HORMONAL REGULATION OF FLUID AND ELECTROLYTE METABOLISM IN ZERO-G AND BEDREST

Joan Vernikos
Life Science Division
M/S 239-11
NASA-Ames Research Center
Moffett Field, CA 94035

Supported by NASA Grant 199-14-12-03

INTRODUCTION:

The study of man in spaceflight has consistently indicated changes in fluid and electrolyte balance. Sodium (Na), Potassium (K) and Calcium (Ca) excretion are increased, accompanied by changes in the levels and responsiveness of adrenal hormones and the sympathetic nervous system (SNS). These hormones and neurohumors are critical to the regulation of blood pressure, blood flow and blood volume. The primary objectives of the research conducted under this task have been to use -6^{0} head down bedrest (BR) as the analog to spaceflight, to determine the long term changes in these systems, their relationship to orthostatic tolerance and to develop and test suitable countermeasures.

Over the course of this work we conducted a series of BR studies designed to:

(1) Determine the physiological response to postural change and to 7 days BR in males;

(2) Compare the effects of 7 days BR in male and female subjects;

(3) Determine the mechanisms underlying these responses during (a) short duration BR (7 days), (b) more prolonged BR (30 days);

(4) Investigate the relationship between the mechanisms regulating fluids and electrolytes during BR and the development of orthostatic intolerance post BR;

(5) Use the information derived to develop and test pharmacological, dietary and other counteractive options.

SIGNIFICANCE:

The importance of the proposed work lies in its ability to provide practical, effective solutions to the problems of post-flight orthostatic tolerance and readaptation to 1G after missions of short or prolonged duration, based on knowledge of the mechanisms underlying the problem. It is obvious that post-flight orthostatic hypotension involves multiple systems which seem to be affected to varying degrees in different individuals. Furthermore, the vasomotor regulatory deficits after relatively short exposures may be more readily compensated for by techniques (such as volume expansion) than those occurring after prolonged missions, when a new state of physiological adaptation to weightlessness has been achieved; nor might a single countermeasure be effective in all individuals.

The importance of postural cues to the regulation of aldosterone secretion and the importance of the secretions of the adrenal gland as a whole and the autonomic nervous system in the homeostatic maintenance of fluid and electrolyte balance have long been recognized. The experiments in this task should contribute to better understanding of the mechanisms that regulate the effective levels of circulating aldosterone, and, in particular, the ways in which other metabolic and neuroendocrine

changes occurring in weightlessness affect the responsiveness of the adrenal to its regulatory influences.

There are few data on these regulatory systems beyond seven days of -6° BR and on fluid volume regulation in general beyond 14 days of horizontal BR (Greenleaf and Kozlowski, 1982; Greenleaf, 1984). Two 56 day horizontal BR studies suggesting reduced sensitivity of endocrine and metabolic target organ responsiveness were conducted almost 20 years ago (Vernikos-Danellis et al., 1974). Indirect evidence from animals and man have also indicated this is probably the case with more prolonged exposures. Antiorthostatic BR (-6°) has proven its usefulness as a simulation for the initial response to weightlessness and physiological changes occur earlier and are more pronounced than they are with horizontal BR. With the advent of the space station era, the understanding of physiological changes occurring in both male and female subjects in weightlessness should form the rational basis for the development of procedures to prevent or control these changes on extended space missions.

PROGRESS:

We use a subject population of healthy volunteers, 30-50 years of age, to best approximate the astronaut corps. Diet is strictly regulated and contains 120 mEq/day Na and 70-80 mEq/day K; three days are allowed at the beginning of each study for equilibration.

The first two studies in the series were identical in design and their primary purpose was to determine the immediate effects of assuming the -6° head down posture and to compare these responses in male and female subjects. Such early responses have not been measured either in flight or in ground studies. In flight, understandably, it has been impossible to do so without interfering with the heavy schedule of the first day. Nor is it likely that such measurements will be possible within the foreseeable future. Furthermore, data on fluid and electrolytes would be inevitably affected by the malaise and/or vomiting of the early phases of the space adaptation syndrome or by medications taken for this. In contrast to investigations using immersion for simulation of space flight, BR studies had not used sufficiently frequent sampling to document the early changes. Yet, the immediate and dramatic responses to simply assuming upright posture, in those systems that regulate blood volume and blood flow, are well known and it could well have been expected that assuming the head down posture would produce equally immediate and marked effects in those systems.

Eight males and eight females were selected from groups of 14-16 after preliminary screening tests which included a PV determination, cardiovascular and endocrine responses to a Standard Posture Test (SPT, one hour supine, one hour standing) and taking into consideration the phase of the menstrual cycles of the females. No significant correlation between menstrual phase and response was evident. Subjects of both sexes were selected to cover the widest possible range of "normal" blood pressures and plasma volumes, so that a fair assessment of the contribution of the initial physiological status to the responses to BR and post BR orthostatic intolerance could be made.

In the SPT, blood samples were drawn before and at 2.5, 5, 15, 30 and 60 minutes after standing for the determination of PRA, A-II, ACTH, AVP, cortisol, aldosterone, Na, K, hematocrit and hemoglobin. The last two parameters were used to obtain a rough index of posture-associated changes in PV using the method of Greenleaf et al., (1977). The data from this test were compared with that of Day 1 of BR and of the first day of recovery (R+1) when upright posture was assumed again.

RESPONSES TO 6° HEAD DOWN BEDREST:

Figures 1 and 2 show the immediate responses to the posture test and to the assumption of the -6° head down position in one group of males. It is quite apparent that the responses to these two postures are mirror images of each other, both qualitatively and temporally.

Similarly, Figure 3 shows that within five minutes of assuming the -6° head down position, there was a significant decline in heart rate ($p<0.05$) that was sustained for the next two hours before gradually increasing toward normal during the next six hours. There were no changes in indirect systolic or diastolic arterial blood pressure or plasma ACTH during the first 24 hours after assuming the head down position. However, there were prompt and sustained decreases in plasma vasopressin (AVP), plasma renin activity (PRA) and plasma aldosterone concentration (PAC) over the first eight hours (all $p<0.01$ by ANOVA). Of note is the finding that PRA reaches a nadir by two hours that is sustained at four and eight hours, but that it increases by 24 hours to values similar to those at 0 time By contrast, the nadir in plasma aldosterone concentration is achieved at four hours and, although the values increase gradually during the next 20 hours, aldosterone levels are still depressed at 24 hours compared to the 0 time value.

