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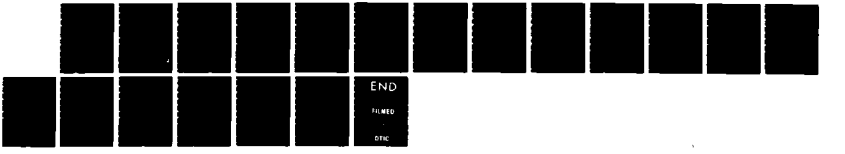

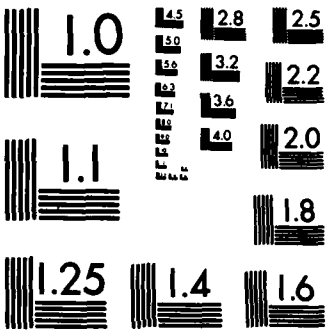

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THE EFFECT OF SPIRONOLACTONE ON THE CARDIOCIRCULATORY RESPONSES TO UPRIGHT TILT AT SEA LEVEL AND AT SIMULATED HIGH ALTITUDE

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The objective of this study was to determine if spironolactone (S) alters the cardiocirculatory responses to upright tilt at sea level (SL;50m) and during 44 hours of simulated altitude (HA;4600m). In a double-blind, crossover-designed study, 9 male subjects (age range:18-25 years) received 25 mg orally, 4x/day of either S or an identically-appearing placebo (P) 2 days prior to and during HA. The crossover was separated by two weeks. Heart rate, stroke volume, cardiac output, calf blood flow, total peripheral resistance and systemic blood pressure were obtained during supine rest and after 10 minutes of 60 degree

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head-up tilt using an impedance monitor and an electro-sphygmomanometer. Twenty-four hour determinations of urinary volume, sodium and potassium as well as venous plasma values for sodium, potassium and chloride were obtained daily. There were no statistically significant differences between P and S treatment periods for: caloric, electrolytes or fluid ingestion; urinary volume or electrolytes; plasma electrolytes; or any of the cardiocirculatory parameters measured in the supine or upright position at SL or during HA. It was concluded that S did not induce a significant diuresis or significantly alter vascular responsiveness to negatively effect the normal cardiocirculatory responses to upright tilt at sea level or simulated high altitude.

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ABSTRACT

The objective of this study was to determine if spironolactone (S) alters the cardiocirculatory responses to upright tilt at sea level (SL;50m) and during 44 hours of simulated altitude (HA;4600m). In a double-blind, crossover-designed study, 9 male subjects (age range: 18-25 years) received 25 mg orally, 4x/day of either S or an identically-appearing placebo (P) 2 days prior to and during HA. The crossover was separated by two weeks. Heart rate, stroke volume, cardiac output, calf blood flow, total peripheral resistance and systemic blood pressure were obtained during supine rest and after 10 minutes of 60^{o} head-up tilt using an impedance monitor and an electro-sphygmomanometer. Twenty-four hour determinations of urinary volume, sodium and potassium as well as venous plasma values for sodium, potassium and chloride were obtained daily. There were no statistically significant differences between P and S treatment periods for: caloric, electrolytes or fluid ingestion; urinary volume or electrolytes; plasma electrolytes; or any of the cardiocirculatory parameters measured in the supine or upright position at SL or during HA. It was concluded that S did not induce a significant diuresis or significantly alter vascular responsiveness to negatively effect the normal cardiocirculatory responses to upright tilt at sea level or simulated high altitude.

INTRODUCTION:

Spironolactone, an aldosterone antagonist, is a mild, potassium-sparing diuretic clinically used for the management of primary hyperaldosteronism or in edematous conditions such as congestive heart failure or cirrhosis of the liver. It is also used in conjunction with other diuretics in the treatment of essential hypertension or for conditions when hypokalemia must be minimized (20). Spironolactone exerts its influence by competitively inhibiting the effects of aldosterone at the distal renal tubules where sodium is normally exchanged for potassium. By blocking this exchange, increased amounts of water and sodium are excreted while the loss of potassium is prevented. The degree of diuresis caused by spironolactone is dependant on the presence of aldosterone (8). In addition to being a diuretic, spironolactone also reduces vascular responsiveness to norepinephrine (20).

