

**N94-11998**

57-52  
182 930  
P-10

**EFFECT OF PROLONGED LBNP AND SALINE INGESTION ON  
PLASMA VOLUME AND ORTHOSTATIC RESPONSES DURING  
BED REST**

Suzanne M. Fortney, Larry Dussack, Tracy Rehbein, Margie Wood, and  
Laura Steinmann

*(NASA JSC Space Biomedical Research Institute (SD5) and KRUG LIFE  
SCIENCES)*

Supported by NASA RTOP 199-14-11-13: "Mechanisms of Orthostatic  
Intolerance", and JSC Director's Discretionary Funds .

## ABSTRACT

Orthostatic intolerance remains a significant problem following space flight despite frequent use of the saline fluid-loading countermeasure and volitional use of an anti-gravity suit during re-entry and landing. The purpose of this project is to examine the plasma volume (PV), endocrine, and orthostatic responses of bed-rested subjects following 2-hr and 4-hr treatments of lower body negative pressure (LBNP) and saline ingestion. Ten healthy men (25 to 41 yrs) underwent 13 days of 60° head-down bed rest. The men were randomly assigned into 2 groups. Group A underwent a 4-hr LBNP/saline treatment on bed rest day 5 and the 2-hr treatment on day 11. Group B underwent the 2-hr treatment on day 6 and the 4-hr treatment on day 10. Blood volume was determined before and after bed rest using radiolabelling. Changes in PV between measurements were calculated from changes in hematocrit and estimated red cell volume. Urinary excretion of anti-diuretic hormone (ADH) and aldosterone (ALD) were measured each day during the study. Orthostatic responses were measured using a ramp LBNP protocol before bed rest, before each treatment, and 24 hours after each treatment. Both 2-hr and 4-hr treatments resulted in a restoration of PV to pre-bed rest levels which persisted at least 24 hours. This increase in PV was associated with significant increases in urinary excretion of ADH and ALD. Twenty-four hours after the 4-hr treatment, the heart rate and pulse pressure response to LBNP were significantly lower and stroke volumes during LBNP were increased. Twenty-four hours after the 2-hr treatment, there was no evidence of improvement in orthostatic responses. These results suggest that a countermeasure which simply restores PV during space flight may not be sufficient for restoring orthostatic responses.

## INTRODUCTION AND BACKGROUND:

LBNP has been used as a procedure to assess orthostatic responses postflight in the Apollo program (1), and in flight during the Skylab program (2). In the Soviet space program LBNP is routinely used inflight both as an assessment procedure and as a countermeasure for postflight orthostatic intolerance (3,4). Cosmonauts perform the LBNP countermeasure while wearing a flexible LBNP suit (the Chibis suit). The LBNP exposures are begun 5 to 21 days before landing, depending on the mission duration, and are combined with fluid and salt ingestion. There is no data

available from the Soviet flight experience which would reveal the precise mechanism by which their LBNP countermeasure acts to improve orthostatic responses.

American research into the possible use of LBNP as a countermeasure began in the 1960s. Lamb and Stevens (5), Stevens et. al (6), and McCally et. al (7) performed studies indicating that prolonged exposures (8-12 hrs daily) to LBNP during bed rest could maintain body fluid balance (5), plasma volume (6), and orthostatic responses (6,7). Hyatt and West (8) were the first to combine the LBNP exposure with fluid ingestion. They reported a restoration of plasma volume and significantly reduced heart rate and blood pressure changes during LBNP, in men after 7 days of bed rest. They concluded that the improvement in orthostatic responses was most likely the result of the increased plasma volume and that further work was required to determine the minimum exposure duration required to provide such improvements.

#### PURPOSE AND HYPOTHESES:

The operational purpose of this project is to determine whether the LBNP/saline countermeasure proposed by Hyatt and West (8) may be reduced to 2 hours and still maintain the beneficial effects on plasma volume and orthostatic responses. In answering this question, we hope to gain a better understanding of potential mechanisms for the loss of orthostatic function during a simulated space flight-- 13 day bed rest--and a greater understanding of the specific mechanisms by which prolonged LBNP during bed rest may reverse some of these changes.