The rapid inhibition in levels of hormones that regulate salt and water metabolism after assumption of the head down position is reflected by the changes in renal fluid and Na excretion during the first days of head down BR in both sexes (Fig. 4 and 5) and an increase in K excretion by the end of the seven day BR period. Fluid and especially Na retention was apparent on becoming ambulatory again. There were no significant sex differences in the parameters measured over a 7 day BR period. With continued bedrest an uncoupling between PRA and aldosterone has been consistently observed. PRA increased and PAC decreased or remained unchanged (see Figure 6).

Measurements of plasma A-II changes did not justify the explanation that the apparent dissociation between PRA and aldosterone could have involved inhibition of lung converting enzyme due to the hemodynamic changes associated with this position, during 7 days of BR. On the other hand in a subsequent 30 day BR study, the data suggested that under resting conditions, both the conversion of angiotensin-I to A-II and the stimulation of aldosterone by endogenous A-II are progressively diminished after 15 days of head down bedrest, (DeCherney et al, 1989).

In addition, BR exceeding 7 days showed the following results. Plasma volume measured using Evans Blue, continued to decline slowly until on d25 it had decreased by 12%. The volume responsive hormones, plasma AVP and PRA remained elevated, but PAC remained at control values throughout the 30d BR period. The response of adrenal aldosterone to graded doses of ACTH or A-II were significantly greater as BR progressed whereas the cortisol response was unaltered by 30d BR. In contrast both the systolic and diastolic blood pressure (BP) responses to A-II (Figure 7 and 8) were greatly reduced by the 16th day of BR. We believe these changes are related to the overall Na deficiency induced by BR. Such enhanced adrenal sensitivity to infused A-II and reduced vascular smooth muscle responses to this peptide have been reported in experimental animals and humans after drastic dietary manipulation of Na. Similarly, the BP response to NE has been reported to be reduced by Na deficiency. In our study the rise in diastolic BP to graded doses of infused NE appeared reduced but the dose of NE was too small to induce significant increases under control conditions. To our knowledge, such observations have only been reported in response to dietary Na manipulations or pathological conditions but not to physiological environmental change (i.e. BR) and are worthy of further pursuit.

Accompanying the changes in the vasomotor hormones involved in fluid and electrolyte changes was a significant reduction in the responsiveness of the carotid sinus cardiac baroreflex response measured using an Eckberg cuff (Figure 9). This effect was evident at d12 of BR and persisted through at least 5 days of ambulatory recovery (Convertino et al, 1990). Furthermore, the buffer capacity of the reflex was reduced as indicated by the decrease in the R-R range. Consequently, not only was the BP response to A-II reduced but the capacity to respond and compensate for moment to moment changes in blood pressure was also reduced by prolonged BR.

POST BEDREST ORTHOSTATIC INTOLERANCE:

During the course of these studies a physiological pattern emerged characteristic of individuals in their normal ambulatory state who are most likely to become syncopal after a period of BR (F). These were subjects showing the lowest resting initial BP's, the highest resting plasma volume (PV); the lowest resting PRA and the smallest decrease in plasma volume on standing. This preservation of an expanded PV becomes a very critical mechanism for the maintenance of BP in these individuals under normal ambulatory conditions (Bannister, 1979) and would therefore be expected to gain importance during any perturbation. There was no correlation between the decrease in PV during BR and post BR orthostatic intolerance but there was a good correlation between the reduced sensitivity of the high pressure baroreflex during BR and post BR orthostatic syncope (Convertino et al, 1990), (Figure 10).

The most significant endocrine differences between these individuals (F) and those who did not become syncopal (NF) became apparent during the effort of individuals to maintain orthostatic control on standing after 7d BR. In NF's there was potentiation of NE, Dopamine and Epinephrine responses to standing after 7d BR as compared to ambulatory controls, suggesting that NF's probably maintain their BP, supported by a large and sustained increase in sympathetic activity. On the other hand F's were

unable either to increase or sustain increased circulating NE and PRA levels (Figures 11 and 12) on standing.

COUNTERMEASURES:

Based on the data from these studies a variety of approaches designed to expand PV and restore baroreflex sensitivity have been and continue to be tested. The results to date from our studies may be summarized as follows:

PV expansion (16%) may be achieved with acute (2 day) administration of fludrocortisone after 7d BR, (Vernikos et al. In Press). It may also be prevented by daily bouts of 30 minutes isotonic exercise (at 50% max VO_2) twice a day during 30d of BR, (Greenleaf et al. In Press).

Increased dietary carbohydrate throughout bedrest was ineffective in increasing the NE response to standing. On the other hand, a combination of dextro amphetamine and atropine together with expanded PV after fludrocrotisone resulted in greatly enhanced and sustained HR, NE and PRA responses. Four of 7 previously documented F's were protected by this treatment.

PLANS:

As a result of these and other findings, we decided to split the work in this task into 2 tasks this year. One task will focus on the PV and progressive baroreflex sensitivity changes during BR periods longer than 30d. The contribution of the low pressure baroreflex and changes in compliance to the development of orthostatic intolerance during BR will be addressed. The countermeasure effectiveness of fludrocortisone will be compared to that of NaCl and water ingestion. On the one hand, the dosage regimes will be refined for maximum effectiveness, and on the other, the mechanism by which fludrocortisone exerts its protective effects in orthostatic intolerance will be investigated. Although it is possible that all of its BP regulating properties may be mediated by its Na retaining activity, it is also likely that it may possess other independent actions on the autonomic or central control of BP, and provides an interesting investigative tool.

