerobic capacity is reached. Evidence of the attainment of a true aerobic capacity is the presence of a plateau in oxygen consumption

with further increase in exercise intensity.

Prior to bedrest in this study, the subjects were able to exercise to their maximal aerobic capacity. Following bedrest however, the criteria for VO2 max was seldom obtained, and thus the postbedrest values are referred to as the "peak VO2." In this study it is unclear what is the primary factor which limits peak VO2 after bedrest. Potentially, the loss of muscle tone during the bedrest might limit the working capacity of the leg muscles. Thus during the VO2 max testing after bedrest, the exercise performance was limited by this local muscle fatigue rather than by a true aerobic capacity limitation. Thus following bedrest without muscle training, it might be impossible to test the decrease in maximal aerobic capacity.

2) Comparison with data in the literature

Previous studies in the literature which claim to have measured VO2 max or peak VO2 changes before and after bedrest report decreases in the range from 17 to 31% (Miller, 1965; Saltin, 1968; Taylor, 1949). The responses of 8 women following bedrest averaged 9.7% following 17 days of bedrest (Convertino, 1977). The decreases in VO2 peak (ml/kg/min) which were measured 24-48 hours after the end of bedrest in the present study, averaged 10% and 5% following bedrests 1 and 2 for the non-premarin group, and 25% in the premarin group. The range of decrease in peak VO2 following bedrest however was great; all the way from no decrease following bedrest to a 31% reduction. Some of this variability may have been related to the experiences of the women during the submaximal exercise tests on the previous day. Subjects who fainted following the submaximal exercise tests appeared to be more cautious and refrain from "going all out" during the post bedrest VO2max test.

3) Lack of influence of premarin treatment

Premarin did not significantly alter VO2 max during the control tests or the decrease in VO2 peak seen following bedrest (Table 8). This is not an altogether unexpected finding as the decrease in plasma volume which occurred in the non-premarin group was almost completely restored by the time the maximal exercise test was performed. For most subjects, postbedrest VO2 peak was determined on the same day that the postbedrest plasma and red cell volume was measured, which was 24-48 hours after the end of the bedrest. Figure 5 illustrates that at this time, the plasma volumes in both the premarin and non-premarin groups were not significantly different from the prebedrest values. Thus if the absolute decrease in plasma volume during bedrest has any effect on the decrease in VO2 peak, this effect would no longer be present at the time of testing in this study. In addition, it would not be expected that alterations in plasma volume alone, without significant alteration in red cell volume, would alter significantly VO2 peak (Kanstrup and Ekblom, 1982).

4) Lack of correlation between VO2 max and the % decrease in VO2 peak

One hypothesis which has been recently tested (Greenleaf, 1982b)

is that a greater reduction in VO2 peak occurs in fit subjects than in unfit subjects following bedrest. Positive correlations between prebedrest VO2 max and the % decrease in VO2 peak have been reported in several studies which examined the responses of male subjects (Chase, 1966; Saltin, 1968; Convertino, 1977). Very little data is available from women (Convertino, 1977), and the correlation found in one study was very low (-0.38). In the present study similar low correlations for this relationship (-0.12 to -0.48) occurred in the non-premarin bedrests. This result may have been due to the narrow range of prebedrest fitness values (28-45 ml/kg/min). Another contributing factor may have been that the exercise was performed in the upright posture, which according to Greenleaf et al (1982b) presents an additional complicating factor in the determination of VO2 peak following bedrest as there are hypothesized differences in blood pressure regulation with differing fitness level. The postitive correlations between prebedrest VO2 max and % change in VO2 peak have been reported from studies in which postbedrest VO2 peak tests were performed in the supine position.

C) SUBMAXIMAL EXERCISE RESPONSES FOLLOWING BEDREST

1) What limits exercise tolerance following bedrest?

The submaximal exercise responses following bedrest would be expected to be reduced because of several concurrent effects. First, deconditioning would be expected to alter the cardiovascular and thermoregulatory responses that were studied. The average prebedrest VO2 max results for the non-premarin and premarin groups were 2.24 and 2.41 liters/min, respectively (a non-significant difference). Exercise intensities for the submaximal tests were calculated to require an oxygen consumption of about 70% of each subject's prebedrest VO2 max. The actual oxygen consumption of each woman during the submaximal exercise was determined during the control tests, and found to average 68 $\pm$ 1.3% VO2 max for the non-premarin group, and 69 $\pm$ 2.7% for the premarin group. Since the average decrease in VO2 peak was 11% in the non-premarin group, then the postbedrest exercise test was performed at an exercise intensity of approximately 76.5% VO2 peak. For the premarin group, the average decrease in VO2 peak was 22% (non-significant from the non-premarin group because of the great variability in responses), and would have resulted in an exercise intensity of about 88.0% VO2 peak during the post bedrest test. Although the decrease in aerobic capacity was probably not as great as suggested by the decrease in VO2 peak following bedrest, the postbedrest exercise was likely performed at a significantly higher relative exercise intensity.

Secondly, in order to assist in subject recruitment, this study was performed during the summer months. Thus during bedrest, it is possible that changes in the state of heat acclimation occurred, which would affect the postbedrest thermoregulatory responses. The magnitude of this effect would be expected to be very small in this study, as all subjects were employed in jobs in which they worked in air conditioned buildings, and none were athletes or consistently exercised out-of-doors. No significant difference was seen in the thermoreguatory data between control and prebedrest responses where the control tests were performed at the end of the study (late August

and early September) in year 1, and at the beginning of the study (end of May and early June) during years 2 and 3.

Third, the decrease in plasma volume which normally occurs during bedrest would be expected to significantly alter cardiovascular, venoconstrictor (Fortney, 1983) and thermoregulatory (Fortney 1981) responses during exercise.

Finally, a loss of venoconstrictor tone during bedrest might result in greater blood pooling in lower body regions, decreasing cardiac return and thus exerting effects similar to the responses seen with hypovolemia.

All of the above effects would be expected to influence the submaximal exercise responses in this study. However, the magnitude of the effects due to losses of training, heat acclimation and venous tone would be expected to be comparable between the varing bedrest conditions. Any change in the cardiovascular or thermoregulatory responses caused by the decrease in plasma volume during bedrest should be evident from comparisons of the responses of the non-premarin (who had a 19.9 % decrease in plasma volume during bedrest) and the premarin subjects (plasma volume decreased only 0.2% during bedrest).

2) Body Fluid Responses during Exercise

In 1969, Hyatt et al proposed that at least part of the postbedrest orthostatic intolerance during tilt was due to a greater loss of plasma volume during the tilt. They speculated that during bedrest the extravascular compartment become dehydrated, and during post-recumbancy tilt, a large transudation of plasma water occurred into the leg tissue spaces. The resultant decrease in plasma volume during tilt would then account for some of the decrement in stroke volume and cardiac output seen after bedrest. It is now known that the extracellular compartment is not dehydrated during bedrest, and thus this mechanism for a greater plasma water filtration after bedrest seems unlikely.

Moderate cycle exercise in a warm environment is also a stress in which decreases in plasma volume occur (Harrison, 1985). Thus if Hyatt's theory is correct, perhaps a greater loss of plasma volume would occur during exercise following bedrest than during the prebedrest tests. In this study, plasma volume decreased during all of the submaximal exercise tests, but the % loss of plasma volume was similar in pre and postbedrest tests (Figure 16). There was no evidence of an increased extravascular fluid loss which may have contributed to the greater cardiovascular and thermoregulatory strain seen in the postbedrest tests. Indeed in the non-premarin group, the same relative decrease in plasma volume occurred in the pre and postbedrest tests, despite the different absolute plasma volumes at the start of the exercise. This suggests that in the hypovolemic condition (postbedrest), a smaller rather than a greater, absolute loss of plasma volume occurred.

3) Cardiovascular responses following bedrest

The cardiovascular responses were altered significantly in all postbedrest exercise tests. Heart rates were higher at all exercise times and stroke volumes were lower during the postbedrest exercise. The increase in heart rate was able to compensate for the lower stroke volume in these tests, and cardiac outputs were not significantly lower postbedrest. For all but one subject, the criteria for shortening a postbedrest exercise test was the attainment of a heart rate of 95% of the prebedrest maximal heart rate value (one subject was stopped early because of a high core temperature). In the non-premarin group, we first speculated that at least part of the elevation in exercise heart rate and reduction in stroke volume was due to the significantly lower plasma volume during the postbedrest test, which presumably would limit cardiac filling. This expectation was based on the similar changes in cardiovascular responses seen in a previous study (Fortney et al, 1983) in which an identical exercise protocol was employed to compare the cardiovascular responses of men during normovolemic exercise, and exercise in which plasma volume was reduced 15% with diuretics prior to the start of exercise. Therefore we were surprised to find that the cardiovascular responses of the premarin group were similar to those seen in the non-premarin group following bedrest. The increase in heart rate, and reduction in stroke volume and endurance time were of a similar magnitude as the non-premarin group, despite significant difference in plasma volume responses during bedrest. Thus a similar increase in cardiovascular strain was seen in these women following bedrest, and it appeared to be independent of the level of pre-exercise hydration.

4) Thermoregulatory Responses following Bedrest

Esophageal temperatures were higher at each exercise time in the postbedrest condition for each subject group, while skin temperatures were not different. Higher core temperatures would be predicted during postbedrest tests, since the subjects exercised at a higher relative exercise intensity (Saltin and Hermanson, 1966). Since core temperature is the primary input for the control of sweating, significantly greater total sweat loss might also be expected during the postbedrest tests, when correction were made for the shorter exercise endurance. However, following a decrease in fitness (Roberts, 1977) or a decrease in plasma volume (Fortney, 1984), sweating sensitivity is reduced. Thus for a given change in core temperature, a reduced sweat production is ellicited. It has also been shown that the threshold for the onset of sweating is influenced by the degree of acclimation of the subject (Roberts et al, 1977). Thus if a significant loss of heat acclimation occurred in these subjects, the sweating threshold would have been shifted so that sweating would to be initiated at a higher core temperature following bedrest. Very few studies have examined thermoregulatory responses following simulated weightlessness and a decrease in heat tolerance during spaceflight could have important consequences for men attempting to work in space.

Greenleaf and Reese (1980) reported significantly higher increases in rectal temperatures in men during submaximal exercise following 2 week bedrests. They suggested that this greater heat intolerance could be due to combined effects of deconditioning and inhibition of

sweating. The results of the present study confirm that core temperature increases to a higher level during exercise following bedrest. Part of the greater increase in core temperature postbedrest, was probably due to the significant decrease in the slope of the sweat rate/core temperature relationship (Table 13). Such a change in sweating sensitivity would be expected because of the bedrest deconditioning. However, the contribution of the decrease in plasma volume to this decreased sweating sensitivity is difficult to identify in this study, because of the variability and small number of non-premarin subjects in whom local sweating records were obtained. Three out of four of the non-premarin subjects, both oral contraceptive subjects, and 6 out of 7 of the premarin subjects had reductions in sweating sensitivity.

In a previous study (Fortney et al, 1981), we postulated that in conditions of hypovolemia, increased titers of anti-diuretic hormone may be released which act either at the sweat gland to reduce sweat output, or centrally in the hypothalmus to inhibit the output of the heat loss thermoregulatory neurons. In this study, we found that following bedrest the sweating sensitivity was significantly reduced despite non-significant changes in blood ADH concentration. These results would tend to present evidence against a role of blood ADH to inhibit sweat gland function. However because of the small number of subjects in whom local sweating records and plasma ADH were obtained it is difficult to draw any firm conclusions.

5) Forearm Venous Compliance Changes after Bedrest

The decrease in orthostatic tolerance following actual or simulated weightlessness as been variously ascribed to the reduction in blood volume, reduced cardiac filling or muscle pumping, reduced arterial mechanoreceptor activity, decreased responses of vascular muscle to adrenergic neural activity, decreased skeletal muscle tone, decreased vascular tone, or increased distensibility of the lower limb veins (Levy and Talbot, 1983). That at least part of the orthostatic intolerance is probably due to factors other than the decrease in blood volume, is evident from studies in which the decrease in orthostatic tolerance persisted following bedrests where plasma volume was restored prior to orthostatic testing, by either oral rehydration (Hyatt, 1977) or administration of a mineralocorticoid (Bohnn et al, 1970).

One hypothesis in the present study was that following bedrest, there might be an attenuation of the sympathetic venoconstrictor response to exercise. The prolonged inactivity combined with a reduction in the lower body vascular volume was predicted to result in a relaxation of the vascular smooth muscle tone in the leg veins and/or a decreased responsiveness to hormonal or sympathetic nervous stimulation. In addition, the increased thoracic blood volume could result in an attenuation of the low-pressure baroreceptor responsiveness, resulting in delayed or unresponsive sympathetic venoconstrictor reflex response. Bevegard and Shepherd (1966) first demonstrated that during exercise, there is a sympathetic venoconstrictor response which is proportional to the intensity of the exercise challenge. Peripheral venous constriction during exercise helps to prevent blood pooling and enhance cardiac filling.

An impairment of these venous reflexes following bedrest would reduce, not only orthostatic, but also exercise tolerance.

In the present study, following bedrest the forearm venoconstrictor response to exercise was not significantly altered from the prebedrest condition. There was no evidence of a delayed or attenuated reflex venoconstriction, either at the beginning or at any time during the exercise test. Instead, following each bedrest there was a greater decrease in forearm venous compliance during exercise. This increased postbedrest venoconstriction might have occured in response to the increased relative exercise intensity (Bevegard and Shepherd, 1965) or in response to the decreased plasma volume (Fortney et al, 1983), at least in the non-premarin group. The similar forearm venoconstriction between the non-premarin and the premarin subjects suggests that either the decrease in plasma volume during bedrest does not alter the venoconstrictor response, or that significant blood pooling may have occurred in both groups following bedrest to negate any beneficial affects of the relatively bigger plasma volume in the premarin group.

These findings of a "normal" exercise venoconstrictor reflex following bedrest, agree with several other studies in which normal sympathetic nervous responses were seen after simulated weightlessness. Chobanian et al (1974) reported no change in postbedrest pressor responses to norepinephrine and angiotension infusions. The plasma catecholamine response to tilt also was unaffected following bedrest and the apparent turnover rate of norepinephrine was normal (Blomquist, 1983). Thus the superficial venoconstrictor responses appear to be maintained following periods of simulated weightlessness. However it is still possible that significant pooling of blood may occur in splanchnic or in dependent deep venous regions, such as in the lower legs. The deeper veins have less smooth muscle and are not as richly innervated as the superficial veins (Ludbrook, 1966). Thus the technique of measuring forearm venous constriction may resolve only that the superficial venoconstrictor reflex is maintained following bedrest, and may even attempt to compensate for the increased blood pooling which may simultaneously occur in dependent deeper veins. Therefore in the present study, as long as the women continued to perform rhythmic leg exercise, there was no problem of orthostatic intolerance. Only after they stopped pedalling, and the muscle pump action was no longer operative, was hypotension and fainting a common occurrence in the postbedrest test.

VI) CONCLUSIONS

The following conclusions may be drawn from this study:

1) Young healthy women have a similar loss of plasma volume during 12-day horizontal bedrest as that reported in the literature from men. In this study the decrease in plasma volume averaged 19.9% after bedrest 1, and 12.4% following the second bedrest in the same women.

2) Menstrual cycle stage has very little effect of the plasma volume changes during bedrest. Just prior to ovulation there is often a water-retaining effect, such that if a bedrest program begins at this

stage of the cycle, the hypovolemic response may be delayed for one or two days. Thereafter, plasma volume is decreased to a level similar to that seen in other women who began bedrest in other stages of the menstrual cycle.

3) Oral contraceptive usage (Ovulin 21 or Orthonovum) in two women did not significantly alter their body fluid responses during bedrest.

4) There was no correlation between the time-course of the decrease in plasma volume and the increase in urine output in this study during the first 5 days of bedrest, suggesting that the decrease in plasma volume is not a simple Henry-Gauer reflex response.

5) Premarin, an estrogen supplement, resulted in a recovery of plasma volume during bedrest and may therefore be used to establish a model whereby the effect of the decrease in plasma volume during bedrest may be separated from other bedrest effects. The premarin ingestion alone did not significantly alter any of the exercise responses studied (as determined from the control studies in the premarin group).

6) Maximal exercise responses following bedrest were not altered by plasma volume retention during the bedrest, were similar to those reported in men following bedrest, and were not correlated to pre-bedrest fitness.

7) Submaximal exercise responses were significantly altered following bedrest. Exercise heart rates were higher, stroke volumes were reduced, core temperatures were higher, blood lactates were higher, and sweating sensitivity was reduced. Cardiac outputs, sweating thresholds, and mean skin temperatures were not different from pre-bedrest tests.

8) No change in the % loss of plasma volume during exercise occurred between pre and postbedrest exercise tests, suggesting no change in capillary permeability following bedrest.

9) Surprisingly, no significant differences were seen between the postbedrest exercise responses of the non-premarin and the premarin groups. Alterations of plasma volume of less than 19.9% before normal ambulatory exercise tests, would significantly alter heart rate, stroke volume, sweating, and body temperature responses in normal ambulatory subjects. In the postbedrest condition, the varying levels of hydration had no influence on these exercise responses.

10) The sympathetic venoconstrictor response to exercise is not significantly altered following bedrest.

VII) RECOMMENDATIONS, DISCUSSION OF UNRESOLVED PROBLEMS, AND PROPOSED COURSES OF ACTION

1) Lack of an increased risk to women in space because of differing

body fluid responses. Need for further studies on menstrual function.

From the results in this study, women do not appear to be at greater risk than men during spaceflight because of differences in body fluid responses to weightlessness. Although women generally tend to have a smaller absolute blood volume, the decreases in plasma and red cell volume found in this study were of a similar relative magnitude as those reported in men. Thus the absolute decrease in plasma volume in these women resulted in a % change in plasma volume similar to the % changes which are reported to occur in men. Menstrual function and oral contraceptive usage had very little affect on the body fluid changes during bedrest. However further studies are needed on the potential effects of weightlessness on menstrual function. It is possible that some aspect of weightlessness (changes in blood volume, protein population, blood flow distribution pattern or organ perfusion, hormonal responses, etc.) might alter normal follicular development and decrease estrogen production. Further work is needed on the potential effects of menstrual dysfuncion with decreases in blood estrogens, on bone mineral losses during long-term exposure to weightlessness.

2) Further study of "fluid loading" countermeasures.

Several recent reports have been published about the success of fluid replacement through the use of salt tablets just prior to re-entry. While this treatment may be useful to prevent orthostatic intolerance in resting subjects, its usefullness in preventing an increased cardiovascular or thermoregulatory strain in men who must perform physical tasks shortly after re-entry is unclear. From the results of this study, following bedrest there was a severe impairment in cardiovascular and thermoregulatory responses to exercise, and these responses were not improved by preventing the decrease in plasma volume during bedrest. The additional factors (other than the decrease in plasma volume) responsible for the decreased postbedrest exercise tolerance (deconditioning, blood pooling, myocardial deconditioning) need to be further identified and methods for their compensation developed. To do these studies, models need to be developed in which weightless responses can be studied both with and without the decrease in plasma volume. It could prove useful to study effects of fluid replacement "acutely", just prior to re-entry vs. "slowly", by maintenance of plasma volume throughout a weightless procedure. Such a protocol might be useful to identify certain mechanisms of orthostatic or exercise intolerance which occur during spaceflight and are not rapidly reversible (ie. alteration of baroreceptor sensitivity, or redistribution of fluid between body fluid compartments). One could also evaluate potential negative effects of preventing the weightless hypovolemia (ie. if plasma volume was maintained at pre-spaceflight levels would facial swelling, headache, increased central venous pressure and thus cardiac preload occur) to determine whether plasma volume maintenance should be a goal during spaceflight.

Fluid loading "treatments" prior to spaceflight might also be explored. Is it possible to alter the plasma, interstitial, or intracellular composition prior to launch and minimize the

alterations in body fluids which occur during spaceflight? Would minimizing such fluid shifts reduce or prolong the initial readjustments to weightlessness? Would it alleviate the problems during re-entry?

3) Potential adaptation to repeated weightless simulations

During the second bedrest, the changes in plasma volume and the submaximal exercise responses were not as severely affected as during the first bedrest, suggesting that some sort of adaption may have occurred. Further studies could be conducted to confirm whether brief programs of simulated weightlessness prior to spaceflight might not decrease some of the discomfort experienced during an individual's actual weightless exposure.

VIII) REFERENCES

Wong,DF, HN Wagner, FR Dannals, JM Links, JJ Frost, et al. Effects of age on dopamine and seratonin recepters measured by positron tomography in the living human brain. Science 226: 1393-1396, 1984.

Wenger,CB, MF Roberts, JAJ Stolwijk, and ER Nadel. Forearm blood flow during body temperature transients produced by leg exercise. J Appl Physiol 38:58-63, 1975.

Wenger,CB, and MF Roberts. Control of forearm venous volume during exercise and body heating. J Appl Physiol 48:114-119, 1980.

Farhi,LE, MS Nesarajah, AJ Olszowka, LA Metildi and AK Ellis. Cardiac output determination by simple one-step rebreathing technique. Resp Physiol 28:141-159, 1976.

Bullard,RW. Continuous recording of sweating rate by resistance hygromentry. J Appl Physiol 17:735-737, 1962.

Van Beaumont, W., JE Greenleaf, and L Juhos. Disproportional changes in hematocrit, plasma volume, and proteins during exercise and bed rest. J Appl Physiol 33: 55-61, 1972.

Dill, DB, and DL Costill. Calculation of percentage changes in volume of blood, plasma, and red cells in dehydration. J Appl Physiol 37: 247-248, 1974.

Abraham, GE, GB Maroulis, and JR Marshall. Evaluation of ovulation and corpus luteum function using measurements of plasma progesterone. Obstet Gynecol. 44: 522, 1974.

Johnson, PC. Fluid volumes changes induced by spaceflight. Acta Astronautica 6: 1335-1341, 1979.

