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RESPONSE AND REGULATION OF VASOPRESSIN AND RENAL  
FUNCTION DURING GRADED EXERCISE

University of Hawaii

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RESPONSE AND REGULATION OF VASOPRESSIN AND RENAL FUNCTION  
DURING GRADED EXERCISE

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RESPONSE AND REGULATION OF VASOPRESSIN AND RENAL FUNCTION  
DURING GRADED EXERCISE

ABSTRACT

Three series of experiments were conducted to study the response and regulation of plasma vasopressin during exercise. The renal handling of water and solutes during exercise was also investigated.

Six male subjects, performed a graded exercise test on a treadmill to voluntary maximal effort. Three additional experiments were performed; a control and 1 hr of exercise at 35 and 70% of maximum heart rate. Blood samples were obtained at 20 and 60 min of exercise and after 1 hr of recovery. Urine samples were also obtained. Plasma vasopressin (P<sub>AVP</sub>) was unchanged during controls and 35% exercise and elevated following 60 min of 70% exercise, from  $0.8 \pm 0.2$  at rest to  $2.1 \pm 0.3$   $\mu\text{U}/\text{ml}$ . This elevation persisted through recovery. Maximal exercise produced an increase in P<sub>AVP</sub> from  $0.9 \pm 0.1$  to  $2.7 \pm 0.7$   $\mu\text{U}/\text{ml}$  after 20 min. Plasma vasopressin returned to resting levels following 1 hr of recovery.

Plasma osmolality, blood pressure, plasma renin activity (PRA), and oral temperature were elevated during exercise. Plasma volume and body weight decreased. Plasma cortisol exhibited no change. A reduction of vasopressin metabolism may have occurred, contributing to the elevation of P<sub>AVP</sub>. There was no consistent relationship of changes in these parameters to the elevation of P<sub>AVP</sub> during exercise.

Urine flow was decreased for both 70% and maximal exercise post-exercise and after 1 hr of recovery. The decrease immediately after

exercise was accompanied by a decrease in creatinine clearance and osmotic clearance ( $C_{\text{osm}}$ ) and an increase in  $C_{\text{H}_2\text{O}}$ . Recovery  $C_{\text{osm}}$  was decreased,  $C_{\text{H}_2\text{O}}$  increased, and creatinine clearance normal.

The response of vasopressin to an elevation in body temperature was studied in seven males. The subjects underwent a 2-hr equilibration period, a 1-hr experimental exposure, and 2 hr of recovery. The experimental exposures were a control, exercise, and passive elevation of body temperature, in a manner similar to that observed during exercise. Five-hour urine samples were obtained. No difference was noted in rectal temperature during exercise and passive temperature elevation. Urine flow was significantly reduced during exercise compared to control values. Vasopressin excretion was increased 22, 79, and 17% for control, exercise, and passive temperature elevation, respectively. The increase in the excretion of vasopressin with exercise occurred in six of the seven subjects with no change seen during passive body temperature elevation.

Seven subjects performed maximal exercise following dehydration (10 hr of fasting) and hydration (ingestion of 300 ml of water). The pre-exercise plasma osmolality of  $283 \pm 2$  mOsm/kg for hydration was lower than that of dehydration ( $288 \pm 2$  mOsm/kg). Following exercise no difference was observed in osmolality. Plasma vasopressin after exercise was elevated,  $0.6 \pm 1$  with hydration and  $1.8 \pm 0.6$   $\mu\text{U/ml}$  with dehydration. No differences in PRA, plasma cortisol, mean arterial pressure, oral temperature, change in plasma volume, or workload and duration were noted between the two treatments.

Urine flow was greater during hydration pre-exercise and post-exercise compared to dehydration. Postexercise urine flow was reduced with dehydration, and for both treatments flow was reduced during recovery. Osmotic clearance was reduced postexercise and through recovery, while  $C_{H_2O}$  was increased postexercise with dehydration.

Plasma vasopressin was elevated during exercise and appeared to be dependent on the hydration state of the individual, work intensity, and duration. Although the regulation of vasopressin during exercise was unclear, the elevation of vasopressin appeared to be independent of the dehydration which occurred during exercise. The elevation of  $P_{AVP}$  apparently was not responsible for the occurrence of the antidiuresis associated with exercise, which was probably due to a reduction in glomerular filtration rate and sodium reabsorption.

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## GENERAL INTRODUCTION

The regulation of body fluids is complex and includes elements of the endocrine, renal, nervous, and cardiovascular systems. Vasopressin, often referred to as antidiuretic hormone (ADH), is the single most important hormone in the regulation of the handling of water by the mammalian kidney. Arginine vasopressin (AVP), found in most mammals, is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior pituitary. The pig and hippopotamus have lysine vasopressin instead of arginine vasopressin. In large doses vasopressin may be a pressor agent; however, its primary action is the conservation of water by increasing the permeability of the collecting duct to water. This may include part of the anatomical distal tubule, as the physiological definition of the collecting duct is that part of the nephron which responds to vasopressin. The mediation of the change in permeability of the collecting duct by vasopressin is unclear; however, cyclic AMP is necessary (Jard et al., 1977; Duosa et al., 1977). Vasopressin release is primarily regulated by plasma osmolality which acts via an osmoreceptor in or near the hypothalamus, and blood volume which functions via atrial stretch receptors and arterial baroreceptors. Other physiological stimuli have also been suggested, such as an increase in body temperature, hypoxia, and cerebrospinal sodium concentration.

Physical exercise results in well-established changes in plasma osmolality, blood volume, blood pressure, and the renin-angiotensin system, all of which have been shown to regulate vasopressin release.

There also are some indications that vasopressin release is stimulated during exercise. In addition, exercise produces an antidiuresis which has been attributed to vasopressin.

## REVIEW OF LITERATURE

Exercise Stimulation of Vasopressin: Rydin and Verney (1938) suggested the presence of an antidiuretic substance associated with exercise when they noted the superficial resemblance of the course of the antidiuresis following exercise by dogs to that after the intravenous injection of pituitary extract. Vera and Croxatto (1954) found an increase in whole blood antidiuretic activity in man after 30 min of exercise on a bicycle ergometer at a workload of 514 kpm/min. Antidiuretic activity was determined by injecting 1 ml of whole blood from the test subject intraperitoneally into at least four rats which were housed together. The rats were then hydrated by 5% of body weight. The urine was then collected every 15 min and production calculated as a percentage of the water ingested. The antidiuretic activity determined in the rats corresponded to the reduction in urine flow postexercise in the subjects. Kozlowski et al. (1967) investigated the antidiuretic activity of plasma following exercise at variable workloads. The method of determining antidiuretic activity was similar to that of Vera and Croxatto (1954) described earlier. At a low workload of 450 kpm/min on a bicycle ergometer, no significant change in plasma antidiuretic activity was noted. However, heavy exercise, 600 and 1200 kpm/min, caused an elevation of plasma antidiuretic activity which was associated with a 5% reduction in the subject's urine flow after the 1200 kpm workload. The ingestion of ethyl alcohol prior to exercise abolished the elevation of antidiuretic activity following heavy exercise in all subjects. Ethyl alcohol was believed by the authors to suppress the activity of the hypothalamohypophyseal antidiuretic system, decreasing the release of

vasopressin. Thus it was concluded that the antidiuresis associated in the exercise was due to an elevation of plasma vasopressin concentration. In the study by Kozłowski et al. (1967), the antidiuretic activity of the plasma was quantified by injecting rats with known doses of Pitressin and comparing the antidiuresis to that occurring with plasma samples. The resting levels of antidiuretic substance were equal to a Pitressin dose of 12  $\mu\text{U}/\text{ml}$  and 31  $\mu\text{U}/\text{ml}$  postexercise. From these findings it was postulated that the antidiuretic substance observed postexercise was vasopressin.

Recently, Legros et al. (1972), using workloads from 75 to 84 percent of the maximum oxygen consumption for up to 20 min, found exercise to elevate plasma neurophysin levels as determined by a radioimmunoassay. Neurophysins, when in the neurosecretory granules of the posterior pituitary, are part of the parent proteins of vasopressin and oxytocin (Zimmerman and Defendini, 1977).

Following 6 min of exercise at 50 and 100% of  $\dot{V}_{O_2}$  max, Sassard et al. (1970) observed the vasopressin response to be variable. Following maximal exercise, vasopressin rose from resting values ranging from undetectable to 8  $\mu\text{U}/\text{ml}$  to a mean of 13  $\mu\text{U}/\text{ml}$  postexercise. Lacour et al. (1970), reporting the same results, raised the question of assay sensitivity. The assay for vasopressin was stated to be a pressor assay; however, the methodology was not clarified. A good pressor assay of vasopressin has a minimum sensitivity of 1000  $\mu\text{U}/\text{ml}$  (Share, 1973).

Beardwell et al. (1975), in testing a radioimmunoassay for vasopressin specificity, employed exercise as a stimulus to which vasopressin was expected to respond. Fifteen minutes of exercise on a bicycle

ergometer at 918 kpm/min for males and 612 kpm/min for females resulted in no significant change in plasma vasopressin concentrations of five subjects. No distinction was made as to the sex of the subjects in the reporting of the results. When 11 hydrated subjects ran up and down a flight of stairs five times, a significant increase was seen in plasma vasopressin from  $2.0 \pm 1.2$   $\mu\text{U/ml}$  standing at rest to  $5.3 \pm 6.5$   $\mu\text{U/ml}$  postexercise. However, as the authors indicated, the elevation of the postexercise sample was due primarily to two subjects with vasopressin levels of 16.5 and 19.5  $\mu\text{U/ml}$ . These high values may be attributed to stimuli other than exercise, possibly pain (Miller and Moses, 1974). If these subjects are disregarded, the postexercise mean would be 2.5  $\mu\text{U/ml}$ . In the validation of a radioimmunoassay for vasopressin, Baylis and Heath (1977) had six subjects exercise vigorously for 5 min on a bicycle ergometer at an unknown workload. Resting plasma vasopressin concentrations were 0.63  $\mu\text{U/ml}$  and rose to 1.91  $\mu\text{U/ml}$  following exercise. There was no established relationship between the change in vasopressin levels and the amount of work done.

Thus, data on exercise and blood antidiuretic activity implicating vasopressin are variable due to assay techniques and lack of standardized workloads. In man, the normal resting concentration of plasma vasopressin is in the range of 0.7 - 1.6  $\mu\text{U/ml}$  (Beardwell et al., 1971; Robertson et al., 1973; Baylis and Heath, 1977). The resting values in many of the exercise studies have exceeded this. In the early studies of Vera and Croxatto (1954) and Kozlowski et al. (1967), the values are questionable as the plasma was not extracted. Therefore, in addition to

vasopressin, other hormones which could alter urine flow such as aldosterone and angiotensin were present. The lack of extraction may also explain the elevated resting values of Sassard et al. (1971) and Lacour et al. (1970) as their methods were not presented. Questions may be raised concerning these data as the minimum sensitivity of the assay method is 500 times their reported values. However, the limited studies of Beardwell et al. (1975) and Baylis and Heath (1977) demonstrated no change or an elevation of plasma vasopressin concentrations with exercise. Thus, the response of vasopressin to exercise is still unclear and may vary with work intensity.

Renal function and exercise: Alterations of urine flow and free water clearance are often used as being indicative of changes in plasma vasopressin concentrations. An antidiuresis as a result of an increased tubular water reabsorption is associated with an increase in vasopressin, while a decrease in tubular water reabsorption is indicative of a decrease in vasopressin.

Studies of renal function during exercise have been carried out by a variety of investigators and have been reviewed by Smith (1951) and Brod (1973). Physical exercise is accompanied by an antidiuresis. Raisz et al. (1959) found running up and down stairs for 30 min to reduce urine flow from 0.48 to 0.18 ml/min. The urine flow returned to control levels during the second hour of recovery. Castenfors (1967) reported urine flow to be reduced following supine work and after an 85 km cross-country ski race. During supine work, the decrease in urine flow was correlated with the increase in heart rate. Similar observations

were made by Refsum and Strömme (1975, 1977) during 70 km cross-country ski races. Urine flow was reduced from a pre-race rate of 0.6 ml/min to 0.4 ml/min. Costill et al. (1976) observed urine flow to decrease from 1.25 ml/min to 0.43 ml/min after 60 min of exercise at 60% of  $\dot{V}O_2$  max, and remain suppressed for 48 hr, with no reference as to water intake. Kachadorian and Johnson (1972), studying renal responses to exercise, found urine flow to decrease in a curvilinear fashion in response to increasing workloads. However, at the mild workload the urine flow was greater than the control flow rate. These observations demonstrate that exercise produces an antidiuresis, the magnitude of which is associated with workload intensity, but at low workloads the urine flow may be greater than at rest.

The amount of urine excreted is a function of the filtered load and the volumes secreted and reabsorbed:  $\text{excretion} = \text{filtration} + \text{secretion} - \text{reabsorption}$ . The antidiuresis seen with exercise may result from a diminished filtration or secretion, an increased reabsorption, or any combination of these factors.

