Eur J Appl Physiol (1983) 51: 121–128

European Journal of
Applied
Physiology
and Occupational Physiology

Acute Albumin-induced Plasma Volume Expansion and Exercise in the Heat: Effects on Hormonal Responses in Men

R. P. Francesconi, M. N. Sawka, R. W. Hubbard, and M. Mager

US Army Research Institute of Environmental Medicine, Natick, MA 01760, USA

Summary. To assess the responses of fluid regulatory and stress hormones to acute expansion of plasma volume and exercise in the heat, 50 g of albumin dissolved in 200 ml normal saline or 200 ml saline alone was administered intravenously to 7 adult, male test subjects followed by exercise (40% $\dot{V}O_2$ max) in the heat (Tdb = 45° C, Twb = 25° C). Blood samples were obtained after sitting in the heat for 1 h, 1 h after completion of infusion which itself required approximately 1.5 h, after standing for 30 min, and 15, 30, 45, and 60 min after commencing exercise. Plasma cortisol levels were generally unaffected by these treatments. Responses of plasma aldosterone levels to postural change and exercise in the heat were attenuated in the albumin trial, and growth hormone levels were unaffected by albumin administration. Angiotensin I levels were significantly decreased at several sampling intervals during the albumin trial, but unaffected by exercise. We concluded from these studies that plasma volume expansion by intravascular albumin administration had no effect on stress hormone responses during exercise in the heat, while regulatory hormone levels were lower in several instances during the albumin trial.

Key words: Cortisol – Growth hormone – Angiotensin I – Aldosterone

Introduction

Exposure of humans to acute heat stress ordinarily results in significant increments in circulating levels of the fluid regulatory hormones, notably aldosterone, vasopressin, and angiotensin I (Bailey et al. 1972; Dumoulin et al. 1980; Follenius et al. 1979; Kosunen et al. 1976). Generally, these responses have been characterized as part of an adaptational process designed to maintain

Offprint requests to: Dr. R. P. Francesconi (address see above)

or increase intravascular fluid volume (Senay 1975) resulting in cardiovascular and thermoregulatory benefits. Additionally, elevations in levels of growth hormone (Okada 1972) as well as cortisol (Collins et al. 1969) have been reported subsequent to acute exposure to heat stress. These latter responses are undoubtedly a reflection of a generalized stimulation of the adrenohypophyseal axis due to exposure to environmental stress.

Acclimatization to heat in humans is characterized by an increased ability to work in the heat subsequent to greater cardiovascular and thermoregulatory efficiency partially attributed to plasma volume expansion (Senay 1970; Wyndham et al. 1968). Senay (1975) demonstrated that the expansion of plasma volume during acclimatization could be explained by an influx of interstitial protein and water into the circulatory system. Fortney et al. (1981) demonstrated the efficacy of intravascular albumin administration to induce significant elevations in circulating plasma volume. Likewise, we (Hubbard et al. 1982) had demonstrated in humans that 1 h after the infusion of hyperoncotic albumin solution, there occurred a significant increase in plasma volume which persisted for approximately 12 h. The purpose of the present investigation was to determine whether acute plasma volume expansion could modulate quantitatively and/or qualitatively the normally anticipated hormonal responses following exposure to the combined stress of exercise and heat.

Methods

Seven adult, unacclimatized volunteer men (Ss) participated in this study after giving their free and informed voluntary consent to all test procedures. Their mean age was 25 ± 4 years ($\bar{X}$ + SDx); their mean weight and height were 77.7 ± 11.3 kg and 176.0 ± 6.7 cm, respectively. Ss retained the right to withdraw from the study for any reason at any time, but none exercised this option.

