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ADVANTAGES AND DISADVANTAGES OF FLUDROCORTISONE OR SALINE LOAD IN PREVENTING POST-SPACEFLIGHT ORTHOSTATIC HYPOTENSION

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Abstract - The purpose of this study was to compare the effectiveness of saline load to fludrocortisone (florinef) as countermeasures for reduced plasma volume and orthostatic intolerance after spaceflight. Eleven males (ages 30-50 yr) underwent a 3-day ambulatory baseline period followed by 7 days of 6° head-down bedrest, during which cardiopulmonary and arterial baroreflex sensitivity and plasma volume (PV) were determined. During pre-bedrest and 2.5 h after treatment on day 8, PV was also measured and subjects underwent a 15-min unsupported stand test. Treatments consisted of 8 salt tablets (1 g NaCl per tablet) and 960 ml of water in 5 subjects and 0.6 mg (0.2 mg x 3) over 24 h in the other 6 subjects. PV decreased by 12% on day 7 of bedrest. This was restored on day 8 by florinef but not by saline load. The effect of florinef on PV was paralleled by decreases in urine volume and the urinary sodium/potassium ratio. Reduced PV was associated with greater vascular resistance for the same drop in central venous pressure, suggesting less vasoconstriction reserve after bedrest. Carotid baroreflex control of heart rate was attenuated after 7 days of bedrest. Both baroreflex functions were restored by florinef but not saline load. Only 1 of 6 subjects showed syncopal symptoms in the florinef-treated group, whereas 4 of 5 subjects did so in the saline-load group. Acute florinef treatment appears to have distinct advantages as a protective measure for post-bedrest orthostatic intolerance, not only through its salt retaining, volume-expanding mineralcorticoid effect, but possibly through its actions on baroreflex and sympathetic functions.

INTRODUCTION

Orthostatic hypotension has been consistently reported in astronauts following spaceflight. Since the accompanying tachycardia has been correlated with the reduction in blood volume after flight [14], the use of fluid replacement just prior to reentry as a possible countermeasure against orthostatic instability has been heavily pursued.

Preliminary results from groundbase and spaceflight experiments suggested that fluid loading with an isotonic saline solution was partially effective in ameliorating post-flight orthostatic tachycardia and hypotension [4,13]. More recent data indicate that this protective effect diminished as the duration of the mission was prolonged [23], perhaps due to less fluid retention. Unfortunately, plasma volumes have not been measured in these astronauts to allow assessment of body fluid retention. The use of mineralcorticoids in groundbase experiments has provided evidence to explore an alternative method to restore plasma volume and provide some protection against orthostatic intolerance following exposure to simulated microgravity [3,19,22].

The purpose of this study was to compare the effectiveness of saline load to fludrocortisone (florinef) as countermeasures for treatment of hypovolemia and orthostatic instability casued by an analog to spaceflight.

METHODS

Subjects. Eleven healthy nonsmoking normotensive men, with a mean (±SEM) age of 38 ± 2 yrs (range 30-45), a mean height of 179 ± 2 cm (range 173-188), and a mean weight of 79 ± 2 kg (range 67-93), gave written informed consent to participate in this study, which was approved by the NASA Human Research Review Boards from both Ames Research Center and Kennedy Space Center. Selection of subjects was based on normal clinical results of a screening evaluation that comprised a detailed medical history, physical examination, psychological tests, complete blood count, urinalysis, 3-h glucose tolerance test, chest X-ray, resting and treadmill electrocardiograms, and a panel of blood chemistry analyses. No subject was taking medication at the time of the study. During a 3-week orientation testing period which preceded the study, all subjects were made familiar with the laboratory, the protocol, and procedures.

Protocol. The experimental protocol comprised 3 d of ambulatory baseline followed by 7 d of 6° head-down bedrest and 2 d of post-bedrest recovery. During bedrest, the subjects remained head-down without interruption and no conventional exercise was performed. During the 12-d experimental period, subjects lived 24 $h \cdot d^{-1}$ in the Human Research Facility at NASA-Ames Research Center and followed the

same controlled diet consisting of an average daily caloric intake of 2500-2800 kcal (45% carbohydrate, 38% fat, 17% protein). Dietary sodium and potassium were held constant at approximately 120 and 60-80 mEq/day. Fluid intake was ad libitum, but restricted to a maximum of 2000 ml/day. The photoperiod was 16 h light to 8 h dark with lights on at 0700 h. The 6° head-down position was chosen since actual flight changes in some cardiovascular responses are closely simulated by this ground-based model [7].