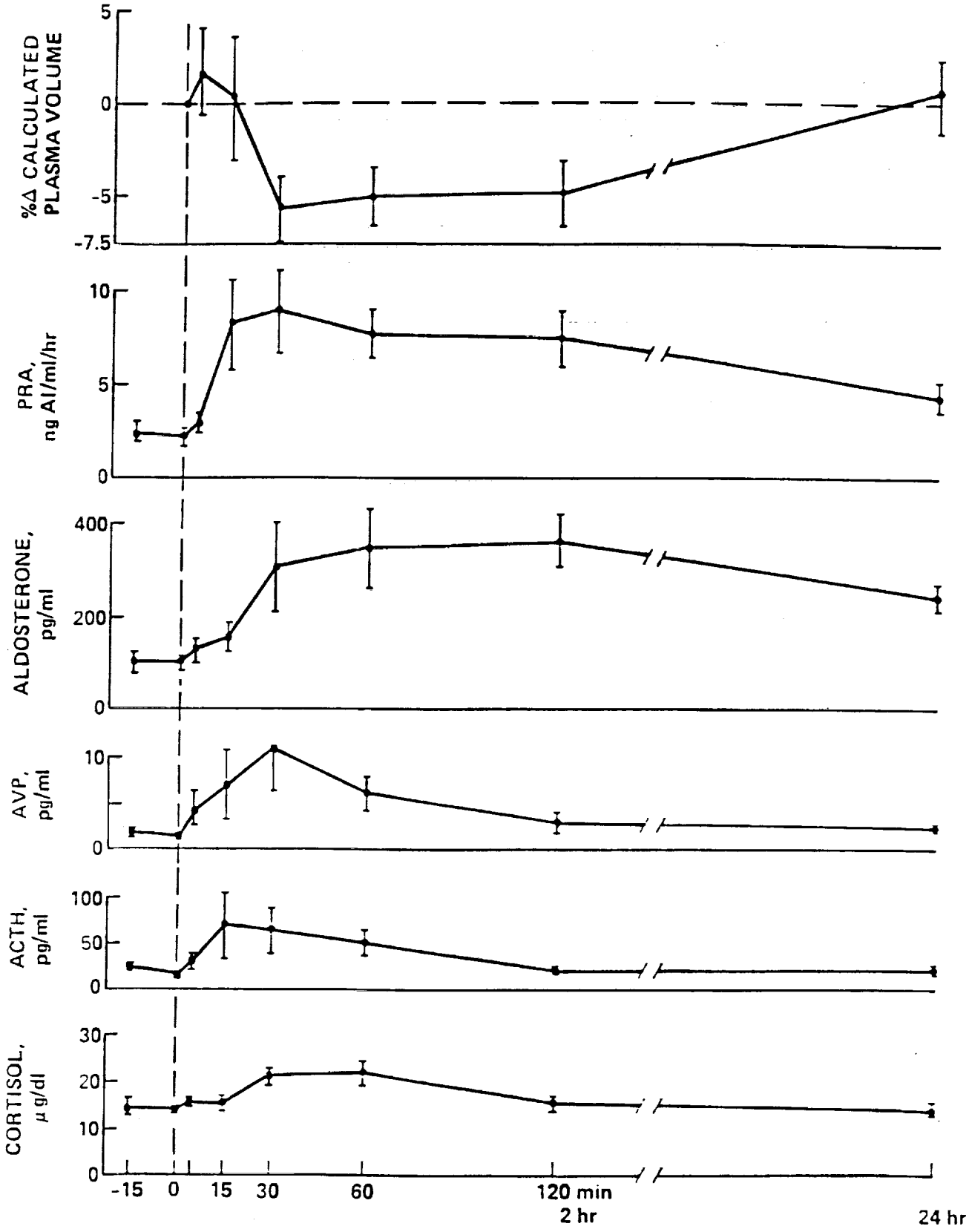
The other task, will focus on the endocrine and neurohumoral regulation of fluids and electrolytes, the uncoupling of endocrine regulating mechanisms, sympathetic nervous system and target organ systems observed in flight and in BR studies, the progression of these changes with more prolonged exposures and the renal consequences of these changes. The role of Na and K in the development of these changes and the relationship of these to the cardiovascular system will continue to be addressed.

BIBLIOGRAPHY:

- Greenleaf, J.E. and Koslowski, S (1982) Physiological Consequences of Reduced Physical Activity During Bedrest: In: Exercise and Sport Science Reviews, vol 10. R.J. Terjung (Ed.) Franklin Institute Press, Philadelphia, pp. 84-119.
- Greenleaf, J.E. (1984) Med. Sci. Sports Exerc., 16:20-25.
- Vernikos-Danellis, J., Winget, C.M., Leach, C.S. and Rambaut, P.C. (1974): Circadian, Endocrine and Metabolic Effects of Prolonged Bedrest; Two 56-Day Bedrest Studies, NASA TM X3051.
- Greenleaf, J.E., Brock, P.J., Haines, R.F., Rositano, S.A., Montgomery, L.D., and Keil, L.C. (1977) Aviation, Space and Environ. Med.:48: 693-700.
- DeCherney, G.S., Dallman, M.F., Keil, L.C., Convertino, V., and Vernikos-Danellis, J. (1989) Proc. Endocrin Soc. p. 1773.
- Convertino, V.A., Doerr, D.F., Eckberg, D.L., Fritsch, J.M. and Vernikos-Danellis, J. (1990): J. Appl. Physiol. 68: 1458-1464
- Bannister, R. (1979) Lancet 2: 404-406
- Vernikos, J. Dallman, M.F., Van Loon, G., and Keil, L.C. (1991) J. Clin. Pharmacol. In Press.
- Greenleaf, J.E., Vernikos, J., Wade, C.E. and Barnes, P.R. (1991) J. Appl. Physiol. In Press.

Plasma Volume and Hormone Responses to Standing in Males.

FIGURE 1



Plasma Volume and Hormone Responses in Males on assuming the 6° Headdown Posture.