Greenleaf,JE, EM Bernauer, HL Young, JT Morse, RW Staley, LT Juhos, and W Van Beaumont. Fluid and electrolyte shifts during bed rest with isometric and isotonic exercise. J Appl Physiol 42: 59-66, 1977.

Witten, CL and JT Bradbury. Hemodilution as a result of estrogen therapy.
Estrogenic effects in the human female. Proc Soc Exp Biol and Med. 73: 626-629, 1951.

Preedy, JRK, and EH Aitken. The effect of estrogen on water and electrolyte metabolism. J Clin Invest 35: 423-429, 1956.

Dignam, WS, J. Voskian and NS Assali. Effect of estrogens on renal hemodynamics and excretion of electrolytes in human subjects. J Clin Endocrinol 16: 1032, 1956.

Gaebelein, CJ and LC Senay, Jr. Vascular volume dynamics during ergometer exercise at different menstrual phases. Eur J Appl Physiol 50: 1-11, 1982.

Greenleaf,JE, and S Kozlowski. Physiological Consequences of reduced physical activity during bed rest. Exercise and Sport Sciences Reviews, 10: 84-119, 1982.

Gauer, OH and JP Henry. Circulatory basis of fluid volume control. Physiol Rev. 43: 423-481, 1963.

Greenleaf, JE. Mechanisms for negative water balance during weightlessness: immersion or bed rest? Physiologist 28: S-38 - S-39, 1985.

Loucks AB, and SM Horvath. Athletic amenorrhea: a review. Med Sci Sports Exerc 17:56-72, 1985.

Hargens, AR. Fluid shifts in vascular and extravascular spaces during and after simulated weightlessness. Med Sci Sports Exerc. 15: 421-427, 1983.

Whittaker, PG, MRA Morgan, PDB Dean et al. Serum equilin, oestrone, and oestradiol levels in postmenopausal women receiving conjugated equine oestrogens. (Premarin). Lancet 1: 14-16, 1980.

Nicogossian, AE, and JF Parker. Space Physiology and Medicine . Chapter 13, NASA publication SP-447, 1982, pg 212-219.

Senay, LC Jr. Changes in plasma volume and protein content during exposures of working men to various temperatures before and after acclimatization to heat: separation of the roles of cutaneous and skeletal muscle circulation. J Physiol 224: 61-81, 1972.

Miller PB, RL Johnson, and LE Lamb. Effects of moderate physical exercise during four weeks of bed rest on circulatory functions in man. Aerosp Med 36: 1007-1082. 1965.

Saltin B, G Blomqvist, JH Mitchell, RL Johnson Jr. K Wildenthal, and CB Chapman. Responses to exercise after bed rest and after training. Circ 38 (Suppl 7), 1-78, 1968.

Taylor, HL, A Henschel., J Brozek, and A Keys. Effects of bed rest on cardiovascular function and work performance. J Appl Physiol 2: 223-239, 1949.

Convertino, VA, RW Stremel, EM Bernauer, and JE Greenleaf. Cardiorespiratory responses to exercise after bed rest in men and women. Acta Astronautica 4: 895-905, 1977.

Kanstrup, I and B Ekblom. Acute hypervolemia, cardiac performance, and aerobic power during exercise. J Appl Physiol 52: 1186-1191, 1982.

Greenleaf, JE and S Kozlowski. Reduction in peak oxygen uptake after prolonged bed rest. Med Sci Sports Exerc. 14: 477-480, 1982b.

Chase GA, C Grave, and LB Rowell. Independence of changes in functional and performance capacities attending prolonged bed rest. Aerosp Med. 37: 1232-1238, 1966.

Fortney, SM, CB Wenger, JR Bove, and ER Nadel. Effect of blood volume on forearm venous and cardiac stroke volume during exercise. J Appl Physiol 55: 884-890, 1983.

Fortney, SM, ER Nadel, CB Wenger, and JR Bove. Effect of blood volume on sweating rate and body fluids in exercising humans. J Appl Physiol 51: 1594-1600, 1981.

Hyatt, KH, LG Kamenetsky and WM Smith. Extravascular dehydration as an etiologic factor in post-recumbency orthostatism. Aerosp Med. 40: 644-650, 1969.

Harrison, MH. Effects of thermal stress and exercise on blood volume in humans. Physiol Rev. 65: 149-209, 1985.

Saltin B and L Hermansen. Esophageal, rectal and muscle temperature during exercise. J Appl Physiol 21: 1757, 1966.

Roberts, MF, CB Wenger, JAJ Stolwijk, and ER Nadel. Skin blood flow and sweating changes following exercise training and heat acclimation. J Appl Physiol 43: 133-137, 1977.

Greenleaf JE and RD Reese. Exercise thermoregulation after 14 days of bed rest. J Appl Physiol 48: 72-78, 1980.

Levy MN and JM Talbot. Cardiovascular deconditioning of space flight. Physiologist 26: 297-303, 1983.

Hyatt, KH and DA West. Reversal of bedrest-induced orthostatic intolerance by lower body negative pressure and saline. Aviat. Space Environ. Med 48: 120-124, 1977.

Bonn, BJ, KH Hyatt, LG Kamenetsky, BE Calder, and WM Smith. Prevention of bed-rest induced orthostatism by 9-alpha-fluorohydrocortisone. Aerosp Med 41:495-499, 1970.

Bevegard BS and JT Shepherd. Reaction in man of resistance and capacity vessels in forearm and hand to leg exercise. J Appl Physiol 21: 123-132, 1966.

Chobanian AV, RD Lille, A Tercyak and P Blevins. The metabolic and hemodynamic effects of prolonged bed rest in normal subjects. Circ 49: 551-559, 1974.

Blomqvist, CG. Cardiovascular adaptation to weightlessness. Med Sci Sports Exerc 15: 428-431, 1983.

Ludbrook J. Venous function in the lower limbs . Charles C Thomas Comp. Springfield, Ill, 1966, pgs 3-87.

ACKNOWLEDGEMENTS

Other individuals whose help was greatly appreciated in the work done in this contract included the following:

Claudia Turner. Graduate student in the School of Public Health
Mat Friedetzky. German exchange student.
The management of the Johns Hopkins Sheraton Hotel.
Clarke Tankersley. Head technician and student, School of Public Health
Kirsti Levine. Technician and student. Johns Hopkins Univerrsity
Bethli Meischer. Post doctoral fellow, School of Public Health
Ajay Carpenter. Visiting research scientist.
Larry Molson. Graduate student, Dept. of Biostatistics.
Em Shivoder. Instrument designer, School of Public Health
John Howell. Instructor, School of Public Health
Howard Zacur. Director, Reproductive Endocrinology Laboratory
Daniel Hanley. Assistant Professor, Dept. Neurology
Dean Wong. Depts. or Radiation Health Sciences and Nuclear Medicine
The subjects, without whose help the study could not have been done.

Appendix 1: Committee on Human Volunteer Forms

Report to Human Volunteers Committee concerning possible complications resulting from continuous bedrest.

Project Title: Bedrest in Healthy Women: Effects of Menstrual Function and Oral Contraceptives.

Principal Investigator: Suzanne Fortney, Assistant Professor, Division of Environmental Physiology.

Subject Involved: Subj. A

Description of Incident:

Subj. A along with six other healthy, non-oral contraceptive pill users, successfully completed the preliminary testing and the first 13-day bedrest procedures. All of Subject A preliminary values, including exercise responses, blood volume, hematocrit, proteins, and electrolytes, were within normal values and similar to the values of the other subjects.

July 9, 1982

Immediately after the bedrest protocol Subj. A performed a submaximal exercise test without unforeseen complications.

July 10, 1982

A maximal exercise test was performed. No problems were reported, and her maximum oxygen consumption was similar to the pre-bedrest value.

July 11, 12

Subj. A noticed swelling and pain in her lower legs and ankles but did not contact anyone in the study.

July 13

Subj. A called my technician, Claudia Turner and reported pain in her legs. She was asked to report to the exercise laboratory where she was examined by Dr. Sol Permutt. Sol further referred her to Dr. Ko-Pen Wang of the Johns Hopkins Hospital in the Division of Respiratory Medicine. Dr. Wang is an individual not directly involved in this study. He reported swelling in both ankles, the right ankle more than the left, but no pain or redness. His impression was that there may have been a mild phlebitis in her right foot and recommended that she continue her usual activities. He felt that anticoagulant therapy was not indicated.

Experimentation on all subjects was cancelled until a full evaluation of Subj. A responses could be made.

Each subject was contacted to see if they reported similar symptoms. One subject, Subj. B , reported pain in her lateral thigh. She was examined by Dr. William Beckett by tests of impedance phlebography of both legs, and by plain x-ray of the right leg and hip. His conclusion was

she may have experienced a slight muscle strain in the right thigh.

July 14, 1982

Dr. Beckett contacted Subj. A and asked to perform an impedance phlebography test to screen for venous occlusion. Although Subj. A had reported to work in the morning, she left early because of a headache and had to postpone the impedance procedure.

July 15, 1982

Dr. Beckett examined Subj. A legs which now had only bilateral trace edema, with no pain or redness. The results from an impedance phlebography test were normal.

July 26, 1982

A meeting was held of a special medical advisory committee composed of Dr. Warren Summer, Dr. Peter Terry, Dr. Harold Menkes, Dr. Bill Beckett and Sol Permutt. The following conclusions and recommendations were made --

1) It is still unclear what triggered the swelling following bedrest in Subj. A Dr. Summer and Dr. Terry thought that the course of the swelling did not suggest clinical deep vein thrombosis, but the possibility of a mild episode of blood clotting could not be ruled out. Another possibility discussed was that muscle tissue damage produced by the severe exercise after prolonged muscle disuse may have caused fluid accumulation in the lower legs.

2) Because of the unexplained reaction to the bedrest procedure it was recommended that Subj. A should not repeat the bedrest. However, because of the importance of further information about possible side effects in other subjects who may also have a similar predisposition to leg swelling after bedrest, it was recommended that Subj. A be allowed to continue with all other aspects of the study - exercise and blood volume tests at various stages of the menstrual cycle. She should not be penalized monetarily because of not completing the bedrest protocol.

3) Each subject will be contacted and informed of the reactions reported by Subj. A and advised of the possible risk of a similar reaction. The consent form will be altered to include special mention of an increased risk of blood clotting or leg swelling following bedrest. Each subject will be asked to sign the new consent form.

4) Careful monitoring of leg size during and after bedrest was advised during further testing. Leg circumference will be measured on alternate days during bedrest, and during the first five days of recovery following bedrest. Venous occlusion plethysmography on a lower leg will be performed on each subject at rest prior to the submaximal exercise tests both before and after bedrest. This test may determine whether there is significant loss of venous tone specifically in the lower legs.

(continued)

5) If in the future a subject complains of leg swelling following bedrest, a 10cc venous blood sample will be obtained to determine plasma creatine phosphokinase levels. Thus we can test for the presence of possible muscle damage which may account for leg swelling. Impedance phlebography will also be performed to test for venous occlusion.

6) The initial medical history of all future studies will include specific questions addressing the occurance of blood clotting disorders in the potential subject or her immediate family.

7) Anticoagulant therapy in future studies was discussed and discouraged. This option was also considered prior to the start of this study and rejected because there is no information present about the efficiacy of administration of heparin to normal subjects during prolonged bedrest, and because of the increased discomfort and added risk of frequent injections (twice a day). A NASA consultant (Dr. Peter Bungo) who has participated in bedrest studies agreed that anticoagulant therapy is inadvisable during bedrest in healthy individuals. Elastic stockings and leg exercise during bedrest were ruled out because these procedures may alter the blood volume responses being studied in the protocol. Leg massage was recommended if subjects complain of leg cramping or tingling during bedrest.

8) The consent form should also point out the additive risk of blood clotting in subjects who use the pill and perform bedrest. Subjects who take oral contraceptives have been shown (Am. J. Epidemiol. 90, 365) to have a 4.4 fold greater risk of pulmonary embolism than non-pill users. This additional risk must be added to the risk of blood clotting induced in the bedrest protocol. (No data is available to evalute the risk of blood clotting in normal healthy individuals confined to bed). Presumably, the risk lies somewhere between the statistics of risk in normal ambulatory women of child bearing age who suffer from blood clots in the legs, about .22 percent/yr (JAMA 219:583); and women who suffer thrombosis in uncomplicated but major surgery, 2% for deep vein thrombosis.

9) In summary, this particular subject was considered to be at increased risk to repeat the bedrest portion of this study and will be asked not to repeat bedrest. All other subjects will be advised of the possibility of lower extremity swelling following bedrest. Although critical data has already been lost pending the decision of the medical advisory committee, it is recommended that the study continue on schedule as determined by the menstrual cycle of each subject and the scheduling difficulties of the bedrest procedure.

Suzanne Fortney
William A Bennett
Peter Bungo
Harold Manker
Wan Sun
Sol Permutt

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September 14, 1982

Arthur Bushel, D.D.S.
Chairman, Committee on Human Volunteers
4041 Hygiene
School of Hygiene

Re: RPN Entitled: "Bedrest in Healthy Women: Effects of Menstrual Functions and Oral Contraceptives"

Dear Art:

Thank you for the report of possible complications in the conduct of the above-referenced research project.

Although phlebitis would be the most worrisome complication, the descriptions of the patients difficulties are not significantly detailed to permit any value judgement on that point. Certainly the studies with impedance plethysmography were performed at a stage when the process was obviously resolved or resolving. My only suggestion for the future would be that specific studies be instituted promptly should this complication reoccur. I suggest that the principal investigator contact Dr. William Bell, Division of Hematology, to determine whether any of the studies of fibrin split products might not provide a more sensitive indication of thrombosis than impedance plethysmography. As you know Dr. Bell's main research interest over the years has been intravascular coagulopathy.

I would like to point out that the printing of the subjects name on the incident report, which receives wide circulation, is a violation of confidentiality. The patient's name is not in any way important in determining the nature of the complication. Therefore, the name should be deleted from all communications regarding the reseach project, its conduct and any adverse effects.

Sincerely yours,

Thomas R. Hendrix, M.D.
Chairman - J.C.C.I.
c/o 127 S/M Admin. Bldg.

TRH:cap

cc: Dr. Faulkner

Received 9/20/82 M.P

Appendix 2: Pulmonary Function Results

EFFECT OF PROLONGED BEDREST ON LUNG VOLUME IN NORMAL INDIVIDUALS

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Running Head: Lung function and bedrest

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ABSTRACT

Pulmonary function was assessed in supine subjects before, during and after three separate bedrest studies of 11 and 12 days duration. Forced vital capacity (FVC) increased during bedrest in each subject. Total lung capacity by helium dilution was measured in one bedrest study and increased in each subject, while residual volume and resting volume of the lung did not change. No change in FVC was found in an ambulatory control group using identical measurement techniques. Maintaining baseline plasma volume during one bedrest by the use of exogenous estrogen did not prevent an increase in FVC, and decreasing plasma volume with diuretics in ambulatory subjects to the same degree as seen in the bedrests did not cause an increase in FVC. We conclude that prolonged bedrest results in a small, significant increase in maximum lung volume, and that this change is not dependent on alterations in plasma volume.

INDEX TERMS: Pulmonary function, lung volume, bedrest

Mechanical function of the normal lung may be altered by changes in the gravitational environment or by altering the body's position within the gravitational field (3,4,12,14,15). Within minutes of going from the upright to the supine position, lung volumes in normal subjects decrease, the largest change being in the residual volume of the lungs at the end of a maximal expiration (17). These postural changes in residual volume (RV) and to a smaller degree in the forced vital capacity (FVC) can be prevented by maneuvers designed to obstruct the transfer of blood from the legs to the upper body -- such as placing tourniquets around the thighs (16). Such immediate changes in lung volume are caused in part by flow of blood from the lower body into the chest; they are considered static changes in lung mechanics, and have been assumed to persist while the supine position is maintained.

Prolonged bedrest places the lungs at 90° to the usual upright relation to the gravitational field for an extended period of time. It has been used as a model of a zero gravity environment to induce decrements in intravascular volumes, orthostatic tolerance, and cardiovascular and skeletal muscular conditioning such as those seen during zero-gravity spaceflight. Previous studies of lung mechanics before and after prolonged bedrest have not detected significant changes other than those seen immediately on lying down (9,19). The purpose of the present studies was to re-examine whether lung function changes occur in normal subjects during eleven to twelve-day bedrests.

Methods and Procedures

Eighteen healthy adults (Table 1) gave informed consent to participate in these studies; twelve in the bedrest studies, and seven in the ambulatory control and diuresis studies. Only one subject in the bedrest studies (number 8)

also participated in the ambulatory control and diuresis studies (number 14). Informed consent was obtained from each subject, and the protocols were approved by the Human Volunteers Committee of the Johns Hopkins Medical Institutions.

Before and after each bedrest study and before the ambulatory control studies absolute plasma volume and absolute red cell volume were determined by radionuclide dilution techniques (technetium labeled human serum albumin for plasma volume and technetium labeled autologous red blood cells for red cell volume). Subsequent changes in blood volume were calculated from alterations in hemoglobin and hematocrit (10). In each study, subjects received one training session for familiarization with the techniques of pulmonary function measurement before the first control session.

I. Bedrest Studies

Subjects remained supine in bed for eleven days in the first two bedrests (BR1 and BR2) and for 12 days in the third bedrest (BR3). Subjects did not exercise while in bed, and were limited to no more than 15 minutes in the seated position per 24 hour period.

The first two bedrests, using the same subjects (No. 1-6, table 1), were conducted consecutively, separated by a four week recovery period. In BR3 a comparable group of six subjects (No. 7-12, table 1) completed the identical protocol except that each received daily oral estrogen supplementation (Premarin, 1.25 mg) to maintain plasma volume under conditions where a spontaneous diuresis of plasma volume would otherwise occur during the first few days of bedrest, resulting in a persistent lowering of plasma volume for the duration of bedrest.

In each bedrest study, two sets of control pulmonary function measurements

C-2

were made on two days prior to the start of bedrest. Tests were repeated daily during bedrest (at approximately the same time of day), one day after the end of bedrest, and after two weeks ambulatory recovery. All pulmonary function measurements, including pre-bedrest control and post-bedrest recovery measurements, were made with subjects in the supine position.

Daily 4 cc blood samples for calculation of plasma volume were taken with free flowing technique at the same time each morning within one hour of pulmonary function tests. Each sample was analyzed for whole blood hemoglobin concentration (cyanmethemoglobin technique in triplicate), hematocrit (microhematocrit technqiue in triplicate), total plasma protein concentration (refractive index in quadruplicate), and plasma osmolality (freezing point depression in duplicate).

Forced expiratory volume in the first second of expiration (FEV_1) and FVC were tested using a Stead-Wells survey spirometer and technique meeting the ATS Snowbird Criteria (1) each day during all bedrests. In BR1 and BR2, the two largest values of three acceptable spirograms were averaged to determine that subject's FEV_1 and FVC for a given day. In BR3, the single largest values from three acceptable spirograms were used as the subject's FEV_1 and FVC for a given day. All spirograms including pre- and post-bedrest studies were performed with subjects in the supine position and were interpreted by the same reader. In BR1 and BR2, single breath diffusing capacity of the lungs for carbon monoxide (D_{LCO}) was measured by the method of Forster, et al. (11), and slope of phase III of the single breath nitrogen washout test was measured by the method of Craig et al. (7), with subjects exhaling at a rate of approximately 500 ml $\cdot$ sec $^{-1}$ into a direct-reading nitrogen analyzer. Records were traced on an X-Y

recorder (Gould), and determinations were the average of two consecutive expiratory maneuvers. Maximal inspiratory pressure at FRC and expiratory pressures at TLC were measured by the method of Black and Hyatt (2). In BR3 measurements of the resting lung volume or functional residual capacity (FRC) by helium dilution, and total lung capacity (TLC) and residual volume (RV) by addition and subtraction of spirometrically measured volumes from FRC (6) were made in addition to measurements of spirometry and diffusing capacity.

II. Ambulatory Control Study

Seven healthy adults served as ambulatory controls for the bedrest study. (Anthropometric data for this group, subjects No. 13-19, are included in Table 1). All pulmonary function measurements of spirometry and diffusing capacity were made in the supine position using the same technicians, technique and equipment as is described under Bedrest Studies, above. Each subject performed six series of pulmonary function tests over a period of nine to thirteen days. Measurements were made at the same time each day, and subjects lay in the supine position for forty minutes to one hour before measurements were made.

III. Diuretic Study

Plasma volume was altered using diuretics followed by intravenous infusion of isoncotic fluid in ambulatory subjects to determine the effect of plasma volume change on pulmonary function.

Following the ambulatory control measurements, subjects No. 13-19 underwent rapid reduction of plasma volume and total body water over several days by taking a diuretic (hydrochlorothiazide 25 mg plus triamterene 50 mg, every 12 hours). Subjects lay in the supine position for forty minutes to one hour prior to measurements, and measurements were made at the same time each day. Samples

of venous blood (5 ml.) were drawn each day with care to maintaining horizontal position of the arm. Analyses of the blood samples were performed as described above under Bedrest Studies. Diuretic treatment was continued until plasma volume loss of 15% or more had occurred, (1-3 days on diuretic). On the last day of diuresis, blood and pulmonary function tests were performed before and immediately after restoration of plasma volume by intravenous infusion of a solution of 5 per cent human serum albumin suspended in isotonic saline and warmed to 37°C. Diuretic administration was then stopped and measurements repeated the following day.

Statistical Analyses

For the bedrest, ambulatory control and diuretic studies, each dependent variable was tested by a one factor factorial analysis of variance with repeated measures across time to determine if bedrest or diuresis caused significant changes (alpha = .05) from control measurements. If the omnibus F indicated significance then post-hoc testing was performed on the ordered means by the Neuman-Kuels technique. Student's t-test was used to compare inspiratory pressures and expiratory pressures before, at the end of, and after bedrest.