At the end of bedrest, the subjects were divided into two treatment groups using a counterbalance design to match them for age, height, and weight. One group consisted of five subjects who ingested a saline load 2 h before standing at the end of bedrest consisting of eight 1-g salt tablets with 960 ml of water designed to make an isotonic saline drink. The second group consisted of six subjects who received 0.2 mg oral dose of fludrocortisone (florinef) at 0800 and 2000 h the day before and 0800 h the day the subjects got out of bed (i.e., 2 h before standing).

Each subject underwent tests for determination of cardiopulmonary baroreflex control of forearm vascular resistance, carotid baroreflex control of heart rate, and plasma volume on the second day prior to bedrest, on the last day of bedrest (BR7), and on day 1 of recovery (R1). During the pre-bedrest baseline tests, 30 min of supine rest preceded each session.

Posture tests. Posture tests were conducted before bedrest and immediately upon the termination of the 7-day bedrest (R1). Pre-bedrest posture tests began with the subject lying supine for 60 min followed by 15 min of active standing. The subjects were instructed to stand still with their feet placed 12 inches apart, with their weight evenly distributed, and to refrain from moving. Thus, contractions of the leg muscles were restricted to those required to support stationary standing. Blood pressure and heart rate were measured continuously throughout standing. At the beginning of each test, a butterfly needle was inserted into an antecubital vein. Venous blood samples were drawn during supine and at 5 and 15 min after standing in both pre- and post-bedrest posture tests for determination of norepinephrine.

Plasma and urine measurements. Baseline plasma volume was measured with an Evans blue dye technique. Plasma norepinephrine was measured before, at 5 min, and at the end of 15 min of pre- and post-bedrest stand tests using high performance liquid chromatography. Urine was measured for total volume and concentrations of sodium and potassium during 2 h immediately after standing.

Carotid-cardiac baroreflex. A stepping-motor driven bellows was used to deliver a series of positive and negative pressure steps to a silastic neck chamber to measure carotid baroreceptor-cardiac reflex response. To avoid respiration-related variations of cardiac vagal outflow, neck-pressure changes were applied only while subjects held their breath at mid-expiration. A pressure of about 40 mmHg was delivered to the chamber and held for 5 R-waves; then, with the next R-wave, the pressure sequentially stepped to approximately 25, 10,-5, -20, -35, -50, and -65 mmHg, and then returned to ambient pressure. Pressure steps were triggered by R-waves so that neck chamber pressure changes were superimposed upon naturally-occurring carotid pulses. This timing was chosen so that experimental baroreceptor stimuli would be as physiologic as possible. During each test session, the stimulus sequence was repeated 5 times and the data averaged for each subject. Blood pressures were taken with a sphygmomanometer at the beginning of each test session. R-R intervals for each pressure step were plotted against carotid distending pressures (systolic pressure minus neck chamber pressure applied during each heart beat). Carotid-cardiac baroreflex function was reduced to calculation of the maximum slope of the stimulus-response relationship. Maximum slopes were determined by application of least squares linear regression analysis to every set of three consecutive points on the response relationship to find the segment with the steepest slope. This maximum slope represented the sensitivity of the baroreflex.

Cardiopulmonary baroreflex. Subjects were required to lie in a lower body negative pressure (LBNP) device in the right lateral decubitus position with the right arm dependent for measurements of peripheral venous pressure (PVP). Prior to initializing the LBNP protocol, a 19-gauge catheter was inserted into an antecubital vein of the dependent right arm. The catheter was then (and periodically) cleared with a 50 u/ml heparinized solution and connected to a Statham model PD23 XL ID pressure transducer, positioned at heart level, for continuous measurement of PVP during the LBNP test. Measurements of alterations in PVP during graded LBNP were used as an estimate of changes in central venous pressure [11,16].

The left arm was raised at heart level and used for forearm blood flow (FBF) measurements. FBF was measured by venous occlusion plethysmography using a Whitney mercury-in-silastic strain gauge placed around the left forearm with circulation to the hand occluded. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure by forearm blood flow and expressed as peripheral resistance units (pru).