Glomerular filtration rate (GFR) is reported to be reduced during exercise (Smith, 1951; Brod, 1973; Refsum and Strömme, 1975). The decrease in filtration during exercise is due at least in part to a reduced renal blood flow (Rowell, 1974; Castenfors, 1978). The reduction in GFR is workload dependent (Kachadorian and Johnson, 1970; Castenfors, 1978). One hour after exercise, GFR had returned to control levels while urine flow remained depressed (Raisz et al., 1959). Thus, the decrease in GFR may contribute to the antidiuresis during exercise;

however, it does not appear to play a role in the observed persistent decrease in urine flow.

Under normal conditions, there is a net reabsorption of 99% of the filtered water; therefore, secretion is not a major consideration in determining urine flow (Vander, 1975). The bulk of the filtered water is reabsorbed passively down an osmotic gradient created by sodium reabsorption in the proximal tubule. In addition, the kidney may reabsorb water without solute. The ability of the kidney to concentrate urine is dependent upon this reabsorption.

Sodium excretion ( $U_{Na}V$ ) is significantly reduced with exercise and remains depressed through three hours of recovery (Raisz et al., 1959; Castenfors, 1967; Costill et al., 1976). The decrease in sodium excretion was assumed to be the result of an increase in sodium reabsorption as the reduction was unrelated to changes in GFR (Castenfors, 1967; Brod, 1973). In later work, Castenfors (1978) measured the reabsorption of sodium during an 85 km cross-country ski race. The percent of filtered sodium excreted was reduced from 0.5% at rest to 0.3% postexercise. This increase in sodium reabsorption accompanied by passive water reabsorption would contribute to the decrease in urine flow during and following exercise.

The tubular reabsorption of water without solute is the mechanism whereby the kidney produces a concentrated urine. Increases in urinary osmolality and decreases in free water clearance are indications of increased tubular water reabsorption. Free water clearance ( $C_{H_2O}$ ) is the theoretical volume of water that would have to be added to (negative  $C_{H_2O}$ ) or subtracted from (positive  $C_{H_2O}$ ) the plasma to change the

osmolality of a volume of urine excreted in a unit of time. Free water clearance may be calculated as:  $C_{H_2O} = \dot{V} - C_{osm}$  where  $\dot{V}$  is urine flow rate and  $C_{osm}$  is osmotic clearance,  $C_{osm} = \frac{U_{osm} \cdot \dot{V}}{P_{osm}}$  (Smith, 1951).

Therefore, when free water clearance is positive there is a net secretion of water, and when it is negative there is a net reabsorption.

Following heavy exercise, urine flow is reduced due to a reduction in osmotic clearance while free water clearance is noted to increase (Raisz et al., 1959; Refsum and Strömme, 1975, 1977). Castenfors (1967), using hydrated subjects with unusually high urine flows, 10-20 ml/min, found free water clearance to decrease 60% following exercise. However, there was not a time control experiment; therefore, the decrease in free water clearance may be due to dehydration. In further work by this investigator in individuals with normal urine flows, free water clearance increased from -1.6 ml/min before exercise to -1.1 ml/min (Castenfors, 1978). This was not a significant change. Kachadorian and Johnson (1972) studied various workloads and observed free water clearance to increase 3.9, 0.4, and 0.8 ml/min following one hour of running at 5.6, 8.0, and 10.0 km/hr, respectively. The decrease in urine osmolality and increase in free water clearance are indicative of a decreased tubular water reabsorption which would lead to an increased urine flow in the absence of a change in osmotic clearance. The decrease in tubular water reabsorption is suggestive of a decrease in plasma vasopressin levels.

Elements of Vasopressin Control and Their Responses to Exercise

Plasma osmolality: The osmolality of body fluids has long been recognized as a major component in the precise regulation of vasopressin

release. Rydin and Verney (1938) first demonstrated this concept by injecting hypertonic saline for 10 sec into the carotid artery of a conscious, hydrated dog and eliciting an antidiuresis. The observed fall in urine output was similar to that seen following the intravenous injection of small amounts of pituitary extract. Based on these findings, Verney postulated an intracranial osmoreceptor which controlled the release of vasopressin (Jewell and Verney, 1957). Various experiments that confirm and extend these early observations have been the subject of extensive review (Share and Claybaugh, 1972; Moses and Miller, 1974; Robertson et al., 1976; Forsling, 1977; Robertson et al., 1977; Share and Grosvener, 1974; Cross and Wakerly, 1977; Schrier et al., 1979).

In man, both the infusion of hypertonic saline or dehydration resulting in an increase in osmotic pressure stimulates vasopressin release (Robertson et al., 1973; Moses and Miller, 1971; Schrier, 1979). Hyperhydration leading to hypotonicity is reported to suppress vasopressin secretion (Czaczkes et al., 1964; Ahmed et al., 1967). In addition, isolated hypothalamic neurohypophyseal complexes in culture respond to an increase in incubation medium osmolality with an increase in the release of vasopressin (Eggena and Thorn, 1970; Sladek and Knigge, 1977). These findings demonstrate a viable osmoreceptor although it has not been anatomically identified. The osmoreceptor is believed to be located in the neurohypophyseal area and is not the hypothalamic nuclei of the neurosecretory cells. Antiadrenergic and ganglionic blocking agents inhibit the release of vasopressin in response to a hypertonic stimuli (Bridges and Thorn, 1970).

The osmoreceptor may also be stimulated by osmotic changes in the cerebrospinal fluid. Andersson et al. (1969), using a variety of osmotically active compounds injected into the third ventricle of goats, noted that some compounds, which elicited vasopressin release when injected in the common carotid artery, were not effective in stimulating vasopressin when injected in the third ventricle. Further, they suggest the osmoreceptor is specific for sodium which, with its anions, contributes more than 95% of the osmotically active components of plasma (Anderson and Olsson, 1973; Olsson, 1975; Olsson and Kolmodin, 1974). Perfusion of the ventriculocisternal system with a hypo-osmolar solution resulted in no change in plasma vasopressin concentration (Mouw and Vander, 1971). This was measured in only three dogs and cannot be considered conclusive. The work of Andersson and co-workers raises the possibility that the receptors which respond to a hyperosmotic stimuli in the cerebrospinal fluid may be different from those which sense changes in the osmolality of cerebral blood. However, other investigators have noted the response of vasopressin to an osmotic stimulus to be elicited in the cerebrospinal fluid and cerebral blood by the compounds which did not respond in Andersson's experiments (McKinley et al., 1974). In addition, isolated neurohypophyseal explants show no significant difference in the osmotic response to sodium chloride or mannitol, suggesting an osmoreceptor rather than a sodium receptor (Sladek and Knigge, 1977).

Attempts have been made to quantify the relationship between plasma osmolality and plasma vasopressin. Several investigators have found highly significant correlations between plasma osmolality and

vasopressin (Aubry et al., 1965; Beardwell et al., 1971; Robertson et al., 1973; Morton et al., 1975; Shimamoto et al., 1976; Weitzman and Fisher, 1977). However, the problem with many of these studies is the difficulty in altering plasma osmolality without changing plasma volume. The responsiveness of the osmoreceptor shows a wide individual variability (Robertson et al., 1976), increases with age (Helderman et al., 1975), and is dependent on the rate of change in osmolality (Athar and Robertson, 1974). The osmotic threshold for the stimulation of vasopressin appears to be 280 mOsm/kg in occidental man (Schrier et al., 1979). From these studies, it appears the osmoreceptor control of vasopressin release is a major factor in its regulation if not the primary control mechanism (Moses and Miller, 1974; Robertson, et al., 1976; Schrier et al., 1979).

Plasma osmolality is found to be elevated with exercise and may reach values of 317 mOsm/kg in man (Delanne et al., 1959; Beaumont, 1973; Refsum and Strömme, 1977). Following heavy exercise, plasma osmolality remains elevated in the absence of fluid replacement (Costill et al., 1976). However, after mild workloads plasma osmolality may return to resting levels within minutes (Greenleaf et al., 1979). The elevation of plasma osmolality with exercise represents a strong stimuli for the increase of vasopressin release.

Blood volume and blood pressure: It is well established that a reduction in effective blood volume will result in an increase in circulating vasopressin levels (Ginsburg and Heller, 1953; Weinstein et al., 1960; Share, 1962; Henery et al., 1968; Share, 1968). Conversely, expansion of the blood volume reduces vasopressin release (Zehr et al.,

1969; Johnson et al., 1970). The volume receptors regulating vasopressin secretion are the left atrial stretch receptors and arterial baroreceptors (Share and Claybaugh, 1972; Share, 1974; Schrier et al., 1976; Share and Grosvenor, 1974; Cross and Wakerley, 1977; Schrier et al., 1979).

Distention of the left atrium resulting in an increase in urine flow led to the postulate that left atrial stretch receptors play an important role in the regulation of vasopressin release (Gauer and Henery, 1963). With a decrease in blood volume there is a reduction in vagal activity from the atrium, which is believed to be responsible for the increase in vasopressin release (Henery et al., 1968). Left atrial pressure may be elevated by 10 mmHg by atrial tachycardia, resulting in diuresis which does not occur under the same conditions in hypophysectomized dogs supplemented with vasopressin (Boykin et al., 1975). These findings suggest atrial tachycardia may suppress vasopressin release. In addition, slight changes in left atrial pressure within the physiological range induced by an indwelling balloon decrease vasopressin release (Johnson et al., 1969). The left atrial baroreceptor appears to regulate vasopressin in response to moderate changes in blood pressure. In man, a blood loss of 9.9% of the estimated total blood volume resulted in no change in heart rate, mean arterial pressure, or circulating vasopressin levels (Goetz et al., 1974). These findings and other studies by this group have been used to refute the role of atrial stretch receptors in the regulation of vasopressin release (Goetz et al., 1975). However, the preponderance of evidence suggests a fine control of blood volume by atrial stretch receptors (Share, 1974). The fact that mean

arterial pressure remains unchanged over a wide range of blood volume changes, while left atrial pressure fluctuates, further suggests regulation by left atrial stretch receptors (Gupta et al., 1966; Share, 1968; Claybaugh and Share, 1973; Share, 1976).

While the left atrial stretch receptors respond to fine changes in blood pressure and volume, the arterial baroreceptors are responsive to coarse changes. The arterial receptors are the aortic and carotid baroreceptors. Considerable attention has been paid the carotid baroreceptor and its role in vasopressin regulation because of its easy accessibility. Occlusion of the common carotid arteries in the vagotomized, anesthetized dog produces an increase in plasma vasopressin (Share and Levy, 1962). This manipulation was ineffective when the vagi were intact. A reduction in pulse pressure while mean arterial pressure is maintained also increased vasopressin levels (Share and Levy, 1966). In conscious dogs, a hemorrhage greater than 10% of the blood volume decreases mean arterial pressure and produces a marked elevation of plasma vasopressin concentration (Henery et al., 1968). Thus, there appears to be an overlap of the control of blood volume mediated by vasopressin between atrial stretch receptors and arterial baroreceptors.

Plasma volume decreases during exercise due to extravascular volume shifts and dehydration as a result of perspiring (Rowell et al., 1966; Kozłowski and Saltin, 1964; Lundvall et al., 1972). Costill and Fink (1974) found 2 hr of exercise at 60-75% of  $\dot{V}O_2$  max resulted in a 16-18% reduction in plasma volume. After 30 min postexercise, the plasma volume was reduced only 9% and remained at this level throughout

180 min of recovery. Wilkerson et al. (1977) found that blood volume reduction in response to 20 min of exercise may be accounted for entirely by changes in plasma volume. Further, the reduction in plasma volume was workload dependent. The decrease in plasma volume was a linear function of work intensity from rest to 60% of  $\dot{V}_{O_2}$  max. However, above 60% a break occurred with the decrease in plasma volume becoming exponential. The observed changes in plasma volume would be effective in stimulating vasopressin at rest; however, with exercise mean arterial pressure is elevated. Systolic blood pressure is elevated in response to exercise with no change in diastolic blood pressure (Åstrand and Rodahl, 1974). The change in systolic blood pressure is linearly related to work intensity and contributes to an increased mean arterial blood pressure and pulse pressure. The elevation of mean arterial and pulse pressure in response to exercise would stimulate arterial baroreceptors, reducing vasopressin release. Stimulation of atrial stretch receptors due to an increased venous return and heart rate during exercise would also suppress vasopressin release (Rowell, 1974).

Thus it would appear that during exercise the decrease in plasma volume is ineffective in stimulating vasopressin, as the sensed parameters, mean arterial pressure, and left atrial pressure are increased, possibly suppressing release. However, following exercise the pressures quickly return to control levels while plasma volume remains decreased. In recovery, the volume receptors may then stimulate vasopressin.

Volume-osmotic interrelationships: The osmoreceptor is believed to be the primary regulator of vasopressin release: however, under extreme conditions fluid volume is maintained at the expense of plasma osmolality.

Therefore, it is of interest to study the interrelationships of osmotic and volume stimuli on vasopressin secretion (Share and Claybaugh, 1972; Moses and Miller, 1974).