Spironolactone has been recommended or used for the prevention or lessening of the symptoms of Acute Mountain Sickness (2,14,23). Sutton et al. (23) has recommended that spironolactone be used by high-altitude sojourners to prevent the hypoxia-induced sodium and fluid retention they had observed. Currie et al. (2) reported that two groups of Tibetan trekkers using spironolactone experienced no symptoms of acute mountain sickness.

It has previously been shown that the normal compensatory hemodynamic responses to upright tilt are altered from those at sea level during altitude exposure (7). Observed reductions in stroke volume, cardiac output and calf blood flow with concomitant increases in blood pressure and total peripheral resistance have been attributed to altitude-induced reductions in plasma and blood volume and/or increased stimulation of the sympathetic nervous system (7,16,17).

In a recent study conducted by our laboratory, spironolactone was found to be benefical in some individuals as a prophylactic agent for the prevention of acute mountain sickness (14). Because of the possibility of spironolactone altering water balance and vascular responsiveness, a tilt-table test was included as part of that study to determine if the normal compensatory responses to a circulatory challenge at sea level and at 4600 meters simulated altitude would be modified. The results obtained from the tilt table tests are reported here.

METHODS:

Nine healthy males (aged 18 to 25 yrs) volunteered for participation in this double-blind, crossover-designed study. Treatment order was randomly assigned by a non-involved third party. The two testing periods were separated by two weeks. During each test period, subjects were given 25 mg orally, q.i.d., of either spironolactone (Aldactone; Searle & Co.) or an identically-appearing placebo two days immediately prior to the hypobaric exposure and continuously for two days (44 hours) during the exposure.

During the two test periods, the subjects were restricted to a diet of known elemental composition. Meals were consumed at designated times of the day; water was available ad libitum. Twenty-four hour values for caloric, water and sodium chloride consumption were calculated for each subject. Daily 24-hour collections of urine were made for the determination of urinary volume, sodium and potassium. Venous plasma values for sodium, potassium and chloride were obtained at sea level and during the two days at altitude. For estimation of blood and plasma volume (4), hematocrit and hemoglobin were determined using samples obtained from an arm vein during rest at sea level and during each day at altitude.

After 1800h of the second day at sea level during each test period, subjects were rapidly decompressed (< 10 min) in a hypobaric chamber to a simulated altitude of 4600m where they remained for 44 hours. Temperature and relative humidity were maintained at 23 $\pm$ 2° C and 45 $\pm$ 5%, respectively. Subjects were sedentary during their period of confinement at sea level and at altitude.

Tilt-Testing Protocol

A tilt-table test was performed daily at sea level and altitude between 1300h and 1500h. Impedance electrodes were placed as described below and then the subject laid supine on a slightly padded 9.5 cm x 30cm 30.0 cm tilt-table surface. Restraining straps and a steel foot rest allowed the subject to remain passive when changing from one position to another. A blood pressure cuff was placed around the subject's right upper arm and impedance monitor cables were connected to the electrodes. When the subject was tilted to the upright position, his right arm rested at heart level on a shelf next to the tilt platform.

Blood pressure and heart rate were determined in the supine position every 2 minutes for the first 8 minutes using an electro-sphygmomanometer (Vita-stat; model 900-s). From minutes 8-10 of supine rest, thoracic and peripheral impedance data were obtained. Blood pressure and heart rate were again measured at minute 12. At minute 13, the subject was tilted (< 2 sec) to a head-up 60° angle. Blood pressure and heart rate were determined immediately and every minute for the first five minutes and at minutes 7 and 9 of tilt. At the end of minute 9 of tilt, upright thoracic and peripheral impedance data were obtained.

Impedance

Impedance data were obtained using an impedance cardiograph (Minnesota; model 304b). The methods and the theoretical basis in determining physiological variables from impedance data have been presented elsewhere (1,3,19). During the present investigation, ECG rather then band electrodes were used. Agreement between these two types of electrodes for impedance measurements has been shown to be excellent (22). A constant sinusoidal current (4mA, rms) with a frequency of 100 kH applied to electrodes located on the forehead and lateral malleolus served as excitation current sources. The four pickup electrodes were located at the base of the neck (3 cm to the right of the first thoracic vertebra), 30 cm directly below on the back and on the lateral segment of the calf 10 and 20 cm above the excitation electrode located on the lateral malleolus. Electrode sites were marked with indelible ink for consistancy of placement from day to day. Thoracic impedance changes recorded via the back electrodes were used to estimate stroke volume and cardiac output while the two lower limb electrodes were used to estimate calf blood flow. To eliminate movement artifacts due to respiration during the collection of the impedance signals, subjects were instructed to hold their breath after a normal exhalation.