After instrumentation for forearm blood flow measurements, the LBNP protocol was initiated. The LBNP protocol began with a 2-min baseline rest period with the LBNP pressure at 0 mmHg followed by continuous decompression of 5 mmHg every 2 min down to -20 mmHg. The PVP was recorded continuously throughout LBNP and forearm blood flow was measured every 10 s. This protocol is designed to elicit forearm vascular responses that result selectively from unloading of cardiopulmonary baroreceptors [21]. Sensitivity of the cardiopulmonary baroreflex was the slope of change in estimated CVP and change of forearm vascular resistance.

Hemodynamic responses to LBNP. Stroke volume and heart rate were measured during each stage of LBNP using impedance plethysmography. Cardiac output was calculated as the product of heart rate and stroke volume.

RESULTS

Orthostatic responses. All but two subjects (one in each group) completed the 15-min stand test during the pre-bedrest ambulatory period. However, four of the five subjects (80%) in the saline-load group experienced syncope or presyncope and could not complete 15 minutes of standing after bedrest while five of the six subjects in the florinef group tolerated the posture test with no noticeable difficulty. Both heart rate and mean arterial pressure increased in a similar manner between saline and florinef groups during the pre-bedrest ambulatory stand test (Fig. 1A and 1B). After 7 days of bedrest, an average elevation in heart rate of 24 bpm in both saline and florinef subjects during standing was greater ($P < 0.05$) than the average 13-bpm increase observed during standing before bedrest. Despite similar elevations in standing

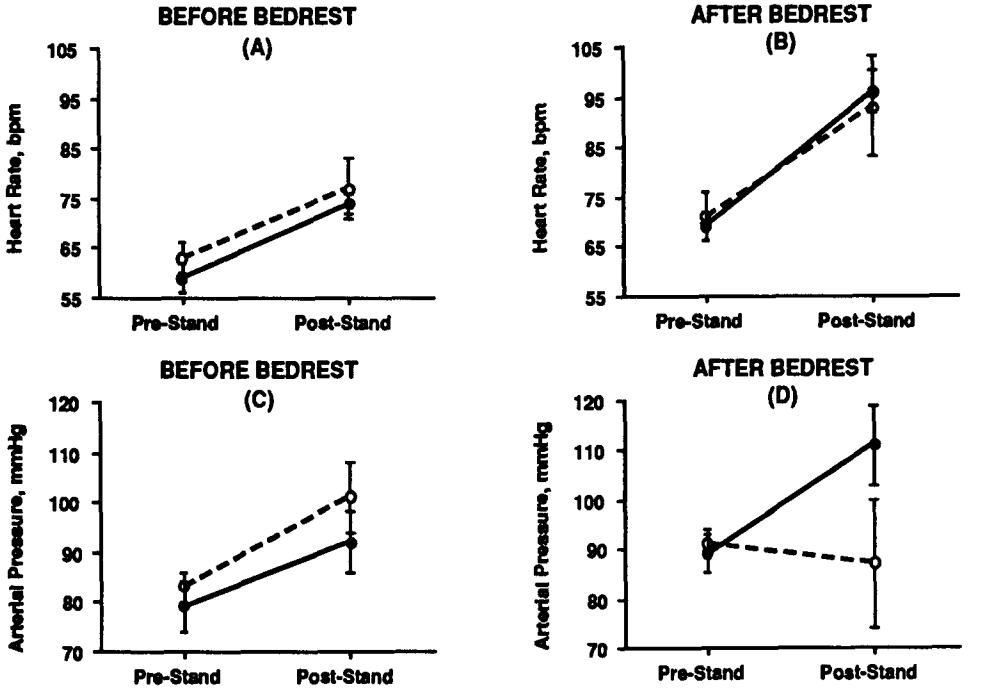

Figure 1. Responses of heart rate (panels A and B) and mean arterial pressure (panels C and D) in subjects during supine rest and at the end of 15 min of standing before (panels A and C) and after (panels B and D) bedrest after treatments with saline (open circles and broken line) and florinef (closed circles and solid line). Symbols represent mean ± SE.