For the diuretic study the six ambulatory control determinations for each lung function test and for plasma volume were averaged for use as the control value for each subject. Immediate pre-infusion and one day recovery values were tested together with the average control value for changes across time and daily measurements of each lung function test were compared with that day's plasma volume by least squares regression techniques. Pearson product-moment correlation coefficients were calculated.

RESULTS

I. Bedrest Studies

Figure 1 shows the rise in FVC and FEV_1 during both BR1 and BR2. During BR1, FVC was significantly greater than control on day three of bedrest ($P<.05$) and remained significantly elevated throughout bedrest with a maximum rise of 270 ml above control. Significant elevation persisted through the one day and two week recovery period. An increase in FVC was seen in each subject during BR1 and BR2. In the second bedrest FVC was significantly increased above control on day 4 ($P<.05$) with a maximum elevation 240 ml above control and remained significantly elevated above control throughout bedrest and the first recovery day. These increases in volume during bedrest represent 6% (BR1) and 3% (BR2) of the mean control FVC.

The time course of increase in FEV_1 (Fig. 1) closely parallels the increase in FVC seen in both BR1 and BR2 indicating that the rise in FEV_1 is a volume dependent flow increase. The ratio of FEV_1/FVC did not change significantly during bedrest.

In BR3, FVC again increased significantly over control values by the third day of bedrest, and remained elevated throughout the remaining days of bedrest, (Figure 2). The maximum mean increase in FVC, seen on day 9 of bedrest, was 206 ml or 5.4% over control. To determine whether the increase in FVC seen in the previous bedrests was due to increased TLC, decreased RV or a combination, lung volumes were measured in this bedrest using helium dilution. Increases in FVC and in TLC were seen in each subject during BR3. TLC was significantly greater than control at the fourth day of BR3 and remained elevated above control through the 12th day. The maximal increase in TLC was 180 ml over

control. One day and two-week recovery values were not significantly greater than controls. The maximal inspiratory and expiratory pressures, an index of respiratory muscle isometric strength measured at FRC for inspiration and TLC for expiration, did not change significantly in BR1 and BR2 comparing pre-bedrest controls to the last day of bedrest and day 1 recovery.

Changes in D_LCO did not follow a consistent pattern. When all bedrest values for diffusing capacity were compared with all control values by analysis of variance, they were found to be significantly lower. The mean decrease in D_LCO during BR1 was -1.7 $cc \cdot min^{-1}_{mmHg^{-1}}$ ($P<.05$) and during BR2 -1.65 $cc \cdot min^{-1}_{mmHg^{-1}}$ ($P<.002$). However, day-by-day analysis of D_LCO changes during bedrest and recovery showed D_LCO was significantly ($P<.05$) lower than controls only on day 1 recovery in BR1, and on bedrest days 5 and 6 during BR2.

Figure 3 shows mean changes in plasma volume, total protein concentration and osmolality during BR1 and BR2, demonstrating the plasma volume diuresis which regularly accompanies prolonged bedrests. During the first bedrest the mean plasma volume for the six subjects decreased a maximum of -20% (-487 ml) in the first six days, and remained decreased from control values during the following days of bedrest. Similarly in the second bedrest, plasma volume decreased by -14% (-317 ml) during the first six days and remained in this range during the remaining days. Plasma volume was significantly lower than control ($P<.05$) on days 2-9 during BR1 and days 2-10 during BR2. At 24 hours after the end of BR1 and BR2, plasma volume had returned to control levels. Total red cell mass decreased by a mean of -5.9% or -121 ml (not significant) during the eleven days of BR1, and by -2.1% or -50 ml (not significant) during BR2. Comparison of the increase in FVC in Figure 1 with the concurrent fall in plasma

volume in Figure 2 suggested an association between changes in total plasma volume and FVC.

These observations motivated the measurements of FVC in studies using slightly different conditions. The first was a repeat of the bedrest studies (BR3) under conditions identical to BR1 and BR2 except that diuresis was inhibited by the use of exogenous estrogen. The second used controlled diuresis of plasma volume in ambulatory subjects, (diuretic study below). No significant overall change in plasma volume occurred in the BR3 subjects taking estrogen, while FVC and TLC increased significantly as noted above.

II. Diuretic Study

Oral diuretics used in ambulatory subjects produced decrements in plasma volume in each of the seven subjects comparable to those measured during bedrest. The mean decrease in plasma volume in the seven subjects was -20.4%, significantly lower than control (Figure 4). During this induced diuresis there was no significant change in FVC compared with control measurements (Figure 4). The maximal decrease in plasma osmolality was -1% (-3 mOsm $\cdot$ l^{-1}) and maximal increase in plasma protein concentration was 19% (+1.3 gm%). Infusion of the saline and albumin solution after diuresis was completed increased plasma volume by a mean of 832 ml to 3% above control plasma volume. After reinfusion, mean plasma osmolality was at 1% below control and plasma protein concentration at 10% above control. No significant relationship between plasma volume changes and FVC, FEV_1, or D_LCO was detected by linear regression analysis of all control, diuresis, re-infusion, and one day post-infusion values. FVC and plasma volume during diuresis are plotted against time in Figure 3. The lack of change in FVC during diuresis is contrasted with the increase in FVC found during all

bedrests (Figures 1 and 2).

DISCUSSION

The mechanical relationships of the static lung volumes requires that the significant increase in FVC found in the three bedrest studies must result either from increased TLC, decreased RV, or a combination of the two. The finding of increased TLC in BR3 with no significant change in FRC indicates that all or most of the increased FVC is due to increased TLC.

Explanations for the increase in FVC and TLC can be divided into three groups: increased neuromuscular force to inflate the lungs, increased chest or lung compliance, or a change in the mechanical relationship of inspiratory muscles to chest wall allowing more negative pleural pressures and greater inflation of the lungs per unit of tension produced by the inspiratory muscles.

Increased neuromuscular force may occur either through increased maximum neural output to the inspiratory muscles or by augmentation of the maximum musclar force of contraction to maximum neural stimulation. Some studies of spirometry in normal subjects have shown small increments in FVC on serial testing which are attributed to a training effect, with better performance through familiarity with the procedure or conditioning of the inspiratory muscles. Three findings of the present studies suggest that neither a learned response in the performance of spirometry nor a muscle conditioning effect can account for all of the observed increase in FVC. First, a significant increase in FVC was found in BR2 in the same subjects already familiarized with the procedure from each completing over 50 spirograms during the BR1 measurements several weeks before. Second, an increase in FVC due to conditioning of inspiratory muscles would be expected to be accompanied by increased isometric muscu-

lar force, which would be reflected in increased maximal inspiratory pressure when breathing against an occluded mouthpiece from FRC. No change in maximal inspiratory pressure was seen during either BR1 or BR2 in these subjects. Third, when the same techniques of measuring supine FVC were followed in a similar group of ambulatory control subjects, no increase in FVC was found, indicating that the measured increase in lung volume in the present studies was related specifically to bedrest and not to a training process.

Increased compliance of the chest wall or the lungs in the presence of unchanged neuromuscular force would also result in increased FVC and TLC. Alteration in airway tone, interstitial water, mechanical properties of the interstitium, or elastic properties of the chest wall as a result of bedrest alone appears unlikely. However, changes in lung volumes due to alterations of central vascular engorgement with blood, leading to alteration in pulmonary compliance or a displacement of air spaces, may occur. Buono (5) has demonstrated that increasing central vascular engorgement either by head-out water immersion or by G-suit inflation to 80 torr about the calves and thighs of normal subjects results in decreases in FVC of -5 to -6% below control. Conversely, Potanin et al. (18) have demonstrated increased vital capacity by applying -30 Torr lower body negative pressure. Because a spontaneous diuresis of plasma volume during bedrest was associated with increased FVC, it was suggested that a decrease in central vascular volume associated with diuresis might account for the increased lung volumes. However, induction of a comparable plasma volume loss by diuretics in ambulatory subjects did not alter lung volumes, indicating that a 20% decrease in plasma volume is not alone sufficient to produce the changes in lung volume seen in bedrest.

Demonstration of these changes repeatedly in the same subjects of BR1 and BR2, with a return toward control levels in the interval between bedrests, suggests a gradual process independent of muscular force or strength. Without change in either neuromuscular output or chest compliance, a shift in the anatomic relationship of the inspiratory muscles to the chest wall that improves their mechanical advantage in generating lower pleural pressure without increasing their maximum tension may have this result. Such anatomical adjustments, occurring gradually over several days after the acute decrease in lung volume on going from the upright to supine position, would represent an opposite and approximately equal compensatory change to the initial postural change in lung volume. The present results would support such a hypothesis, but do not indicate the mechanism for such a gradual compensation.

These changes were not seen in one previous study of pulmonary function in four subjects during bedrest (8), although small non-significant increases in FVC and TLC were found in another five healthy subjects after 20 days bedrest (19). Our study of a larger number of subjects or the use of more consistent measurement with subjects always supine may explain why these changes were seen in the present but not the previous studies.

In conclusion, a small increase in maximum lung volume (TLC) demonstrated during prolonged bedrest in normal subjects appears to be a true alteration in lung mechanics and not the result of decreased plasma volume alone.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the technical assistance of Louis Wilkinson, Michael Soaper, Thomas Cross, Debbie Gerke, and Clarke Tankersley.

This research was partially supported by NASA, NIH grants HL 10342 and HL 07534, and NIOSH.

REFERENCES

1. ATS Snowbird Workshop: Standardization of Spirometry. Am. Rev. Respir. Dis., 199: 831, 1979.

2. Black, LF, and RE Hyatt. Maximal respiratory pressure: normal values and relationship to age and sex. Am. Rev. Respir. Dis. 99: 696-702, 1969.

3. Bryan, AC, WD MacNamara, J Simpson and HN Wagner. Effect of acceleration on the distribution of pulmonary blood flow. J. Appl. Physiol. 20: 1129-1132, 1965.

4. Bryan, AC, J Milic-Emili and D Pengelly. Effect of gravity on the distribution of pulmonary ventilation. J. Appl. Physiol. 21: 778-784, 1966.

5. Buono, MJ. Effect of central vascular engorgement and immersion on various lung volumes. J. Appl. Physiol. 54: 1094-1096, 1984.

6. Meneely, AR, and NL Kaltreider. The volume of the lung determined by helium dilution. Description of the method and comparison with other procedures. J. Clin. Invest. 28: 129, 1949.

7. Craig, D, W Wahra, H Don, J Couture, and M Becklake. Closing volume and its relation to gas exchange in seated and supine positions. J. Appl. Physiol. 31: 717, 1971.

8. Dietlein, L and W Judy. Experimental M-2 cardiovascular conditioning. In: Manned Space Flight Experiments, Interim Report, Gemini V Mission. National Aeronautics and Space Administration. Washington, D.C. January 6, 1966.

9. Dietrick, JE, GD Whedon, E Shorr, V Toscani and VB Davis. Effect of immobilization upon various metabolic and physiologic functions of normal men. Am. J. Med. 4: 3-35, 1948.

10. Dill, DB, and DL Costill. Calculation of changes in volumes of blood plasma and red cells in dehyration. J. Appl. Physiol. 37: 247-248, 1974.

11. Forster, RE, WS Fowler, DV Bates and B Van Lingen. The absorption of carbon monoxide by the lungs during breathholding. J. Clin. Invest. 33: 1135-1145, 1954.

12. Glazier, JB, JMB Hughes, JE Maloney, and JB West. Effect of acceleration on alveolar size in the lungs of dogs. Aerosp. Med. 39: 282-288, 1968.

13. Michels, DB and JB West. Distribution of pulmonary ventilation and perfusion during short periods of weightlessness. J. Appl. Physiol. 19: 212-216, 1964.

14. Milic-Emili J, JA Henderson, MB Dolovich, D Trop and K Kaneko. Regional distribution of inspired gas in the lung. J. Appl. Physiol. 21: 747-759, 1966.

15. Milic-Emili, J, J Mead, and JM Turner. Topography of esophageal pressure as a function of posture in man. J. Appl. Physiol. 19: 212-216, 1964.

16. Mills J. The influence upon the vital capacity of procedures calculated to alter the volume of blood in the lungs. J. Physiol. London. 110: 207-216, 1949.

17. Moreno, B, and H Lyons. Effect of body posture on lung volumes. J. Appl. Physiol. 16: 27-29, 1961.

18. Potanin, C, S Morehead, WW Neblett, and BC Sinclair-Smith. Respiratory mechanics with lower body negative pressure (LBNP) a simulation of the erect posture. Aerosp. Med. 40: 1101-1104, 1969.

19. Saltin, B, G. Blomquist, JH Mitchell, RL Johnson, K Wildenthal, and C. Crapman. Response to exercise after bedrest and after training. Circulation 38 Suppl VII: VII-1 through VII-78, 1968.

20. Sawin, CF, AE Nicogossian, JA Rummel, and EL Michel. Pulmonary function evaluation during the Skylab and Apollo-Soyuz Missions. Aviat. Space and Env. Med. 47: 168-172, 1976.

21. West, JB and FL Matthews. Stresses, strains and surface pressures in the lung caused by its weight. J. Appl. Physiol. 32: 332-345, 1972.

22. West, JB and CT Dollery. Distribution of blood flow and ventilation-perfusion ratio in the lung, measured with radioactive CO_2. J. Appl. Physiol. 15: 405-410, 1960.

LEGENDS

Figure 1: Mean forced vital capacity of the lungs (FVC) and mean forced expiratory volume in one second (FEV_1) for six subjects as a function of time measured daily during pre-bedrest control (C), bedrest days 1-11, one day post-bedrest recovery (R1), and two weeks post-bedrest recovery (R2). Circles indicate days on which values were significantly ($P<.05$) greater than control during the first bedrest (BR1), and squares days on which values were greater than controls during the second bedrest (BR2) in the same six subjects.

Figure 2: Mean total lung capacity (TLC) forced vital capacity (FVC) and residual volume (RV) of the lungs of the six subjects in the third bedrest study (BR3). Circles indicate days on which volume was significantly greater than control ($P<.05$). There was no significant change in RV.

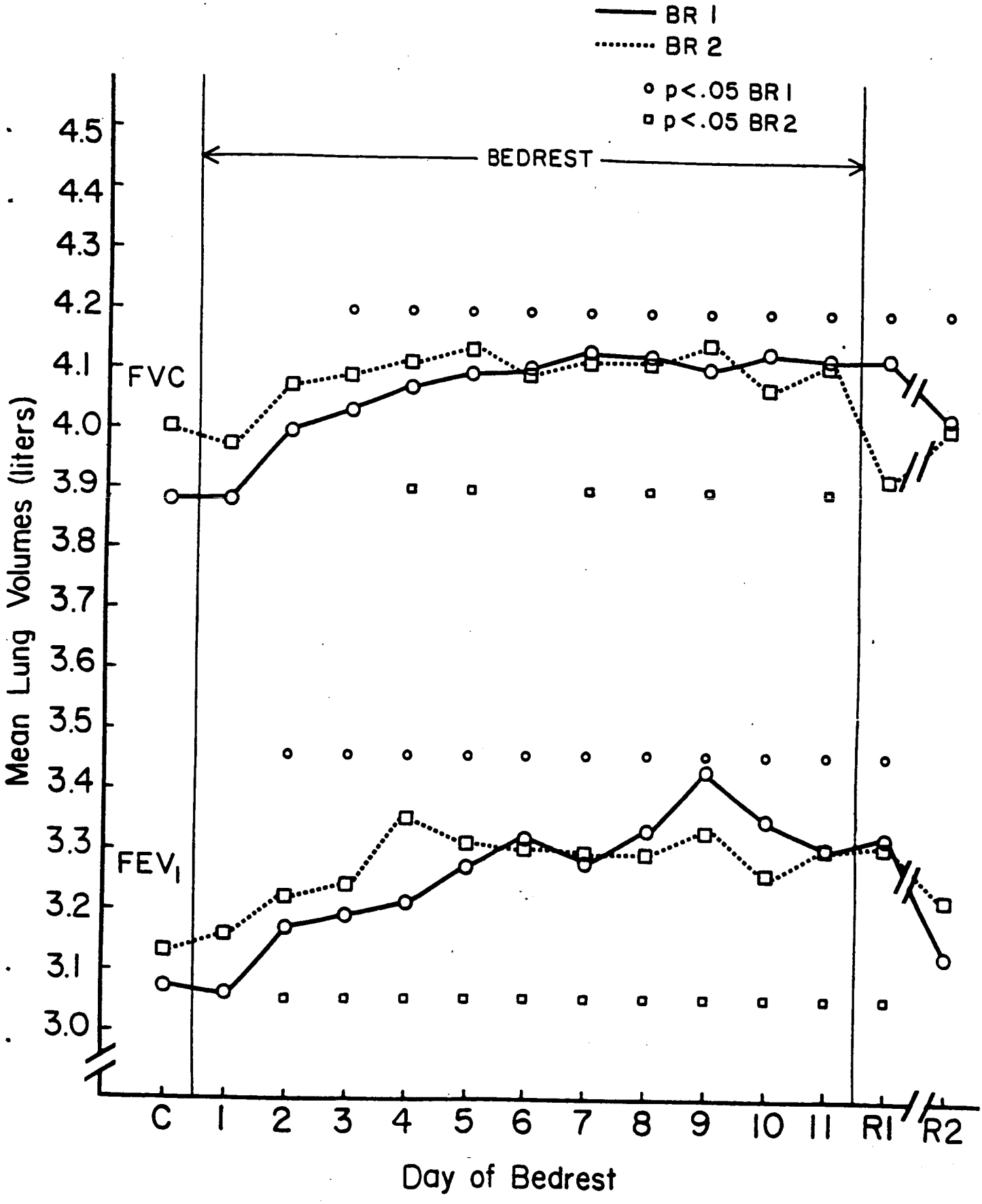
Figure 3: Mean values for absolute plasma volume (ml), plasma osmolality, and plasma protein concentration (gm%) for the same six subjects as a function of time during bedrest 1 and bedrest 2. Circles indicate days on which values were significantly ($P<.05$) different from controls during bedrest 1, and squares during bedrest 2.

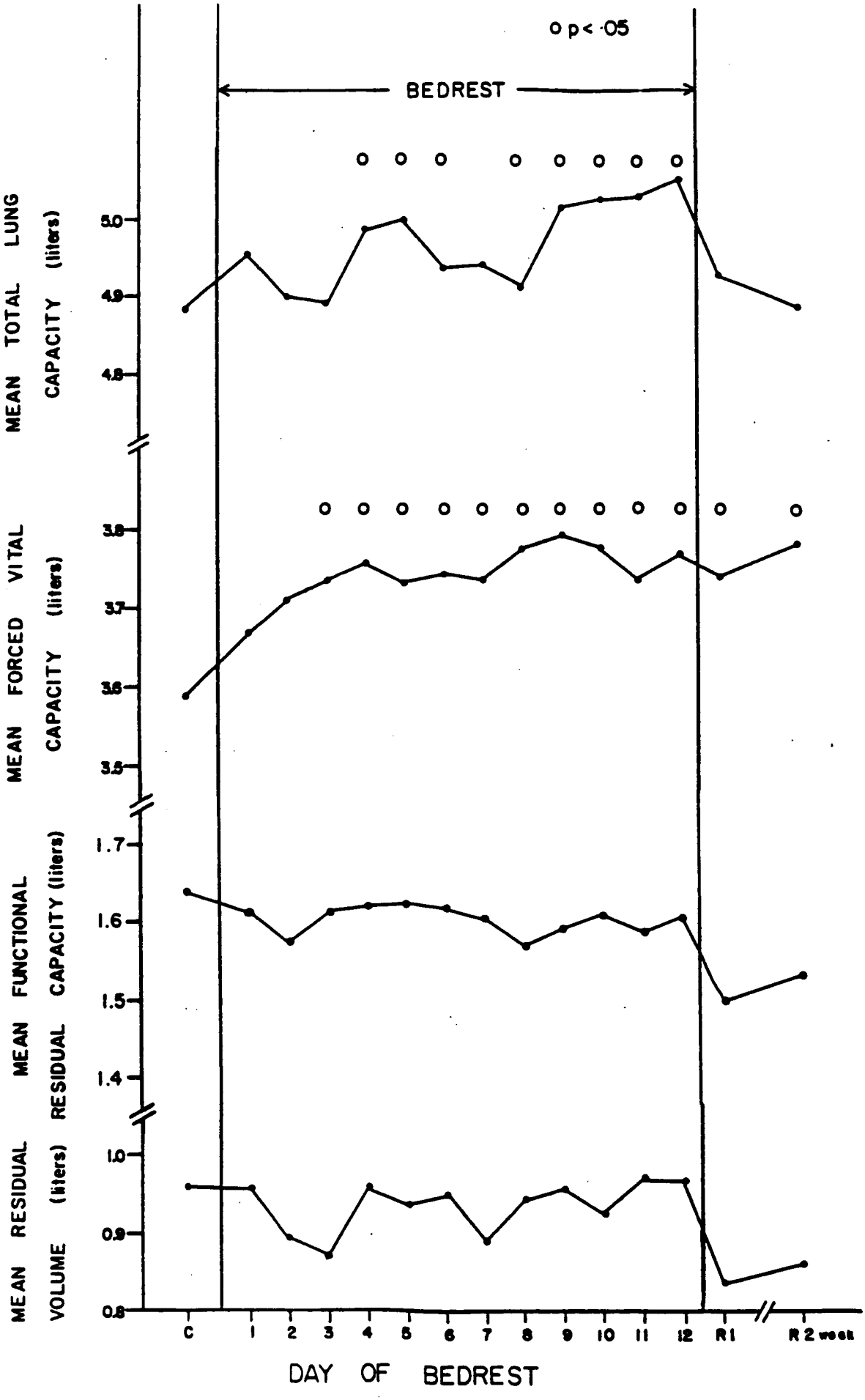
Figure 4: Forced vital capacity (FVC, mean $\pm$ S.E.M.) and absolute plasma volume (PV, mean $\pm$ S.E.M.) for seven subjects during pre-diuresis control measurements, after diuresis (prior to re-infusion of