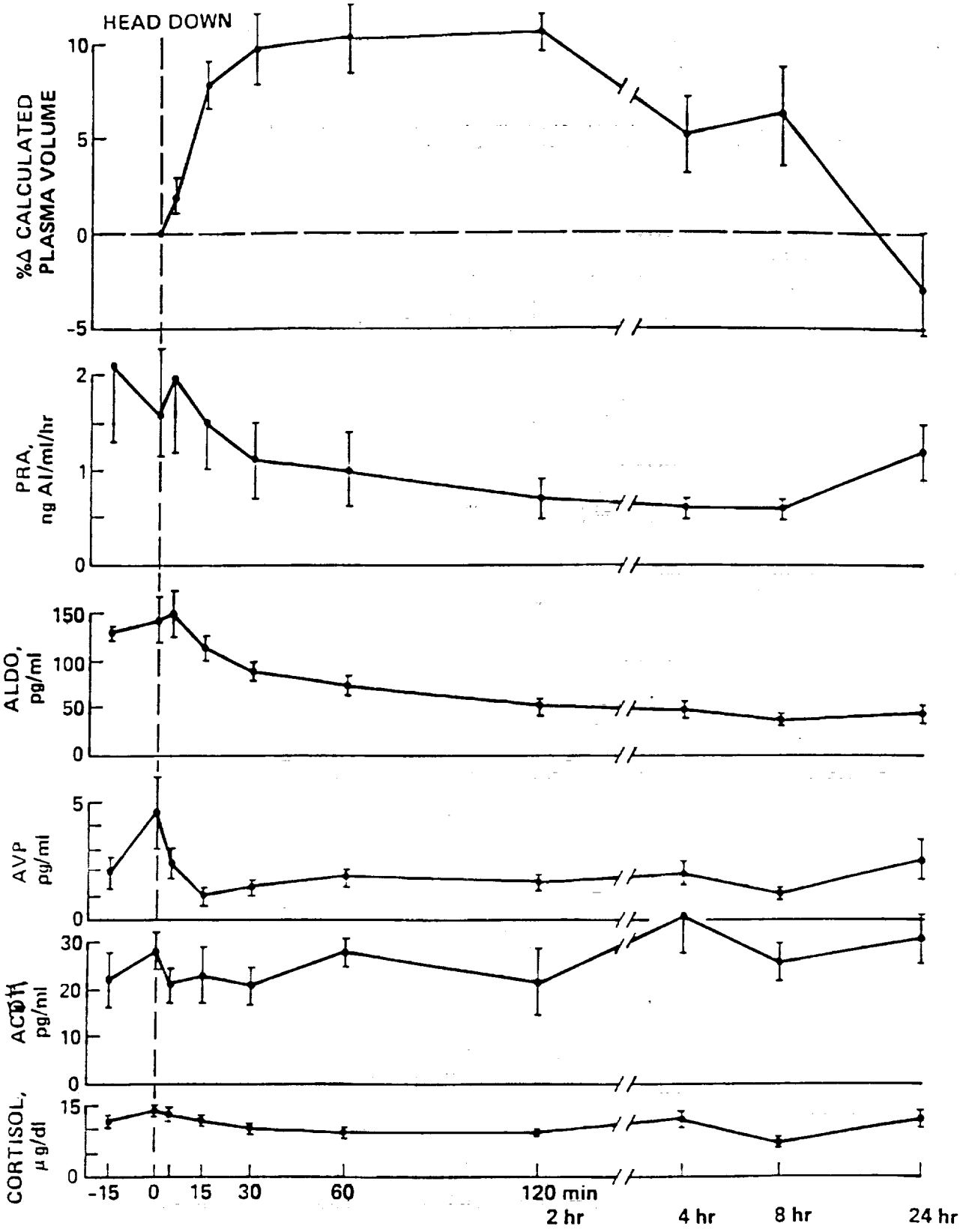
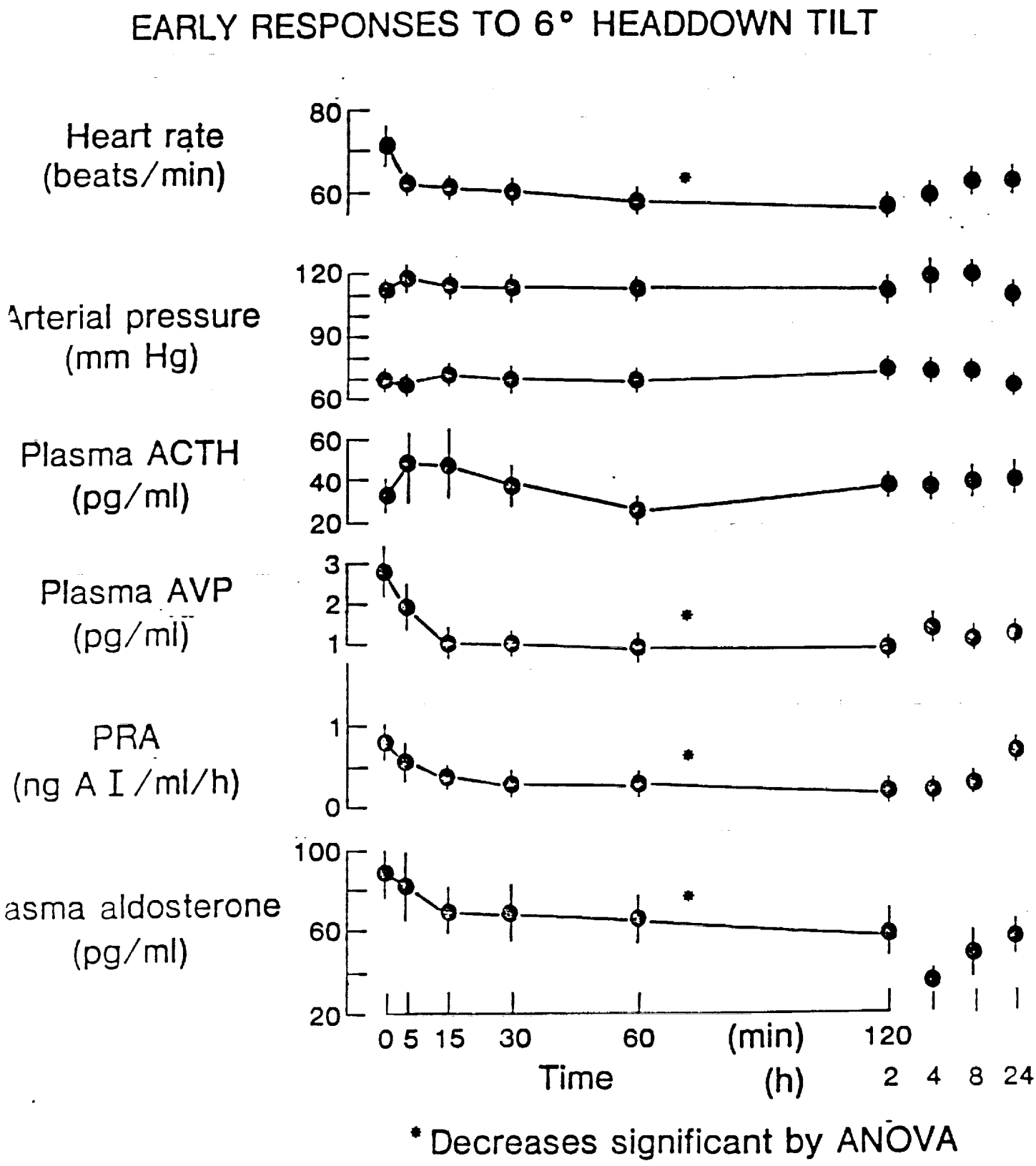