Ss were awakened at 06.00 h, provided with juice and a standard breakfast, and entered the heat chamber (Tdb = 45° C, Twb = 25° C) at approx. 07.00 h. Upon entry, Ss remained seated quietly while a pediatric type catheter was inserted into an antecubital vein of both arms. Following this (approx. 1 h after entering the chamber), a resting blood sample (6 ml) was taken from the right arm, and each subject received an infusion of either human albumin (50 g in 200 ml isotonic saline) or saline alone (200 ml). This infusion procedure required approx. 100 min during which all Ss were required to remain seated quietly in the heat. Following completion of the infusion procedure, Ss remained seated for an additional 60 min after which a second resting blood sample was taken. Thus, the two blood samples taken while sedentary were separated by approx. 160 min. Ss were then asked to stand for 30 min after which a third blood sample was obtained; the standing blood sample was taken to account for the effects of posture on the hormones in question. Each subject was then requested to complete an exercise bout (1.56 m · s^{-1}, treadmill, at a grade that elicited 40% $\dot{V}O_2$ max, previously determined under moderate environmental conditions) designed to last for 90 min. At the start of both trials man T_{re} was 37.3° C and mean T_{sk} approx. 35° C. During the exercise period Ss consumed 200 ml cool water at 20 min intervals; plasma osmolalities were virtually unchanged throughout the experiment. Ss were required to undergo this entire procedure on two separate occasions, once receiving albumin and once receiving saline, in a randomized order and separated by at least one week. Tests were halted if heart rate exceeded 180 bt · min^{-1} or rectal temperature reached 39.5° C or greater. By 60 min two subjects had dropped out of both groups reducing the n to 5. During exercise, blood samples (6 ml each) were obtained at 15 min intervals, centrifuged (10,000 *g*, 4° C), the plasma removed, frozen (−20° C) and stored for subsequent analysis. Plasma volume changes were estimated from appropriate hemoglobin and hematocrit values (Dill and Costill 1974).

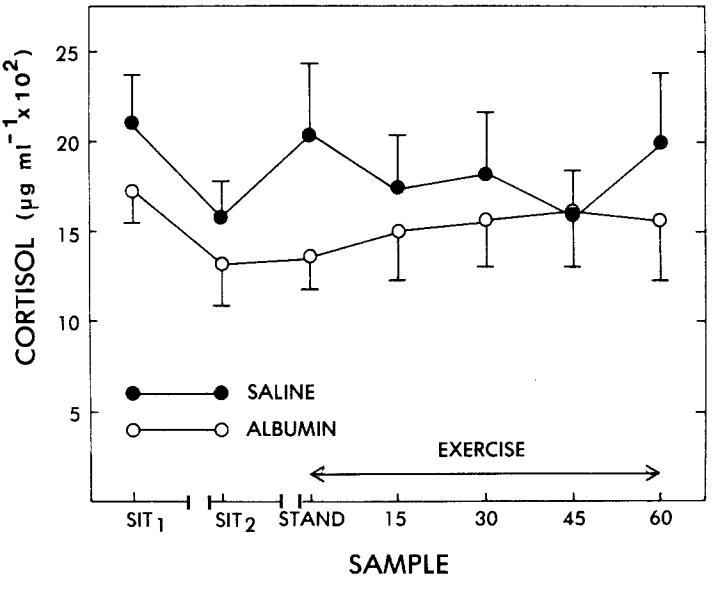

Fig. 1. Effects of heat exposure, plasma volume expansion, and exercise in the heat on plasma levels of cortisol. Mean values ± SEM are recorded for $n = 7$ at all sampling times except $n = 6$ at 45 min (sal), $n = 5$ at 60 min (sal) and $n = 5$ at 60 min (alb). The first sample, sit 1, was taken 60 min after entering the chamber and sit 2 was obtained 60 min following completion of infusion. Test volunteers then stood in place for 30 min at which the "stand" sample was obtained. The remaining samples were taken at the appropriate time after initiation of exercise. The albumin treatment consisted of 50 g of albumin in 200 ml sterile saline and in the control trial, sterile, isotonic saline was infused equivolumetrically

Aliquots of the frozen plasma were assayed by radioimmunoassay techniques for cortisol, aldosterone, angiotensin I, and growth hormone. Cortisol was quantitated using radioimmunoassay test kits (Damon Diagnostics, Needham, MA); aldosterone and growth hormone levels were also measured by radioimmunoassay test kits (International CIS, Sorin-Biomedica, Saluggia, Italy). Angiotensin I was likewise estimated by pre-prepared test kit (New England Nuclear Corp., No. Billerica, MA). All of these assays were performed according to procedures and methods outlined in the respective technical bulletins. For an assay with representative variability (aldosterone) intraindividual variation (duplicate assays of the same standard) averaged about 2% while a series of duplicate or triplicate assays of the same normal human serum elicited a variability of 7.8%. Interindividual variation (assays of four samples of normal human serum) averaged 5.7%.