We hypothesize that during prolonged LBNP exposures, fluid is redistributed from the thoracic region of the body to the lower body, thus stimulating cardiopulmonary mechanoreceptors. The unloading of these receptors due to the decrease in central blood volume results in an increased secretion of ADH and ALD. Increased levels of ADH and ALD result in fluid and electrolyte retention during the 24 hour period after the LBNP/saline countermeasure. In addition, the accumulation of fluid in the lower body during LBNP may result in the filtration and sequestration of fluid in the lower body tissues. This fluid is later reabsorbed, and in the presence of elevated ADH and ALD may contribute to the plasma volume expansion. The restoration of plasma volume will result in a larger stroke volume,

lower heart rates, higher blood pressures, and a larger cardiac output during a graded orthostatic stress such as LBNP.

#### METHODS AND PROCEDURES:

Ten men (25 to 40 yrs; 169 to 182 cm. height; 66 to 90 kg weight; and 45 to 59 ml/min/kg maximum oxygen consumption) participated in this study.

The study protocol involved a crossover design with the subjects randomly assigned to two groups, group A and group B. The experimental protocol is shown in **Figure 1**. Each subject was exposed to one 4-hr and one 2-hr LBNP/saline treatment, with half the subjects exposed to the 4-hr treatment first and the 2-hr treatment second (group A), and the other half exposed to the 2-hr treatment first and the 4-hr treatment second (group B). During each treatment, the subject was exposed to a continuous negative pressure exposure of -30 mm Hg and ingested one liter of isotonic saline between exposure minutes 30 and 90.

Blood volume was calculated as the sum of red cell volume (RCV) and PV measurements obtained before and on the last day of bed rest. RCV was determined with  $^{51}\text{chromium}$  sulfate and PV was determined with  $^{125}\text{iodinated}$  human serum albumin. PV was calculated for each bed rest day from the daily RCVd (RCVd = pre bed rest RCV minus the accumulative loss of red cells due to daily blood draws) and the daily hematocrit value; where  $PV = (RCVd/(hct/100)) - RCVd$ .

Pre-syncopal LBNP tests (graded LBNP exposures in 3 min. stages which continued until pre-syncopal symptoms were observed) were done before and after bed rest. LBNP response tests (graded LBNP exposures in 5 min. stages from 0 to -60 mm Hg in 10 mm Hg steps) were performed pre-bed rest, before each treatment, and 24 hours after each treatment.

FIGURE 1 : BEDREST PROTOCOL					
BEDREST DAY	BLOOD DRAWN	HORMONES DETERMINED	BLOOD VOLUME	LBNP PROCEDURE	
				GROUP A	GROUP B
- 2	YES		YES	PSL-LBNP	PSL-LBNP
- 1	YES	YES		LBNP	LBNP
1	YES				
2	YES	YES			
3	YES	YES			
4	YES	YES		LBNP	LBNP
5	YES	YES		4HR LBNP	
6	YES			LBNP	2HR LBNP
7	YES				LBNP
8	YES	YES			
9	YES			LBNP	LBNP
10	YES				4HR LBNP
11	YES	YES		2HR LBNP	LBNP
12	YES			LBNP	
13	YES		YES	PSL-LBNP	PSL-LBNP
R1	YES	YES		LBNP	LBNP
R2	YES	YES		LBNP	LBNP

Each subject underwent a 13-day, 6° head-down bed rest, two days of ambulatory control before bed rest, and two days of ambulatory recovery after bed rest. Throughout bed rest fluid, salt, and food intake were maintained at 2500 ml of rehydration fluid/day, 4 grams of salt/day, and 2500 Kcal/day. Twenty-four hour urine collections were obtained each day of the study from which volume, electrolytes, ADH, and ALD concentration were measured. Venous blood samples were obtained without stasis each morning and before each LBNP test. Hematocrit and hemoglobin concentration were determined from each sample.