FIGURE 2

FIGURE 3


EARLY RESPONSES TO 6° HEADDOWN TILT
Heart rate (beats/min)
80
60
Arterial pressure (mm Hg)
120
90
60
Plasma ACTH (pg/ml)
60
40
20
Plasma AVP (pg/ml)
3
2
1
PRA (ng A I /ml/h)
1
0
asma aldosterone (pg/ml)
100
60
20
0 5 15 30 60 (min) 120
Time (h) 2 4 8 24
* Decreases significant by ANOVA

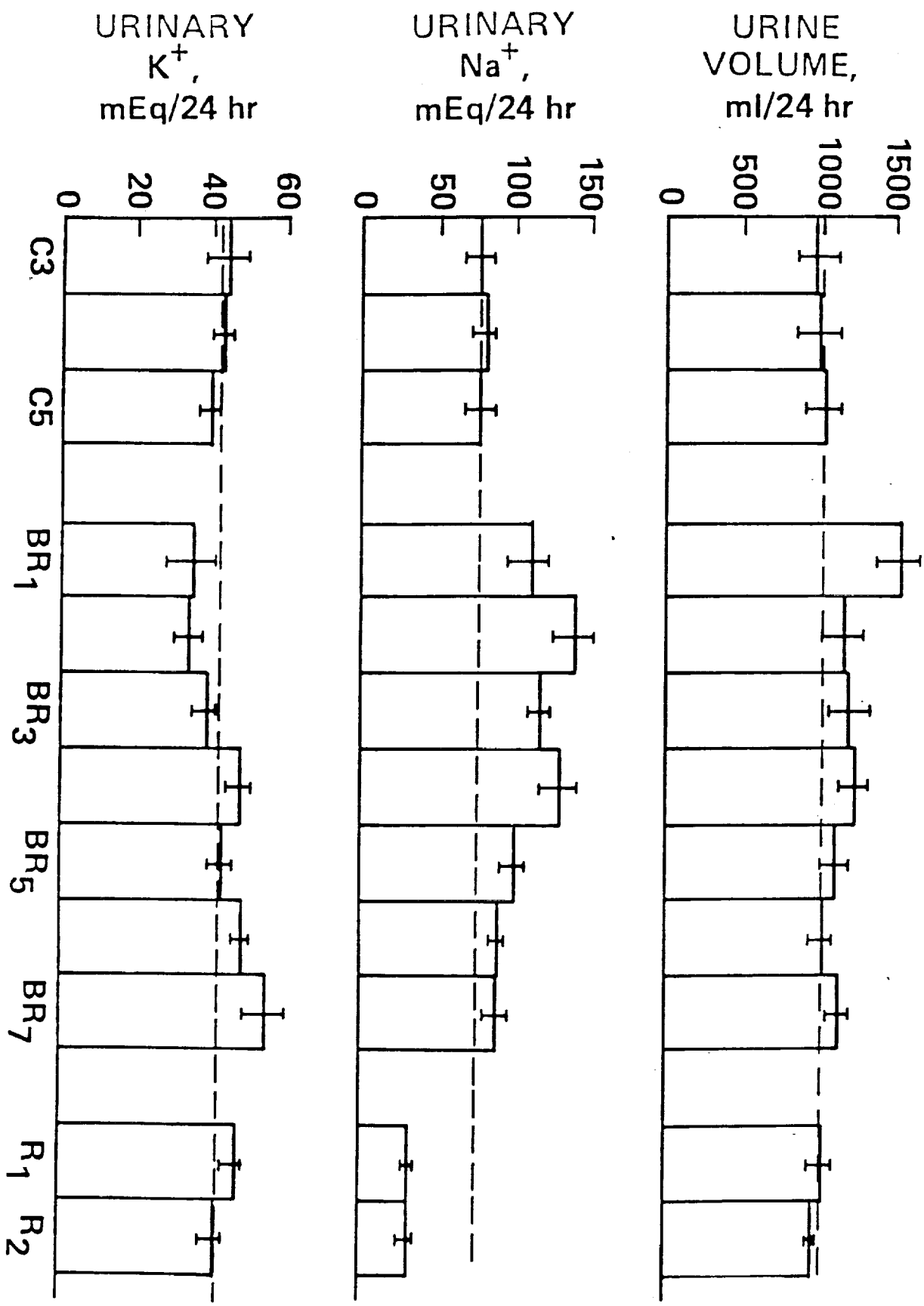

URINARY
K+,
mEq/24 hr
0
20
40
60
URINARY
Na+,
mEq/24 hr
0
50
100
150
URINE
VOLUME,
ml/24 hr
0
500
1000
1500
C3
C5
BR1
BR3
BR5
BR7
R1
R2

FIGURE 4

Fluid and electrolyte excretion in rats during -6° headdown bedrest
FIGURE 5
URINARY
mEq/24 hr
URINARY
mEq/24 hr
URINE
VOLUME
ml/24 hr
C3
C5
BR1
BR3
BR5
BR7
R1
R2