Student's *t*-test was used to evaluate the significance of the means of paired data. Analyses of variance were used to assess the significance of the difference of the means of the consecutive samples; critical differences were established by Tukey's test (Li 1964; Lindquist 1953). The null hypothesis was rejected at $p < 0.05$.

Results

Plasma volume (sit 1 to sit 2 sample, all figures) was increased by 13.9% in test volunteers when hyperosmotic albumin was administered; in the saline trial plasma volume was virtually unaffected during this interval and as a result of

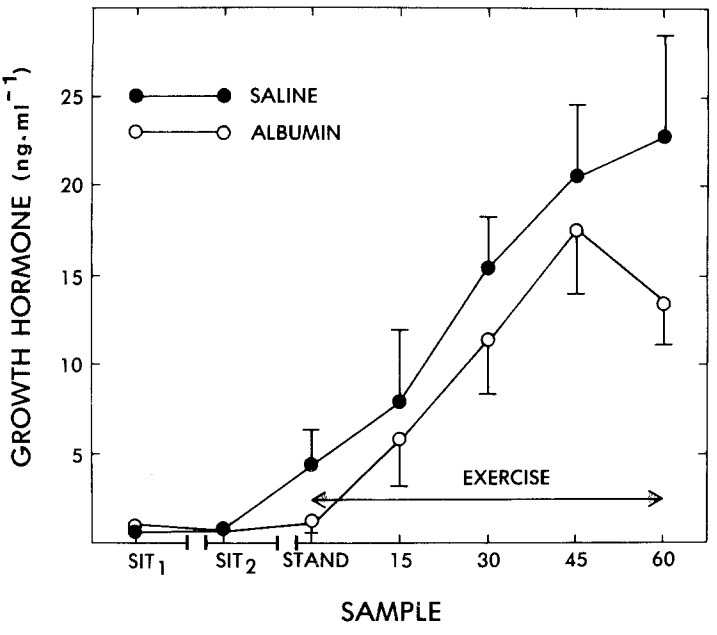

Fig. 2. Effects of heat exposure, plasma volume expansion, and exercise in the heat on plasma levels of growth hormone. Significant effects were noted as follows: saline – sit 1, sit 2, stand vs 45, 60 min exercise, $p < 0.05$; albumin – sit 1, sit 2, stand vs 30, 45, 60 min exercise, $p < 0.05$. All conditions are as noted in Fig. 1

infusion of 200 ml isotonic saline. Following standing for 30 min plasma volumes were reduced in both tests, but a 13.7% difference in plasma volume persisted between the albumin and saline trials. During the exercise intervals euhydration was maintained in both trials and no further alterations in plasma volume were observed.

Figure 1 demonstrates the effects of both albumin and saline infusion followed by exercise in the heat on plasma levels of cortisol. The relatively high concentrations of cortisol recorded in both groups in the initial resting samples reflect the fact that these samples were obtained during the early morning hours when plasma cortisol levels are highest in the circadian cycle. Statistical analysis confirmed that there were no significant differences between the albumin and saline trials nor were there any significant changes over time for either trial.

Figure 2 depicts the effects of exercise in the heat on circulating levels of growth hormone (GH). In the experiment with saline infusion, exercise led to a significant ($p < 0.05$; sit 1, sit 2, stand vs 45, 60 min exercise) increase in GH levels. With albumin infusion, GH levels were slightly, but not significantly lowered; thus, the response to exercise was unaffected by plasma volume expansion.