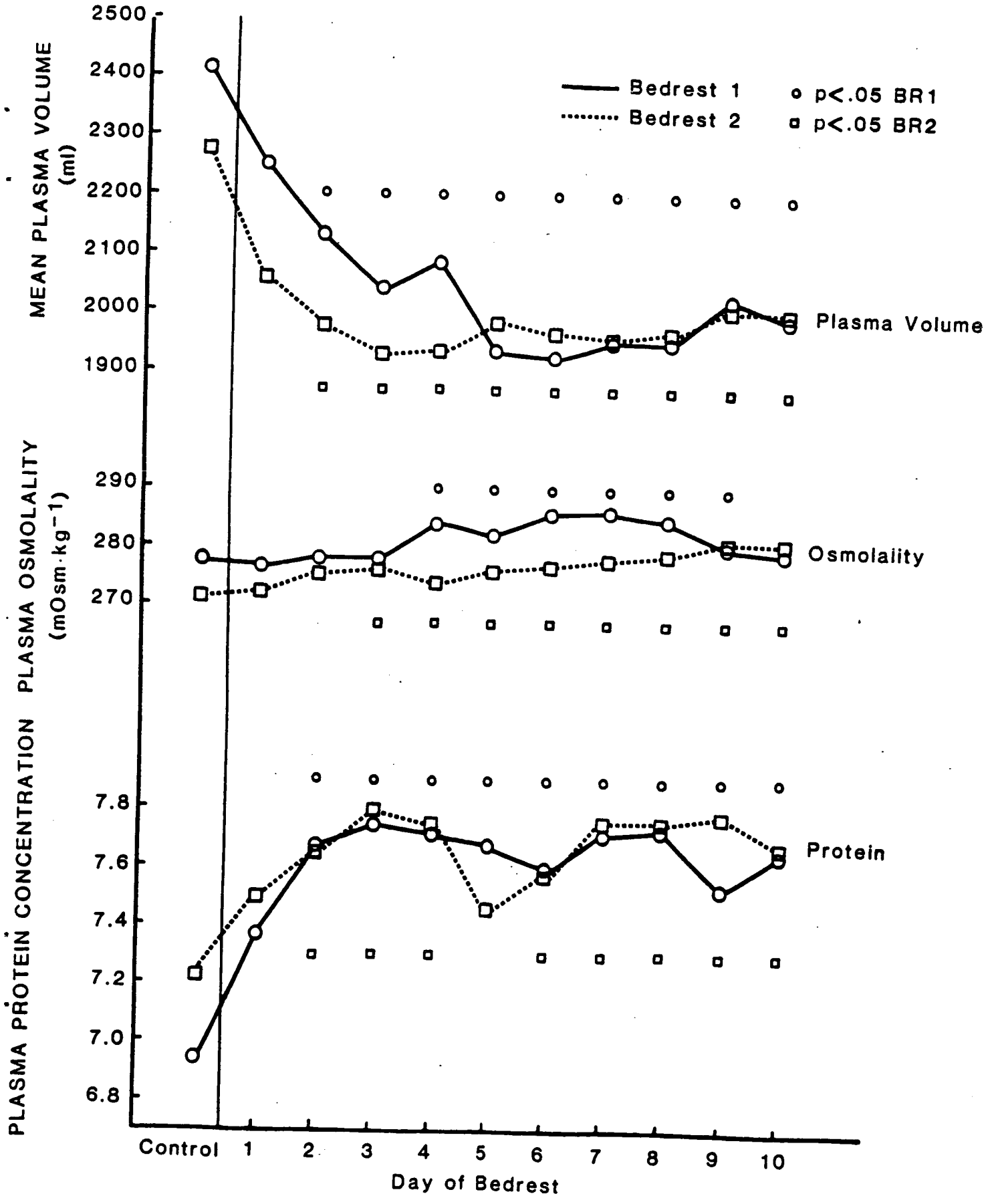
plasma volume), immediately after re-infusion of plasma volume, and one day after re-infusion. PV, but not FVC, was significantly different from control after diuresis.

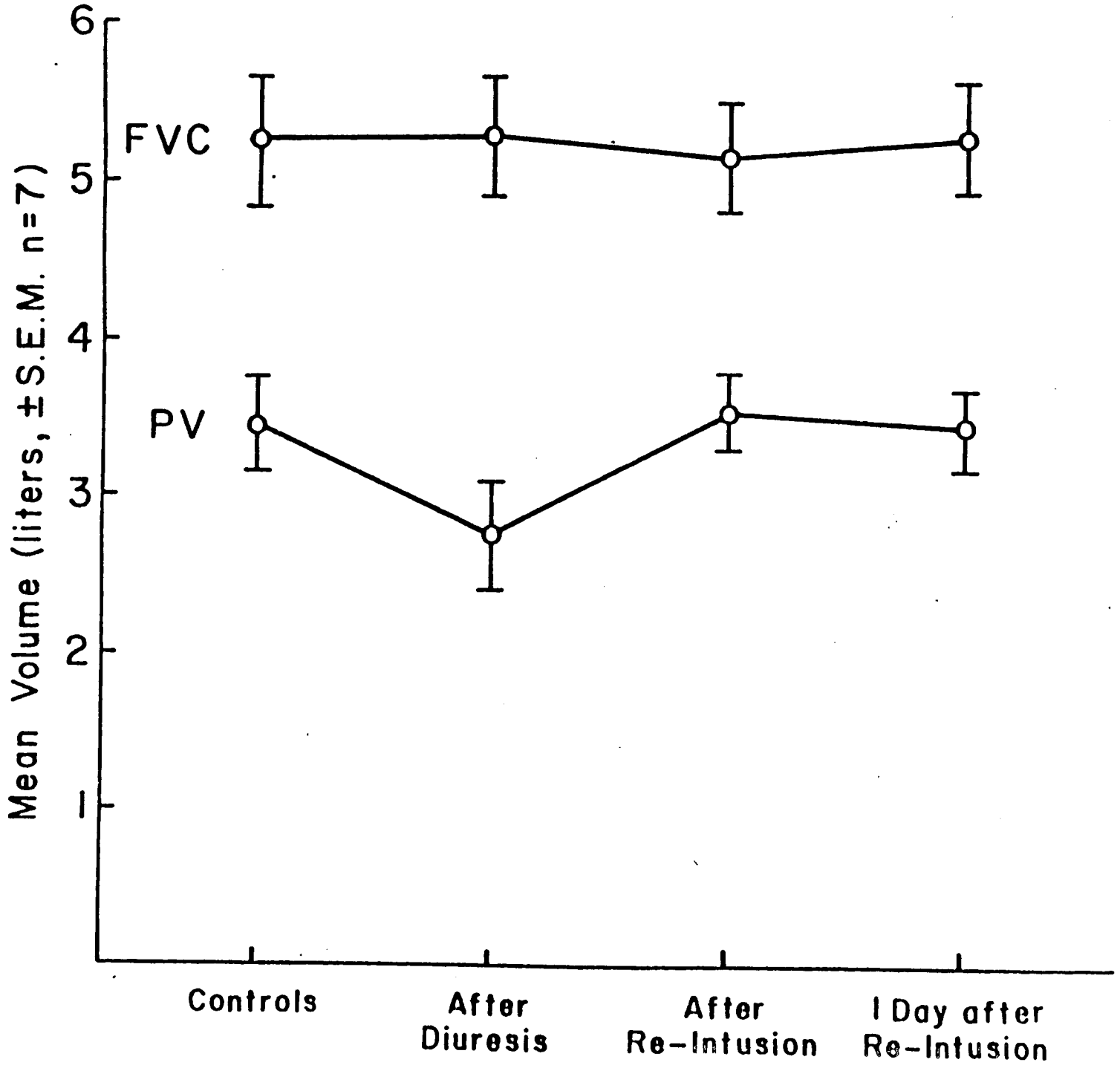
TABLE 1: Physical characteristics of subjects in bedrest 1 and 2 (No. 1-6), 3 (No. 7-12) and ambulatory diuresis (No. 13-19).

SUBJECT (No.)	SEX	AGE	HEIGHT (cm)	WEIGHT (kg)
(Bedrest 1 and 2)				
1	F	27	168	57
2	F	27	155	75
3	F	24	166	59
4	F	26	161	50
5	F	36	172	60
6	F	23	175	66
Mean ± S.D. BR1 (n = 6)		27 ± 5	166 ± 7	61 ± 8
(Bedrest 3)				
7	F	23	166	57
8	F	33	173	68
9	F	24	158	47
10	F	28	161	57
11	F	26	169	74
12	F	24	178	68
Mean ± S.D. (n = 6)		23 ± 4	168 ± 7	62 ± 9
(Ambulatory Diuresis)				
13	M	32	184	73
14	F	33	173	68
15	M	30	183	71
16	M	38	187	87
17	M	25	193	79
18	M	31	163	87
19	F	40	172	56
Mean ± S.D. (n = 7)		33 ± 5	179 ± 10	74 ± 11


BR 1
BR 2
p<.05 BR1
p<.05 BR2
BEDREST
FVC
FEV1
Mean Lung Volumes (liters)
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
C
1
2
3
4
5
6
7
8
9
10
11
R1
R2
Day of Bedrest


o p< ·05
BEDREST
MEAN TOTAL LUNG CAPACITY (liters)
5.0
4.9
4.8
MEAN FORCED VITAL CAPACITY (liters)
3.8
3.7
3.6
3.5
MEAN FUNCTIONAL RESIDUAL CAPACITY (liters)
1.7
1.6
1.5
1.4
MEAN RESIDUAL VOLUME (liters)
1.0
0.9
0.8
C
1
2
3
4
5
6
7
8
9
10
11
12
R1
R2 weeks
DAY OF BEDREST


MEAN PLASMA VOLUME (ml)
2500
2400
2300
2200
2100
2000
1900
Bedrest 1
Bedrest 2
p<.05 BR1
p<.05 BR2
Plasma Volume
PLASMA OSMOLALITY (mOsm·kg⁻¹)
290
280
270
Osmolality
PLASMA PROTEIN CONCENTRATION
7.8
7.6
7.4
7.2
7.0
6.8
Protein
Control
1
2
3
4
5
6
7
8
9
10
Day of Bedrest


6
5
4
3
2
1
FVC
PV
Mean Volume (liters, ±S.E.M. n=7)
Controls
After Diuresis
After Re-Infusion
1 Day after Re-Infusion

Appendix 3: Publications from this Contract

83 FASEB Abstract Form

Fed. Proc. 42(3) 584, 1983

ORIGINAL PAGE IS OF POOR QUALITY

Mail to your society of membership (i.e. ASPET, AAP, AIN or AAI; Members of ASBC, BMES & SEBM send to APS.)
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T CATEGORY NUMBER & TITLES
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ALTERATION OF VENOUS RESPONSES DURING EXERCISE FOLLOWING BED REST. Fortney, S., Beckett W.*, Turner, C.*, Vroman, N.*, Wilkinson, L. The Johns Hopkins Medical Institutions, Baltimore, MD 21205.

Prolonged bedrest produces a decrease in exercise tolerance, which has been partly attributed to a decreased cardiovascular responsiveness. In this study we tested the hypothesis that the venoconstrictor response to exercise is attenuated following bedrest. Seven untrained women underwent 3 day bedrests (BR). Submaximal exercise tests (70% $\dot{V}O_2$max, 30°C) were performed before and immediately after BR. Measurements of esophageal temperature (T_{es}), heart rate (HR), and forearm venous volume (FVV) were obtained during submaximal tests. Although $\dot{V}O_2$max was not significantly changed by BR (2.05 ± 0.07 $\ell \cdot min^{-1}$ pre BR; 1.97 ± 0.06 $\ell \cdot min^{-1}$ post BR), submaximal exercise endurance was reduced from 30 min to 20 min following BR, and T_{es} and HR were higher at any given exercise time. Venoconstriction occurred during all exercise tests, and FVV was significantly reduced (20-40%) below pre-tests following BR. After exercise, there was a 3-4 min delay in the release of this venoconstrictor response as compared pre-BR, and 5 subjects experienced light-headedness or fainting in this interval. In summary, exercise venoconstriction was potentiated, rather than attenuated during submax. exercise following BR. The delay in recovery of FVV after exercise may be representative of a general delay in venous readjustments which maintain cardiac filling after exercise. (Supported by NASA).

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PLASMA VOLUME RESPONSES DURING EXERCISE FOLLOWING BEDREST.

W. Beckett*, S. Fortney, C. Turner*, and N. Vroman*. The Johns Hopkins Medical Institutions, Baltimore, MD 21205.

Although decreased exercise tolerance following prolonged bedrest has been attributed to transient diuresis resulting in loss of plasma volume (PV), it is unclear whether factors other than hypovolemia, such as changes in plasma proteins or capillary permeability, affect the control of PV during exercise. In this study we tested the hypothesis that following bedrest, a change occurs not only in the resting plasma volume but also in the rate of intravascular fluid loss during exercise. Exercise studies (70% $\dot{V}O_2max$, 30°C, 40% rh) were performed on 7 untrained women before and after duplicate 12-day bedrests separated by 1 month recovery. Absolute red cell volume (RCV) and plasma volume (PV) were determined using Technetium-labelled red cells and albumin before and after bedrest. Relative changes in plasma volume during bedrest and exercise were determined from changes in hematocrit and hemoglobin concentration. PV significantly decreased 18.5 ± 5.8% during bedrest 1 (BR1), and 9.5 ± 4.6% during the second bedrest (BR2) without significant changes in RCV or plasma osmolality. During pre-bedrest exercise, PV decreased 13.3 ± 1.3 and 12.6 ± 1.3% and 9.3 ± 1.0 and 10.4 ± 4.3% following bedrest. Although the % loss of PV was similar during exercise, the absolute loss was less post-BR. We conclude that although BR results in hypovolemia, specific effects of BR on the control of PV during exercise are minimal. (Supported by NASA).

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PLASMA VOLUME RESPONSES DURING BEDREST IN HEALTHY WOMEN

S. Fortney, H. Drew, and N. LaFrance
The Johns Hopkins Medical Institutions

Decreases in plasma volume (PV) occur during spaceflight which could potentially compromise an astronauts' blood pressure maintenance during reentry. Such losses of PV are usually attributed to a cephalic shift of body water during low gravity exposure, and subsequent stimulation of low-pressure baroreceptors which initiate a diuretic response (3). The purpose of this study was to critically examine PV responses in healthy women during simulated weightlessness (bedrest). We tested the hypothesis that the loss of PV during bedrest (BR) is influenced by menstrual function, specifically by the water-retaining properties of plasma estrogens.

Six women 23 to 37 years of age who did not use oral contraceptives gave their informed consents and underwent two 12-day periods of enforced BR, where each BR period was separated by four weeks of ambulatory recovery. A seventh woman participated in the first bedrest (BR1), but was prevented from participating in the second bedrest (BR2) because she unexplainably developed pronounced lower leg edema a couple days after BR. The possibility of such complications following spaceflight was predicted recently by Hargens et al. (1)

Bedrest procedures were timed to occur at opposing stages of the menstrual cycle for each woman. Menstrual cycles were divided into four separate stages where -

Stage 1 = cycle day 2 (day 1=first day of bleeding) until 6 days prior to ovulation (ovulation was estimated from morning temperatures and by counting back 14 days from day 1). This is a stage of low estrogens and progesterones.

Stage 2 = five days prior to ovulation until one day after ovulation. During this stage there is a large estrogen peak while plasma progesterones remain low.

Stage 3 = two to 9 days after ovulation. Estrogen and progesterone concentrations both gradually increase.

Stage 4 = ten days after ovulation until cycle day 1. Estrogens and progesterones gradually decrease.

Each morning of BR, a 3ml venous blood sample was drawn to determine relative changes in PV during BR (from hematocrit and hemoglobin concentrations), total protein concentration (refractometry), and plasma osmolality (freezing point depression). Periodic 10cc blood samples were drawn to monitor blood estrogen and progesterone (radioimmunoassay), and morning temperatures and personal diaries were obtained to monitor menstrual function.

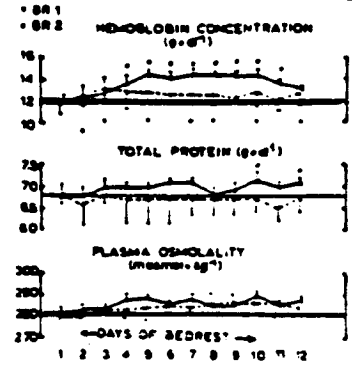
Prior to each BR, and within 48 hours after BR, absolute Red Cell Volume (RCV) and PV were determined using radioactive dilution techniques with Technetium (Tc)-labelled red blood cells and Tc-labelled Human Serum Albumin as the labels respectively. Absolute PV during each day of BR was calculated based on the TC-determined PV and hematocrits obtained during the pre-BR TC test, and on the hematocrits obtained on the first day of BR.

The technetium test results are shown in the following table. Red cell mass did not significantly change during either BR, although there was a progressive tendency towards decreasing levels during the eight-week program. Plasma volumes, which significantly decreased an average 17.4 + 2.1% during BR1 and 9.3 + 1.7% during BR2, were not significantly different from pre-BR levels 24-48 hours after BR. Such findings agree with the rapid recovery of PV reported in earlier BR studies (5).

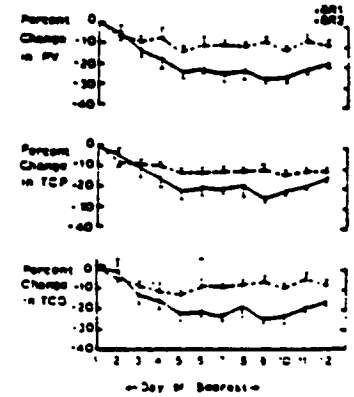
Table 1
Plasma and Red Cell Volumes Before and Within 48 hours after Bedrest (mean±S.E., n=6)

	Pre-BR1	Post-BR1	Pre-BR2	Post-BR2
RCV	1419±57	1371±52	1366±37	1301±42
PV	2305±143	2247±107	2257±121	2324±72

During BR, blood hematocrit increased significantly, plasma osmolality remained unaltered, and total protein concentration increased significantly during BR1 but not during BR2 (see Fig. 1)

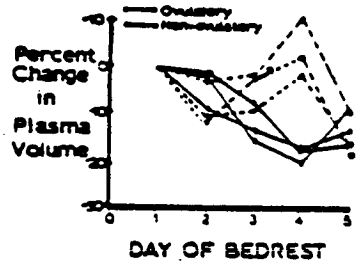


Plasma volume decreased rapidly during the first 4-5 days of BR, then remained fairly stable during the last 7 days of BR (see Fig.2). Also during BR, there was a net loss of Total Circulatory Proteins (TCP=PV times the total protein concentration), and Total Circulatory Osmols (TCO=plasma water times plasma osmolality).

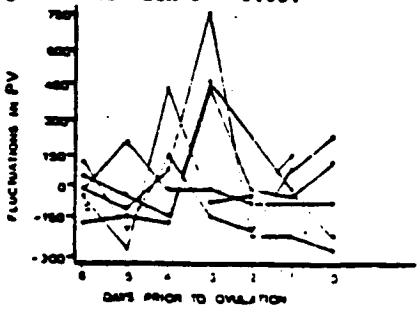


The loss (percent decrease) of PV during the first five days of BR was analyzed in terms of menstrual cycle stage (see Fig.3). The loss of PV during BR days 1-5 was progressive and showed a similar pattern for each woman who began BR while in menstrual cycle stage 1, 3, or 4. However, in the three women who began BR while in cycle stage 2, there was a transient attenuation in the loss of PV. Illustrated in Figure 3 are the relative losses of PV in the six women during BR2. The dotted lines illustrate PV responses for the 3 women in stage 2, while the solid lines represent PV responses for the other three women.

During BR1 none of the women were in stage 2, and all had PV responses similar to the solid lines in Figure 3.



Next, PV data from BR days 5-12 were analyzed in terms of menstrual stage. The effect of BR on PV at this period was minimal (see Fig.2). During the last 7 days of BR, ovulation occurred during six BR periods. Figure 4 illustrates the PV responses in these women, where days 0-6 represent the seven days prior to ovulation with day 0 calculated as ovulation. Fluctuations in PV were calculated by subtracting the mean PV for a given subject during each 7-day period, from her daily PV. The data were centered in this manner in order to adjust for differing absolute levels of PV among subjects, thus enabling visual comparison of changes in PV during the days preceeding ovulation. For each subject, a transient increase in PV occurred in this interval before ovulation. These changes in PV were analyzed through a two-way analysis of variance, where observations were classified by subject and by day prior to ovulation. Inspection of the data suggested testing for a quadratic response (i.e., a temporary fluctuation from baseline) in this interval before ovulation. The calculated F-value of 4.36, based on 1 and 30 degrees of freedom, was significant with $P < 0.05$.



We began this study with the hypothesis that elevated blood estrogens, just prior to, and after ovulation would attenuate or reverse the decreases in PV seen during BR. We postulated that as long as blood estrogen concentrations were elevated, their water-retaining properties would oppose the diuretic effects of BR. We failed however to account for the transient nature of the water-retaining properties of estrogens. Several authors (3, 4) have studied the effects of estrogens on body fluid responses. Estrogen administration consistently results in a reduction in urinary excretion of sodium and chloride and reduces urinary volume. Preede and Aitken (4) studied urinary excretion during eight days of daily injections of estradiol in women. While there was an increased water retention during the first five days of treatment, on the sixth day the kidney "escaped" from the effects of estradial, and a diuresis occurred. Such an escape phenomena may help to explain why only transient changes in PV occurred in this study during periods of expected prolonged elevation in blood estrogens. Thus the water-retaining effects of estrogens were only evident during menstrual cycle stage 2, where an initial large, transient rise in estrogens occur in most women. During stages 3 and 4, the smaller, and slower rise in estrogens was much less effective in preventing the decrease in PV associated with BR.

In conclusion, the overall PV responses seen in these women during BR were of a similar magnitude as that reported for men during two-week bedrest procedures (2). Only small transient fluctuations in PV occurred just prior to ovulation which may have been due to the influence of increasing blood estrogen titers. Therefore, the protective (water-retaining) effects of estrogens on PV losses during weightless conditions are probably only small and transient.