FIGURE 6

PLASMA RENIN ACTIVITY INCREASES AND ALDOSTERONE DECREASES DURING HEADDOWN BEDREST

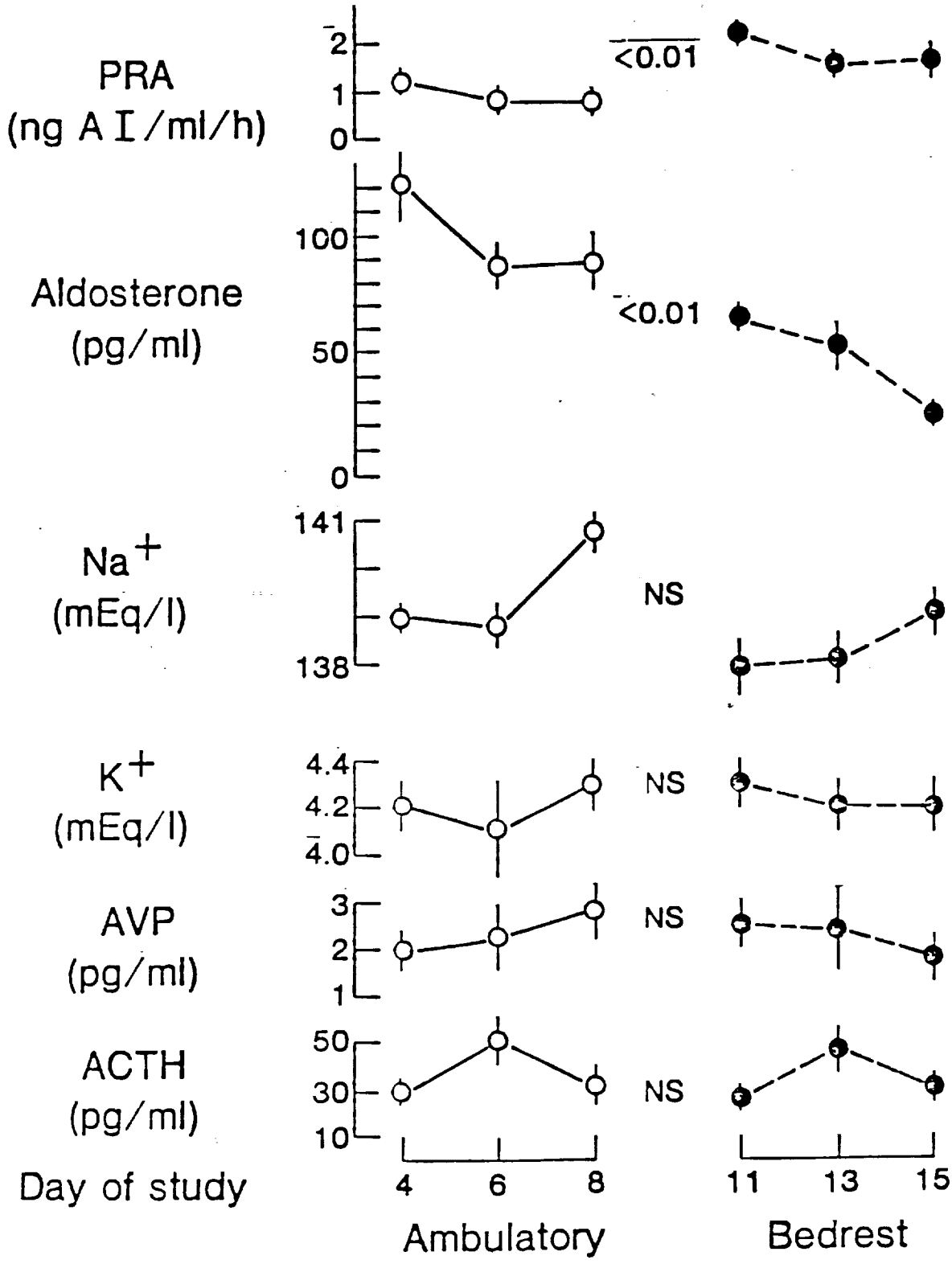


FIGURE 7

Subject descriptions and changes in plasma and blood volumes during head down bedrest (Males).

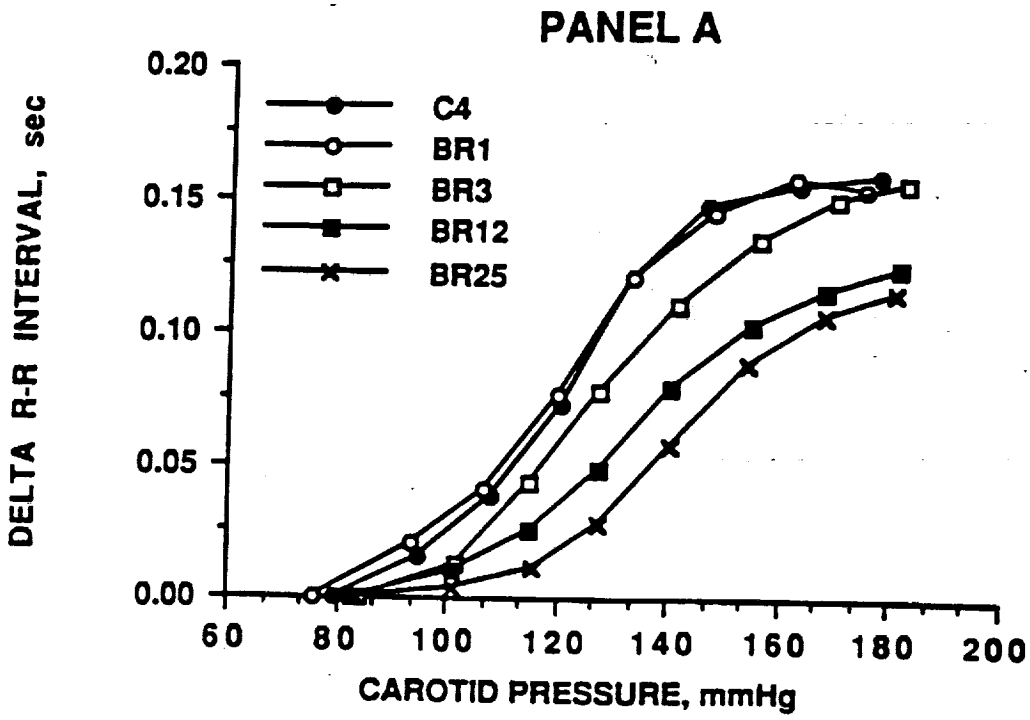
Subject #	Age (Yrs)	Height (Cm)	Weight (Kg)	Decrease in Plasma Volume		Decrease in Blood Volume	
				(ml)	%	(ml)	%
72	49	165	68.2	66	2.9	195	5.0
160	45	188	94.0	177	5.5	342	6.3
161	38	178	75.5	143	5.6	360	8.3
162	38	188	83.2	146	3.8	168	2.7
163	50	180	56.4	423	15.2	440	9.8
164	42	185	84.0	460	13.0	539	9.5
165	38	188	85.0	719	18.2	1138	17.5
166	38	170	68.2	190	6.8	381	8.2
$\bar{X}$	42	180	76.7	290.5	8.9	445	8.4
$\pm$ SEM	2	3	4.2	78.6	2.0	108	1.6