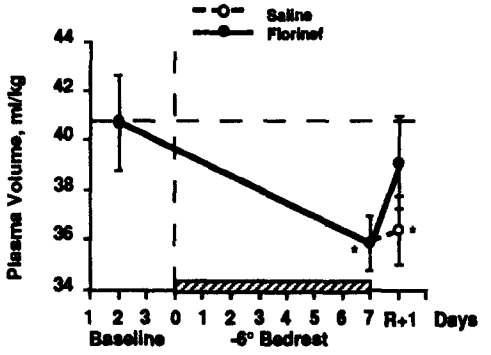

Figure 2. Plasma volume before and at the end of bedrest, and after treatment with saline (open circle and broken line) and florinef (closed circle and solid line). Symbols represent mean ± SE. Asterisk indicates $P < 0.05$ compared to pre-bedrest baseline level.

heart rate, saline loading failed to maintain mean arterial pressure during post-bedrest standing compared to that observed during pre-bedrest standing and with post-bedrest florinef treatment (Fig. 1C and 1D).

Plasma volume responses. Mean resting plasma volume decreased ($P < 0.05$) by approximately 12% by BR7 in both saline and florinef groups (Fig. 2). Following the treatments, florinef returned plasma volume to within 4% of baseline (NS) while saline failed to restore plasma volume ($P < 0.05$).

Catecholamine responses. Baseline pre-stand norepinephrine levels were similar between pre- and post-bedrest and between treatment groups (Fig. 3). Average elevation of plasma norepinephrine to 725 ± 66 pg/ml ($P < 0.05$) induced by 5 min of posture change from supine to standing before bedrest (left panel) was accentuated to 1049 ± 122 pg/ml ($P < 0.05$) during 5 min of standing after bedest (right panel). There were no group differences in the norepinephrine response to standing before or after bedrest.

Carotid baroreflex responses. The changes in carotid baroreflex sensitivity in all eleven subjects after bedrest before treatments have been published elsewhere [6]. Briefly, maximum slopes of the carotid-cardiac stimulus-response relationship decreased from 3.4 ± 0.6 ms/mmHg before bedrest to 2.2 ± 0.4 ms/mmHg at the end of 7 days of bedrest ($P < 0.05$). Average carotid baroreflex response relationships for all subjects in each group after their treatments at the end of bedrest compared to before bedrest are depicted in Figure 4. The responses demonstrate that the maximum slope of the stimulus-response relationship remained depressed after saline load (Fig. 4, left panel) at 2.5 ± 0.6 ms/mmHg compared to pre-bedrest ($P < 0.05$). Maximum slope of the stimulus-response relationship returned to pre-bedrest level at 4.1 ± 0.8 ms/mmHg after florinef treatment (Fig. 4, right panel). Baseline systolic, diastolic, mean arterial and estimated carotid distending pressures did not change with bedrest.

Cardiopulmonary reflex responses. Average maximum slopes of the cardiopulmonary baroreceptor-forearm vascular resistance stimulus-response relationship in all eleven subjects after bedrest before treatments increased from -1.6 ± 0.3 pru before bedrest to -2.8 ± 0.7 pru at the end of 7 days of bedrest ($P < 0.05$, ref. 6). Average cardiopulmonary baroreflex response

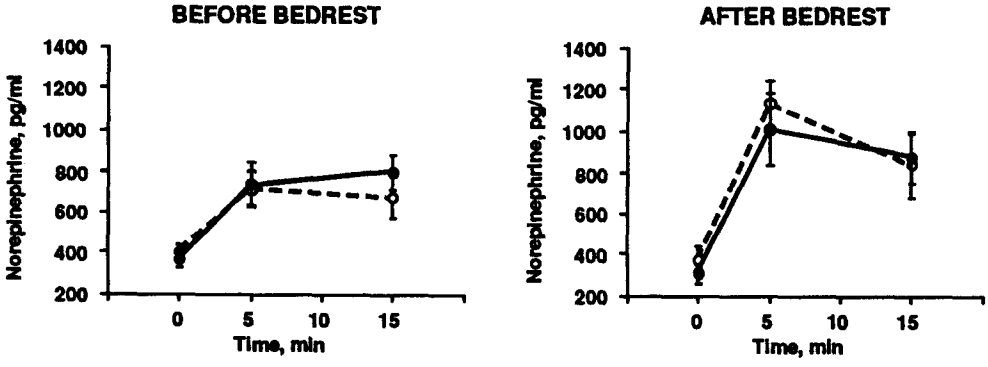

Figure 3. Plasma norepinephrine responses in subjects during supine rest and at 5 and 15 min of standing before (left panel) and after (right panel) bedrest following treatments with saline (open circles and broken lines) and florinef (closed circles and solid line). Symbols represent mean ± SE.