*The authors gratefully acknowledge the statistical assistance of Lawrence Moulton.
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References

1. Hargens, A.R., B.J. Tucker, and C.M. Tipton. 1982. Fluid shifts in vascular and extravascular compartments of humans during and after simulated weightlessness. Physiologist 25:S63-S64, Suppl.
2. Greenleaf, J.E., E.M. Bernauer, H.L. Young, J.T. Morse, R.W. Staley, L.T. Juhos, and W. VanBeaumont. 1977. Fluid and electrolyte shifts during bedrest with isometric and isotonic exercise. J. Appl. Physiol.:Respir. Environ. Exercise Physiol. 42:59-66.
3. Piemme, T.E. 1968. Body fluid volume and renal relationships to gravity. In: Hypodynamics and Hypogravics, ed. M. McCally, Acad. Press, pp. 133-161.
4. Preedy, J.R.K. and E.H. Aitken. 1956. The effect of estrogen on water and electrolyte metabolism. J. Clin Invest. 35: 423-429.
5. Taylor, H.L., L. Erickson, A. Henschel, and A. Keys. 1945. The effect of bedrest on the blood volume of normal young men. Am. J. Physiol. 144:227-232.

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EFFECTS OF ALTERATION OF PLASMA VOLUME ON PULMONARY FUNCTION.

W. Beckett*, N. Vroman*, S. Fortney, and J. Wilkerson.
The Johns Hopkins Medical Institutions, Baltimore, Md. 21205

In a previous study of prolonged bedrest we demonstrated a 15% decrease in plasma volume due to spontaneous diuresis, concomitant with a statistically significant increase in forced vital capacity (FVC) of about 200 ml and decrease in diffusing capacity of the lung (D_LCO) of 2 cc/min/mmHg during the first 3 to 4 days of bedrest. Both changes resolved rapidly after bedrest. These findings suggested that decreased pulmonary vascular volume might account for these changes by increasing lung compliance and decreasing capillary perfusion. In the present study we tested the hypothesis that changes in plasma volume can cause alterations in lung function including FVC and D_LCO. Control total red cell and plasma volumes were measured by radionuclide dilution in seven healthy adults. Control measurements of hematocrit, hemoglobin, protein concentration and osmolality, FVC and D_LCO were taken after one hour supine rest on six normovolemic control days, following plasma reduction with diuretic, and after plasma volume restoration by infusion of an isotonic saline and albumin solution. Plasma volumes calculated from hemoglobin and hematocrit decreased by a mean of 20% during the diuresis, while protein concentration and osmolality were not changed by diuresis or infusion. FVC and D_LCO did not change significantly from controls following either diuresis or re-infusion of plasma volume. Thus changes in FVC and D_LCO with bedrest are not due to decreased plasma volume.

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DEVELOPMENT OF TOLERANCE TO REPEATED BEDRESTS. S.M. Fortney, W.S. Beckett, and N.B. Vroman. Johns Hopkins Univ., Baltimore, MD 21205.

Intro: Deconditioning, as measured by reduction in maximum oxygen uptake ($\dot{V}O_2MAX$), usually occurs following exposure to weightless conditions. We examined this deconditioning response following programs of simulated weightlessness (bedrest) to test for 1)an effect of a previous bedrest exposure on the deconditioning response to a second bedrest, and 2)for a relationship between initial fitness level and the degree of deconditioning following bedrest. Methods: Twelve women, with $\dot{V}O_2MAX$ from 26.3 to 45.8 ml/min/kg, performed duplicate 11-day programs of horizontal bedrest. Each woman began the second bedrest (BR2) about 6 weeks after the start of the first bedrest (BR1), and between bedrests resumed normal daily activity. $\dot{V}O_2$ MAX was measured before each BR, and after 1 day, 2 weeks, and 4 weeks of recovery from BR. $\dot{V}O_2MAX$ was determined as no further increase in $\dot{V}O_2$ (<2 ml/min/kg) with increase in exercise intensity. Results: One day after bedrest $\dot{V}O_2MAX$ (ml/min/kg) decreased 10.0 ± 2.5 per cent following BR1, and 4.0 ± 2.3 per cent following BR2. The decrease in $\dot{V}O_2MAX$ was significant ($P<0.002$) following BR1 but not following BR2 ($P<0.12$), despite almost complete recovery (to within -0.9 ± 2.4 per cent) of pre BR1 $\dot{V}O_2MAX$ level prior to the start of BR2. The relationship between Pre-BR fitness ($\dot{V}O_2MAX$ in ml/min/kg), and the decrease in $\dot{V}O_2MAX$ (per cent change between Pre-BR and Post-BR $\dot{V}O_2MAX$) following BR, was not significant; where the regression for this relationship was $Y= -0.49X + 8.3$, $R= -0.31$. Conclusions: The observation that there was a smaller reduction in $\dot{V}O_2$ following the second bedrest (i.e., less deconditioning) indicates the development of tolerance.

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INCREASED VITAL CAPACITY AND DIMINISHED DIFFUSING CAPACITY DURING PROLONGED BEDREST. W. Beckett, N. Vroman, D. Nigro, and S. Fortney, Division of Environmental Physiology, Johns Hopkins Medical Institutions, Baltimore, MD.

Previous studies indicate that prolonged bedrest results in loss of plasma volume, a redistribution of extravascular fluid, and deconditioning of muscles. Since these may affect lung function, we studied the effects of prolonged bedrest on forced expiratory volume and flow, diffusing capacity for carbon monoxide, and the single breath nitrogen test. Seven healthy subjects underwent duplicate twelve-day bedrests (BR1 and BR2) separated by four weeks recovery. Forced expiratory volume in one second (FEV_1), vital capacity (VC), diffusing capacity (DCO), nitrogen washout slope of phase III (SPIII) and closing volume (CV) were measured on three ambulatory control days, daily during bedrests, one day after bedrest, and after two weeks recovery. Maximal inspiratory and expiratory pressures were measured before and after bedrest. All pulmonary functions were measured in the supine position at approximately the same time each day. During the first five days of bedrest, mean plasma volume decreased 20% (BR1) and 15% (BR2). Red cell mass was decreased by 5.9% ($p<.05$) in BR1 and 2.1% (N.S.) in BR2. During both bedrests, VC rose during the first five days (BR1 mean change 228 ml $\pm$ 28 ml S.D., $p<.05$, BR2 mean change 107 ml $\pm$ 51 ml S.D. $p<.05$), DCO decreased compared with control values (BR1 mean change -1.7 cc/min/mmHg, $P<.05$, BR2 mean change -1.65 cc/min/mmHg, $P<.002$). No consistent change was measured in SPIII, CV or maximal inspiratory and expiratory pressures. Plasma volume values increased to pre-bedrest control levels by 24 hours after the completion of bedrest, and VC decreased toward control values at 24 hours post-bedrest. We speculate that the increase in vital capacity reflects a fall in thoracic intravascular plasma volume due to the spontaneous diuresis during bedrest.

Supported by NASA, NIOSH, and NIH grants HL 10342 and HL 07534.

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PLASMA VOLUME MAINTENANCE DURING BEDREST IN WOMEN RECEIVING PREMARIN. S.M. Fortney, J.A. Rock, N.B. Vroman, H. Drew, and N. LaFrance. Johns Hopkins Medical Institutes, Baltimore, Maryland 21205.

INTRODUCTION: Decreases in plasma volume have been reported in both men and women during simulated weightlessness (bedrest), and are believed associated with the decrease in exercise and orthostatic tolerance following spaceflight. In a previous study we reported an attenuation in plasma volume loss during bedrest during the immediate pre-ovulatory phase, which we suggested may be attributed to the water-retaining properties of estrogens in this phase of the menstrual cycle. In the present study, we further studied the effects of female sex steroids to prevent bedrest hypovolemia. METHODS: Nineteen healthy women (21 to 39 yrs) underwent a 12-day horizontal bedrest. Plasma and Red Cell Volumes were determined using technetium-labels before and after bedrest to verify red cell mass stability during bedrest. Daily plasma volumes were calculated from hematocrit and hemoglobin ratios. Twelve women did not receive estrogen supplement, while seven additional women received 1.25mg Premarin daily. RESULTS Plasma volume significantly decreased by an average - 20.1 ± 3.9% between the first and last day of bedrest in the non-premarin group, and was not reduced (+0.3 ± 2.8%) in the premarin users. CONCLUSION: Premarin, an estrogen-containing preparation, effectively prevented the decrease in plasma volume associated with bedrest, and may serve as a useful model to study the role of the decreasing plasma volume on post-bedrest responses. Supported by NAS9-16703

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TOTAL LUNG CAPACITY INCREASES DURING PROLONGED BEDRES INDEPENDENT OF PLASMA VOLUME CHANGES. S. Thompson Gorman, K Beckett, and S. Fortney. Johns Hopkins Stress Physiolog Laboratory, Baltimore, MD 21205.

We have previously shown that significant increases i forced vital capacity (FVC) of approximately 6% occur whe using prolonged bedrest as a model for spaceflight. In th present study, seven healthy adult females were studie during 12 days of bedrest to clarify the mechanism of thi increase. FVC, functional residual capacity (FRC), tota lung capacity (TLC), residual volume (RV), and single breat diffusing capacity for carbon monoxide (D_LCO) were measure on two ambulatory control days, during each day of bedrest one day post-bedrest, and after two weeks recovery. Al tests were done with the subject in the supine position Subjects received exogenous estrogen (1.25 mg/day). Plasm volume (measured immediately before bedrest by technetiu label, and calculated daily from hematocrit and hemoglobi values) did not decrease significantly during bedrest as i had in the previous studies without estrogen. A significan ($p < .05$) increase in FVC occurred by the third day o bedrest which persisted throughout the rest of the study with a maximal mean increase of 206 ml (5.4%). TLC als increased significantly by the fourth day of bedrest an remained elevated through day 12, with a maximal mea increase of 180 ml. Post-bedrest TLC values were not signi ficantly different from control at one day and two week recovery. There was no significant change in D_LCO, RV an FRC. These results indicate that the increase in FVC is th result of an increase in TLC and not a decrease in RV, an that these mechanical changes are not dependent on changes i plasma volume. (Supported by NASA).

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FOREARM VENOCONSTRICTOR RESPONSES FOLLOWING BEDREST. J.E. Davis, N.B. Vroman, C.G. Tankersley, and S.M. Fortney. The Johns Hopkins Medical Institutions, Baltimore, MD 21205.

INTRODUCTION. We have previously observed that simulated weightlessness (bedrest) augments resting and exercise venoconstriction, as measured by decreases in forearm venous compliance (FVC). This was attributed to a low pressure baroreceptor reflex response to bedrest (BR)-induced hypovolemia. The purpose of the present investigation was to determine if maintaining plasma volume (PV) during BR would result in an attenuation of resting and exercise venoconstriction. METHODS. FVC was measured (venous occlusion plethysmography) in 19 healthy women (21-39 yrs) at rest and during 30 minutes of cycling (70% $\dot{V}O_2$max) in a warm environment (30°C, 40% RH) before and after BR. Seven subjects were given Premarin (P) to prevent BR-induced hypovolemia, and 12 subjects received no Premarin (NP). PV was calculated from hematocrit ratios and technetium dilution determinations. RESULTS. PV, prior to exercise, decreased after BR in NP (2389 to 1957 ± 317 ml) but not in P (2667 to 2537 ±497 ml). Resting FVC was reduced after BR in NP (3.72 to 2.97 ±.8 cc/100cc) and in P (3.30 to 2.29 ±.6 cc/100cc). Venoconstriction during the first 10 minutes of exercise was greater after BR for NP (2.18 to 1.64 ±.7 cc/100cc) and P (2.14 to 1.21 ±.6 cc/100cc). Although PV was maintained in P after BR, there was a greater venoconstriction in P than NP at rest (30.6% to 20.2% ±8%) and during exercise (44% to 25% ±6%). CONCLUSIONS. Venoconstriction following BR is independent of PV suggesting that other variables, e.g. peripheral pooling, may contribute to the greater venoconstriction. Supported by NAS.9-16703.

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THE LACK OF AN AFFECT OF ELEVATED ESTROGENS ON EXERICSE THERMOREGULATION. Fortney, SM, JE Davis, AJ Carpenter, and JA Rock. Johns Hopkins Stress Physiology Lab, Baltimore, MD.

One proposed explanation for the lower sweating response of women than of men, is that estrogens inhibit sweating. Te test this hypothesis and to explore other potential estrogenic effects on exercise responses, 5 women cycled with and without 7-10 days pretreatment with a natural estrogen supplement, 1.25 mg premarin per diem. Each subject exercised (70% V02max) for 30 minutes in a warm (30°C, 60% RH) environment. Non-premarin tests (NP) occured in the follicular phases of 2 subjects, the luteal phases of 2 subjects, and in both phases of the menstrual cycle of 1 subject. Esophageal temperatures (Tes) did not differ significantly between NP and premarin (P) tests during exercise, nor was there a significant difference in the rise in Tes; NP=1.05 ± 0.41°C, and P=1.07 ± 0.39°C, mean ± SE. No significant differences were seen in mean skin temperatures, skin conductances, total body sweat losses, Tes sweating thresholds, the slopes of the Tes/sweat rate relationship, heart rates, stroke volumes, or blood lactates. Plasma volume did not differ significantly between NP and P at rest or during exercise. We conclude that estrogen supplementation with premarin at this dosage does not alter thermoregulatory responses during moderate exercise in a warm environment either by inhibiting sweating, or by altering plasma volume. (Supported by NAS9-17199.)

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THERMOREGULATORY RESPONSE TO EXERCISE AT DIFFERENT PHASES OF THE MENSTRUAL CYCLE. E. Miescher, A.J. Carpenter, C.G. Tankersley, K. Levine, S.M. Fortney. Johns Hopkins Medical Institutions, Stress Physiology Laboratory. Baltimore, MD

It has been suggested that thermoregulatory responses differ with the phase of the menstrual cycle. Thermoregulatory responses to exercise were measured in the early follicular (progesterone <1.0ng/ml, 17-B-estradiol <100 pg/ml) and midluteal (progesterone >6ng/ml, 17-B-estradiol 70-150pg/ml) phases in 8 women with regular (28 ±4 days) and endocrinologically normal cycles. Each subject exercised for 30 minutes at 70% VO2max in a warm (30°C, 60% RH) environment. Exercise tests were performed between 8:00 and 14:00h, at the same time of day for each woman. Esophageal temperatures (Tes) at rest were greater in the luteal phase (37.25 ±0.16°C) than in the follicular phase (36.91 ±0.15°C). Tes was approximately 0.3°C higher in luteal than in follicular phase at all times during the exercise test. Thus, heat storage during exercise was similar in either phase of the menstrual cycle. Neither evaporative heat loss estimated from total body sweat loss, nor skin conductance in response to exercise differed significantly as a function of the menstrual cycle. In addition, plasma volumes, exercise cardiac outputs, heart rates, stroke volumes and metabolic rates did not differ significantly. Thus, although there is a consistant upward shift in body temperature during the luteal phase of the menstrual cycle both at rest and in response to moderate exercise, no difference in the heat loss mechanisms measured was detected in this study.

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Medical and Surgical Considerations for Women in Spaceflight

JOHN A. ROCK[1] and SUZANNE M. FORTNEY[2]

Division of Reproductive Endocrinology, The Johns Hopkins Hospital,[1] and Department of Environmental Health Sciences, The Johns Hopkins University School of Public Health and Hygiene,[1,2] Baltimore, Maryland

With the development of the space shuttle program, both men and women will serve as astronauts. Space flights will be made available to specialists in science and technology to conduct experiments in planned orbital laboratories. Recently, Sally K. Ride was the first woman astronaut to enter the weightless environment aboard the space shuttle Challenger (Fig. 1). Consideration should now be given to the impact of weightlessness on the reproductive act.

This report also reviews the current methods for simulation of weightlessness and hypodynamic spaceflight. With these investigative models in mind, the physiologic adaptive processes both predicted and observed at zero-gravity are presented. Results of current investigations into these adaptive processes with respect to the gynecologic endocrine system will be discussed and recommendations for future gynecological investigation presented.

Simulation of Weightlessness and Hypodynamic Spaceflight

The need to ascertain whether a human can survive experiences of long-term spaceflight without harmful effects has prompted the use of methods that provide a simulation of certain aspects of weightlessness (Table 1). Current methods may provide reasonable complete negation of certain aspects of gravity tissue interaction. However, they are frequently of no use in approximating other aspects of the weightless state.

True alterations in gravity cannot be achieved on this planet but the simulation of one or more of the predictable effects of zero-gravity is possible. Immobilization (i.e., casts, splints, prolonged bed rest) has been used to simulate effects on the cardiovascular system. Other simulations include tumbling, immersion, direct acceleration, and opposing acceleration (i.e., suborbital and paraboiic flight).

Bed rest has been a common method for simulating zero-gravity. This is a valuable technique, because 1) less work is required for postural support while a diminished load is supplied to the body structure, and 2) there is a reduction in the effective length of the major fluid columns. There are generally four general physiologic responses to bed rest: bone demineralization, circulatory deconditioning, fluid and electrolyte alterations, and muscular atrophy. Disadvantages include prolonged studies (minimum 12-day bed rest) and the psychological stress factor associated with this simulation.

Parabolic trajectories have also been used to simulate conditions of weightlessness. The use of inertial properties of a mass in producing a weightless state can be extended to greater time periods if one takes advantage of the physical characteristics of trajectile motion. The duration of fall can be extended and the problems with air frictional resistance overcome using an aircraft. The flight pattern during which weightlessness occurs is called a Keplerian trajectory. The parabolic form of such a trajectory is that of an ellipse with one focus at the center of the gravitation or traction (Fig. 2). In this maneuver the aircraft dives to gain speed and then pulls up onto one leg of the appropriate parabola with the power of the engines used to negate air friction. The maximum duration of exposure possible with this technique is about 1 minute. The disadvantages of this simulation include an exposure of intense G-fields just before the period of brief weightlessness. This

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Fig. 1. Sally K. Ride aboard space shuttle Challenger, June 1983. Courtesy of NASA; Lyndon B. Johnson Space Center, Houston, Texas.

TABLE 1 Simulation of specific anticipated effects of weightlessness

Direct reduction of mechanical force in localized areas (i.e., partial immobilization results in bone demineralization and muscle atrophy). This may be accomplished with the use of plaster casts.
Reduction by mechanical support of forces required to oppose gravity.
Bed rest
Immersion and buoyant support
Frictionless devices (support of subjects by jets of air)
Opposing accelerations
Opposing linear accelerations—dropping devices
Parabolic trajectories
Opposition primarily by radial acceleration: orbital flight

Adapted from: Wunder, C. C., Culling, E., and Burgess, H.: Methods of simulating weightlessness in hypodynamics and hypogravics. In *Hypodynamics and Hypogravics*, edited by M. McCally. Academic Press, New York, 1965, p. 71.

technique has been used primarily for studies of sensory patterns which respond rapidly to changing inertial fields.

Immersion and buoyant support of a subject in a fluid also provide a method of simulating the weightless state. The buoyant support provided to limbs and trunk reduce the work necessary in normal posture and support without great restriction in motion, as with bed rest. Subjects exposed to immersion or Keplerian parabolic flight report that sensations are similar; that is, astronauts actually execute only slow, cautious movements in either system. Nevertheless, the unnatural external environment of immersion produces some experimental difficulties. Primarily, prolonged experimentation is quite difficult. Furthermore, the high specific heat of water results in abnormal heat exchange with the environment. Therefore, body temperature must be carefully monitored if temperature artifacts are not to confuse the studies.

The methods of simulation of weightlessness which have been discussed suffer from one or more disadvantages. Although the systems are less than optimal, important predictions can be made concerning the adaptation of man in spaceflight. Many of the observed responses to spaceflight have been predicted using these simulations.

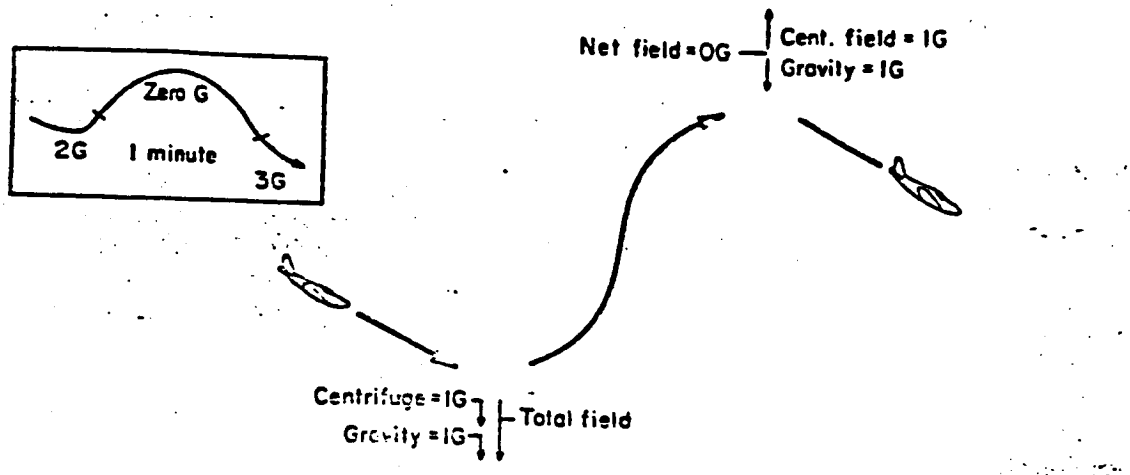

Fig. 2. Parabolic flight.

Physiologic Adaptive Processes at Zero-Gravity

The Musculoskeletal System

Muscle structure and, therefore, function is strongly determined by the combined stresses to which the muscle is exposed. During conditions of spaceflight, the stress provided by gravity is removed and alterations in muscle structure become evident within the first week. The most gross evidence of changing muscle structure is seen by the overall decrease in body mass. Although most of the decrease in body weight during short-term (1–14 days) spaceflight is due to decreases in body fluids, about one-third of the weight loss results from decreases in lean body mass and fat (1).