Moses et al. (1967) studied the interrelationship of volume and osmotic stimuli in man. The response to the infusion of hypertonic saline was determined with or without blood volume expansion by infusion of 500 ml of dextran. The renal response was used as being indicative of plasma vasopressin. The antidiuresis in response to constant saline infusion occurred later and at a higher plasma osmolality following blood volume expansion. Further studies by this group led to the conclusion that a decrease in blood volume lowers the osmotic threshold, while an increase in volume elevates the osmotic threshold for vasopressin release (Moses and Miller, 1971).

Recent studies measuring plasma vasopressin confirm the earlier observations and suggest that plasma osmolality is the dominant variable in the regulation of vasopressin secretion (Robertson and Athar, 1976; Kimura et al., 1976). However, Johnson et al. (1970), in studying conscious sheep, found conflicting stimuli of a 10% hemorrhage on top of 1.2% reduction in plasma osmolality to produce no change in plasma vasopressin or urine flow. These findings suggest the lack of dominance of any one system.

Plasma osmolality is increased during exercise, and volume receptors appear to be stimulated, presenting conflicting stimuli for vasopressin release. If plasma osmolality is the dominant input in man as suggested, the net result would be stimulation of vasopressin release in response to exercise.

Angiotensin: The role angiotensin II plays in the release of vasopressin is controversial and has been of considerable interest since being proposed by Bonjour and Malvin (1970). It was suggested that angiotensin II stimulates vasopressin release. Infusion of angiotensin II into the common carotid artery of anesthetized dogs failed to stimulate vasopressin, yet the response to an osmotic stimulus was potentiated (Claybaugh et al., 1972; Shimizu et al., 1973). An increased vasopressin release in response to angiotensin II infusion has been demonstrated in conscious dogs and man (Bonjour and Malvin, 1970; Uhlich et al., 1975; Ramsey et al., 1978). Tagawa et al. (1971) reported Pitressin infusion may suppress renin secretion in conscious sodium-depleted dogs. These findings suggest a negative feedback relationship between vasopressin and the renin-angiotensin system. If this mechanism exists, it provides integration of body water and electrolyte regulation.

The renin-angiotensin system is stimulated during exercise (Kotchen et al., 1971; Kosunen and Pakarinen, 1976). Maher et al. (1975) showed the elevation of renin and angiotensin II to be workload dependent. The increase in angiotensin II with exercise may provide a stimulus for vasopressin release.

Stress and the adrenocortical hormones: In 1938, Rydin and Verney demonstrated an antidiuresis in the unanesthetized dog in response to sensory and emotional stimuli. A similar antidiuresis is seen in response to ischemic muscle pain, nausea, and emotional stress (Konzett et al., 1971; Schrier et al., 1979). Studies of men during the performance of mental tests resulted in the urinary excretion rate of vasopressin, epinephrine, and norepinephrine being elevated (Konzett et al., 1971).

However, under all conditions there was no change in urine flow. Conflicting studies have more recently been reported by Keil and Severs (1977). In their study, rats were stressed by exposure to ether or acceleration and showed no change in plasma vasopressin levels when hydrated, but a significant decrease was noted in dehydrated rats. Rydin and Verney (1938) in their studies of dogs found the antidiuresis to be reduced as the animals became familiar with the stress. The conflicting results may therefore be due to a training response to the induced stress.

The stress response is associated with the adrenocorticotrophin (ACTH) adrenal axis as ACTH, epinephrine, and norepinephrine are elevated. This system is also of interest as adrenal insufficiency results in the inability to excrete a waterload (Williams, 1974). It was therefore postulated that adrenocortical hormones suppress vasopressin release. Green et al. (1970) adrenalectomized rats with hereditary diabetes insipidus and found the excretion of a waterload to be impaired. Subsequent studies in man resulted in similar findings (Berl et al., 1974). Therefore, the impaired renal handling of water was not entirely due to an elevated plasma vasopressin concentration. However, exogenous norepinephrine is known to suppress circulating vasopressin levels (Schrier et al., 1976). Intravenous norepinephrine results in a diuresis only in animals with an intact source of vasopressin, and the release is believed to be mediated by the baroreceptor mechanism in response to changes in blood pressure (Share and Travis, 1970; Schrier, 1979).

Cortisol is directly mediated by ACTH and therefore is indicative of ACTH release. Intravenous injections of vasopressin have been shown

to stimulate ACTH release (Cross and Wakerly, 1977; Yasuda et al., 1978). Cortisol suppresses the release of vasopressin in response to osmotic stimuli, as well as dampening the pressor potentiating effect of vasopressin (Aubry et al., 1965; Karmazyn et al., 1978). In addition, administration of cortisol produces a marked increase in free water clearance in the absence of vasopressin (Kleeman et al., 1958; Green, 1970). This suggests a direct effect of cortisol on the renal tubule to decrease water reabsorption.

Stimulation of the ACTH-adrenal axis could result in the suppression of vasopressin release via changes in blood pressure. Further, the effectiveness of vasopressin may be muted by an increase in cortisol.

Epinephrine and norepinephrine are both elevated during exercise (Åstrand and Rodahl, 1974). Cortisol is reported to be increased, unchanged, or decreased during exercise (Tharp, 1974; Few, 1974; Sutton, 1978). The response of adrenocortical hormones to exercise is dependent on the work intensity and degree of training (Maher et al., 1975; Sutton, 1978; Winder et al., 1979). Therefore, with exercise vasopressin release may be suppressed and its action inhibited due to the elevation of adrenocortical hormones dependent on the degree of emotional stress, training, and work intensity associated with the exercise performed.

Temperature: Exposure to high environmental temperatures results in an antidiuresis which is associated with the stimulation of vasopressin release (Hellman and Weiner, 1953; Segar and Moore, 1968; Collins and Weiner, 1968). The increased plasma vasopressin may be due to the redistribution of blood volume (Segar and Moore, 1968; Costill and Fink,

1974) or an increase in plasma osmolality (Senay, 1978). Szczepanska-Sadowska (1974) found local preoptic heating, elevating brain tissue temperature 0.5-2.4° C., 1.5 mm from the probe, to increase circulating plasma vasopressin levels from 2.4 to 24.0  $\mu$ U/ml in the dog. These findings suggest a direct effect of temperature on vasopressin release. However, MacFarlane and Robinson (1957) found no relationship between the urinary concentration of vasopressin and increases in skin or body temperature in man.

There is an elevation of core temperature which may reach 42° C. during prolonged exercise (Michaels and Horvath, 1977). The increase in body temperature is linearly related to work intensity (Åstrand and Rodahl, 1974). The elevation of body temperature during exercise is also correlated with increase in plasma osmolality (Greenleaf, 1973) and a decrease in plasma volume (Rowell, 1974). Both factors would provide input into vasopressin release and mask any direct effect of temperature.

Hypoxia: A variety of studies have shown vasopressin release to be altered by hypoxia (Forsling and Ullmann, 1977; Forsling, 1977; Anderson, et al., 1978). Share and Levy (1966) stimulated the isolated carotid chemoreceptors of anesthetized dogs by perfusion in the deoxygenated blood. This resulted in a suggestive increase in plasma vasopressin levels. Neither an increase in lung or chest movements nor a fall in arterial CO<sub>2</sub> pressure provides an immediate stimulus to vasopressin; therefore arterial hypoxia was concluded to be the stimulus (Forsling and Ullmann, 1977). Recent studies by Claybaugh et al. (1978) in spontaneously breathing men demonstrated a suppression of vasopressin in response to hypoxia.

With exercise there is a mild but functionally insignificant hypoxia. Arterial oxygen remains unchanged from control values (100 mmHg) during submaximal exercise (Ekblom et al., 1975). During maximal exercise, arterial oxygen pressure may decrease to 94 mmHg. The observed hypoxia during exercise appears to be insufficient to alter vasopressin release.

Metabolism of vasopressin: The metabolism of vasopressin occurs in the liver and kidney with a half-life of approximately 8 min in man (Lauson, 1974; Share et al., 1977; Walter and Simmons, 1977). In the conscious dog, the kidney accounts for 67% of the total clearance of vasopressin, and the liver the other 33% (Lauson et al., 1965; Usami and Chien, 1963; Little et al., 1966; Harvey et al., 1967). In both organs the clearance is dependent on the rate of blood flow (Lauson, 1974). The clearance of vasopressin by the kidney is due to filtration and secretion which appears to be receptor mediated (Shade and Share, 1977; Weitzman and Fisher, 1978).

The clearance of vasopressin is dependent on renal and hepatic blood flow, both of which are reduced in man during exercise (Rowell, 1974). The possible decrease in clearance during exercise would lead to elevated plasma vasopressin levels in the presence of a constant release.

Summary: The regulators of vasopressin release are work-intensity dependent. Some respond in a linear fashion while other parameters exhibit a log function response. Directional, diagrammatic representations of these parameters are presented in figure 1. The variability of the change in regulators to exercise may account for differences observed in vasopressin concentration.

### RESPONSES OF STIMULI OF VASOPRESSIN TO WORK INTENSITY

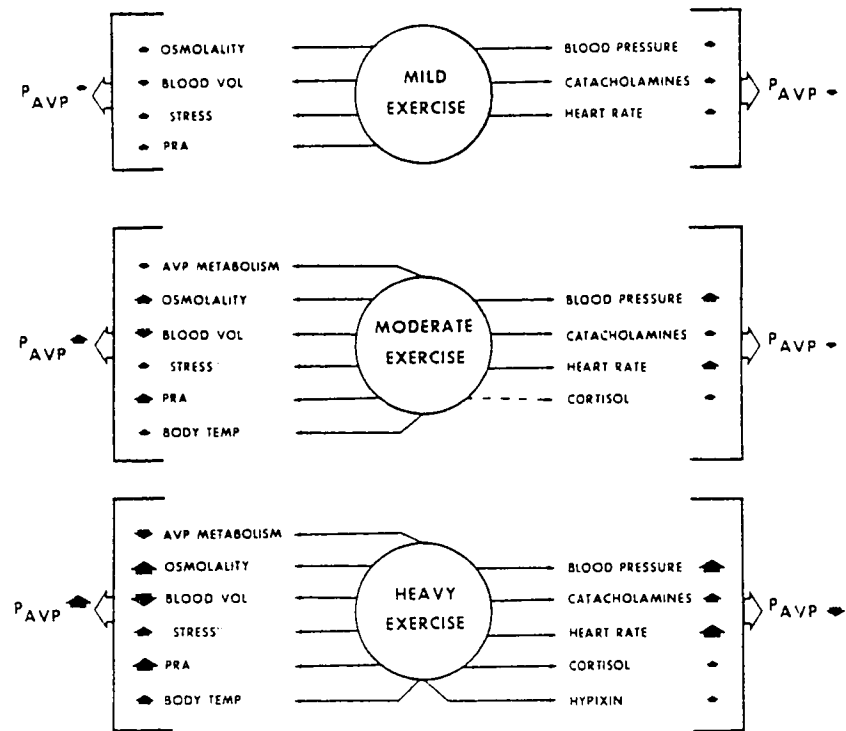


Figure 1: Present here are the known responses of various regulators of vasopressin to exercise. The arrows represent a decrease or increase with the size being indicative of the magnitude of change in response to work intensity. Plasma renin activity and plasma vasopressin concentration are shown as (PRA) and (P<sub>AVP</sub>), respectively.

## STATEMENT OF PROBLEM

The response of vasopressin release to exercise is unclear. Studies of renal function during exercise have suggested a suppression of vasopressin release as there is a diuresis at low workload and an increase in free water clearance at all workloads. Limited studies report plasma vasopressin concentrations to be unchanged at moderate workloads and to be elevated following "vigorous" exercise. The anti-diuresis which occurs following most exercise has been attributed to vasopressin; however, these findings suggest vasopressin release to be work-intensity dependent with a suppression during submaximal work and an elevation following maximal exercise.

It is possible that a dose-dependent release of vasopressin to exercise may explain some of the variability noted in the literature. Thus the present study is undertaken to investigate the regulation of vasopressin release in response to various intensities of exercise and evaluate its effectiveness in regulating renal handling of water. Alteration of the various regulators of vasopressin release will be measured and the primary regulator during exercise possibly identified. Manipulations effecting changes in blood volume and osmolality prior to exercise and the passive elevation of body temperature identical to that observed during exercise will be conducted to obtain further information on the control of vasopressin secretion during exercise.

## MATERIALS AND METHODS

Experiment I: The response and regulation of vasopressin and renal function to graded exercise.

**Subjects:** The subjects were six physically active males, 25-38 years of age and 165-190 cm in height with means of  $31 \pm 2$  yr and  $178 \pm 5$  cm, respectively. The subjects were free of renal and circulatory disease. The subjects were fully informed and familiarized with all procedures prior to any experiments, and consent forms were obtained. The subjects were requested to abstain from tobacco, alcohol, food, and water for 12 hr prior to the experiments.