A minicomputer (MINC; Digital Equipment Corp) was used to digitize, store and later analyze the impedance signals. Calculations of volume and flow were made according to Nyboer and others (19,22,25) using the systolic downstroke extrapolation method. Most studies utilizing the impedance technique use constant values for blood resistivity which assumes little or no change in hematocrit (11,18,22,26). However, because of the possibility that hematocrit would be altered either due to the altitude exposure or to spironolactone treatment, a value for blood resistivity for use in the impedance

equations was determined daily from the hematocrit (9). Heart rate was calculated from the impedance pulse recording. Cardiac output and peripheral blood flow were determined by multiplying heart rate by the volume values obtained from the back or calf electrodes, respectively. Systolic and diastolic blood pressure were determined using the electro-sphygmomanometer. Mean arterial pressure was calculated as 1/3 pulse pressure plus diastolic blood pressure. Total peripheral resistance was calculated as mean arterial pressure divided by cardiac output. The data were analyzed using a repeated measures ANOVA and, where appropriate, the Neuman-Keuls post hoc test. Statistical significance was chosen at $p < .05$.

RESULTS:

Table 1 presents the values for the cardiovascular parameters obtained from the test subjects while in the supine and upright tilt positions at sea level and after 20h and 44h of hypobaric exposure with either placebo or spironolactone treatment. All values are the means ($\pm$ S.E.) of 9 subjects.

Table 1 here

There were no statistically significant differences due to spironolactone treatment in any of the parameters measured in the supine or upright position at sea level or during the altitude exposure.

In the supine position after 20 and 44 hours of hypobaric exposure, heart rate, total peripheral resistance, diastolic and mean blood pressure were increased while stroke volume was decreased relative to sea level. Cardiac output and calf blood flow during the altitude exposure were not altered from sea level values.

In the upright position, heart rate was increased and stroke volume was decreased after 20h of altitude exposure. Cardiac output, total peripheral resistance and systolic blood pressure were not statistically altered from sea level. During the exposure, mean arterial blood pressure was higher during spironolactone treatment and calf blood flow was higher during placebo treatment relative to sea level.

Table 2 here

Caloric, fluid and electrolyte intake did not differ between the placebo and spironolactone treatment at sea level or at altitude. During the altitude exposure, both treatment groups demonstrated a reduction in potassium, sodium and calories consumed. However, fluid intake at altitude did not differ from sea level.

Urine volume and urinary sodium and potassium excretion as well as the serum sodium, potassium and chloride concentration did not differ between the placebo and sprionolactone treatment periods at sea level or at altitude. Urine volume and urinary electrolyte excretion were reduced while serum chloride concentration was greater at altitude. Serum sodium and potassium concentrations were not altered by the altitude exposure. Hematocrit and hemoglobin were increased while estimated values for blood and plasma volume were decreased at altitude. The increases in hematocrit and hemoglobin were greater during spironolactone treatment then with placebo. However, no significant differences were found between treatments for blood and plasma volume reduction.

DISCUSSION

Cardiocirculatory responses to upright tilt are altered from sea level during exposure to high altitude (7). These changes have been attributed primarily to reduced plasma and blood volumes and increased stimulation of the sympathetic nervous system (7,17). Because spironolactone has the potential to further reduce blood volume and to alter vascular responsiveness, the present investigation was undertaken to determine if the normal responses to upright tilt during hypobaric exposure would be exacerbated.