Figure 3 demonstrates the effects of albumin infusion and exercise in the heat on circulating aldosterone levels. In the saline trial the postural effects on

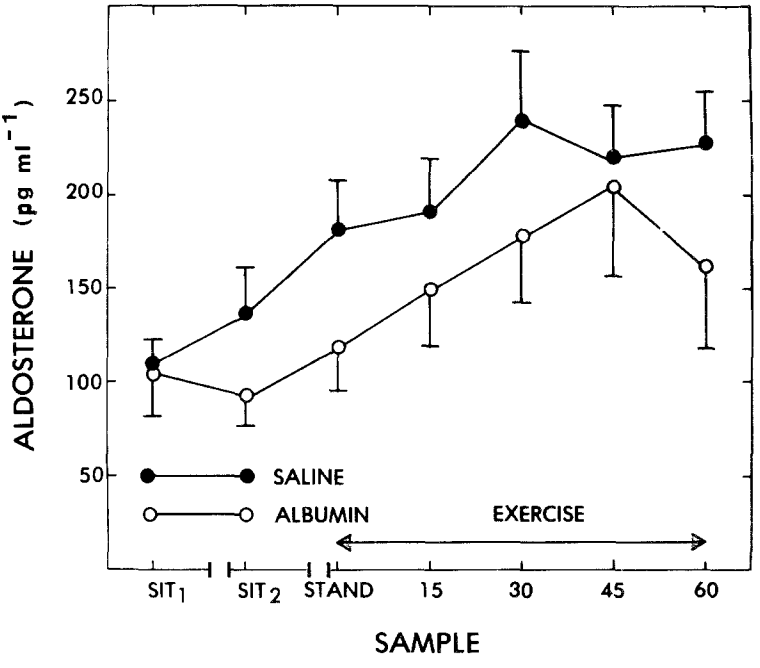

Fig. 3. Effects of heat exposure, plasma volume expansion, and exercise in the heat on plasma levels of aldosterone. Significant effects were noted accordingly: saline − sit 1, sit 2 vs stand, $p < 0.05$; albumin vs saline − stand, 15 min, $p < 0.05$. All conditions are as noted under Fig. 1

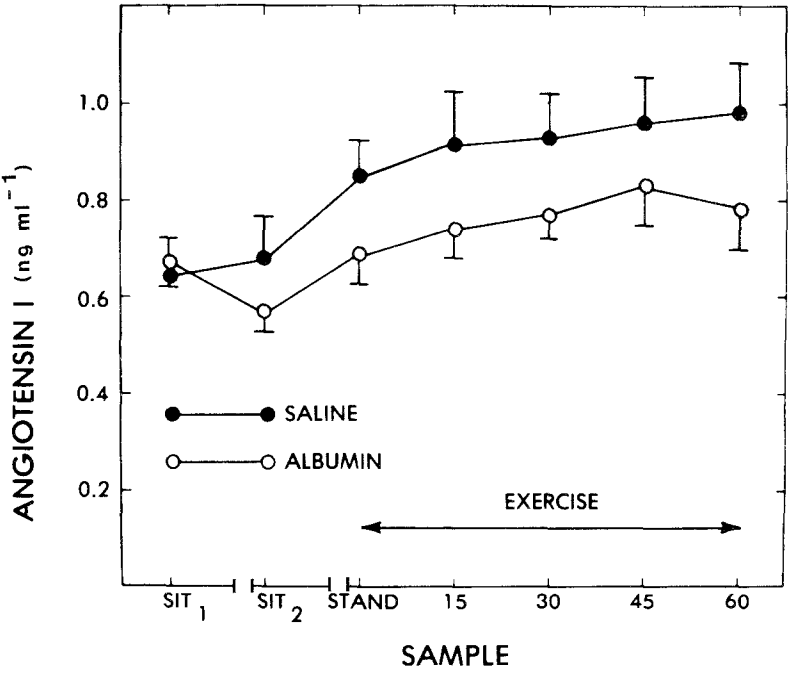

Fig. 4. Effects of heat exposure, plasma volume expansion, and exercise in the heat on plasma levels of angiotensin I. Significant effects were noted: albumin vs saline-stand, 30 min, $p < 0.05$. All conditions are as noted under Fig. 1

aldosterone levels are noted in a significant ($p < 0.05$) increment between the sit and stand samples in this group. However, effects of exercise are insignificant when compared with the stand sample in the saline as well as the albumin trial. In the albumin trial aldosterone levels in the stand stample are not elevated as in the saline trial, leading to a significant difference ($p < 0.05$) between trials in this and the 15 min sample. This is indicative of an albumin effect on aldosterone levels.