**Protocol:** The subjects reported to the laboratory in the morning following 12 hr of fasting. A voided urine specimen was obtained and the experimental control period begun. An hour later a control urine and blood sample, 45 ml of venous blood, were taken. The desired exercise protocol was then undertaken. At submaximal workloads, a blood sample was taken after 20 min of exercise. Postexercise urine and blood samples were obtained 3 min after the cessation of exercise. An hour following exercise, samples were again taken and are referred to as recovery samples (Fig 2). Body weight, blood pressure, and oral temperature were also measured at each sampling period.

Exercise was performed on a motor-driven treadmill under the supervision of a cardiologist at Tripler Army Medical Center. Heart rate and ECG were continuously monitored throughout the exercise test and for 6 min of recovery. A graded exercise test with 3-min stages was performed to voluntary maximum. The starting speed was 4 mph with a grade of zero percent. The speed was increased to 6 mph with subsequent



grade elevations of 2.5% until a maximum grade of 10% was attained. The speed was then increased 1 mph until voluntary maximum. The maximum was defined as the workload at which the subject voluntarily ceased exercising. In all cases, this followed a plateauing of heart rate in response to an additional workload. This plateau was taken as the maximum heart rate.

The subsequent submaximal workloads were performed on the basis of heart rate. The resting heart rate represented a zero workload and the maximal heart rate a 100% workload. The performance heart rates for the 35% and 70% workloads were calculated using a method which corrects for resting heart rate so that the work performed is correlated with the percent of the maximum oxygen uptake (Karvonen et al., 1957; Davis and Convertino, 1975):

$$HR_{\text{submax}} = [(HR_{\text{max}} - HR_{\text{rest}}) \times \% \text{ workload desired}/100] + HR_{\text{rest}}$$

Throughout the 1-hr submaximal exercise test, heart rate was maintained at the predetermined rate by varying the speed of the treadmill with a constant grade of 0%. The resting values, 0% workload, were obtained following the submaximal protocol.

Experiment II: Effects of hydration on the response and regulation of vasopressin to maximal exercise.

Subjects: Seven physically active males, six whom had participated in experiment I, volunteered to participate as subjects. The age ranged from 25-38 yr with a mean of  $30.6 \pm 1.6$  yr. The mean height was  $179 \pm 4$  cm with a range of 165-191 cm. The subjects were informed of the purpose of the study and the testing procedures.

Protocol: Following 10 hr of fasting, the subjects reported to the laboratory. The subjects delivered a voided urine specimen and then

ingested 300 ml of tap water (hydrated) or received no water (dehydrated). The sampling procedures and maximal exercise test were the same as those previously described for experiment I. The order in which the experiments were performed was alternated between subjects, and tests were separated by at least 10 days.

Experiment III: Renal function and vasopressin excretion in response to submaximal exercise and passive elevation of body temperature. (This experiment was a cooperative study with Nema Frye, Department of Nutrition, University of Hawaii.)

Subjects: Seven males who were actively training for marathon races volunteered as subjects. The mean age was  $23 \pm 2$  yr, height  $180 \pm 2$  cm, and the average training  $47 \pm 8$  mi/wk. Informed consent forms were obtained from each individual after he was familiarized with the purpose and procedures of the experiment.

Protocol: The study consisted of three 5-hr experimental procedures: control, exercise, and thermal exposure. For all tests, the subject arrived in the laboratory with an overnight urine sample following 8 hr of fasting. The subject then voided and inserted a rectal temperature probe 10 cm into the rectum. The voided sample was combined with the overnight urine sample. A blood sample for the determination of hematocrit was then obtained. The subjects were then administered 120 ml of tap water. The experiment was started consisting of a 2-hr equilibration period, the desired treatment for 1 hr and a 3-hr recovery period. Throughout the experiment, rectal temperature (Ernest Turner, Model #7055), pulse rate, and blood pressure were monitored. Body

weights were measured at the start of the experiments, following exposures, and at the end of the experiment. A pooled urine sample was collected throughout the 5-hr procedure. At the end of 5 hr another blood sample was obtained. Blood samples were analyzed for hematocrit, hemoglobin, and creatinine.

The subjects remained in a prone position throughout the equilibration and recovery periods. During the control experiment the subjects maintained this position. The exercise periods consisted of 60 min of running on the treadmill at a zero grade. The subjects varied the speed of the treadmill to simulate a training workout. The thermal exposure was performed to passively elevate body core temperature to the same rate and extent as observed during exercise. The core temperature was passively elevated using a hyperthermic suit which allows the air surrounding the skin to be heated or cooled (Weiner and Lourie, 1969). This regulation of ambient temperature allows for the control of core temperature change.

Sample Handling: Immediately after the venous blood sample was obtained the blood was dispensed into three heparinized test tubes and a tube containing EDTA. Aliquots for hematocrit levels were then taken in heparinized microcapillary tubes and 2 ml of blood dispensed into a tube containing EDTA for the determination of hemoglobin. A 1 ml aliquot of whole blood was placed in a tube containing 2 ml of 0.6M perchloric acid for the measurement of lactate. All samples were immediately placed on ice. At the end of the experiment, all samples except those for hemoglobin and hematocrit were centrifuged at 2,000 rpm (1,120 x G)

for 20 min at 4° C. The plasma samples treated with EDTA were drawn off and stored for the determination of plasma renin activity (PRA). The supernatant from the lactate tube was drawn off and stored. Plasma from the heparinized tubes was decanted and centrifuged again. Ten to 15 ml of plasma, treated with 0.1 ml of 1 N HCL per ml of plasma, were stored for the measurement of vasopressin. A 2.3 ml aliquot of plasma was taken for the determination of osmolality, creatinine, sodium, and potassium. A 0.3 ml sample was also saved for the determination of cortisol. All samples were frozen at -5° until the desired measurements were made. Urine specimens were measured for total volume, and aliquots of 3 and 25 ml taken. The 25 ml sample for the determination of urinary vasopressin was pH adjusted to 4.5 with glacial acetic acid and frozen until extracted. The 3 ml untreated sample was saved for the measurement of urinary osmolality, creatinine, potassium, and sodium.

Techniques used for sample analysis:

All samples were analyzed for osmolality by freezing-point depression with a Fiske Osmometer (Model 330D), for sodium and potassium by a flame photometer employing lithium as an internal standard (Instrumentation Laboratories, Model 343) and for creatinine by the Jaffe reaction employing the methods of Owens et al. (1954). Hematocrit was determined in triplicate by the microcapillary method using an International Equipment Company microcapillary centrifuge and reader. Hemoglobin was measured with the cyanomethemoglobin method (Coulter Hemoglobinometer). Plasma lactic acid levels were determined using Calbiochem-Behring Rapid Lactate Reagents.

A variety of radioimmunoassays were used to determine hormone concentrations. Plasma cortisol was determined using Clinical Assays Gammacoat cortisol radioimmunoassay kits. The coefficient of variability within assay was 4.2% and 10.0% between assays. Plasma renin activity was measured with a radioimmunoassay for angiotensin I from New England Nuclear. The within-assay coefficient of variability for PRA was 10.7%, while the between-assay coefficient was 14.2%.

An analysis of variance for repeated measures in the same subject and Duncan's multiple range test were used to determine significant differences within an experimental procedure (Winer, 1971). Student "t"-test was used to determine between protocol differences (Steel and Torrie, 1960). In addition, correlations were determined by linear regression analysis using the method of least squares (Sokal and Rohlf, 1969). Values in text are mean  $\pm$  SE. A probability of less than 0.05 was accepted as being significant.

#### Methods of the extraction of and assay for vasopressin:

Antibody production: A conjugant of vasopressin and thyroglobulin was produced using the procedures of Skowsky and Fisher (1972). Rabbits were injected subcutaneously with 1 ml of the conjugant, containing 0.625 mg of arginine vasopressin, at 10-14 day intervals. The animals were bled after at least a 3-booster series. The serum was heated to 56° C. for 30 min to destroy the complement and the titer checked. The boosters were continued over a 6-month period with titer usually improving.

Antibody ClayAb-09, 6/20/78, was used to assay plasma samples and has a cross-reactivity with oxytocin of 1:800. Urine samples were assayed using ClayAb 11, 11/24/74, which has a cross-reactivity with oxytocin of 1:1100.

Iodination of vasopressin: The iodination of arginine vasopressin was performed using a modification of the lactoperoxidase method of Thorell and Johansson (1971). The iodinated hormone and possible fragments were separated from free iodide by a 10 cm DEAE column. One ml aliquots were collected. The tube of peak activity was added to a 20 cm sephadex G-25-40 column and 1 ml aliquots collected. The two tubes on the falling side of peak activity were used in the assay. The radioactivity was diluted to obtain 2,500 cpm/50  $\mu$ l.

Assay procedures: The assay procedures were similar to those described by Skowsky et al. (1974) and Moses and Miller (1972). Arginine vasopressin was used in the generation of the standard curve and control samples were run with each assay. The radioimmunoassay had a coefficient of variability of 11.6% within assay and 16% between assays. Plasma samples were assayed at three doses in single and urine at two doses duplicated. Both free and bound counts were obtained.

Plasma extraction: The bentonite extraction procedure for plasma vasopressin is a modification of the methods used in the laboratories of Drs. Miller and Share (personal communication). The sample was prepared by adding 0.1 ml of 1 N HCL for each 1 ml of plasma. This may be stored by freezing. Normal sample volume is 10 ml.

TABLE 1: Percent recovery of vasopressin in plasma samples with known quantities of arginine vasopressin added. Values are the means of two determinations assayed at three doses each.

VASOPRESSIN ( $\mu$ U/ml)	RECOVERY (%)
20	95
40	90
50	108
80	71
100	101
150	78
200	72

- (1) Add 30 mg of Fisher bentonite and shake for 30 min.
- (2) Rinse sides and cap of tube with 0.1 N HCL and centrifuge for 20 min at 2,000 rpm.
- (3) Decant supernatant and add 5 ml of 1 N HCL. Resuspend the bentonite button and spin at 2,000 rpm for 20 min.
- (4) Decant supernatant and add 5 ml of cold distilled water. Resuspend the pill and spin at 3,000 rpm for 20 min.
- (5) Decant supernatant and add 5 ml of 80% acetone - 20% 1 N HCL. Shake for 30 min. Rinse the sides and cap in the acetone-HCL solution and spin at 2,000 rpm for 20 min.
- (6) Decant the supernatant into a 45 mm Buchner funnel with 42 Whatman filter paper. Collect the sample in a siliconized round-bottom flask.
- (7) Repeat step 5, pouring the samples through the same filter.
- (8) Rinse each funnel three times.
- (9) Dry the sample down and then reconstitute with 1 ml solution of 0.9% NaCl, 0.1% BSA, and 0.03% acetic acid.

The sample may be stored by freezing. Table 1 gives the results of recoveries of spiked samples. A normal plasma sample of 10 ml would contain 10-30  $\mu$ U/ml of vasopressin well within the range of maximum recovery. A control and a sample spiked with vasopressin were run with each extraction to determine recovery. The mean recovery was  $83 \pm 5\%$ . Samples were not corrected for recovery.

Urine extraction: The urine extraction is a modification of the method of Miller and Moses (1972) to determine urine vasopressin concentration. Samples were prepared by being pH adjusted to 4.5 with glacial

acetic acid. The resin, Mallinkrodt CG-50, AR grade, 200-400 mesh, was prepared by washing out the fines and making a 1:1 solution of resin and water. The following procedure was then used.

- (1) Place 7 ml of 1:1 (resin:water) in conical centrifuge tubes.
- (2) Centrifuge at 2,000 rpm for 5 min, decant and discard water.
- (3) Measure 25 ml aliquots of urine into the conical centrifuge tubes.
- (4) Cap tightly and vortex gently (no foaming).
- (5) Place tubes on a conical rack and shake for 30 min.
- (6) Centrifuge for 10 min at 2,000 rpm. Decant urines.
- (7) Add 10 ml of distilled water, vortex gently (no foaming).
- (8) Centrifuge for 10 min at 2,000 rpm. Decant water.
- (9) Add 20 ml of 75% ETOH pH adjusted to 2.0 with 50% HCL (make extra for rinsing walls of tubes after centrifugation).
- (10) Shake for 30 min.
- (11) Rinse walls and cap of the tubes with 75% pH 2.0 ETOH.
- (12) Centrifuge 15 min at 2,000 rpm.
- (13) Decant ETOH into siliconized round-bottom flasks.
- (14) Dry down sample and resuspend with 2 ml of 0.9% NaCl, 0.03 acetic acid, and 0.1% bovine serum albumin.

All urine extractions were performed with a control and a sample spiked with pituitary extract to determine extraction recovery. The mean recovery was  $93 \pm 4\%$ . Samples were not corrected for recovery.

#### Calculations and statistics:

Explanations of the derivations of these formulae related to renal function may be found in Vander (1975) and Rose (1977).

(1) Urine flow rate ( $\dot{V}$ ) = ml/min.

(2) Urinary excretion rate of electrolytes ( $U_xV$ ): mEq/min  $U_xV = [X] \cdot \dot{V}$  ([X]; Urinary concentration of X : Na, K, osm).