From the results obtained in this study, it appears that spironolactone had little effect on the fluid and electrolyte balance either at sea level or at altitude, and consequently did not alter the normal hypoxic responses to upright tilt. During sea level therapy, this lack of effect on fluid and electrolyte balance was not surprising as spironolactone is not a potent diuretic (21), especially in the presence of normal aldosterone levels (20). During the altitude exposure, the potency of spironolactone as a diuretic was not as predictable. Reports of aldosterone levels at altitude have not been consistant, probably due to differences in age, diet, exercise and elevation (6,10,12,13,15,24). Aldosterone was not measured in the present study. However, in studies where the age of the subjects, altitude and diet restrictions were similar to the present, plasma and/or urinary aldosterone levels were reported to be reduced from sea level (10,13,15). Further, the high levels of sodium consumption present during both placebo and spironolactone treatment suggest that all subjects were fully salt replete during this investigation. With normal or reduced aldosterone secretion, spironolactone would not be expected to induce sufficient diuresis to negatively effect the normal cardiocirculatory responses to upright tilt.

With upright tilt or high altitude exposure, there is increased sympathetic activity as evidenced by increased plasma norepinephrine and urinary catecholamine levels (5,7,16,17). Increased sympathetic tone is associated with an increase in resting blood pressure and arteriolar constriction (7,17). In the present study, there were no consistant differences measured between placebo and spironolactone therapy at sea level or altitude for total peripheral resistance, calf blood flow or blood pressure in either the supine or upright position. These findings suggest that spironolactone in the quantity given did not significantly alter vascular responsiveness to norepinephrine.

In conclusion, under the contraints of this investigation, spironolactone administration did not alter the normal circulatory responses to upright tilt at sea level or altitude when compared to placebo. Caution must be exercised however, not to compare these results to other, non-controlled situations, e.g., prolonged and physically demanding treks, where dietary supplementation may not be adequate to allow body fluid levels to normalize. If depletion is severe enough, aldosterone secretion would be increased, causing a compensatory retention of sodium and fluid. If spironolactone is administered under these conditions, it may effect fluid and electrolyte status and, thereby, circulatory responses to tilt.

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TABLE 1

The Response of Cardio-circulatory Variables to Upright Tilt at Sea Level and During 20h and 44h of Hypobaric Exposure with and without Spironolactone

Variable	Position	S.L.		S.L.		Alt 20		Alt 44	
		P	S	P	S	P	S	P	S
Heart rate (beat/min)	supine	53 ± 2	53 ± 3	53 ± 3	53 ± 3	78 ± 3*	81 ± 6*	73 ± 3*	77 ± 7*
	tilt	86 ± 7#	82 ± 7#	90 ± 7#	88 ± 6#	113 ± 6#*	116 ± 7#*	116 ± 7#*	124 ± 8#*
Stroke volume (ml/beat)	supine	96.9 ± 6.6	97.9 ± 8.3	90.1 ± 7.0	94.0 ± 7.6	66.7 ± 5.2*	66.2 ± 5.0*	64.9 ± 3.7*	60.4 ± 5.7*
	tilt	59.3 ± 5.4#	61.6 ± 6.3#	52.9 ± 5.1#	60.0 ± 7.0#	48.2 ± 5.9*	48.2 ± 4.5#*	41.7 ± 5.2#*	42.4 ± 6.0#*
Cardiac output (l/min)	supine	5.52 ± 0.24	5.30 ± .43	5.11 ± .24	5.29 ± .37	5.25 ± .39	5.16 ± 0.36	4.88 ± 0.27	4.70 ± 0.89
	tilt	4.85 ± 0.21#	4.79 ± .36	4.51 ± .24#	4.99 ± .41	5.19 ± .43	5.45 ± 0.40	4.60 ± 0.39	4.93 ± 0.47
Total Peripheral Resistance (mmHg/l/min)	supine	14.37 ± .92	15.81 ± 1.37	15.77 ± .95	15.39 ± 1.23	17.13 ± 2.08	17.29 ± 1.71	19.78 ± 1.23*	18.97 ± 1.08*
	tilt	18.30 ± .92#	18.35 ± 1.68	19.06 ± 1.20	18.77 ± 1.53#	16.92 ± 1.65	16.99 ± 1.79	21.14 ± 1.91	21.51 ± 3.26
Calf blood flow (ml/min/100ml)	supine	7.01 ± .61	8.82 ± .74	5.77 ± .60	5.97 ± .58	8.92 ± .94	8.90 ± 0.65	7.35 ± 0.58	7.56 ± 0.93
	tilt	4.24 ± .42#	5.68 ± 1.05#	4.31 ± .35#	4.37 ± .45#	5.85 ± .53*	6.33 ± 0.79#	6.14 ± 0.59*	5.00 ± .57#
Systolic blood pressure (mmHg)	supine	117 ± 4	119 ± 3	121 ± 3	115 ± 6	131 ± 4*	124 ± 4	131 ± 4*	123 ± 3
	tilt	110 ± 5	113 ± 5	106 ± 3#	117 ± 4	108 ± 4#	112 ± 6	119 ± 3	124 ± 6
Diastolic blood pressure (mmHg)	supine	61 ± 3	60 ± 3	59 ± 2	60 ± 4	61 ± 3	66 ± 4	75 ± 3*	69 ± 3*
	tilt	77 ± 4#	71 ± 4#	73 ± 3#	77 ± 4#	73 ± 3	77 ± 5#	77 ± 3	83 ± 4#
Mean arterial blood pressure (mmHg)	supine	79 ± 2	79 ± 1	78 ± 2	78 ± 2	84 ± 2	85 ± 3*	94 ± 2*	87 ± 2*
	tilt	88 ± 4#	84 ± 4	84 ± 3#	89 ± 4#	84 ± 3	88 ± 4	91 ± 2	95 ± 4*