## RESULTS AND DISCUSSION:

### A. Pre-syncopal LBNP Results--Pre vs. Post Bed Rest

The effect of 13 days of bed rest on LBNP tolerance is shown in Figure 2; where "LBNP tolerance" is defined as the LBNP pressure tolerated for at least one minute without pre-syncopal symptoms. Not all subjects had a decrease in LBNP tolerance during bed rest and

there was no significant correlation between changes in LBNP tolerance and changes in blood volume (measured via radiolabelling on the morning of PSL-LBNP testing). However, there was a significant correlation between the the change in LBNP tolerance during bed rest and the pre-bed rest LBNP tolerance (Figure 3). Subjects with high LBNP tolerance had a greater decrease in LBNP tolerance during bed rest than subjects with low LBNP tolerance.

FIGURE 2

Lowest Pressure Attained, Pre vs. Post Bed Rest

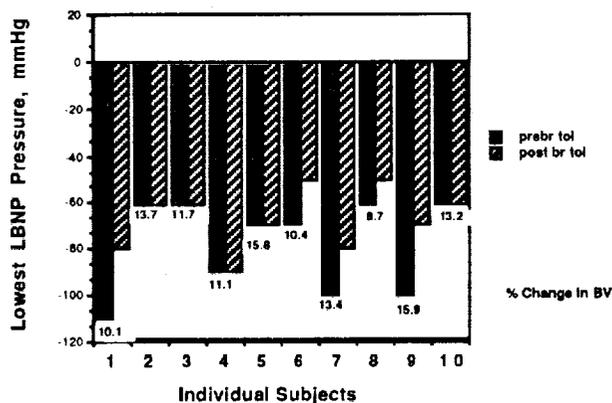
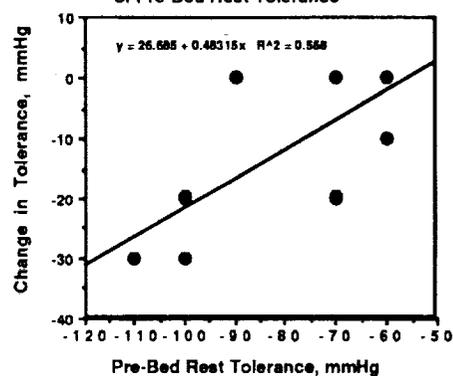


FIGURE 3

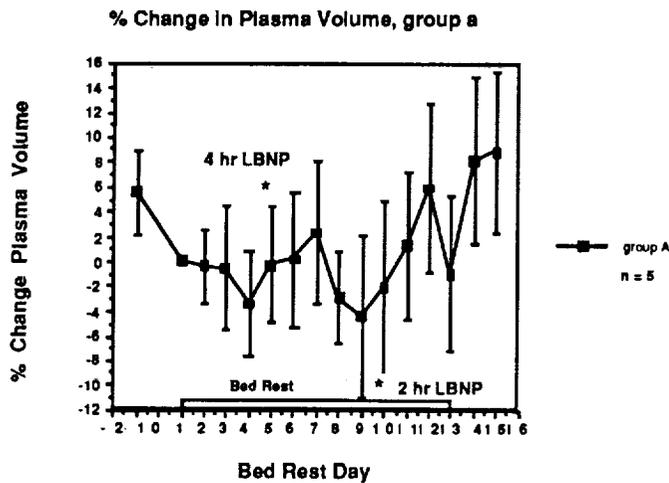
Change in LBNP Tolerance as a Function of Pre-Bed Rest Tolerance



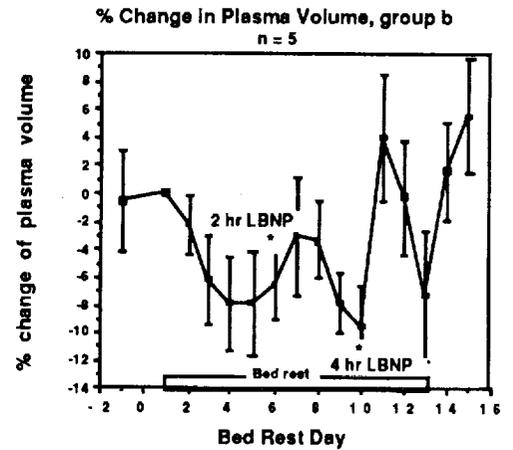
B. Changes in Plasma Volume During Bed Rest--Effect of the 2-hr and 4-hr LBNP and saline ingestion treatments.