(3) Creatinine clearance ( $C_{Cr}$ ): A measure of glomerular filtration rate: ml/min,  $C_r = U_{Cr} \cdot \dot{V} / P_{Cr}$  ( $P_{Cr}$ : plasma concentration of creatinine, mg %.  $U_{Cr}$  urinary concentration of creatinine, mg %).

(4) Osmolar clearance ( $C_{Osm}$ ): The volume of water required to make urine solutes isotonic to plasma: ml/min.  $C_{Osm} = U_{Osm} \dot{V} / P_{Osm}$  ( $P_{Osm}$ : plasma osmolality, mOsm/kg.  $U_{Osm}$ : urine osmolality, mOsm/kg).

(5) Free water clearance ( $C_{H_2O}$ ): The net excess or deficit of water beyond osmolar clearance: ml/min.  $C_{H_2O} = \dot{V} - C_{Osm}$

(6) Fractional excretion of filtered solute (X%).

$X\% = C_x / C_{Cr}$  ( $C_x$  the clearance of the X. X = Na, K, osm).

(7) Changes in plasma volume (% $\Delta$ PV) were calculated using hematocrit (van Beaumont, 1972):

$$\% \Delta PV = \frac{100}{100 - Hct_{pre}} \times \frac{100 (Hct_{pre} - Hct_{post})}{Hct_{post}}$$

( $Hct_{pre}$  is the pre-exercise hematocrit and  $Hct_{post}$  is the hematocrit postexercise.)

(8) Mean arterial pressure (MAP): mmHg

$$MAP = [(S - D) \times 0.33] + D$$

(The systolic blood pressure is S, and D is the diastolic blood pressure in mmHg.)

(8) Calculations for the radioimmunoassay are fully developed in Odell and Daughaday (1971). Standard curves and unknown samples were calculated simultaneously using a logit versus log dose transformation to obtain a linear regression curve. Calculations were performed using a Wang 2200B computer.

## RESULTS

Experiment I: The response and regulation of vasopressin and renal function to graded exercise.

Gradation of the exercise: The mean endurance time for the maximal exercise test was  $24 \pm 2$  min. The mean maximal heart rate was  $181 \pm 4$  beats/min. The grading of the exercise test was demonstrated by the increase in heart rate and lactate levels following 20 min of exercise (Table 2). The heart rates during the submaximal workload were maintained within 5 beats/min of the calculated prescribed rate throughout the 60 min of exercise.

Renal function: With increasing work there was a reduction in urine flow that persisted through the 1-hr recovery period for workloads of 70% and greater (Fig 3). The decrease in urine flow immediately postexercise was due in part to a reduced glomerular filtration rate as indicated by creatinine clearance (Fig 4). The observed antidiuresis 60 min following the 70% workload was due in part to a continuation of the reduction in filtration based on the change in creatinine clearance. Osmotic clearance was reduced postexercise and following recovery from the 70 and 100% workloads (Fig 5). The decrease in glomerular filtration contributed to a lower osmotic clearance postexercise at 70 and 100% and in recovery for the 70% workload.

A reduced sodium excretion ( $U_{Na}V$ ) postexercise, due to a reduction in filtration rate and an increased sodium reabsorption during recovery, was seen at the 70 and 100% workloads (Fig 6). The increase in sodium reabsorption was shown by a reduction in the percent of the filtered load excreted. The increase in sodium reabsorption contributed to the

TABLE 2: Heart rate and lactic acid concentration following 20 min of exercise demonstrating the grading of exercise.

WORKLOAD (% max)	HEART RATE (beats/min)	LACTIC ACID (mM)
0	58 ± 2	0.93 ± 0.18
35	104 ± 3	0.63 ± 0.07
70	142 ± 6	1.32 ± 0.17
100	181 ± 4	5.82 ± 1.11

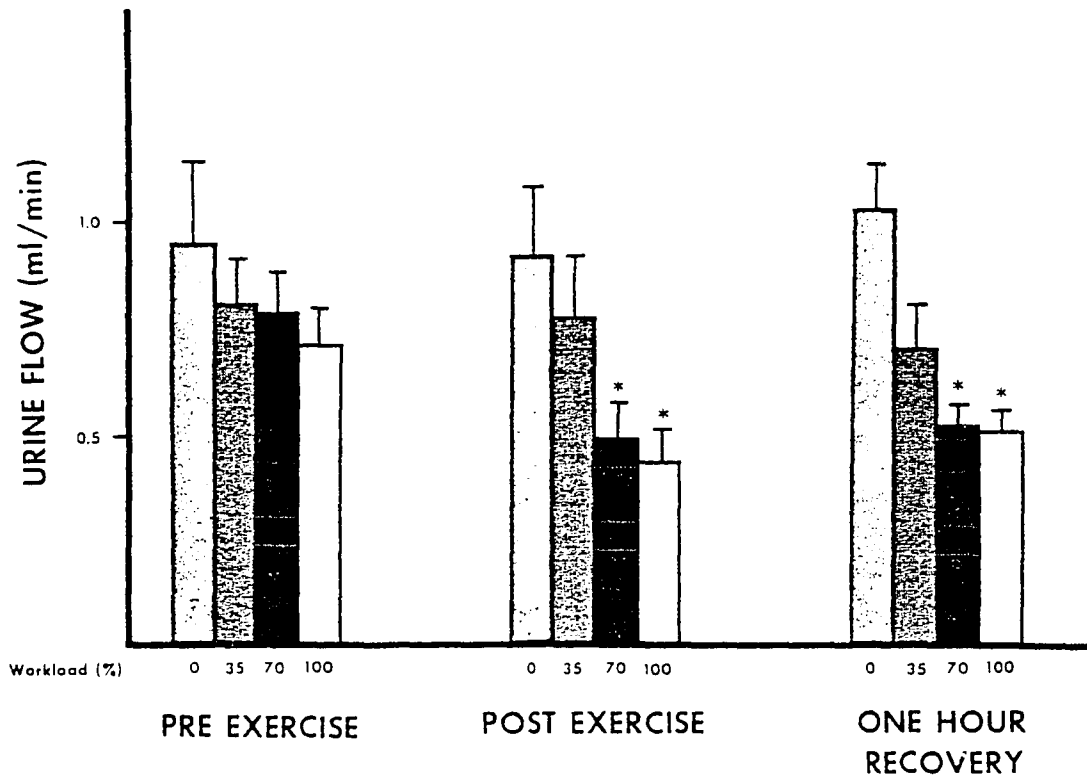


Figure 3: Urine flow for the various workloads with the pre-exercise control values for each experiment, postexercise, and following 1 hr of recovery. \*Significantly different from that workload ( $P < 0.05$ ).

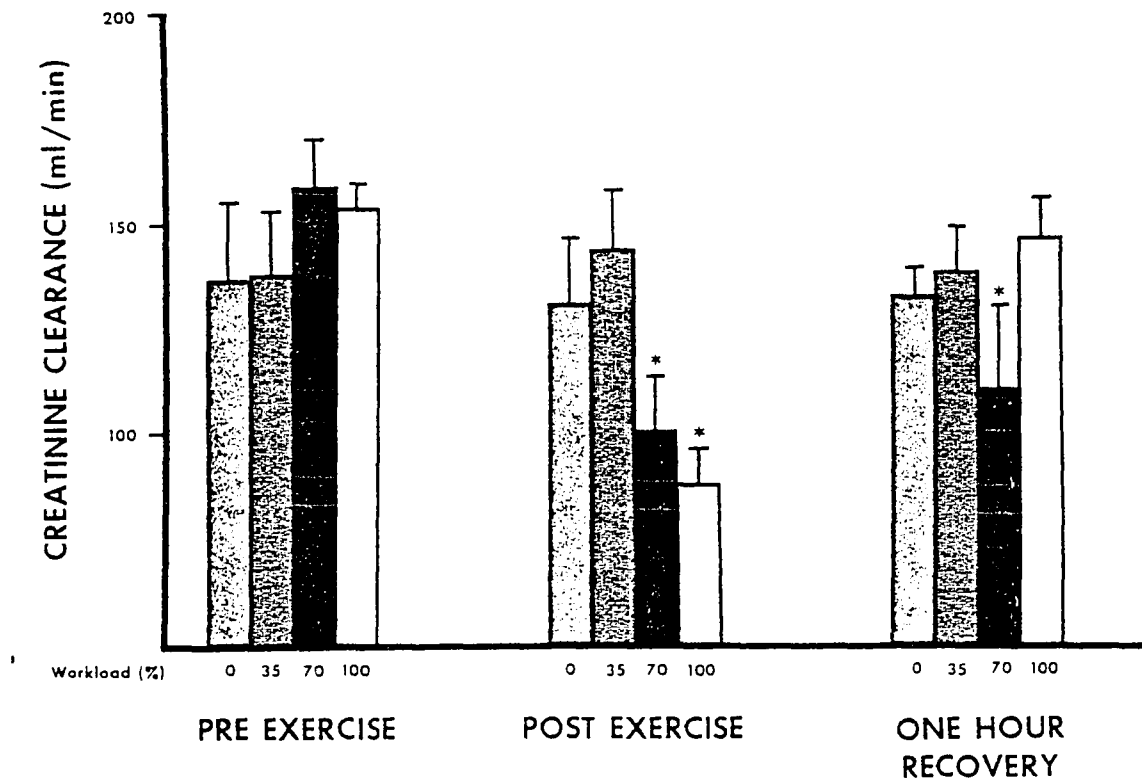


Figure 4: Creatinine clearance, which is indicative of glomerular filtration rate, for the various workloads. \*Significantly different for the pre-exercise values for that workload ( $P < 0.05$ ).

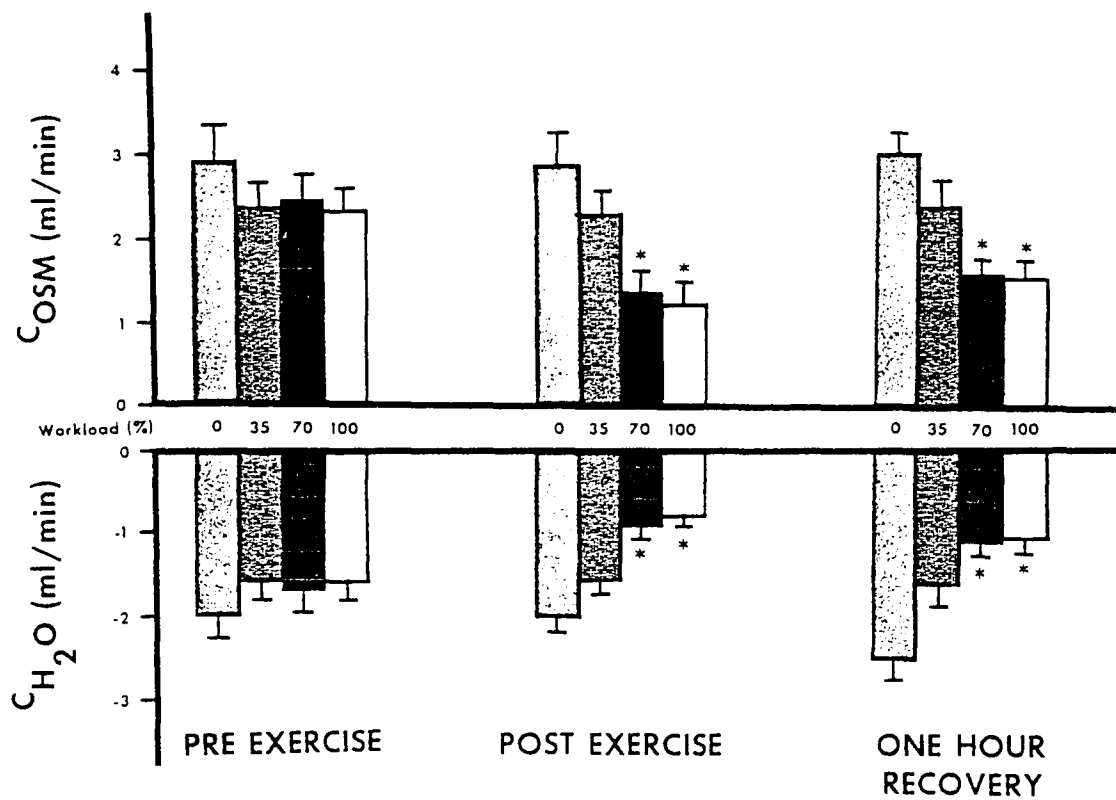


Figure 5: Osmotic ( $C_{OSM}$ ) and free water clearance ( $C_{H_2O}$ ) for the graded workloads. Values are compared to the pre-exercise controls to determine significance for that workload (\* $P < 0.05$ ).