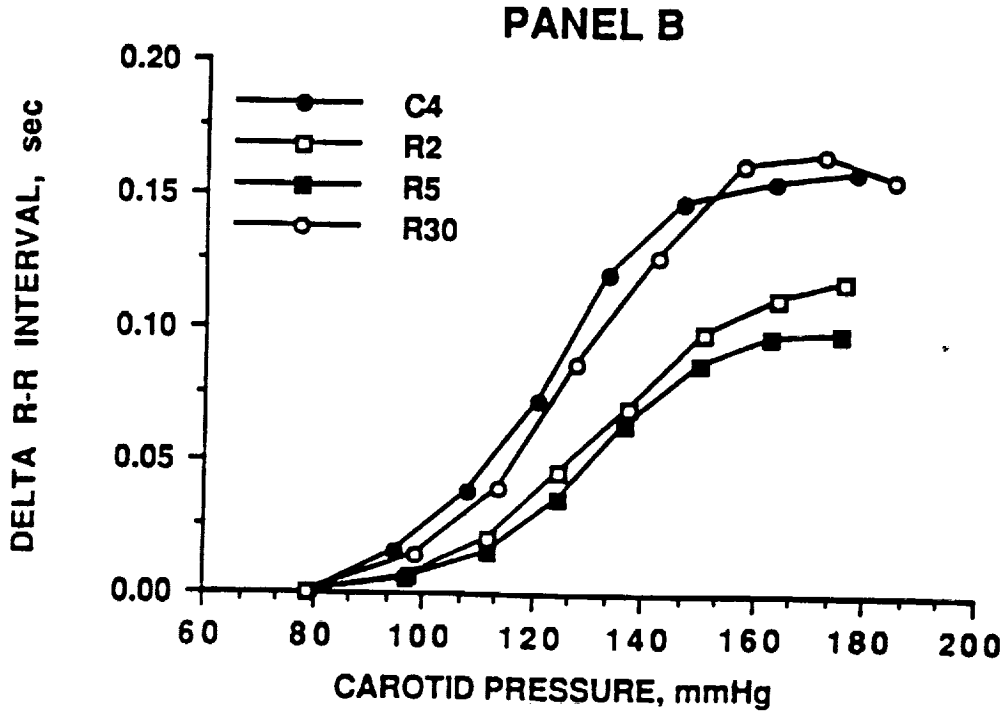
FIGURE 8

Subject descriptions and changes in plasma and blood volumes during head down bedrest (Females).

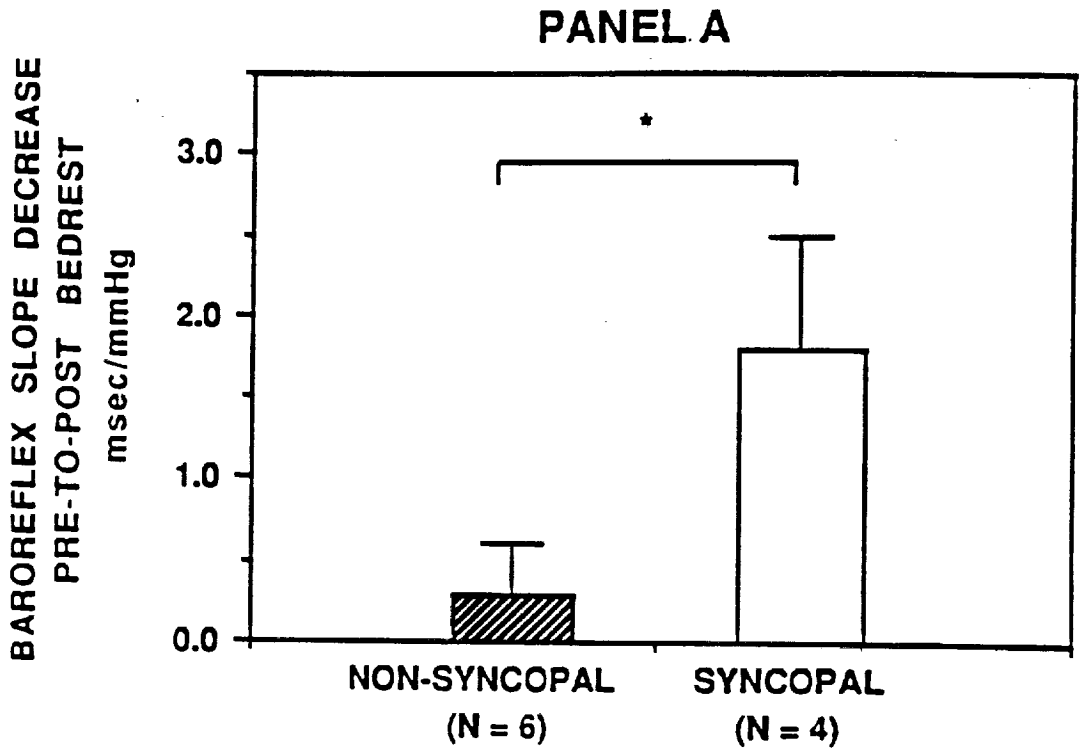
Subject #	Age (Yrs)	Height (Cm)	Weight (Kg)	Decrease In Plasma Volume (ml)	Decrease In Plasma Volume %	Decrease In Blood Volume (ml)	Decrease In Blood Volume %
198	41	157	49.6	270	10.5	476	12.0
200	36	173	76.6	170	7.3	240	6.5
201	30	138	58.9	163	5.7	306	6.9
202	35	173	84.8	259	8.7	402	8.8
204	37	158	63.9	553	18.6	693	15.3
205	44	161	63.9	255	10.4	515	13.5
207	34	166	50.5	119	4.7	81	2.1
209	40	157	63.6	304	12.0	290	7.7
M	37	160	64.0	262	9.7	375	9.2
SEM	1.6	4.0	4.2	47.3	1.55	66.6	1.6