As the length of exposure to weightlessness continues, further evidence of an atrophic muscle effect appears, especially in muscles involved in control of posture and weight bearing. After the Salut 6/Soyuz prolonged flights, significant atrophy of the rear calf, long and wide calf muscles was seen (2). Morphologic changes in muscle tissues following simulated weightlessness show a decrease in muscle mass brought about by decreases in muscle fiber size and also a smaller decrease in muscle capillary density. Oxygen transport time between capillaries and tissues is not believed to be reduced and arterial-venous O_2 differences during exercise in bed-rested muscles were not significantly different from pre-bed rest values (3).

Biochemical changes in muscles during simulated weightlessness suggest a net decrease in those enzymes and cofactors necessary to support oxidative capacity. One week of bed rest was associated with a 12–18 per cent reduction in oxidative enzyme activity and 2 weeks with a 30 per cent reduction. During spaceflight, increases in plasma calcium, phosphorous, and creatinine occurred. In the urine, increases in these factors as well as sodium, magnesium, total hydroxylysine, N-methylhistidine, and most amino acids suggest a generalized muscle atrophy. The time course of these biochemical changes precedes measured changes in maximum work capacity in bed-rested subjects. An earlier sign of decreasing muscle function was a deteriorating capacity for endurance exercise (3).

During the Skylab missions, metabolic balance studies were conducted to assess whether catabolic biochemical conditions would persist in the presence of ample dietary intake of key muscle-maintaining elements. Despite carefully monitored intake of calcium, nitrogen, phosphorous, magnesium, potassium, and sodium, a negative or only slightly positive balance was found for these elements.

The changes in muscle structure reported above were also associated with changes in muscle function. Decreases in muscle strength, especially in extensor and leg muscles, with little change in arm muscles, occurred both in-flight and immediately postflight (1). These decreases in strength could be ameliorated but not prevented by exercise programs. Even an extremely vigorous exercise protocol did not reverse the loss of total body nitrogen and phosphorous. Electromyogram changes occur during spaceflight which indicate increasing susceptibility to fatigue and possibly reduced muscular efficiency (1). Muscle reflexes during and after spaceflight are characterized as a condition of "generalized hyperreflexia." During the long-term Soviet flights there was a reduction in threshold in tendon reflexes, and the Skylab results suggest an increase in duration of the Achilles tendon reflex, which returned to preflight levels only after a month or more (1).

One of the most serious complications of space-

flight is the continuing loss of bone mineral. Like muscle, bone is a dynamic tissue which maintains a mass dependent upon the level of overall daily stresses. The greatest stresses for bone result from forces caused by weight and inertia. Passive standing exerts a force proportional to an individual's body weight and the surrounding gravitational field, such that a 132-pound man will generate a force equivalent to 66 pounds on the tibia/fibula bones. This force, however, is small compared to the forces caused by muscle counterforces during exercise. Jogging or running may provide forces exceeding 1000 pounds of transient force on the bones of the foot (4). Conditions of spaceflight or simulated weightlessness remove most of the major forces from the musculoskeletal system so that only a fraction of the inertial forces remain. The major medical hazards of prolonged spaceflight on bone include a lengthy recovery of lost bone mass following spaceflight, possible irreversible bone loss, bone fractures, and toxic effects on soft tissues such as the kidney due to increased release of calcium and phosphorous (1).

Loss of skeletal mass becomes an important consideration, however, only in long-term spaceflights. Changes in bone density were found even during short-term spaceflights, but the rate of loss of demineralization was gradual. Evidence from the longer Apollo and Skylab flights support the hypothesis that bone mineral loss occurs only in weight-bearing bones during spaceflight (1). The mechanism of bone degeneration is still unknown but may involve changes in electrochemical properties, and in hormonal and neural factors. In-flight animal studies suggest that the loss of bone mineral is due to an inhibition of new bone formation. In man, however, it is unclear whether there is reduced bone formation or increased bone resorption during spaceflight. Autopsies of three Russian cosmonauts who died after 21 days of spaceflight revealed evidence of anatomical bone changes suggesting increased bone resorption (1).

Studies on the reversibility of bone loss following spaceflight are inconclusive. If the decrease in bone mass is simply due to a temporary imbalance in bone turnover, then bone loss would be replaced at a later time, perhaps following spaceflight. On the other hand, an alteration in the functions of individual bone cells could result in irreversible bone loss (5).

Part of the difficulty in determining the mechanism of bone loss with weightlessness is that, so far, simulation techniques do not mimic the results during spaceflight. During bed rests, a negative calcium balance appears within a few days. Urinary calcium increases and plateaus after about 5 weeks, while fecal calcium increases until about 10–12 weeks and then plateaus. During spaceflight, urinary calcium plateaus after about 30 days, but fecal calcium loss does not appear to plateau. Extrapolated calcium losses from the Skylab spaceflights suggest that within 1 year an astronaut would lose about 25 per cent of the total body calcium pool. Extrapolated bed rest data give values of only 6 per cent (6).

The results reported from long-term Soviet spaceflights suggest that the calcium loss does not continually increase during long-term weightlessness, but slows considerably between the third and sixth month when vigorous exercise programs are conducted (2). The effectiveness of exercise as a countermeasure is still uncertain, however, as during Skylab 3 and 4, weight-loading exercise reduced bone loss in only three of the six astronauts. Soviet findings regarding the effects of exercise as a countermeasure are more hopeful (Nicogossian and Parker, 1982; 1). Other countermeasures which have been proposed include dietary supplements and pharmacological agents. One drug, clodronate disodium, effectively prevented negative calcium balance in human bed-rested subjects but was discontinued from use because of evidence of possible carcinogenic properties (6).

Comparisons of bone mineral losses in men and women suggest that women had significantly less calcium loss than similarly stressed men. Further studies are needed to verify this finding and to establish the mechanism for such differences (7).

Respiratory System

The changes that occur in the respiratory system during actual or simulated weightless conditions appear to be slight and of little overall physiological significance. Pulmonary function measurements obtained from five men during a 20-day bed rest protocol revealed nonsignificant changes in total lung capacity, forced vital capacity, 1-second forced expiratory volume, residual volume, and the diffusing capacity of the lung for carbon monoxide. It was unclear in this study, however, whether all measurements were controlled for posture (8). In a recent study in which six women underwent duplicate 11-day bed rests, small but significant increases in vital capacity and 1-second forced expiratory volume occurred during the first 5 days of the bed rest protocol, continued to be elevated throughout the remainder

of the bed rests, and returned toward supine pre-bed rest levels during 2 weeks of ambulatory recovery. It was postulated by these authors that the changes in vital capacity and 1-second forced expiratory volume may have been associated with the 15–20 per cent decreases in plasma volume which occurred in the same time interval. Presumably decreased plasma volume would be reflected in a similar proportioned decrease in thoracic blood volume and an increase in lung compliance during the first few days of bed rest (9). A follow-up study, in which a 20 per cent decrease in plasma volume was induced in seven ambulatory subjects through the use of diuretics, failed to establish a correlation between changes in plasma volume and changes in vital capacity or 1-second forced expiratory volume (10).

No consistent changes in pulmonary function have been reported during spaceflights of 28–84 days' duration. During one spaceflight, vital capacity on most days averaged about 10 per cent lower than preflight controls in three astronauts, but returned to preflight levels rapidly after landing (11).

Body Fluids

With the removal of hydrostatic pressure gradient during conditions of weightlessness, body fluids are redistributed such that fluid redistributes from the lower extremities in a cephalad direction. The resulting increase in thoracic blood volume is believed to initiate a Gauer-Henry reflex, whereby stretch receptors in the left atrium inhibit the release of antidiuretic hormone. As a result, a spontaneous diuresis occurs, resulting in a decrease in plasma volume and electrolytes. During 2-week bed rest studies in seven men, this diuresis was seen during the first 4–5 days and resulted in a 13 per cent reduction in plasma volume (12). A similar relative loss of plasma volume was reported in bed-rested women during 11-day bed rests. However, it was observed that, when bed rest was begun in the immediate preovulatory stage of a woman's menstrual cycle, either an increase or only a small decrease in plasma volume was seen during the first 4 days of bed rest. These results suggest that the hormones associated with the preovulatory stage may transiently prevent the diuresis associated with bed rest (13).

During actual spaceflights, however, this early-onset diuresis has not been seen probably because of problems in obtaining urine samples during flight, and because of a reduced fluid intake due to motion sickness and anti-motion sickness drugs. Measurements of the net water balance during Skylab flights indicate, however, that although fluid intake is reduced, urine output is not reduced to a comparable level, resulting in a negative water balance during the first 6 days of flight. In-flight increases in urinary sodium, potassium, and chloride, and decreases in antidiuretic hormone lend support for the diuresis theory of the plasma volume decrease during weightlessness (1).

These fluid losses are believed to contribute to the postflight orthostatic intolerance seen in most astronauts and cosmonauts. Countermeasures to prevent the diuresis include vigorous exercise programs and water and electrolyte supplements during spaceflight or just before reentry. During long-term Soviet flights, the water and electrolyte supplementation was combined with lower-body negative pressure administration to ensure that the ingested fluids were retained within the vascular space (2). Mineralocorticoid (9-α-fluorohydrocortisone) ingestion during bed rest studies has successfully prevented the loss of plasma volume but the effects on orthostatic tolerance following bed rest have been indecisive (14, 15).

Besides the loss of plasma volume, red cell volume also decreases during weightlessness. The effect, however, now appears to be self-limiting, where with long-term spaceflight, the red cell mass decreased until about 60 days into the mission and then gradually began to recover (1). Along with the loss in cell mass, there is a change in the shape of the red cells. Preflight, 80–90 per cent of the red cells had a biconcave (discocyte) shape. During the Soyut 6 flight, there was an increase in number of ellipsoidal and spherical shaped cells. These changes were rapidly reversible postflight (1).

The most accepted theory to explain the decrease in red cell mass is that in-flight there is a suppression of new red cell production by a direct inhibitory effect on bone marrow. The reduction in proportion of reticulocytes during early spaceflight would confirm this hypothesis. Findings from the Apollo-Soyuz flight dispute other theories that increased red cell destruction or selective sequestration of red cells cause the decreased red cell mass (1).

Cardiovascular System

It is especially difficult to simulate the effects of weightlessness on the cardiovascular system since simulation procedures, such as bed rest and water immersion, produce physical deconditioning in addition to the hypogravic responses. Most of this review will, therefore, focus on cardiovascular responses

seen during or after spaceflight. Three major changes in cardiovascular function following weightlessness include decreased orthostatic tolerance, changes in cardiac electromechanics, and changes in exercise capacity postflight. In addition, some morphological changes have been reported in the heart following prolonged spaceflight.

One early controversy centered around how the cardiovascular system would deal with the cephalad shift in body fluids. It was feared that a chronic elevation in central venous and left atrial pressures would persist during weightless exposures, potentially compromising cardiac function. Recent evidence of only transient increases in central venous pressure during head-down tilt simulations and normal cardiac function curves during the Skylab missions argue against this theory (16, 17). Recently, it has become possible to collect data to examine the effect of long-term spaceflight on cardiac structure and function. Electrocardiographic studies after the Skylab missions found decreases in left ventricular dimensions without significant change in contractile properties (17). Following Salyut 7, electrocardiography studies revealed a small but reversible decrease in left ventricular muscle mass which was restored within 7 days postflight. The rapidity of muscle mass restoration suggests that the changes were due to alteration in myocardial intercellular hydration rather than to myocardial muscle degeneration (18).

Decreases in orthostatic tolerance are consistently reported during and after spaceflight. At least part of the intolerance to tilt, lower body negative pressure, or quiet standing postflight is due to the blood volume losses associated with weightlessness. This 250–500 ml fluid loss, however, is too small to account for the degree of cardiovascular dysfunction reported. Also, replacement of the volume loss before orthostatic tolerance testing did not completely restore orthostatic tolerance (15).

Other mechanisms that may contribute to the decreased orthostatic tolerance may include an increase in venous compliance, especially in the lower body or abdominal regions, or changes in the neurogenic or hormonal control mechanisms that regulate blood pressure. Venous compliance measurements during Skylab flights revealed an increase in compliance during the first 10 days of flight, then a slow decrease with continuing spaceflight. The time course of these compliance changes did not concur with accompanying changes in tolerance to lower body negative pressure (1).

Data describing changes in autonomic function after spaceflight or bed rest are inconclusive. Upon tilt or lower body negative pressure challenge after spaceflight, the cardiovascular responses are exaggerated with greater increases in heart rate and a greater fall in mean arterial pressure. However, the normal vasoconstrictor responses appear intact. Injections of norepinephrine or angiotensin produce similar pressor responses during 2–3 week bed rests. Although plasma catecholamines are reduced during bed rest, their response during tilt is unchanged (19). The venoconstrictor response of forearm blood vessels during exercise was found to be potentiated rather than reduced following bed rest, suggesting normal sympathetic venoconstrictor function. The increased venoconstriction was proportioned to the reduction in plasma volume during bed rest (20).

Electrocardiographic and vectorcardiographic data, at rest and during lower body negative pressure challenge during Skylab missions, showed an increase in the QRS maximum vector, which may be related to increases in thoracic blood volume and a prolongation of the P-R interval, possibly due to an atrioventricular conduction slowdown caused by an increased vagal tone. Frequent arrhythmias during spaceflight may also result from sympathetic-parasympathetic imbalance or may be due to fluid or electrolyte imbalances induced by the weightless state (1). During Salyut 6 flights, kinetocardiographic measurements also revealed a significant shortening of isometric contraction and relaxation of ejection and postfilling phases (2).

Exercise capacity is severely reduced following spaceflight. After the 8–11 day Apollo flights, decreases in exercise intensity, oxygen uptake, and cardiac output were observed at an exercising heart rate of 160 beats per minute. Oxygen consumption for a given exercise intensity (muscle efficiency) was not altered postflight. Following the longer Skylab flights, similar decreases in exercise capacity were found but were restored within 3 weeks of recovery (1).

One unexpected finding, however, was the improvement in exercise tolerance during spaceflight. Once the mechanical problems of exercising in weightless conditions were negotiated, astronauts during Skylab flights were able to accomplish higher exercise intensities than were possible in a one-gravity environment. An increased maximum oxygen uptake in zero-gravity conditions is probably not indicative of a training response as in normal condi-

tions, but may have been due to the effect of an increased venous return and maximum cardiac output resulting from the increased central blood volume. As a linear relationship exists between absolute work output and cardiac output, a higher exercise intensity would be attainable. Oxygen consumption may also increase because of an increased active muscle mass in zero-gravity as the arms play a more active role during exercise. Fixed submaximal exercise intensities were accomplished with lower heart rates and blood pressures than preflight. A more rapid recovery of heart rate after exercise in the weightlessness environment was probably due to the greater venous return. Therefore, in order to maintain a stable fitness level while in-flight, training exercise intensities must be adjusted in an upward direction (21).

Endocrine System

The endocrine response during spaceflight reflects the combined effects of stresses induced through the removal of gravity, effects from motion sickness, changes in diet, and the psychological stresses associated with space travel. Because so many stresses are simultaneously combined, the hormonal responses are often difficult to interpret.

Head-down bed rest studies (22) have been conducted in an attempt to identify some of the transient hormonal fluctuations associated with changes in the hydrostatic gradient exerted on the body. Within the first 2 hours after lying down, there is an increase in central venous pressure which probably triggers the decrease in plasma concentrations of antidiuretic hormone, angiotensin, and aldosterone. In this same time interval, sympathetic activity is decreased as reflected by decreases in concentrations of epinephrine and norepinephrine. Glomerular filtration rate is also transiently decreased. After 4 hours of bed rest, central venous pressure returns to pre-bed rest levels and then continues to decrease. The glomerular filtration rate returns to baseline only after about 8 hours, at which time plasma aldosterone and angiotensin levels have also recovered and may even exceed the pre-bed rest level.

Data from astronauts in the space shuttle program revealed increased plasma and urinary aldosterone, angiotensin, and urinary antidiuretic hormone postflight, similar to the results reported after 8 hours of head-down bed rest. The plasma levels of these hormones in-flight, however, have also been shown to be influenced by salt and water intake. Urine antidiuretic hormone concentration during long-term Skylab flights was reduced during the first 40–50 days of flight, then began to return toward preflight levels (23). These hormonal fluctuations undoubtedly occur in response to the fluid shifts with exposure to weightlessness.

During Skylab spaceflights, parathyroid hormone was slightly elevated (6.4 per cent) above preflight levels (23). Parathyroid hormone normally functions to increase plasma calcium by first increasing bone resorption, second by increasing resorption of calcium in the kidney and decreasing excretion, and third by increasing calcium resorption from the intestine. Increased parathyroid hormone may function during spaceflight to oppose the effects of increasing cortisol which exerts a negative calcium balance effect. The action of parathyroid hormone requires the presence of vitamin D. It is not yet known what happens to vitamin D levels during spaceflight, although in bed rest studies urinary concentrations of 1,25 dihydroxycholecalciferol, and vitamin D metabolites were decreased.

Increased cortisol levels in spaceflight may have a significant role in the muscle degeneration. Thyroxine and thyroid-stimulating hormone were both found to be increased during spaceflight and may also contribute to an increased metabolism of proteins, carbohydrates, and fats (23).

Catecholamine excretion decreased during the Skylab flights, which is within the observation of reduced sympathetic responsiveness. During bed rest studies, the reduction in norepinephrine excretion could be prevented by exercise (23).

Both American and Soviet spaceflights have shown evidence of a change in energy utilization and production. Fasting blood glucose levels increase initially, then decrease below preflight levels. Plasma insulin concentrations decreased during Skylab flights (23) but were reportedly increased in the Salyut 6 cosmonauts (3).

Fundamental changes in carbohydrate metabolism are evident after only 2 days of bed rest. Dolkas and Greenleaf (24) found that the degree of glucose intolerance during bed rests is proportional to the degree of immobility as assessed by the total energy expenditure each day, and is probably not due to a hydrostatic effect. Exercise during bed rests was effective in reducing glucose intolerance. A possible mechanism of this decreased glucose tolerance is that, during deconditioning or bed rest, there is a decreased sensitivity of the tissues to insulin action through modification of the insulin receptors.

Reproductive System

Little work has been done to evaluate the effect of weightlessness on the female reproductive tract. Rock and Fortney (25) have documented the reduction of plasma volume during bed rest in women. Interestingly, a normalization of plasma volume was observed at midcycle with a preovulatory estrogen peak. Rising estrogens were thought to have salt-retaining property that prevented the loss of plasma volume.

Recently, Rock and Fortney (25) have studied the menstrual cycle in the bed rest patient. A luteal phase deficiency as defined by Abraham et al. (26) was documented in 3 of 12 patients (Fig. 3).

Further investigations using subjects as their own controls are needed to establish that weightlessness may result in diminished progesterone secretion. Furthermore, studies of the hypothalamic-pituitary-ovarian axis may further elucidate a pathophysiologic mechanism.

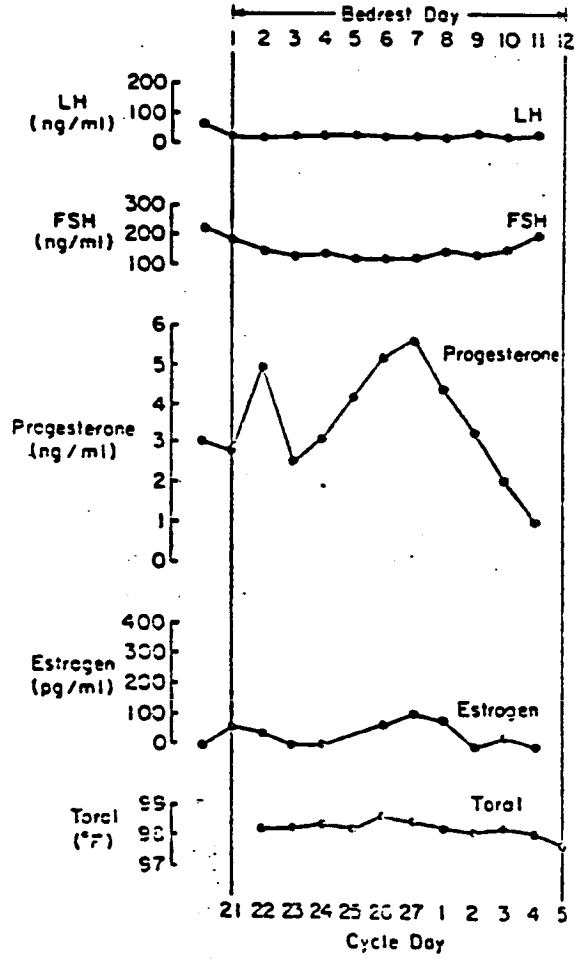

Fig. 3. Endocrine parameters of a woman at bed rest for 12 days. An insufficiency of progesterone secretion was documented according to the method of Abraham. Plasma volume decreased by 22 per cent.

Recent studies have documented an increased incidence of endometriosis among monkeys exposed to proton irradiation similar to that which would be experienced by an astronaut (27). Thus, it has been hypothesized that astronauts may be at increased risk for the development of endometriosis. Furthermore, in an environment of weightlessness, the normal egress of menstrual fluid may be less optimal and tubal reflux more frequent.

Aberration of menses may occur in the weightlessness environment due to anovulation. This may be particularly true in long-term spaceflight. Alterations in the metabolism, clearance of steroids, and secretion of gonadotropins may result in chronic anovulation. Menometrorrhagia and hypermenorrhea may be serious as it is unknown whether the normal hemostatic mechanisms associated with the menstrual period are operative in conditions of weightlessness.