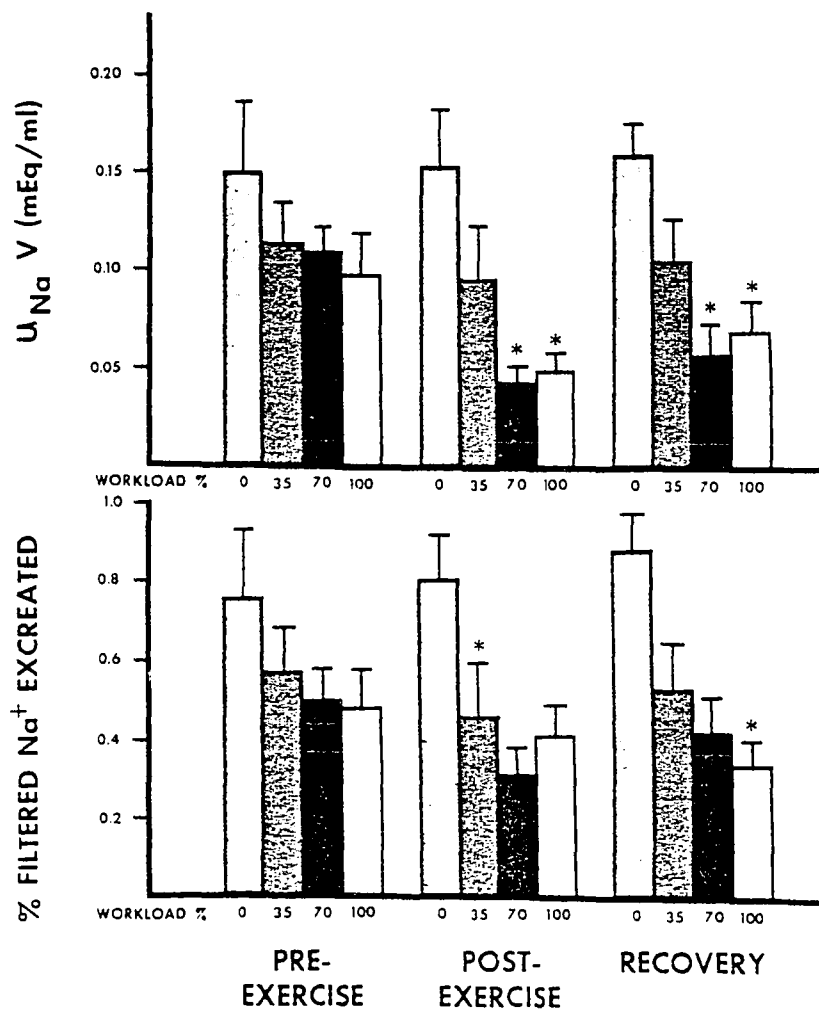


Figure 6: Urinary excretion of sodium ( $U_{Na}V$ ) and the percent of the filtered sodium excreted for the various grades of exercise. \* $P < 0.05$  significantly different from pre-exercise control for that workload. (Correction: The 35% postexercise is not significant; however, the 70% workload is significantly different from its control for the percent of the filtered load excreted.)

reduction in osmotic clearance and, following recovery from the 100% work effort, was almost entirely due to this. The decrease in potassium excretion ( $U_{kV}$ ) postexercise and during recovery was the result of a decrease in flow rate (Fig 7). However, the percent of the filtered load excreted was not changed with exercise. The reduction in osmotic clearance was accompanied by an increase in free water clearance, which remained elevated over the initial values through the 60 min of recovery for the 70 and 100% workloads, although there was a tendency to decrease (Fig 5).

The observed antidiuresis was not workload related. However, the decrease in creatinine clearance postexercise was inversely correlated with work intensity ( $r = 0.51$ ,  $P < 0.05$ ). This relationship was not maintained during the recovery period.

Plasma constituents: Plasma osmolality, sodium, and potassium are presented in Table 3. Plasma osmolality was significantly elevated during exercise at the 70 and 100% workloads. Following the 1-hr recovery period, the plasma osmolality was elevated only at the 100% work intensity. Plasma sodium showed no significant changes (Table 3). Plasma potassium, however, was reduced after the recovery period at the 0, 70, and 100% exercise treatments (Table 3).

After 20 min of exercise plasma osmolality was elevated at the 70 and 100% workloads. The change in osmolality during 20 min of exercise was 0.8, 3.5, and 7.7 mOsm/kg for the workloads of 35, 70, and 100%, respectively. This change in osmolality was significantly correlated with work intensity ( $r = 0.74$ ,  $P < 0.01$ ).

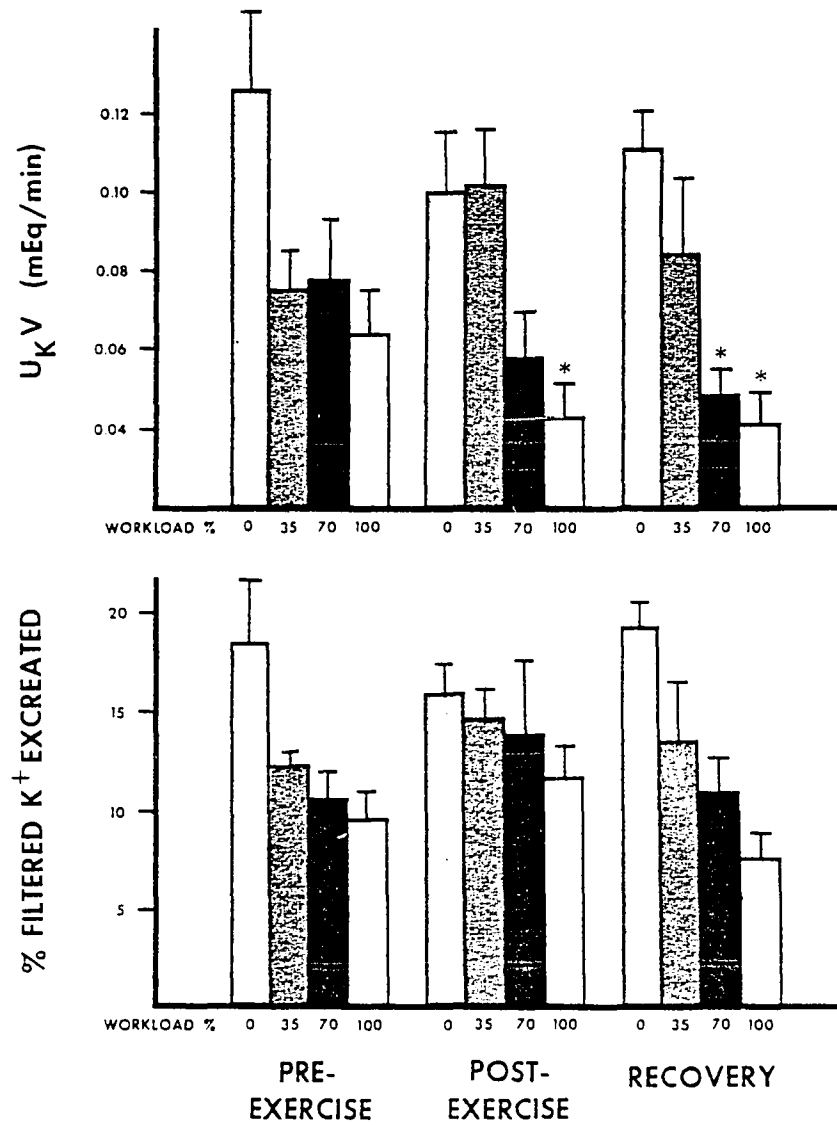


Figure 7: Urinary excretion of potassium ( $U_{k}V$ ) and the percent of filtered potassium excreted for the various workloads. \* $P < 0.05$  significantly different from pre-exercise control.

TABLE 3: Plasma constituents.

	WORKLOAD	CONTROL	20-MIN EXERCISE	60-MIN EXERCISE	60-MIN RECOVERY
Plasma Osmolality (mOsm/kg)	0	283 ± 2	283 ± 2	285 ± 2	286 ± 2
	35	286 ± 2	286 ± 2	287 ± 3	286 ± 2
	70	284 ± 1	289 ± 1*	288 ± 2*	287 ± 2
	100	289 ± 2	297 ± 3*	-----	292 ± 2*
Plasma Sodium (mEq/l)	0	147 ± 4	145 ± 4	145 ± 4	144 ± 5
	35	142 ± 3	142 ± 4	145 ± 5	139 ± 3
	70	142 ± 3	139 ± 2	143 ± 3	144 ± 3
	100	133 ± 1	131 ± 1	-----	132 ± 2
Plasma Potassium (mEq/l)	0	5.0 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	4.4 ± 0.1*
	35	4.5 ± 0.2	4.8 ± 0.3	5.0 ± 0.2	4.6 ± 0.2
	70	5.0 ± 0.1	4.0 ± 0.1	-----	4.0 ± 0.1*

\*Significantly different from control (P<0.05)

Plasma volume and blood pressure: Exercise resulted in a hemo-concentration with increases in hematocrit and hemoglobin observed. Plasma volume change tended to decrease following 20 min of exercise, but returned to resting values after 60 min of submaximal exercise (Fig 8). Following recovery exercise, a tendency for plasma volume to increase was noted; however, this was not significant.

There was a reduction in body weight during all experiments (Table 4). When corrected for urine loss, the rates of change in body weight during the exercise periods were 184, 673, 931, and 2,194 g/hr for the 0, 35, 70, and 100% workloads, respectively. The loss of body weight calculated in this manner is indicative of perspiration and insensible water loss.

Systolic blood pressure was significantly elevated following 20 min of exercise at all workloads and remained elevated with the prolonged submaximal exercise at the 35% workload. However, at 60 min of 70% exercise a significant reduction from 20 min was seen. Following recovery, no significant difference was noted from pre-exercise values. Diastolic blood pressure showed no significant change in response to exercise. Therefore, the mean arterial pressure and pulse pressure were increased during exercise (Table 4). Of interest is the reduction in the mean arterial pressure after 60 min of recovery from the exercise, accompanied by an increase in plasma volume.

The reduction in plasma volume and elevation of mean arterial pressure with 20 min of exercise appear to be work-intensity related (Fig 9). However, with further submaximal work this relationship did not continue.

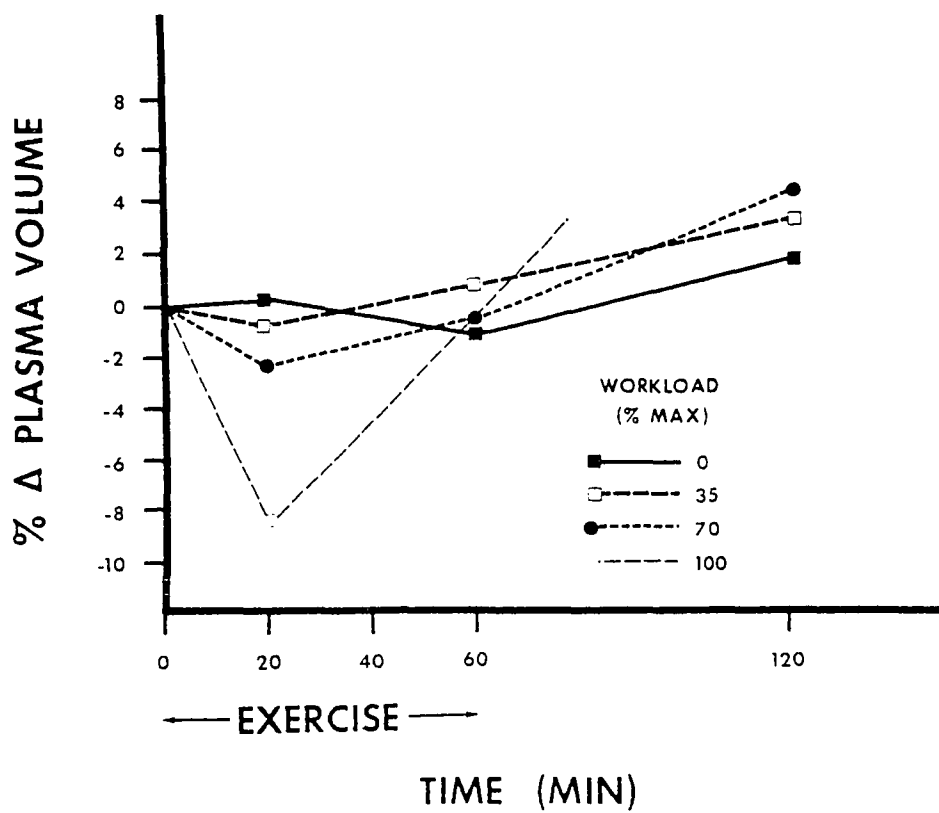


Figure 8: Percent change in plasma volume calculated from hematocrit. The 100% workload shows a significant reduction after 20 min of exercise.

TABLE 4: Body weight, mean arterial pressure, and oral temperature for the various workloads.