Plasma levels of angiotensin I (Fig. 4) initially demonstrated no effects of plasma volume expansion with no significant differences noted between sit I and sit 2 samples or saline and albumin trials. Interestingly, the increment noted after postural change was more pronounced during the saline trial leading to significant inter-trial differences ($p < 0.05$) in the stand and 30 min samples.

Discussion

Absolute concentrations of hormones were reported with no adjustments made for hemodilution. This was decided since physiologically the osmotic, regulatory, and metabolic effects of these hormones are dependent upon their absolute concentrations. Further, if albumin administration and plasma volume expansion were to have effects on the hormonal responses to exercise in the heat, this would be determined from intra-trial comparisons at the various sampling times.

The initiation of exercise in the heat was timed to coincide with maximal plasma volume expansion, approx. 95 min subsequent to the completion of the albumin infusion (Hubbard et al. 1982). While cortisol levels are generally not affected by moderate heat stress, there have been reports of increased adrenocortical activity as a result of exercise stress. White et al. (1976) demonstrated that the intensity of the exercise and level of physical fitness may affect this adrenocortical response. Statistical evaluation of the present data indicated no significant effects on levels of plasma cortisol, but it is important to note that during the time period of this experiment, significant diurnal decrements would ordinarily occur in circulating cortisol levels (Krieger et al. 1971). Thus, it may be reasonable to conclude that the experimental regimen prevented the normally occurring circadian decrease in plasma cortisol. Interestingly, Follenius and Brandenberger (1974) showed similar effects on cortisol rhythms after only 20 min of exercise on a bicycle ergometer.

Growth hormone has been reported to increase pursuant to heat exposure (Okada et al. 1972) and exercise (Kuoppasalmi et al. 1976); in both these studies, as in our own, interindividual values and responses for this hormone were highly variable. The present work corroborates the earlier observation that growth hormone may be one of the more sensitive hormonal indices of stress perception and response in humans (Kuoppasalmi et al. 1976). These workers also suggested that increments in circulating levels of growth hormone during exercise may be inversely proportional to the level of fitness.

The data indicated significant effects of posture, exercise in the heat, and plasma volume expansion on aldosterone levels. While we did observe moderate increases in plasma levels of aldosterone during exercise in both trials, these increments were smaller than those reported by Melin et al. (1980). In the latter study Ss exercised at 80% $\dot{V}O_2$ max until exhaustion at which time the final blood sample was obtained; evidently, the intensity of the plasma aldosterone response may be correlated with exercise intensity. Angiotensin I levels were slightly, but significantly, lowered in several samples following plasma volume expansion after albumin administration, but unaffected by exercise in the heat following either trial. These decrements apparently arose as a result of an attenuation of the response to postural change when plasma volume was expanded following albumin administration.

In an earlier experiment designed to separate the thermal and exercise factors effecting hypervolemia, Convertino et al. (1980) partially attributed the greater exercise effects to an increased secretion of arginine-vasopressin. While heat stress alone has been reported to elicit acute increments in levels of the hormones currently under consideration, the intensity of these hormonal responses has been greatly augmented by severe heat (Kosunen et al. 1976) or sodium depletion (Follenius et al. 1979). In the current study the levels of heat and exercise stress apparently were sufficient to induce moderate and specific hormonal responses rather than generalized, inclusive effects.

We have concluded from these experiments that exercise in the heat may prevent the normally occurring circadian reduction in plasma cortisol levels during the morning hours. While aldosterone was affected by volume expansion, posture, and exercise, GH concentrations were significantly increased as a result of exercise in the heat in both trials. The increased plasma volume appeared to have a significant effect on angiotensin I levels, but these were unaffected by mild exercise. Under the exercise and environmental conditions of the current experiment, plasma volume expansion had relatively minor effects on hormonal response.