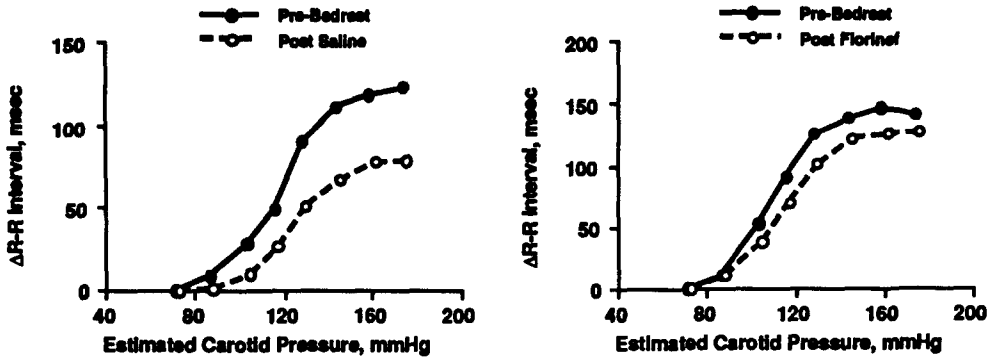

Figure 4. Average carotid baroreceptor-cardiac reflex response relationships before bedrest (solid circles and solid line) and after treatments with saline (left panel) and florinef (right panel) at the end of bedrest (open circles and broken lines).

relationships for all subjects in each group after their treatments at the end of bedrest compared to before bedrest are depicted in Figure 5. The responses demonstrate that the maximum slope of the stimulus-response relationship was elevated after saline load (Fig. 5, left panel) at -4.3 ± 3.3 pru compared to pre-bedrest ($P < 0.05$). Maximum slope of the stimulus-response relationship returned to a pre-bedrest level of -1.5 ± 0.3 pru after florinef treatment (Fig. 5, right panel). Estimated central venous pressure at baseline was reduced ($P < 0.05$) from 8.4 ± 1.4 mmHg before bedrest to 5.7 ± 0.7 mmHg after bedrest in all subjects and was not affected by either treatment.

Hemodynamic responses. Stroke volume before bedrest and after treatments at baseline and each level of LBNP are presented in Figure 6. Stroke volume decreased ($P < 0.05$) as a function of LBNP. Before treatment, bedrest decreased stroke volume by an average of 12 ± 2 ml at all levels of LBNP [6]. Stroke volume remained depressed ($P < 0.05$) after saline ingestion, an effect which was greater at lower levels of LBNP (Fig. 6, left panel). Stroke volume after florinef treatment was not different at all levels of LBNP compared to pre-bedrest (Fig. 6, right panel). The average difference in stroke volume across LBNP levels in the saline load group (8 ± 3 ml) was 4 times greater ($P < 0.05$) than that under florinef treatment (2 ± 1 ml).

Renal responses. Saline loading increased urine volume (411 ± 115 ml) during the 2 h following assumption of the standing posture after bedrest compared with the pre-bedrest level (163 ± 60 ml). Urine [Na^+] was similar between before (18.4 ± 5.5 mEq/L) and after (14.2 ± 2.3 mEq/L) bedrest. Urine Na^+/K^+ ratio was similar after bedrest (1.2 ± 0.1) compared to before

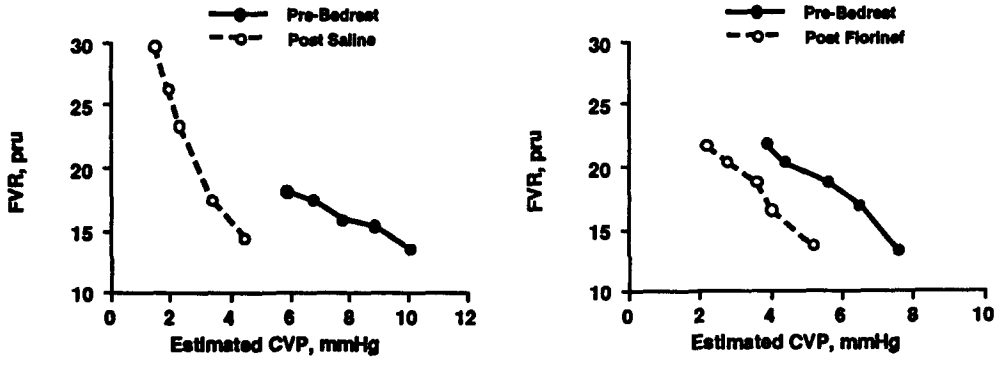

Figure 5. Average cardiopulmonary baroreceptor-forearm vascular resistance reflex response relationships before bedrest (solid circles and solid line) and at the end of bedrest (open circles and broken lines) following treatment with saline (left panel) and florinef (right panel).