	WORKLOAD (% max)	INITIAL	PRE-EXERCISE	20-MIN EXERCISE	60-MIN EXERCISE	RECOVERY
Body weight (kg)	0	78.0±3.8	77.9±3.8	--	77.7±3.8	77.4±3.8*
	35	76.2±3.8	76.0±3.8	--	75.2±3.8*	75.2±3.7*
	70	75.7±3.9	75.7±3.8	--	74.8±3.8*	74.3±3.7*
	100	76.9±3.7	76.6±3.7	75.9±3.7*	--	75.6±3.7*
Mean arterial pressure (mmHg)	0	91±3	92±3	91±3	90±1	91±3
	35	86±0	87±1	96±3*	94±2*	88±1
	70	89±2	89±1	110±3*	98±1*	85±4
	100	90±2	86±4	110±7*	--	89±3
Oral temperature (°C)	0	36.4±0.1	36.7±0.1*	36.7±0.1*	36.7±0.1*	36.6±0.1*
	35	36.4±0.0	36.6±0.1	36.8±0.2*	36.9±0.1*	36.8±0.1*
	70	36.5±0.1	36.5±0.1	36.8±0.2	36.9±0.2*	37.0±0.1*
	100	36.6±0.1	36.5±0.1	37.2 0.2*	--	37.4±0.2*

\*Significantly different from initial value (P<0.05)

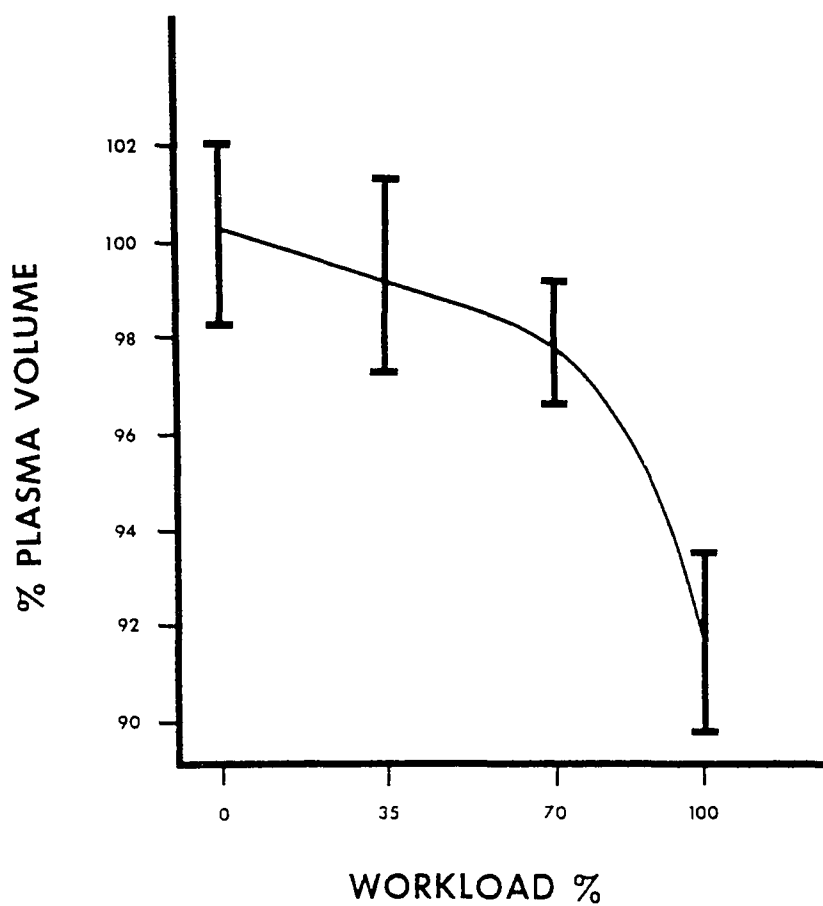


Figure 9: The percent change in plasma volume calculated from hematocrit following 20 min of exercise. A linear relationship is seen until approximately a 60% workload, then a break occurs which follows a "fold" catastrophe model (Wilkerson et. al., 1977).

Oral temperature: Oral temperature increased significantly with exercise and remained elevated throughout the recovery period (Table 4). Although there were no differences noted in the response to exercise between the 35 and 70% workloads, the steady increase through recovery following the 70% workload suggests a greater metabolic heat generation which may not be alleviated (Table 4). At the end of the recovery periods the oral temperature was work-intensity related.

Hormones: Plasma cortisol showed no significant change in response to any workload (Table 5). No differences were noted among any of the exercise protocols.

Plasma renin activity (PRA) showed no significant difference through the control experiment (Table 5). Following 60 min of 35% exercise, PRA was significantly elevated, but returned to control levels during the recovery period (Table 5). Plasma renin activity was elevated at both 20 and 60 min of exercise during and through recovery after the 70% workload. Maximal exercise resulted in PRA being elevated after 20 min, but PRA was not significantly different from control levels following recovery.

The plasma vasopressin concentrations during the control periods of all workloads ranged from 0.42 to 2.92  $\mu\text{U}/\text{ml}$  with a mean value of  $1.1 \pm 0.1 \mu\text{U}/\text{ml}$ . The responses to the various workloads are presented in Table 5. Plasma vasopressin tended to decrease throughout the zero workload, but no significant differences were noted. With a workload of 35% there was an initial nonsignificant trend of suppression of vasopressin, with a tendency of a rise later in exercise. However, no significant difference was observed. At the 70% work intensity, plasma

TABLE 5: Hormonal responses to the various work intensities.

	WORKLOAD (% MAX)	PRE-EXERCISE	20-MIN EXERCISE	60-MIN EXERCISE	RECOVERY
Plasma Cortisol (ng %)	0	14.0 ± 2.5	12.7 ± 2.0	11.2 ± 0.7	10.1 ± 0.7
	35	13.1 ± 1.5	12.8 ± 1.6	10.1 ± 0.9	12.4 ± 1.6
	70	14.3 ± 1.5	15.7 ± 1.3	15.9 ± 1.2	14.9 ± 2.4
	100	15.1 ± 0.9	14.9 ± 0.8	----	14.3 ± 1.1
Plasma Renin Activity (ng Angio I/ ml/hr)	0	0.28 ± 0.04	0.31 ± 0.07	0.25 ± 0.03	0.33 ± 0.06
	35	0.29 ± 0.06	0.57 ± 0.09	0.80 ± 0.16*	0.45 ± 0.11
	70	0.38 ± 0.06	1.95 ± 0.37*	2.60 ± 0.47*	1.09 ± 0.17
	100	0.29 ± 0.06	2.48 ± 0.50*	----	0.79 ± 0.18
Plasma Vasopressin (μU/ml)	0	1.5 ± 0.4	1.4 ± 0.3	1.1 ± 0.2	1.1 ± 0.2
	35	1.1 ± 0.2	1.0 ± 0.1	1.3 ± 0.1	1.3 ± 0.2
	70	0.8 ± 0.2	1.1 ± 0.1	2.1 ± 0.3*	1.6 ± 0.1*
	100	0.9 ± 0.1	2.7 ± 0.7*	----	1.5 ± 0.2

\*Significantly different from control (P<0.05)

vasopressin levels increased throughout exercise, being significantly elevated after 60 min. After recovery, the levels dropped significantly from the previous values, but remained above the initial levels through the recovery period. Vasopressin levels were significantly increased following maximal exercise, and after 60 min of recovery were not significantly different from pre-exercise values. Plasma vasopressin levels following 20 min of exercise were significantly correlated with work intensity ( $r = 0.75$ ,  $P < 0.01$ ).

Summary: Exercise at a workload greater than 70% resulted in an antidiuresis. The causes of the decreased urine flow were a reduced glomerular filtration rate and an increase in sodium reabsorption. The net result was a reduction in osmotic clearance which was large enough to overcome an increase in free water clearance and result in a net reduction in urine flow.

Plasma osmolality was elevated immediately following exercise as were body temperature and mean arterial pressure. Plasma renin activity and vasopressin concentration were increased following 70% and maximal workloads, and no change was noted in cortisol.

During the recovery period, most parameters returned to pre-exercise levels. Plasma vasopressin 60 min after the end of maximal exercise was not significantly different from pre-exercise, while plasma osmolality was elevated. Further, mean arterial pressure which was elevated during exercise also returned to control levels.

Experiment II: Effects of hydration on the response and regulation of vasopressin to maximal exercise.

**Workload:** There was no significant difference in heart rate, lactate, or endurance time between hydrated and dehydrated maximal runs (Table 6). Therefore it is assumed there was no difference in the work performed.

**Renal function:** The osmolality of the voided urine samples before hydration were  $811 \pm 99$  and  $945 \pm 37$  for the hydrated and dehydrated exposures, respectively. The lack of a significant difference suggests a similar state of initial hydration prior to the experiments. One hour after the ingestion of the 300 ml water load, the urine flow was significantly greater in the hydrated experiment (Fig 10). Immediately post-exercise, a significant antidiuresis was noted in the subjects only during dehydration with a significant difference noted between treatments. There was an antidiuresis during recovery in both dehydrated and hydrated subjects. At this time there was no significant difference between groups.

Creatinine clearance was significantly reduced with exercise independent of the state of hydration and returned to pre-exercise values upon recovery (Table 7). Osmotic clearance was significantly reduced postexercise and through recovery in both experiments. No significant difference was noted in free-water clearance in the hydrated group in response to exercise, while dehydration resulted in an increase which continued through recovery.

**Plasma constituents:** Plasma osmolality was significantly lower in the hydrated study prior to exercise,  $283 \pm 2$  versus  $288 \pm 2$  mOsm/kg for

TABLE 6: Heart rate, endurance time, and lactate levels following dehydrated maximal exercise.

	HYDRATION	DEHYDRATION
Heart rate (beats/min)	184±5	182±3
Endurance time (min)	22±1	25±2
Lactate (mM)	7.0±1.0	6.8±0.5

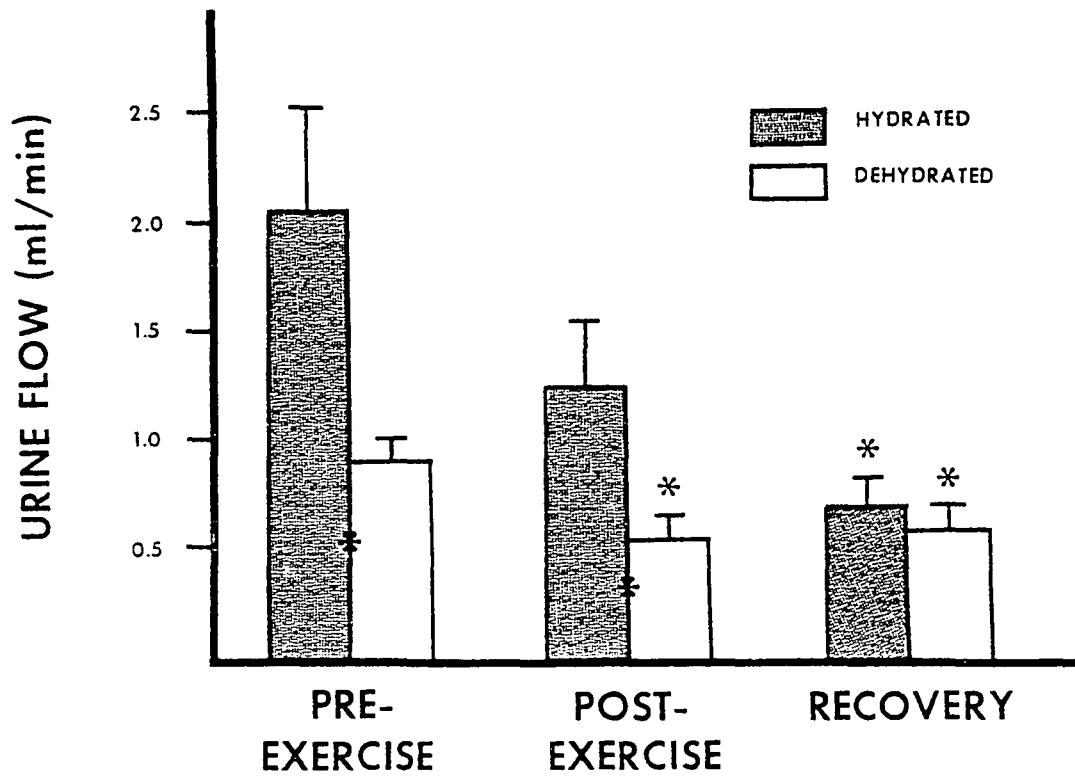


Figure 10: Urine flow for dehydrated and hydrated maximal exercise.  
\*P<0.05 significant differences between groups and for the initial pre-exercise control.

TABLE 7. Renal function during hydration and dehydration.

		PRE-EXERCISE	POSTEXERCISE	RECOVERY
C <sub>Cr</sub> (ml/min)	hydrated	151±11	100±17*	142±10
	dehydrated	160± 8	89± 8*	150± 9
C <sub>osm</sub> (ml/min)	hydrated	3.3±0.4	1.8±0.3*	1.8±0.2*
	dehydrated	2.5±0.3	1.5±0.3*	1.7±0.2*
C <sub>H<sub>2</sub>O</sub> (ml/min)	hydrated	-1.1±0.7	-0.5±0.2	-1.1±0.1
	dehydrated	-1.7±0.1	-0.9±0.1*	-1.1±0.1

\*Significantly different from pre-exercise (P<0.05)

the subject during dehydration. Postexercise, plasma osmolalities were found to be significantly elevated for both exposures,  $292 \pm 3$  and  $295 \pm 2$  mOsm/kg for hydration and dehydration, respectively, which were not statistically different from one another. Following recovery the plasma osmolality of the hydration treatment,  $285 \pm 3$  mOsm/kg, fell and was not significantly different for the pre-exercise value. The plasma osmolality with dehydration,  $291 \pm 2$  mOsm/kg, decreased during recovery from the values observed postexercise, but was significantly greater than pre-exercise osmolality.