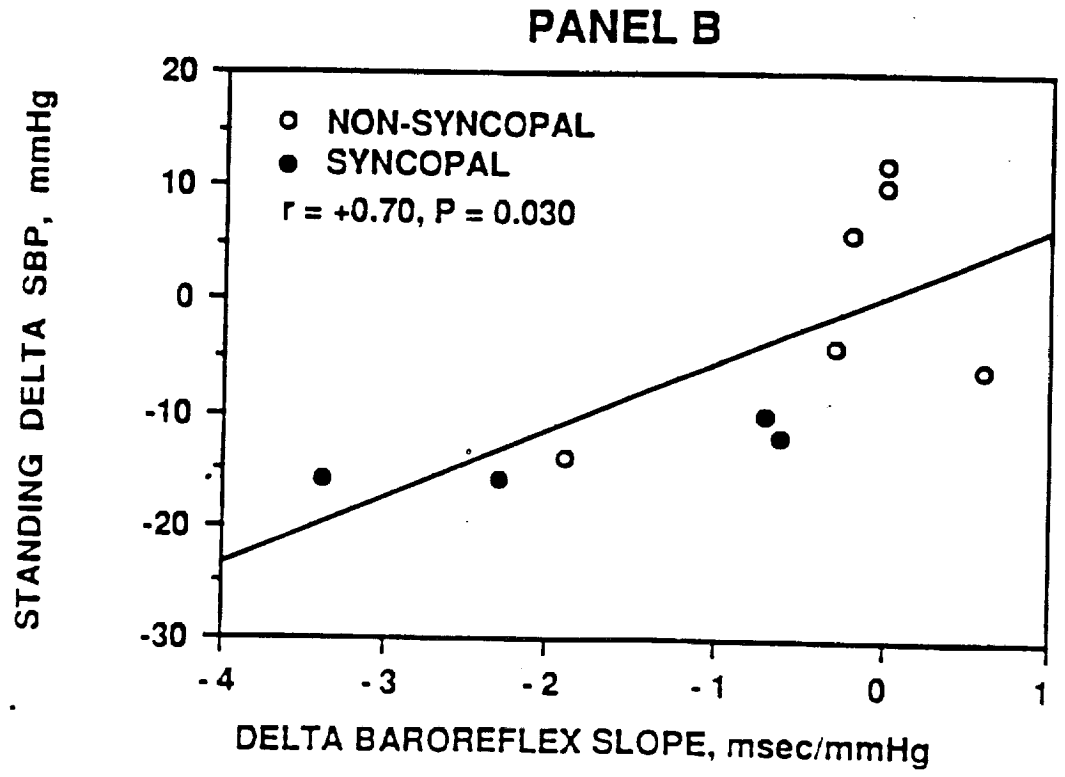
FIGURE 9





Carotid baroreceptor-cardiac reflex response relationships. Panel A depicts relations generated on days 1, 3, 12, and 25 of bedrest (BR) and the pre-bedrest control day (C4). Panel B depicts relations generated on days 2, 5 and 30 of post-bedrest ambulatory recovery (R) and C4.





Reduction in the maximum slope of the carotid baroreceptor-cardiac relationship after bedrest in non-syncopal and syncopal subjects (Panel A) and the relationship between the change in maximum slope and the change in systolic blood pressure (SBP) during the post-bedrest stand test (Panel B). Asterisk indicates differences at $P < 0.05$.

FIGURE 11

Plasma Renin Activity Responses to Standing in Female F and NF Subjects before and after -6° Bed Rest.

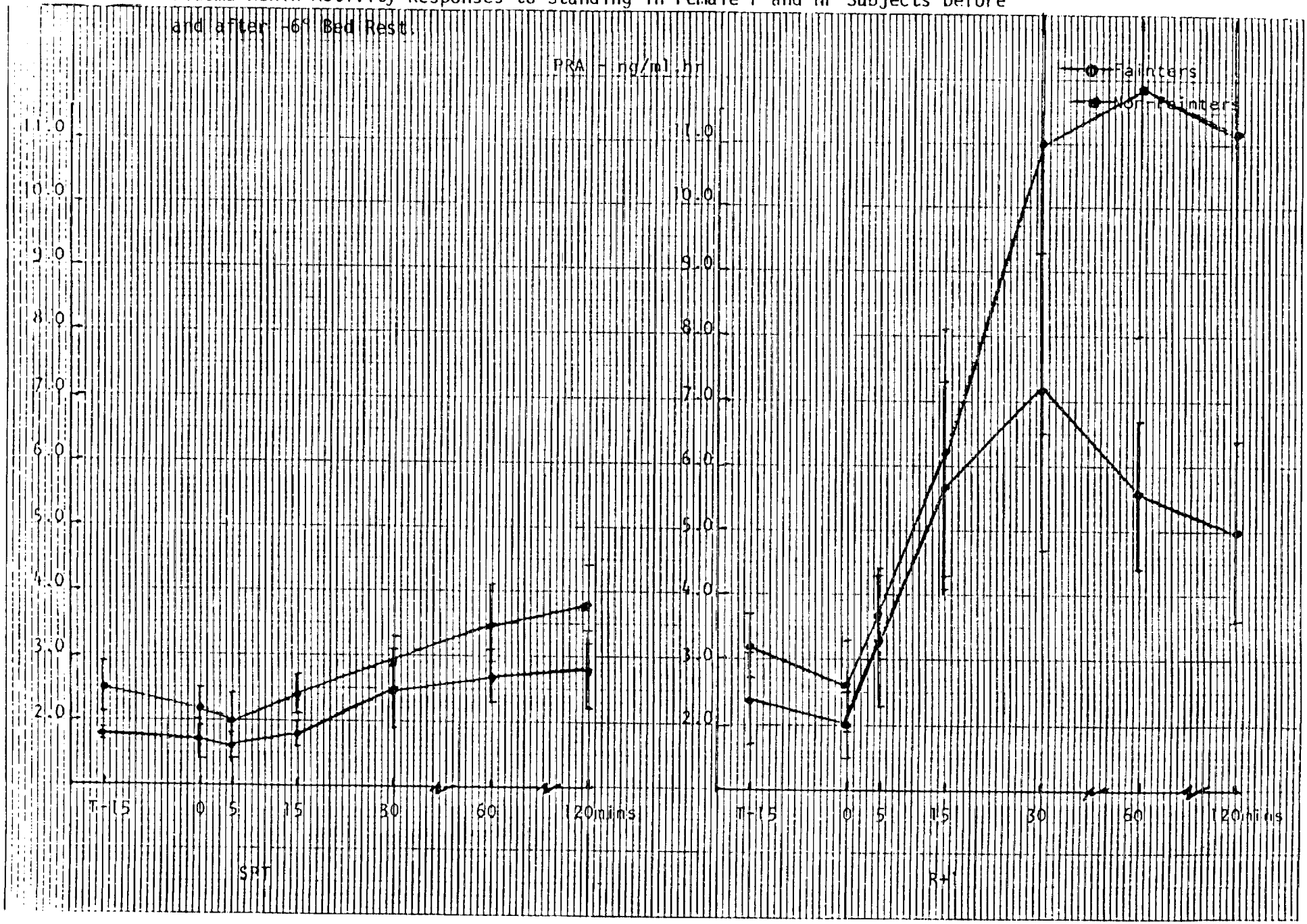


FIGURE 12

Plasma Norepinephrine Responses to Standing in Female F and NF Subjects before and after -6° Bed Rest.