Surgery in Conditions of Weightlessness

With the increasing frequency and duration of extraterrestrial travel in an environment of weightlessness, the need for medical and surgical care will most likely increase. In particular, if an injury occurs, surgical techniques should be developed for rapid hemostasis and tissue closure at zero-gravity if the mission profile precludes the prompt return of an injured crew member to earth for treatment. Furthermore, problems related to surgical technique and weightlessness should be resolved before planetary missions, which preclude the return of a crew member to earth for surgery.

In-flight surgery has been tested aboard aircraft in Keplerian parabolas by the Soviet Union (28, 29). Special transparent containers were used to perform surgical laparotomy on rabbits under local anesthesia. Cutting the mesentery of the small intestine was accompanied by vigorous blood flow. The blood did not pump out and scatter into the atmosphere but flowed around injured vessels in the form of puddles. Arterial blood flow tended to scatter. Contamination of the cabin atmosphere may be prevented by careful clamping of tissue before the incision. The Soviets reported the necessity of limiting the abdominal incision initially to avoid eventration. The surgeons noted, however, that eventration eliminated the need for retractors.

Thus, this preliminary work brought about the

realization that surgery could be performed in the weightlessness environment. Although our understanding of the effect of weightlessness have rapidly advanced, the available literature on surgical techniques at zero-gravity is sparse. Studies are primarily in the Russian literature and observational in nature (29, 30).

Upon entering zero-gravity, there is a slowing down of speed and accuracy for a purposeful movement. In particular, there are errors in trying to hit the center of the target (deviation of hits upward). There is, however, rapid adaptation as motor coordination habits usually develop quite easily (31–33). Specifically designed instruments may be required to perform complex motor reactions required for delicate surgical maneuvers.

Stazhadze et al. (30) suggested that the limitations of the size of the cosmic craft and the reduced immunoreactivity of man in space requires a soft surgical antibacterial chamber made of transparent fluorplastic film and having two to three pairs of built-in sleeves with surgical gloves. The authors stressed the need for developing a compact set of lightweight surgical instruments meeting the requirements for surgical intervention at zero-gravity.

Rock (34) has suggested an expandable chamber for minor surgery in conditions of weightlessness. Major considerations in developing such a system for use in a spacecraft were to provide a sterile environment as well as to prevent contamination of the cabin with blood and other debris while performing the surgery.

The module is a self-contained system with a cuff tourniquet and insufflator. The sterile gloves are built into the system so that the environment within the capsule is sterile, containing both gloves and instruments, which are attached with Velcro straps to the clear vinyl walls of the capsule (Figs. 4 and 5). In the event of an arm injury, the arm would be inserted through the cuff tourniquet; the tourniquet would then be inflated to achieve hemostasis. The capsule then may be insufflated and the surgeon's hands inserted into the gloves, the instruments grasped, and the surgery performed. The surgical area may be prepped and local anesthesia administered within this surgical environment. The bleeders may either be clipped or suture ligated. As normal hand tying movements may be difficult under conditions of weightlessness, clip systems may be more appropriate to achieve vessel ligation and hemostasis. Contamination of the spacecraft with blood and tissue debris is thus avoided, maintaining a clean environment.

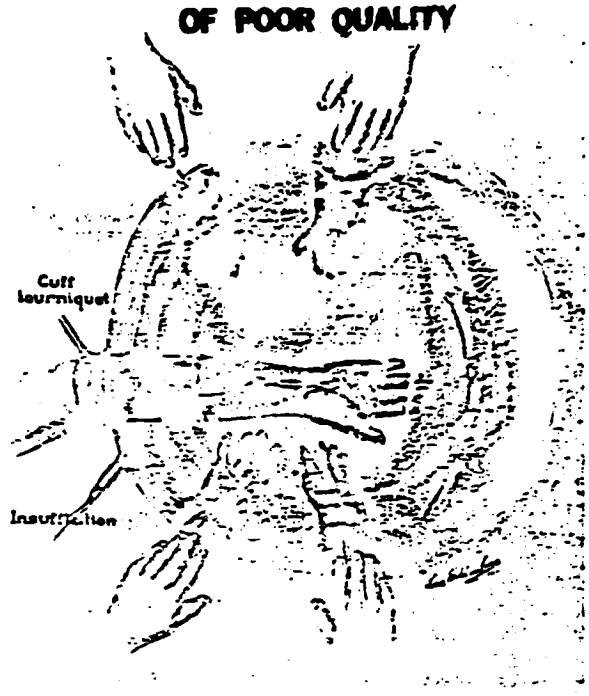

Fig. 4. An expandable chamber for surgery in conditions of weightlessness. Instruments and suture material are stored in pockets within the chamber. From Rock, J. A.: An expandable surgical chamber for use in conditions of weightlessness. Aviat. Space Environ. Med. 55: 403, 1984. Reproduced with permission of the Aerospace Medical Association, Washington, DC.

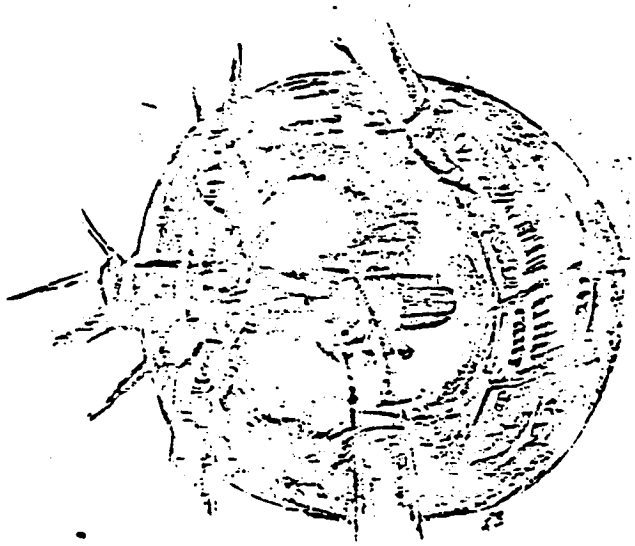

Fig. 5. The injured limb is inserted through the cuff tourniquet, the tourniquet inflated, the surgeon's hands inserted into the gloves, instruments grasped, and surgery performed. From Rock, J. A.: An expandable surgical chamber for use in conditions of weightlessness. Aviat. Space Environ. Med. 55: 403, 1984. Reproduced with permission of the Aerospace Medical Association, Washington, DC.

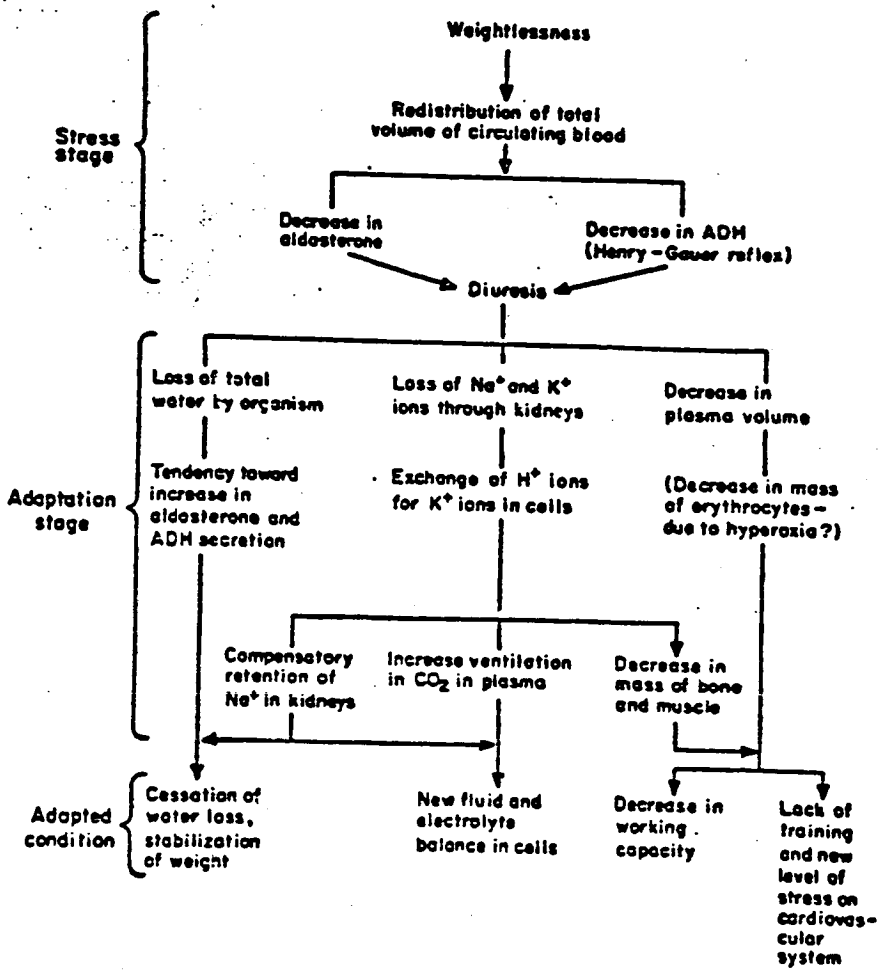

Fig. 6. The process of adaptation of man at zero gravity. ADH, antidiuretic hormone. Adapted from: Leach, C. S., Alexander, W. C., and Fischer, C. L.: Compensatory change during adaptation to the weightless environment. Physiologist 13: 246, 1970.

Future Clinical Investigation

Although the process of adaptation to zero-gravity in the human has been studied (Fig. 6), the effects of prolonged weightlessness on the menstrual cycle are unknown; thus, a new field of gynecologic investigation is apparent. In particular, using bed rest for simulation, the hypothalamic-pituitary-ovarian axis may be carefully studied and the metabolic clearance of steroids elucidated. Long-term spaceflight may allow dynamic testing in "skylabs."

Immersion in water or the Keplerian parabola will provide a method of simulation for testing surgical modules. Ideally, the "skylab" will allow careful study of the technical difficulties in performing minor surgery. Major surgery will be addressed in the space stations of the future.

The influence of the process of adaptation on surgery may be of great importance. The reduction of plasma volume and increase in central venous pressure may result in a critical margin of safety.

REFERENCES

1. Nicogossian, A. E., and Parker, J. F.: *Space, Physiology and Medicine*. NASA, SP-447, U.S. Government Printing Office, Washington, DC, 1982.
2. Vorobyov, E. I., Gazenko, O. G., Genin, A. M., and Egorov, A. D.: Medical results of Salyut-6 manned spaceflights. Aviat. Space Environ. Med. 54(suppl. 1): S31, 1983.
3. Saltin, S., and Rowell, L. B.: Functional adaptations to physical activity and inactivity. Fed. Proc. 39: 1506, 1980.
4. Thorton, W. E.: Rationale for exercise in spaceflight. In *Conference Proceedings: Spaceflight Deconditioning and Physical Fitness*, edited by J. F. Parker, Jr., C. S. Lewis, and O. G. Christensen. Prepared by Bio-Technology Inc. under contract No. NASW-3469 for National Aeronautics and Space Administration, Washington, DC, August 1981, pp. 13–31.
5. Wronski, T. J., and Morey, E. R.: Alterations in calcium homeostasis and bone during actual and simulated spaceflight. Med. Sci. Sports 15: 410, 1983.
6. Dietlein, L. F., and Johnson, R. S.: U.S. manned spaceflight: The first 20 years. A biomedical status report. Acta Astronaut. 8: 693, 1981.
7. Rose, G. A.: Immobilization osteoporosis. A study of the extent, severity, and treatment with bendrofluazide. Br. J. Surg. 53: 769, 1966.
8. Saltin, B., Blomquist, G., Mitchell, J. H., et al.: Response to exercise after bedrest and after training. Circulation 38(suppl.

VII): VII-1, 1968.
9. Beckett, W., Vroman, N., Nigro, D., et al.: Increased vital capacity and diminished diffusing capacity during prolonged bedrest. Am. Rev. Respir. Dis. 129: A266, 1984.
10. Beckett, W., Vroman, N., Fortney, S., et al.: Effects of alteration of plasma volume on pulmonary function. Fed. Proc. 43: 297, 1984.
11. Sawin, C. F., Nicogossian, A. E., Rummel, J. A., et al.: Pulmonary function evaluation during the Skylab and Apollo-Soyuz missions. Aviat. Space Enviom. Med. 47: 169, 1976.
12. Greenleaf, J. E., Bernauer, E. M., Young, H. L., et al.: Fluid and electrolyte shifts during bedrest with isometric and isotonic exercise. J. Appl. Physiol. Respir. Environ. Exercise Physiol. 42: 59, 1977.
13. Fortney, S., Drew, H., and LaFrance, N.: Plasma volume responses during bedrest in healthy women. Aerosp. Med. Assoc. Preprints 1983, p. 245.
14. Bohm, B. J., Hyatt, K. H., Kamenetsky, L. C., et al.: Prevention of induced orthostatism by 9-alpha-fluorohydrocortisone. Aerosp. Med. 41: 495, 1970.
15. Stevens, P. M., Lynch, T. N., Johnson, R. L. et al.: Effects of 9-alpha-flurohydrocortisone and venous occlusion cuffs on orthostatic deconditioning of prolonged bedrest. Aerosp. Med. 37: 1049, 1966.
16. Blomqvist, C. G., Gaffney, F. A., and Nixon, J. V.: Cardiovascular responses to head-down tilt in young and middle-aged men. Physiologist 26(suppl.): S81, 1983.
17. Henry, W. L., Epstein, S. E., Griffith, J. M., et al.: Effect of prolonged spaceflight on cardiac function and dimensions. In *Biomedical Results from Skylab*, edited by R. S. Johnson and L. F. Dietlein. NASA, SP-377, U.S. Government Printing Office, Washington, DC, 1977.
18. Nicogossian, A. E., Pool, S. L., and Rambaut, P. C.: Cardiovascular response to spaceflight. Physiologist 26(suppl.): S78, 1983.
19. Grobanian, A. V., Lille, R. D., Tercyak, A., et al.: The metabolic and hemodynamic effects of prolonged bedrest in normal subjects. Circulation XLIX: 551, 1974.
20. Fortney, S., Beckett, W., Turner, C., et al.: Alteration of venous responses during exercise following bedrest. Fed. Proc. 42: 584, 1983.
21. Bergman, S. A., Johnson, K. L., and Hoffler, G. W.: Evaluation of the electromechanical properties of the cardiovascular system after prolonged weightlessness. In *Biomedical Results from Skylab*, edited by R. S. Johnson and L. F. Dietlein. NASA, SP 377, U.S. Government Printing Office, Washington, DC, 1977.
22. Leach, C. S., Johnson, P. C., and Suki, W. N.: Current concepts of spaceflight induced changes in hormonal control of fluid and electrolyte metabolism. Physiologist 26(suppl.): S24, 1983.
23. Leach, C. S., Altchuler, S. I., and Cintron-Trevino, N. M.: The endocrine and metabolic respones to spaceflight. Med. Sci. Sports Exercise 15: 432, 1983.
24. Dolkas, C. B., and Greenleaf, G. E.: Insulin and glucose responses during bedrest with isotonic and isometric exercise. J. Appl. Physiol. Respir. Environ. Exercise Physiol. 43: 1033, 1977.
25. Rock, J. A., and Fortney, S. M.: Unpublished data, 1984.
26. Abraham, G. E., Maroulis, G. B., and Marshall, J. R.: Evaluation of ovulation and corpus luteum function using measurements of plasma progesterone. Obstet. Gynecol. 44: 522, 1974.
27. Wood, H. D., Yochmowitz, M. G., Salmon, Y. L., et al.: Proton irradiation and endometriosis. Aviat. Space Environ. Med. 54: 718, 1983.
28. Berry, C. A.: Medical care of space crews in flight. In *Foundations of Space, Biology and Medicine*, edited by M. Calvin and O. G. Gazenko. NASA, U.S. Government Printing Office, Washington, DC, 1975, p. 3425.
29. Yaroshenko, G. L., Terent'ev, V. G., and Mokov, M. D.: Characteristics of surgical intervention under conditions of weightlessness. Voenno-Med. Zh. 10: 69, 1967.
30. Stazhadze, L. L., Goncharov, I. B., Neumyvakin, I. P., et al.: Problems of anesthesia, surgery and resuscitation during manned spaceflights. Kosm. Biol. Aviakosm. Med. 16: 9, 1982.
31. Berry, C. A.: The medical legacy of Apollo. Presented at the 21st Congress on Aviation and Space Medicine at Munich, Germany, September 1973.
32. Pestov, I. D., and Gerathewohl, S. J.: Weightlessness. In *Foundations of Space, Biology and Medicine*, edited by M. Calvin and O. G. Gazenko. NASA, U.S. Government Printing Office, Washington, DC, 1975, vol. 2, book 1, p. 305.
33. Terent'ev, V. G., and Kreysina, T. N.: Medical and prophylactic safety at space crews. Akad. Nauk SSSR, Moscow, 1970. NASA TIF-13.1949.
34. Rock, J. A.: An expandable surgical chamber for use in conditions of weightlessness. Aviat. Space Environ. Med. 55: 403, 1984.

THERMOREGULATORY ADAPTATIONS TO INACTIVITY

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ABSTRACT

Exercise conditioning is usually accompanied by increases in blood volume and improvements in heat tolerance. Deconditioning on the other hand, especially when produced by extended periods of bedrest, is accompanied by a decrease of blood volume. In this study, the effects of bedrest deconditioning on exercise thermoregulatory responses were studied, both with and without an accompanying reduction in plasma volume. Two groups of women underwent identical 12-day bedrest protocols. Group 1 (n=12) was administered no hormonal treatment, and their plasma volumes were significantly reduced (19.9%) at the end of the bedrest. Group 2 (n=7) received daily estrogen supplementation (1.25 mg premarin) during bedrest, and they did not suffer a significant reduction in plasma volume during the last days of bedrest. Both groups however had impaired thermoregulatory responses after bedrest. Therefore deconditioning, even if unaccompanied by a reduction in plasma volume, results in an impairment of thermoregulatory function.

INTRODUCTION

Although many studies have examined the effect of increasing fitness level on heat tolerance[1-5], very few[6] have looked at the effect of deconditioning. There are many reasons to suspect that heat tolerance would be impaired following periods of inactivity, especially if that inactivity involved physical confinement, for example, as often occurs in patients confined to bed for several days or weeks. Bedrest results not only a reduction in fitness level, but also is known to result in pronounced reduction in body fluid compartments.[7,8] Hypovolemia both with and without electrolyte losses, has been shown to alter significantly both the vasodilatory and the sweating heat loss responses in exercising humans.[9-11]

The effect of increasing fitness level on local sweating and skin blood flow responses was studied by Roberts and co-workers.[12] The local sweat response was measured with sweat capsules placed on the chest and connected to a resistance

hygrometry sweat system. The local sweat rate was then plotted as a function of the internal body temperature, which was measured with a thermocouple placed in the esophagus at heart level. A plot of the chest sweat rate (SR) as a function of the rise in deep body temperature (T_{es}) characterized the effect of increased fitness. An increase in the slope of this SR/T_{es} relationship indicated that the sensitivity of the sweating response increased during the training program, which produced an 11% increase in the maximum oxygen uptake (VO_{2max}) in these subjects. The T_{es} threshold at which sweating began was reduced significantly. The skin blood flow (SkBF) response was measured by electrocapacitance plethysmography. Again this thermoregulatory response was characterized by plotting the skin blood flow values as a function of the rise in T_{es}. The slope of the SkBF/Tes relationship was only slightly altered following training. However the T_{es} threshold at which vasodilation occurred, was significantly reduced during the training program.

Thus changes in fitness level may be expected to alter both the sweating and the skin blood flow responses. We would hypothesize further, that after deconditioning, the internal temperature during an exercise challenge would be elevated to a greater extent than before deconditioning. The higher core temperature would be due to a reduction in the slope of the sweating response, and an elevation in the thresholds of the sweating and skin blood flow responses. Deconditioning as a result of bed confinement would be expected to result in even further impairment of heat tolerance. The combined effects of hypovolemia and deconditioning during bedrest would be predicted to act in an additive manner to impair thermal exercise responses.

EXPERIMENTAL METHODS AND RESULTS

To test our hypothesis that thermoregulatory responses would be impaired following deconditioning, we studied the exercise responses of twelve young healthy women before and after 12-day programs of horizontal bedrest. Then to further test the contribution of hypovolemia on the impairment of exercise thermal responses, a second

group of 7 women performed an identical 12-day bedrest protocol, except they were given a daily estrogen supplement (premarin) several days before and during the bedrest. The estrogen supplement resulted in an attenuation of the loss of body fluids during bedrest so that deconditioning responses might be separated from hypovolemic effects.

Table 1 illustrates the physical characteristics of the two groups of women. All the women in this study reported a normal menstrual cycle history, with a total cycle length consistently between 25 and 32 days. Group 1 was composed of 12 women who did not regularly take medication of any kind, including oral contraceptives. They were between 21 and 39 years of age, with a group mean age of 27. They were of average fitness as determined by VO_{2max} testing. Group 2 had similar physical characteristics, but had at some point in their lives used an estrogen-containing oral contraceptive without suffering significant side effects. These women were instructed to ingest one tablet (1.25 mg) of premarin each morning starting on the third cycle day (where day 1 is the first day of bleeding) immediately before the bedrest, and to continue this treatment until two days after the bedrest.

The bedrest procedure consisted of 12 days of horizontal bedrest. Each woman maintained a horizontal position during all but 18 minutes in each 24 hour interval. These 18 minutes were spent in the sitting position and this was the total accumulative time in which the subjects traveled by wheelchair to and from the bathroom. At no time did a subject support her weight by standing or walking. At the same time each morning during the bedrest, a blood sample was drawn without stasis to determine the hematocrit and hemoglobin concentration. These values were used to calculate[13] the relative changes in plasma volume between the first and each succeeding day of the bedrest.

The absolute red cell volume and plasma volume of each woman was determined by radioisotope dilution.[14] ^{99}M technetium pertechnetate was used to label a sample of

each subject's red blood cells to determine absolute red cell volume, and ^{99}M technetium-labelled human serum albuman was used to determine absolute plasma volume. Absolute red cell and plasma volume determinations were performed one day before and within 48 hours after each bedrest.