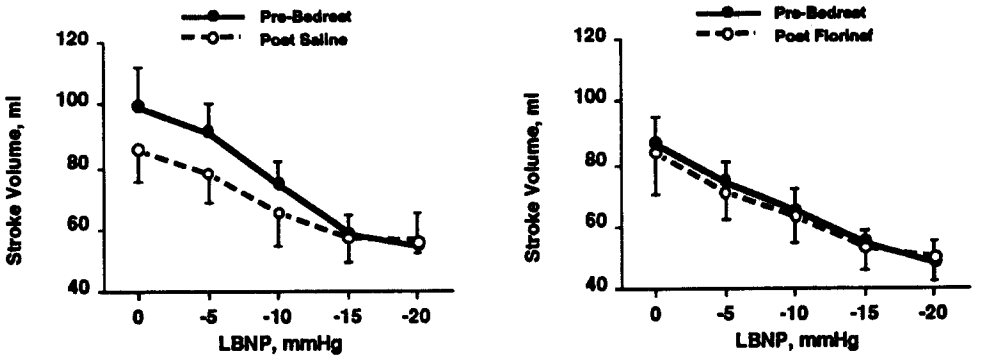

Figure 6. Stroke volume responses at rest and during selective graded orthostatic challenge induced by lower body negative pressure (LBNP) before bedrest (solid circles and solid line) and at the end of bedrest (open circles and broken lines) following treatments with saline (left panel) and florinef (right panel). Symbols represent mean ± SE.

bedrest (1.1 ± 0.5).

In contrast to the effects of saline load, florinef decreased urine volume (73 ± 57 ml) during the 2 h following assumption of the standing posture after bedrest compared with the pre-bedrest level. Urine [Na^+] was decreased from 12.8 ± 6.9 mEq/L before bedrest to 1.1 ± 0.9 mEq/L after bedrest. Urine Na^+/K^+ ratio was reduced after bedrest (0.2 ± 0.1) compared to before bedrest (0.6 ± 0.4).

DISCUSSION

In the present study, we used a groundbase model to compare saline ingestion currently used for fluid replacement at the end of spaceflight with a pharmacological alternative to test the efficacy of these procedures as potential countermeasures for reduced blood volume and orthostatic hypotension following spaceflight. Saline loading was unsuccessful in providing protection against presyncope after 7 days of exposure to simulated microgravity. Its use was associated with inability to restore plasma volume to pre-bedrest level, maintain stroke volume and increase mean arterial pressure during orthostatism, and reverse baroreflex alterations. In contrast, florinef restored plasma volume, stroke volume during LBNP, mean arterial pressure during standing, and baroreflex sensitivities. It is clear that the current use of saline loading as a countermeasure against post-flight hypovolemia and orthostatic hypotension is tenous while a protective effect of florinef proved promising.

Chronic reduction in baseline central venous pressure during bedrest in both saline and florinef groups (Fig. 3) was similar in magnitude to measurements obtained from two astronauts on the seventh day of the D-1 Space Shuttle mission [7,15]. If lower central venous pressure represents a resetting of the stimulus-response mechanism associated with regulation of blood volume [6], it might become more difficult to retain a fluid load with a reduced operating point for central venous pressure under microgravity conditions. Our data support this notion. Two hours after saline loading, plasma volume remained depressed at post-bedrest levels (Fig. 2) while urine volume was increase by nearly three-fold. In contrast, a restoration of plasma volume by florinef treatment was accompanied by average reductions of 55% in urine volume and 73% in the urinary Na^+/K^+ ratio. Florinef is a mineralcorticoid with potent salt-retaining action on the kidney. The effectiveness of florinef treatment over simple saline loading in replacing vascular volume in the present study underscores the importance of providing a physiological mechanism to enhance renal capacity for retention of a fluid and sodium load which is otherwise excreted as excess volume against a lower central venous pressure stimulus.