a = Tilt-test was performed 5 hours after 1st medication was distributed; subsequent tilt-tests were performed at 24 hour intervals

All sea level to altitude comparisons were made between the first sea level tilt-test and the corresponding treatment period altitude tilt-test.

* $p<.05$ from corresponding sea level value

TABLE 2

Comparison of Physiological and Biochemical Parameters Between
Placebo and Spironolactone Treatment at Sea Level, 20h and 44h of Hypobaric Exposure

	Sea level		Alt20		Alt44	
	P	S	P	S	P	S
URINARY VALUES						
Sodium (Meq/24h)	168 ± 31	165 ± 23	94 ± 23*	84 ± 22*	47 ± 11*	56 ± 18*
Potassium (Meq/24h)	54 ± 8	45 ± 8	27 ± 6	24 ± 6*	19 ± 4*	19 ± 5*
Volume (ml)	992 ± 99	1018 ± 192	691 ± 183	501 ± 130*	329 ± 71*	364 ± 99*
BLOOD VALUES						
Sodium (Meq/L)	142 ± 1	----------	148 ± 3	147 ± 3	147 ± 3	147 ± 3
Potassium (Meq/L)	4.10 ± .10	----------	4.20 ± .12	4.40 ± .13	4.34 ± .15	4.64 ± .26
Chloride (Meq/L)	107 ± 1	----------	114 ± 3	113 ± 3*	115 ± 2*	112 ± 2*
Hematocrit (%)	47.6 ± 1.2	47.4 ± 1.2	47.4 ± 1.0	49.1 ± 1.2#*	51.2 ± 1.1a	53.1 ± 1.0a
Hemoglobin (gm/dL)	15.74 ± .38	15.66 ± .39	15.49 ± .35	16.17 ± .43#*	16.73 ± .46a	17.38 ± .37a
Blood Volume reduction (%)	----------	----------	0	3.1 ± 1.2	4.5 ± 2.0+	9.3 ± 2.0+
Plasma Volume reduction (%)	----------	----------	0	6.0 ± 2.4	8.5 ± 4.0+	17.4 ± 4.0+
INGESTED						
Potassium (Meq)	62 ± 9	67 ± 7	----------	17 ± 7*	----------	----------
Sodium Chloride (Meq)	153 ± 20	159 ± 12	51 ± 17*	50 ± 18*	----------	----------
Sodium (Meq)	168 ± 22	202 ± 22	51 ± 19*	61 ± 22*	----------	----------
Calories(Kcals)	2085 ± 330	2240 ± 257	759 ± 248*	690 ± 266*	----------	----------
Fluid (ml)	1299 ± 156	991 ± 80	1142 ± 132	793 ± 110	----------	----------

Values are means (± S.E.); n=9 unless otherwise indicated
a = 6 subjects
* $p < .05$ from sea level value
# $p < .05$ from placebo value
+ $p < .05$ from Alt20 reduction

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