Although significant reductions in red cell volume have been reported during longer bedrest procedures[15], in this study there was a tendency to reduce red cell volume during bedrest, but these differences were not significant ($P<0.05$ from t-test determinations). Red cell volume averaged 1474 $\pm$ 44 and 1326 $\pm$ 95 before bedrest for Groups 1 and 2 respectively. The red cell volumes for the two groups averaged 1389 $\pm$ 42 and 1240 $\pm$ 90 ml after bedrest.

Figure 1

Figure 1 illustrates the changes in plasma volume during the two bedrest procedures. Plasma volume decreased significantly during the first 4-5 days of bedrest in the women who did not receive estrogen supplement (Group 1). A markedly different pattern however was seen in Group 2. Plasma volume decreased significantly during the first two days of bedrest. Then the decrease in plasma volume was attenuated and even reversed, such that, the plasma volume in the group of women who received estrogen supplement was not significantly different ($P<0.05$, Duncan Multiple Range comparisons) from their first day of bedrest during 7 of the last 8 days of the bedrest.

Submaximal exercise tests were performed in a warm (30 degrees C, 50-60% relative humidity) temperature-controlled room, one day before and immediately after bedrest. The exercise intensity on the low-sit cycle ergometer was adjusted to 70% of each subjects pre-bedrest $\dot{V}O_{2max}$, which was determined previously and defined by a plateau in the oxygen consumption/exercise intensity relationship measured during progressive cycle exercise tests. The submaximal tests continued for 30 minutes, or until a subject's heart rate exceeded 95% of her pre-bedrest maximum heart rate

value.

Submaximal exercise tolerance was reduced significantly in both groups of women following bedrest, despite the marked differences in plasma volume decrease during bedrest between Groups 1 and 2. Whereas, before bedrest each woman was able to comfortably complete the 30-minute exercise task, following bedrest, only one woman in Group 1, and none of the women in Group 2 could complete the thirty minutes of exercise without being instructed to stop because their heart rate had reached 95 percent of their maximal heart rate.

Figure 2

The heart rate responses during these submaximal tests are illustrated in Figure 2. The average $\pm$ standard error values for the first group of women are shown in the top panel of this figure, for both pre-bedrest and post-bedrest exercise. Since the submaximal exercise tests were performed immediately after bedrest, a postural stress was induced by the assumption of the sitting position in the low-sit cycle for 30 minutes before the start of exercise. Thus even at rest, heart rates were significantly higher than pre-bedrest values in the post-bedrest tests. Initially, we attributed at least part of the increase in heart rate after bedrest to a hypovolemic effect. The average plasma volume at the start of exercise was 432 ml lower during the post-bedrest test than during the pre-bedrest test.

However, the results in the bottom half of Figure 2 illustrate the heart rate responses in the second group of women. The average difference in plasma volume at the start of exercise between the pre-bedrest and the post-bedrest tests was only 130 ml (non-significant). Yet an examination of the heart rate responses following bedrest, shows a similar pattern as seen in Group 1, that is a similar increase in heart rate post-bedrest.

Figure 3

Continuous measurement of body core temperature was obtained during each exer-

cise test from a thermocouple placed in the esophagus at the level of the heart and these results are illustrated in Figure 3. Again the responses from Group 1 are shown in the top panel of this figure. Like the heart rate responses, the esophageal temperature (T_{es}) already was elevated significantly above pre-bedrest levels before the start of the post-bedrest test. T_{es} remained higher than pre-bedrest time-matched values throughout exercise following bedrest. A similar pattern of T_{es} response occurred in the pre- and post- bedrest tests in Group 2 (bottom panel). However, the rise in T_{es} during post-bedrest exercise was significantly greater than before bedrest in group 1 ($p < 0.02$), but not in the group 2 ($p < 0.67$).

The total sweat output was estimated in these exercise tests, by accurately weighing each subject in dry cotton clothing before and after exercise. The changes in body weight are shown in Table 2.

Table 2

The total change in body weight (g) was less in the post-bedrest tests, in part due to the shorter exercise period. When the sweat rate was expressed as a weight loss per minute of exercise, (g/min), the total sweat rate was significantly higher in the post-bedrest tests for both groups 1 and 2. It appears that the sweating response was not inhibited by deconditioning following bedrest, and that the higher post-bedrest sweat rate would be expected to accompany the higher T_{es} values. We had predicted an inhibition of sweating in the hypovolemic exercise condition (Group 1, post-bedrest), as compared to the normovolemic post-bedrest conditions (Group 2). Although there was a tendency for the sweat rates to be lower in Group 1 than in Group 2 following bedrest, these differences just barely were not significant ($P<0.06$).

DISCUSSION

In these studies we have developed a model to examine the effects of bedrest, both with and without plasma volume reduction, on submaximal exercise responses. We

predicted that exercise tolerance would be reduced following bedrest for two reasons. First, a certain degree of physical deconditioning would be expected following 2 days of bedrest; then, since the same absolute exercise intensity (70% of the pre-bedrest $\dot{V}O_{2max}$) was used in the pre- and post-bedrest tests, post-bedrest exercise was performed at a higher relative exercise intensity. Second, it has been reported in men during bedrest[15], that a spontaneous diuresis occurs in the first few days of a bedrest procedure. Presumably a Henry-Gauer type of reflex is illicited[16] by an increase in central blood volume caused by the cephalad movement of body fluids with the assumption of the horizontal position. Cardiopulmonary stretch receptors are then stimulated resulting in an increased urine output and a decrease in total body fluids. In this study the decrease in plasma volume averaged about 20% in Group 1. In previous studies[10,11,17] in which plasma volume was reduced to a similar degree through the use of diuretics or by blood withdrawal before submaximal exercise, the thermoregulatory responses were impaired significantly. The surprising finding in this study was that exercise responses following bedrest were equally impaired in these subjects, whether the plasma volume was reduced (by about 20%), or restored to the pre-bedrest level before exercise testing. An attempt was made to measure the decrease in $\dot{V}O_{2max}$ within 48 hours after the end of the bedrest procedure. However, following bedrest, we were not able to attain consistently our criteria for determination of $\dot{V}O_{2max}$: that is, a plateau of the oxygen consumption/exercise intensity curve. Only peak oxygen uptake values could be obtained, because most subjects stopped the progressive exercise test due to leg fatigue rather than a cardiovascular limitation. The peak $\dot{V}O_2$ value obtained following bedrest in group 1 averaged an 11.5% reduction from the pre-bedrest values. Group 2 showed a 21.5% average reduction. There was tremendous variation in the responses of the individual subjects in each group, and so the decrease in peak $\dot{V}O_2$ seen following bedrest was not statistically different ($p < 0.05$) between Group 1 and Group 2. Thus there is no reason to

believe that the deconditioning effect was different between the two groups.

An alteration in thermoregulatory responses was evident after bedrest even before the start of exercise. The higher resting core temperature and heart rate in the post-bedrest tests occurred before the initiation of the sweating reflex. This fact, together with the lack of a significant reduction in the sweat rate following bedrest, argues against the idea that deconditioning may have inhibited the sweating response, and thus been responsible for the higher body temperatures after bedrest.

There are two other possible explanations for the impaired heat tolerance after bedrest. The first is that there was a change in the resting metabolic rate after bedrest, such that the total body heat production increased both at rest and during exercise. This explanation seems unlikely, as one would expect that if any change occurred in the resting oxygen consumption during bedrest, VO_2 would decrease, not increase.

The second more likely explanation is that there was an alteration in vasomotor tone following bedrest, producing a greater vasoconstriction which decreased heat exchange between the skin surface and the environment. Indirect evidence to support this hypothesis is the greater venoconstriction we reported in a group of women at rest and during exercise following bedrest.[18] At the time of this report, we suggested that following bedrest, there was an increase in peripheral venoconstrictor tone which helped to compensate for the reduction in plasma volume, and which functioned to maintain central blood volume. Although in this previous study we measured an increase in forearm venous tone, we might also expect a greater cutaneous arteriolar tone, since both venous and arteriolar constrictor responses are produced by the increased sympathetic drive which occurs with the onset of exercise. Although the cutaneous vessels may show an increase in tone following bedrest, a decrease in the tone may occur in the deeper blood vessels of the lower extremities or of the splanchnic region. Thus following bedrest when the subjects in this study sat up-

right just prior to the exercise tests, blood may have pooled in dependent body regions, illiciting a vasoconstrictor response and impairing cutaneous heat exchange. The potential for blood pooling following bedrest may be so great, that even when the plasma volume was restored during bedrest (Group 2), blood still pooled in the lower extremities, producing a vasoconstrictor response and impairing heat loss. Thus even an expansion of plasma volume following bedrest may not improve exercise tolerance, but may simply lead to greater blood pooling, and in extreme cases, may produce lower body edema.

CONCLUSIONS

Bedrest in healthy young women resulted in impairment of thermoregulatory responses both at rest and during exercise in a warm environment. The higher body temperature following bedrest may have been due to effects caused by deconditioning or to effects caused by the hypovolemia which normally accompanies bedrest. In this study the sweating responses were not significantly altered following bedrest. It is most likely that the higher body temperatures were caused by a cutaneous vasoconstrictor response which functioned to oppose blood pooling in the lower extremities. Restoring blood volume to pre-bedrested values was ineffective in reversing the impairment of thermoregulatory responses.

ACKNOWLEDGEMENTS

This work was supported by NASA Contract NAS9-16703. Thanks to Clarke Tankersley, Kirstin Levine, and Kay Chadwell for their help in the preparation of this manuscript.

REFERENCES

1. Strydom, N.B., Wyndham, C.H., Williams C.G., Morrison, J.F., Bredell, G.A.G., Benade, A.J.S. and Von Rahden, M. Acclimatization to humid heat and the role of physical conditioning. J. Appl. Physiol. 21: 636, 1966.

2. Piwonka, R.W., Robinson, S., Gay, V.L. and Manalis, R.S. Preacclimatization of men to heat by training. J. Appl. Physiol. 20: 379, 1965.

3. Pandolf, K.B. Effects of physical training and cardiorespiratory physical fitness on exercise-heat tolerance: recent observations. Med. Sci. Sports 11: 60, 1979.

4. Gisolfi, C. and Robinson, S. Relations between physical training, acclimatization, and heat tolerance. J. Appl. Physiol. 26: 530, 1969.

5. Henane, R., Flandrois, R.L and Charbonnier, J.P. Increase in sweating sensitivity by endurance conditioning in man. J. Appl. Physiol. 43: 822, 1977.

6. Greenleaf, J.E., and Reese, R.D. Exercise thermoregulation after 14 days of bedrest. J. Appl. Physiol. 48: 72, 1980.

7. Taylor, H.L., Erickson, L., Henschell, A. and Kaye, A. The effect of bedrest on the blood volume of normal young men. Am. J. Physiol. 144: 227, 1945.

8. Hargens, A.R. Fluid shifts in vascular and extravascular spaces during and after simulated weightlessness.

9. Horstman, D.H., and Horvath, S.M. Cardiovascular and temperature regulatory changes during progressive dehydration and euhydration. J. Appl. Physiol. 33: 446, 1972.

10. Nadel, E.R., Fortney, S.M., and Wenger, C.B. Effect of hydration state on circulatory and thermal regulations. J. Appl. Physiol. 49: 715, 1980.

11. Fortney, S.M., Nadel, E.R., Wenger, C.B., and Bove, J.R. Effect of blood volume on sweating rate and body fluids in exercising humans. J. Appl. Physiol. 51: 1594, 1981.

12. Roberts, M.F., Wenger, C.B., Stolwijk, J.A.J., and Nadel, E.R. Skin blood flow and sweating changes following exercise training and heat acclimation. J. Appl. Physiol. 43: 133, 1977.

13. Dill, D.B. and Costill, D.L. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. J. Appl. Physiol. 37: 247, 1974.

14. Glass, H.I. Standard techniques for the measurement of red-cell and plasma volume. Br. J. of Haematology 25: 801, 1973.

15. Greenleaf, J.E. Physiological responses to prolonged bedrest and fluid immersion in humans. J. Appl. Physiol. 57: 619, 1984.

16. Gauer, O.H., Henry, J.P. and Sieker, H.H. Cardiac receptors and fluid volume control. Prog. in Cardiovas. Des. 4: 1, 1961.

17. Fortney, S.M., Nadel, E.R., Wenger, C.B., and Bove, J.R. Effect of acute alterations of blood volume on circulatory performance in humans. J. Appl. Physiol. 50: 292, 1981.

18. Fortney, S.M., Beckett, W., Turner, C., Vroman, N.B. and Wilkinson, L. Alteration of venous responses during exercise following bedrest. Fed. Proc. 42: 584, 1983.

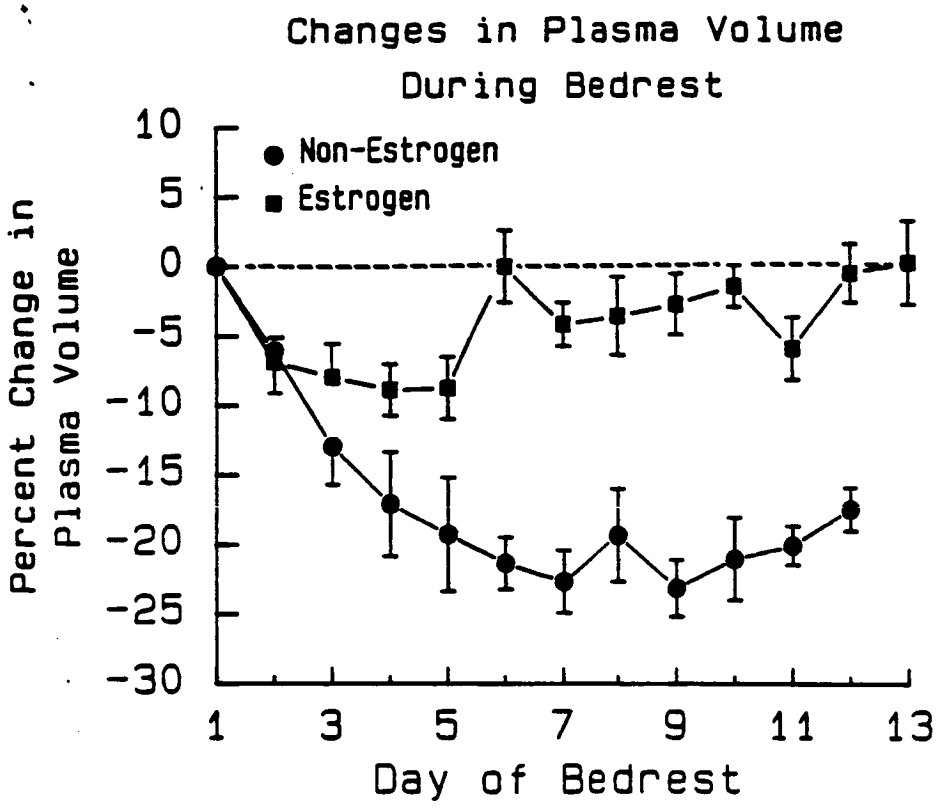
Table 1: Physical Characteristics of the Subjects

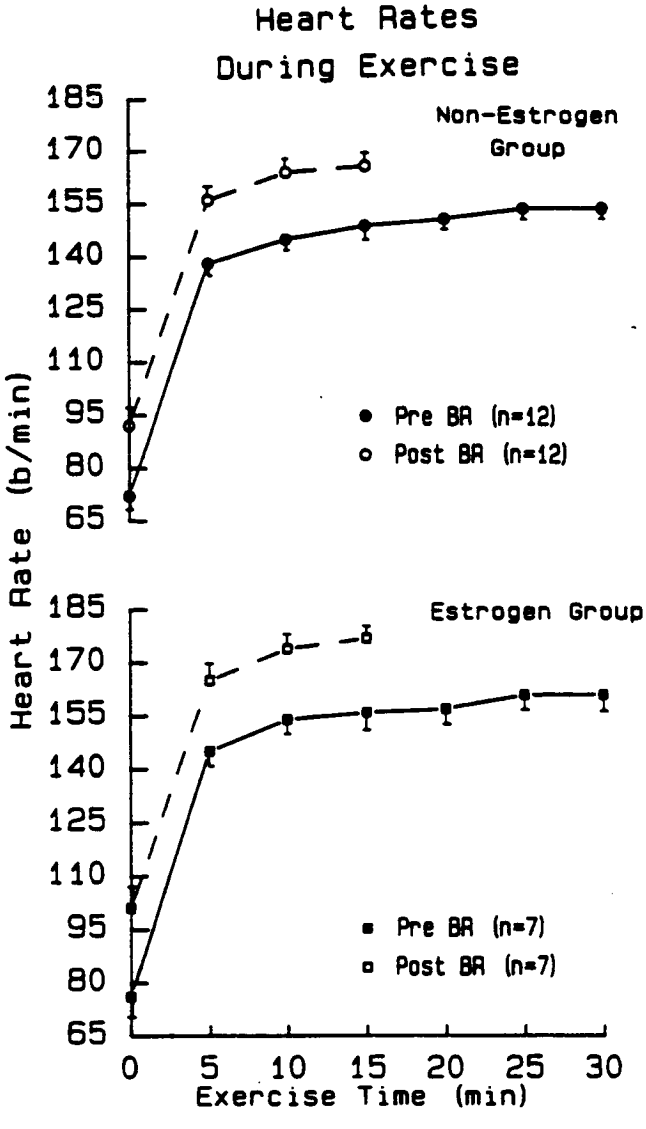
	Group 1 (n=12)	Group 2 (n=7)
Mean weight (kg)	60.5	62.7
± SD	8.0	9.8
Mean age (yrs)	27	26
± SD	6	4
Pre-Bedrest VO_{2max}	37.5	37.2
(ml/kg/min)	5.7	7.7
± SD		

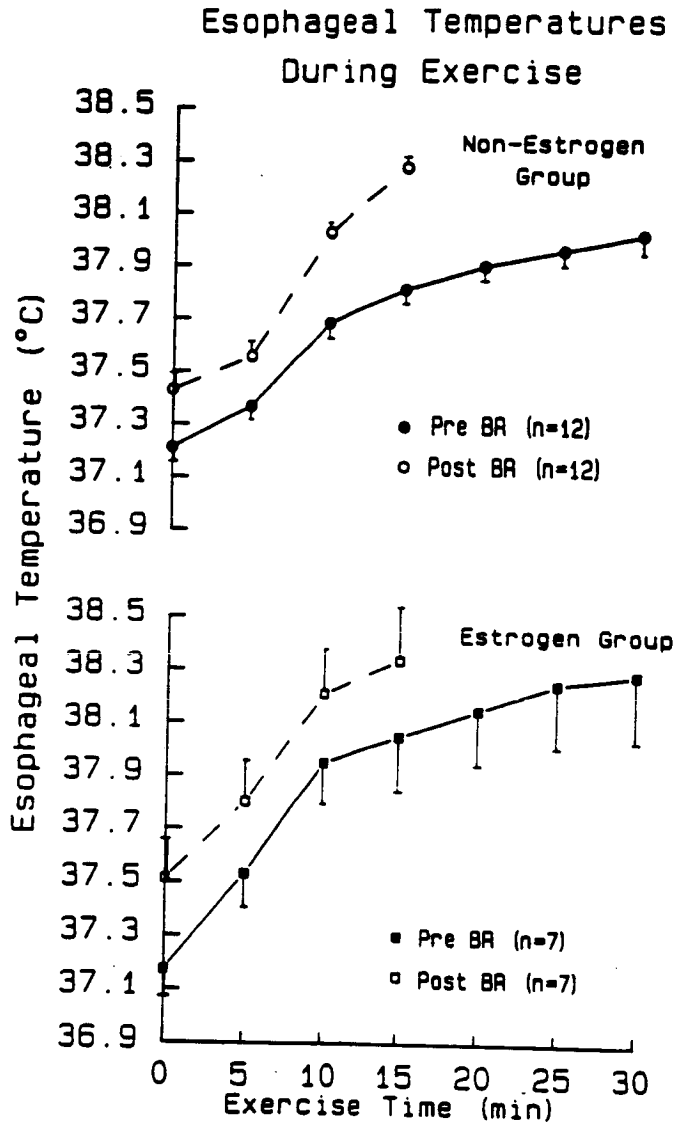
Table 2: Total Body Sweat Losses During Exercise

	Group 1 (Non-estrogen)		Group 2 (Estrogen)	
	Pre-Bedrest	Post-Bedrest	Pre-Bedrest	Post-Bedrest
Change of body wt.	512	*436	486	409
± S.E.	20	19	33	47
(g)				
Minutes of exercise	30	* 21	30	* 16
± S.E.	0	2	0	2
(min)				
Total Sweat Rate	17.31	* 22.19	16.19	* 26.84
± S.E.	2.56	4.59	2.73	5.00
(g/min)				
Increase in T_{es}	0.62	* 0.78	0.89	0.83
± S.E.	0.06	0.07	0.16	0.09
(^{o}C)				

* Post-Bedrest value significantly different from Pre-Bedrest value ($P \leq 0.05$). Paired t/test comparison.


Changes in Plasma Volume
During Bedrest
Non-Estrogen
Estrogen
Percent Change in
Plasma Volume
10
5
0
-5
-10
-15
-20
-25
-30
1
3
5
7
9
11
13
Day of Bedrest


Heart Rates
During Exercise
Non-Estrogen
Group
Pre BR (n=12)
Post BR (n=12)
Estrogen Group
Pre BR (n=7)
Post BR (n=7)
Heart Rate (b/min)
185
170
155
140
125
110
95
80
65
0
5
10
15
20
25
30
Exercise Time (min)


Esophageal Temperatures
During Exercise
Non-Estrogen
Group
Pre BR (n=12)
Post BR (n=12)
Estrogen Group
Pre BR (n=7)
Post BR (n=7)
Esophageal Temperature (°C)
38.5
38.3
38.1
37.9
37.7
37.5
37.3
37.1
36.9
0
5
10
15
20
25
30
Exercise Time (min)