During pre-bedrest standing, elevated heart rate was associated with increased blood pressure and orthostatic stability in both groups. Florinef treatment protected this response after 7 days of bedrest. In contrast, subjects who received saline load increased their heart rates to the same degree as that of florinef subjects despite a greater unloading of carotid baroreceptors (i.e., a lower mean arterial blood pressure, see Fig. 1D). This relationship between a similar heart rate elevation in response to a

lower blood pressure stimulus during the stand test is consistent with impairment of carotid-cardiac baroreflex function after saline loading compared to restored function with florinef treatment (Fig. 4). Thus, our results are consistent with previous findings that carotid-cardiac baroreflex function is impaired following exposure to microgravity and is associated with orthostatic hypotension [5,6].

Increasing levels of LBNP reduced stroke volume, a response typical of that observed during orthostatism [2,6]. In addition to the LBNP effect, bedrest produced lower stroke volume [6], an effect which persisted after treatment with saline compared to the pre-bedrest response. The bedrest effect was eliminated by florinef treatment. However, even in the saline-load subjects, bedrest effects on stroke volume converged at higher levels of LBNP. These results indicate that the association between maintenance of vascular volume and mechanisms of cardiac filling and stroke volume did not distinguish between the treatments, and fail to provide an explanation for the protective effect of florinef during orthostatic challenges following adaptation to microgravity in the present study.

There is little known about the effects of spaceflight on the cardiopulmonary baroreceptor stimulus-FVR response relationship, but head-down bedrest provided the opportunity to examine this mechanism in a simulated microgravity posture. An increased slope of the cardiopulmonary baroreflex stimulus-response relationship was induced by bedrest [6] and continued after saline loading (Fig. 5). This relationship demonstrated a more responsive reflex increase of FVR for the same stimulus (i.e., ΔCVP) compared to pre-bedrest baseline, and supports previous observations that acute [20] and chronic [1] plasma volume reductions were associated with greater vasoconstriction compared to a normovolemic state. Increased responsiveness (i.e., slope) was eliminated in the florinef group who had restored their plasma volume, suggesting that the baroreflex response is volume dependent [16,20]. The vascular system has finite vasoconstrictive capability [20]. Increased slope of the cardiopulmonary baroreflex stimulus-response relationship has been interpreted to represent a greater utilization of vasoconstrictive reserves [20] and, depending on the degree of hypovolemia, may significantly compromise the capacity to provide adequate increases in vascular resistance during orthostatic challenges after adaptation to microgravity. In this perspective, it is clear that the capacity to further increase vascular resistance and defend arterial pressure was compromised in the volume-depleted, saline-loaded subjects while blood volume repletion by florinef restored vasoconstrictive reserve capacity. In light of similar responses in heart rate and stroke volume between treatment groups, our data suggest that increasing the reserve for vascular resistance may distinguish one of the primary mechanisms by which florinef provided protection from post-bedrest orthostatic hypotension in the present study.

In addition to replacing vascular volume and vasoconstrictive reserve, florinef elevates blood pressure by a direct effect on increasing total peripheral resistance [8,9,17,18]. The mechanism of enhanced vasoconstrictive response with florinef is unclear. Circulating catecholamines do not offer a resonable explanation for increased blood pressure during post-bedrest standing in the florinef group since florinef inhibits norepinephrine release [9,10,14,17] and both treatment groups exhibited similar plasma norepinephrine levels and heart rates at rest and during standing after bedrest (Fig. 1 and 3). There are compelling data, however, to suggest that florinef may have enhanced the orthostatic response observed in the present study by augmenting the responsiveness of vascular smooth muscle receptors to norepinephrine [8,10,18].

The major finding of this study was that treatment with saline loading following 7 days exposure to an analog of microgravity failed to reverse lowered plasma volume, impaired carotid-cardiac baroreflex function, increased gain and reduced reserve capacity of cardiopulmonary baroreflex control of forearm vascular resistance, and lowered central venous pressure. All of these physiological alterations were associated with greater orthostatic intolerance after bedrest despite saline loading. Florinef treatment, however, was successful in eliminating all of these changes and orthostatic hypotension. Therefore, acute florinef treatment during the final 24 h of spaceflight appears to have distinct advantages over the present use of saline loading as a protective measure for orthostatic instability, not only through its salt-retaining, volume-expanding mineralcorticoid actions, but probably through direct actions on baroreflex function and vascular smooth muscle.

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