The changes in PV determined from each morning blood sample are shown in Figure 4 for Group A and in Figure 5 for Group B. In both groups, PV decreased initially during bed rest and returned towards the pre-bed rest level for one to two days following each LBNP treatment.

**FIGURE 4**



**FIGURE 5**



**C. ADH, ALD, and PV during Bed Rest: effect of LBNP and saline ingestion:**

There were no significant differences between the two groups in any of the treatment or bed rest responses (analysis of variance). Therefore, the data from both groups was combined to compare the effect of the LBNP and saline ingestion treatments on PV, endocrine, and orthostatic responses. PV was calculated from blood samples drawn immediately before each LBNP response test and ADH and ALD secretion were determined from 24-hr urine samples (Table 1). PV was significantly reduced from pre-bed rest levels before each LBNP treatment, but, 24 hours after each treatment PV was no longer significantly different from pre bed rest. On the day of each LBNP treatment, there was a significant increase in the secretion of both ADH and ALD (compared to pre-treatment) which may have contributed to the plasma volume expansion.

**TABLE 1**

<u>Variable</u>	<u>PreBR</u>	<u>Pre 4hr</u>	<u>Post 4hr</u>	<u>Pre 2hr</u>	<u>Post 2hr</u>
PV (ml)	3157(161)	*2918(132)	3144(173)	*2987(131)	3109(146)
UV (ml)	2506(250)	2538(155)	+2923(111)	2258(162)	+2788(191)
ADH (ng)	136(33)	114 (15)	+177 (26)	93 (18)	+155 (42)
ALD (ng)	16(4)	*35(4)	+*54(5)	*37(7)	+*46(7)

\* = Different from pre bed rest,  $P < 0.05$ .

+ = Different from pre treatment (pre 4hr or pre 2hr),  $P < 0.05$ .

D. Orthostatic Responses during Bed Rest--effect of LBNP and saline treatments:

The results in Table 2 illustrate the orthostatic responses (mean  $\pm$  S.E.) for all 10 subjects by presenting specific cardiovascular variables during the final (-60 mm Hg) LBNP exposure level. Heart rates were significantly higher than pre bed rest during all pre and post LBNP treatment tests, although post treatment, the heart rates were lower than pre treatment. Pulse pressure was significantly reduced during bed rest without LBNP treatment but not after treatment. Stroke volume was reduced significantly during bed rest without treatment, but not following treatment. Cardiac output (measured by continuous wave Doppler at the suprasternal notch) was not affected by either bed rest or LBNP treatment.

TABLE 2

<u>Variable</u>	<u>Pre-BR</u>	<u>Pre-4hr</u>	<u>Post-4hr</u>	<u>Pre-2hr</u>	<u>Post-2hr</u>
Heart rate (bpm)	111(5)	*134 (4)	*128 (5)	*144 (5)	*134 (5)
Pulse Pressure (mm Hg)	25 (3)	*16(2)	19 (2)	*18 (3)	19 (3)
Cardiac Output (l/min)	4.2 (0.4)	3.7 (0.2)	3.8 (0.4)	3.6 (0.3)	4.0 (0.3)
Stroke Volume (ml/beat)	39 (5)	*27 (2)	29 (3)	*27 (3)	29 (3)

\* = Different from pre bed rest value, P < 0.05.

Figures 6 and 7 illustrate the mean  $\pm$  S.E. heart rate response to the entire LBNP ramp test (0 to -60 mm Hg) and they compare this response pre bed rest, during bed rest before treatment (pre 2-hr and pre 4-hr) and 24 hours after the 4-hr and 2-hr treatments.

After the 4-hr treatment, the heart rate response was significantly elevated from pre-bed rest, but significantly improved from pre treatment (pre 4-hr). The effectiveness of the treatment to lower heart rate diminished with increasing LBNP exposure.

After the 2-hr treatment, the heart rate response was significantly elevated from pre bed rest and there was no significant improvement after the treatment.