Acknowledgements. The authors which to thank Sandra Beach, Lianne Gallerani, Pat Basinger and Julie Cyphers for typing the manuscript. Numerous technical support personnel at the USARIEM contributed greatly to the successful completion of the experiment and we are grateful for all their efforts, especially to Ms. Natalie Maslov for the radioimmunoassays. We express our thanks to H. Michael Kimes, M.D. for the expert medical assistance and to all the test volunteers who participated in these experiments.

The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

References

Bailey RE, Bartos D, Bartos F, Castro A, Dobson R, Grettie D, Kramer R, Macfarlane D, Sato K (1972) Activation of aldosterone and renin secretion by thermal stress. Experientia 28: 159–160

Collins KJ, Few JD, Forward TJ, Giec LA (1969) Stimulation of adrenal glucocorticoid secretion in man by raising the body temperature. J Physiol (Lond) 202: 645–660

Convertino VA, Greenleaf JE, Bernauer EM (1980) Role of thermal and exercise factors in the mechanism of hypervolemia. J Appl Physiol 48: 657–664

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

Dumoulin G, Nguyen, N, Henriet, M, Bopp J, Berthelay S (1980) Variations des electrolytes plasmatiques et de leurs hormones de regulation, lors d'une exposition aigue a la chaleur. Etude au cours du sauna finlandais chez l'Homme. Compt Rendus 174: 146–150

Follenius M, Brandenberger G (1974) Influence de l'exercice musculaire sur l'evolution de la cortisolemie et de la glycemie chez l'homme. Eur J Appl Physiol 33: 23–33

Follenius M, Brandenberger G, Reinhardt B, Simeoni M (1979) Plasma aldosterone, renin activity, and cortisol responses to heat exposure in sodium depleted and repleted subjects. Eur J Appl Physiol 41: 41–50

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

Hubbard RW, Matthew WT, Horstman D, Francesconi R, Mager M, Sawka M (1982) Effects of I.V. albumin administration on plasma volume expansion in the heat. Fed Proc 41: 1348

Kosunen KJ, Pakarinen A, Kuoppasalmi K, Adlercreutz H (1976) Plasma renin activity, angiotensin II, and aldosterone during intense heat stress. J Appl Physiol 41: 323–327

Krieger DT, Allen W, Rizzo F, Krieger P (1971) Characterization of the normal temporal pattern of plasma corticosteroid levels. J Clin Endocrin Metab 32: 266–284

Kuoppasalmi K, Naueri H, Rehunen S, Harkonen M, Adlercreutz H (1976) Effect of strenuous anaerobic running exercise on plasma growth hormone, cortisol, luteinizing hormone, testosterone, androstenedione, estrone, and estradiol. J Ster Biochem 7: 823–829

Li CC (1964) Introduction to experimental statistics. Mc Graw-Hill, New York, p 425

Lindquist EF (1953) Design and analysis of experiments in psychology and education. Houghton-Mifflin, Boston, pp 56, 269

Melin B, Eclache J, Geelen G, Annat G, Allevard A, Jarsaillon E, Zebidi A, Legros J, Gharib C (1980) Plasma AVP, neurophysin, renin activity, and aldosterone during submaximal exercise performed until exhaustion in trained and untrained men. Eur J Appl Physiol 44: 141–151

Okada Y, Matsuoka T, Kumahara Y (1972) Human growth hormone secretion during exposure to hot air in normal adult male subjects. J Clin Endocrin Metab 34: 759–763

Senay LC (1970) Movement of water, protein and crystalloids between vascular and extravascular compartments in heat-exposed men during dehydration and following limited relief of dehydration. J Physiol (Lond) 210: 617–635

Senay LC (1975) Plasma volumes and constituents of heat-exposed men before and after acclimatization. J Appl Physiol 38: 570–575

White JA, Ismail AH, Bottoms GD (1976) Effect of physical fitness on the adrenocortical response to exercise stress. Med Sci Sports 8: 113–118

Wyndham CH, Benade AJA, Williams CG, Strydom NB, Goldim A, Heyns AJA (1968) Changes in central circulation and body fluid spaces during acclimatization to heat. J Appl Physiol 25: 586–593

Accepted November 12, 1982