FIGURE 6

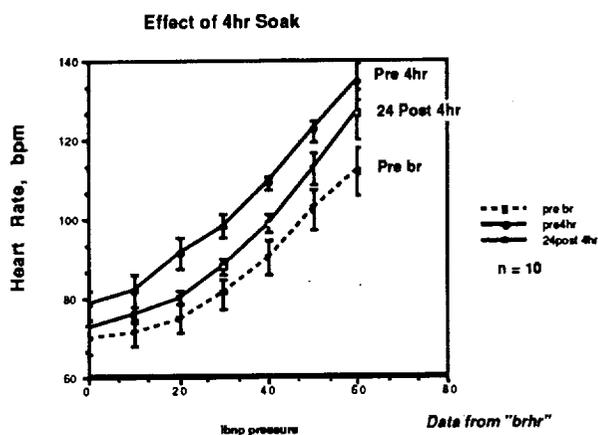
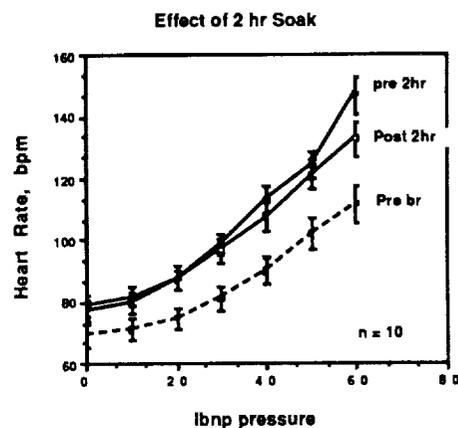


FIGURE 7



CONCLUSIONS:

- 1) The loss of tolerance to LBNP after 13 days of bed rest is most marked in individuals with high LBNP tolerance pre bed rest.
- 2) Prolonged LBNP exposures during bed rest effectively increase PV for at least 24 hours and this expansion may be related to an increased secretion of ADH and ALD.
- 3) 4-hr LBNP exposures combined with salt water ingestion may provide some improvement of orthostatic responses for approximately 24 hours. 2-hr exposures are less effective.

SIGNIFICANCE:

Prolonged LBNP and saline ingestion may provide an effective means to restore PV during space flight. However, with this particular protocol (LBNP pressure and fluid ingestion) a 2 hour LBNP exposure is not sufficient to restore orthostatic responses.

REFERENCES:

- 1) Hoffler, GW, and RL Johnson. Apollo flight crew cardiovascular evaluations. In: Biomedical Results of Apollo. Edited by RS Johnston, LE Dietlein, and CA Berry, NASA SP-368, 1975, pg. 227-264.

- 2) Johnson, RL, GW Hoffler, AE Nicogossian, SA Bergman, and MM Jackson. Lower body negative pressure: third manned skylab mission. In: Biomedical Results from Skylab. Edited by RS Johnston and LF Dietlein. NASA SP-377, 1977, pgs. 284-312.
- 3) Mikhaylov, VM, Pometov, YD, and VA Andretsov. LBNP training of crew members on main missions aboard salyut-6 orbital station. Kosm. Biol. i. Aviakosm. Med. 18: 29-33, 1984.
- 4) Kakurin, LI, BS Katkovskiy, VA Tishler, GI Kozyrevskaya, VS Shashkov, VS Georgiyevskiy, AI Grigor'yev, VM Mikhaylov, OD Anashkin, GV Machinskiy, AA Savilov, and YP Tikhomirov. Substantiation of a set of preventive measures referable to the objectives of missions in the salyut orbital station. Kosm. Biol. i Aviakosm. Med. 12: 20-27, 1978.
- 5) Lamb, LE, and PM Stevens. Influence of lower body negative pressure on the level of hydration during bed rest. Aerospace Med. 36: 1145-1151, 1965.
- 6) Stevens, PM, PB Miller, CA Gilbert, TN Lynch, RL Johnson, and LE Lamb. Influence of long-term lower body negative pressure on the circulatory function of man during prolonged bed rest. Aerospace Med. 37: 357-367, 1966.
- 7). McCally, M, TE Piemme, RH Murray. Tilt table responses of human subjects following application of lower body negative pressure. Aerospace Med. 37: 1247-1249, 1966.
- 8) 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.