Plasma volume and blood pressure: There was no significant difference between treatments in the pre-exercise hemoglobin and hematocrit. The calculated change in plasma volume postexercise for the hydration exercise,  $-8.6 \pm 1.7\%$ , was similar to that of dehydration,  $-9.6 \pm 1.8\%$ . There was no difference noted between groups in the trend of change in body weight (Table 8).

Systolic blood pressure was significantly elevated postexercise in both experiments, with no change in diastolic pressure. There was no difference between treatments. Mean arterial pressure postexercise was  $115 \pm 6$  mmHg with hydration and  $107 \pm 7$  mmHg with dehydration, significantly elevated above pre-exercise.

Oral temperature: Oral temperature was significantly elevated for both treatments during exercise and through the recovery period. With dehydration the increase in temperature with exercise,  $0.7 \pm 0.4^\circ \text{C}$ ., was significantly greater than the  $0.3 \pm 0.3^\circ \text{C}$ . rise seen in the hydration treatment. However, no significant difference in oral temperature was noted between treatments.

TABLE 8: Changes in body weight, blood pressure, and oral temperature for hydration and dehydration exercise treatments.

		INITIAL	PRE-EXERCISE	POSTEXERCISE	RECOVERY
Body weight (kg)	hydrated	75.8±3.4	75.9±3.4	75.3±3.4*	75.0±3.3*
	dehydrated	76.5±3.1	76.2±3.2*	75.5±3.2*	75.1±3.1*
Systolic BP (mmHg)	hydrated	111±7	109±9	171±17*	106±8
	dehydrated	115±4	114±4	188±6*	111±3
Diastolic BP (mmHg)	hydrated	76±4	71±3	80±6	68±3
	dehydrated	74±3	68±4	67±7	75±3
Mean arterial pressure (mmHg)	hydrated	89±3	86±2	115±5	83±2
	dehydrated	88±3	84±4	107±6*	87±3
Oral temperature (°C)	hydrated	36.5±0.1	36.6±0.1	37.0±0.2*	37.1±0.1*
	dehydrated	36.6±0.1	36.5±0.1	37.3±0.2*	37.4±0.2*

\*Significantly different from initial (P<0.05)

Hormones: Plasma cortisol levels did not respond to exercise and exhibited no difference between treatments (Table 9). Plasma renin activity (PRA) increased during exercise; however, the response was independent of the state of hydration.

Plasma vasopressin was significantly elevated in response to exercise in both treatments. No significant difference was seen between treatments; however, the change from pre-exercise values was significantly greater in the dehydration exercise,  $1.82 \pm 0.56 \mu\text{U/ml}$ , compared to  $0.62 \pm 0.13 \mu\text{U/ml}$  for the hydrated treatment.

The response of vasopressin to osmolality was compared during hydration and dehydration (Fig 11). Although the change in osmolality was similar for both treatments, going from 282 to 292 mOsm/kg in the hydrated and 288 to 295 mOsm in the dehydrated treatment, dehydration resulted in a greater change in plasma vasopressin in response to exercise. The slopes relating plasma osmolality ( $P_{\text{Osm}}$ ) to plasma vasopressin ( $P_{\text{avp}}$ ) during the dehydration treatment were significantly steeper than those for hydration.

Summary: Hydration, ingestion of 300 ml of tap water, produced a significant increase in urine flow which depressed the antidiuresis associated with exercise. A decrease in urine flow was observed 60 min postexercise.

The response of vasopressin was significantly muted during hydration, although the osmolality, mean arterial pressure, temperature, cortisol, and PRA postexercise were the same as those for dehydration. During the dehydration treatment, the recovery plasma vasopressin level was not significantly greater than that observed pre-exercise. However, plasma

TABLE 9: Hormonal responses to exercise with hydration and dehydration.

		PRE-EXERCISE	POSTEXERCISE	RECOVERY
Plasma Cortisol (ng %)	hydrated	16.0 ± 2.0	15.8 ± 1.7	15.9 ± 1.3
	dehydrated	14.5 ± 1.0	14.0 ± 1.1	13.8 ± 1.1
Plasma PRA (ng of Angio I/ ml/hr)	hydrated	0.23 ± 0.06	1.65 ± 0.43*	0.48 ± 0.05
	dehydrated	0.29 ± 0.05	2.41 ± 0.43*	0.75 ± 0.15
Plasma AVP (μU/ml)	hydrated	1.06 ± 0.22	1.68 ± 0.30*	1.25 ± 0.18
	dehydrated	0.85 ± 0.08	2.67 ± 0.60*	1.36 ± 0.22

\*significantly different from pre-exercise (P<0.05)

values are  $\bar{x} \pm se$

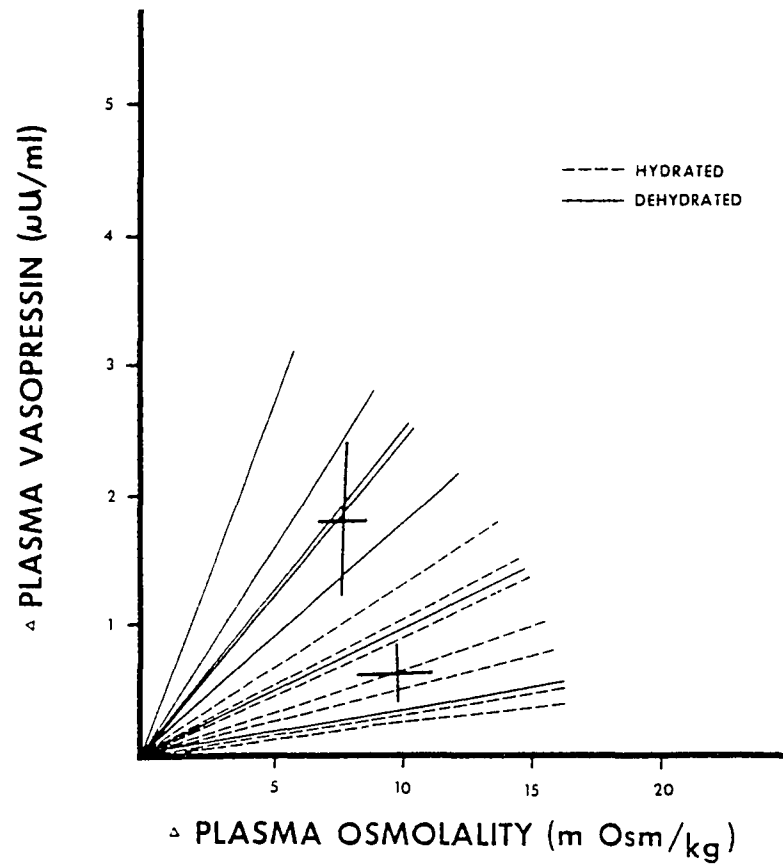


Figure 11: The slopes of the change in plasma vasopressin and osmolality following hydrated and dehydrated maximal exercise. Means  $\pm$  SE are presented for both groups with dehydration having a significantly greater plasma vasopressin concentration.

osmolality remained significantly elevated, and mean arterial pressure returned to control values.

Experiment III: Renal function and vasopressin excretion in response to submaximal exercise and passive elevation of body temperature.

General observations: There was no significant change in body temperature during the control, while significant increases were noted during exercise and hyperthermia. The rise in rectal temperature during passive temperature elevation was similar to that during exercise (Fig 12). No significant difference in rectal temperature was noted between exercise and passively induced hyperthermia.

Renal function: Urine flow was significantly reduced during exercise protocol compared to control (Table 10). However, no difference was observed between exercise and thermal exposure. Creatinine clearance, urine osmolality, and potassium excretion rate exhibited no differences in response to any of the three protocols. Sodium excretion rate was significantly reduced during exercise and thermal exposures compared to control (Table 10).

Plasma volume and blood pressure: No significant differences were noted in hematocrit or hemoglobin between pre and postexposure samples in any groups. Thus, the calculated change in plasma volumes showed no significant differences between exposures (Table 11).

Body weight decreased through all exposures, with the reductions during exercise and hyperthermia being significantly greater than control. No difference was seen between exercise and thermal treatments.

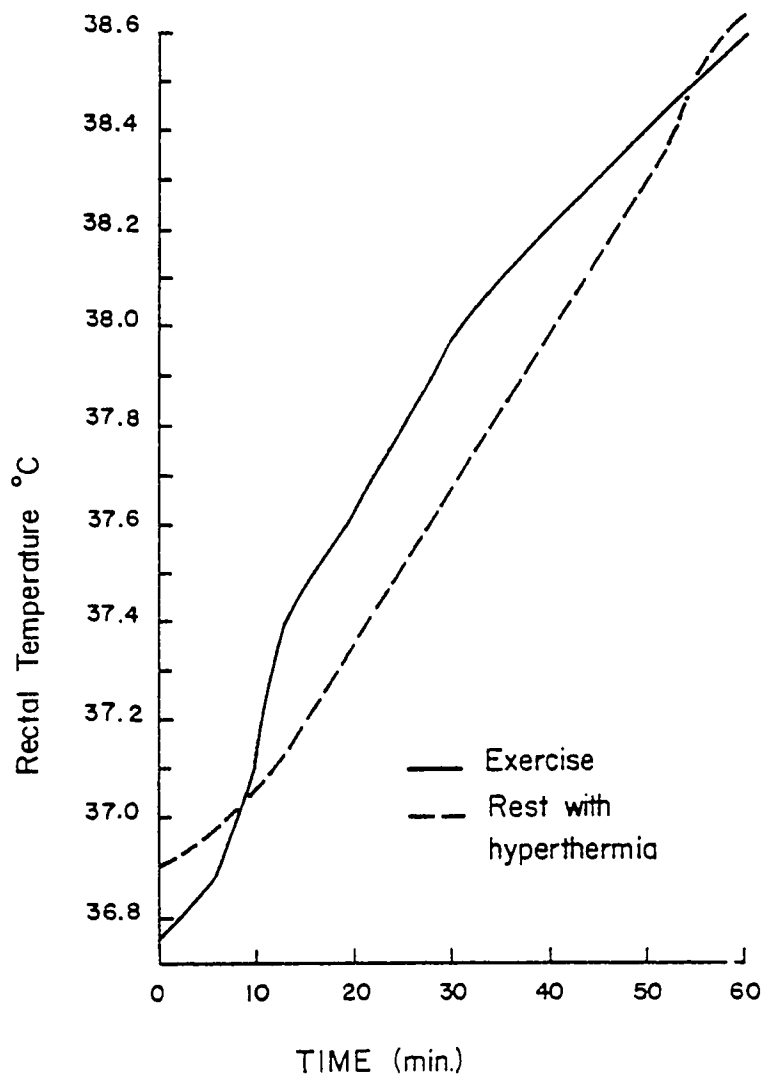


Figure 12: The elevation of rectal temperature during exercise and passive elevation by external heating. No difference was seen between the two treatments.

TABLE 10: Renal function for control, exercise, and thermal exposures.

	CONTROL	EXERCISE	TEMPERATURE
$\dot{V}$ (ml/min)	1.7 ± 0.3	1.0 ± 0.2*	1.2 ± 3
$U_{Osm}$ (mOsm/kg)	545 ± 135	586 ± 78	704 ± 49
$C_{Cr}$ (ml/min)	116 ± 7	103 ± 8	103 ± 8
$U_{Na}\dot{V}$ (μEq/min)	163.1 ± 16.2	80.4 ± 14.2*	86.4 ± 16.4*
$U_{K}\dot{V}$ (μEq/min)	80.3 ± 6.2	69.9 ± 4.0	63.2 ± 11.3

\*Significantly different from control (P<0.05)

TABLE 11: Change in plasma volume and weight, and mean cortisol pressure for cortisol, exercise, and thermal exposures.

	CONTROL	EXERCISE	TEMPERATURE
$\Delta PV$ (%)	$-2.53 \pm 1.42$	$-0.11 \pm 1.22$	$-3.83 \pm 2.78$
$\Delta Wt$ (kg)	$-0.3 \pm 0.1$	$-0.87 \pm 0.1^*$	$-0.93 \pm 0.2^*$
MAP (mmHg)	$92 \pm 3$	$101 \pm 3^*$	$94 \pm 4$

\*Significantly different from control ( $P < 0.05$ )

Mean arterial pressure at the end of the exposure period was greater than control for exercise but not for thermal exposure. The exercise mean arterial pressure was also significantly higher than that observed during the thermal exposure.

Vasopressin excretion: Vasopressin excretion corrected for filtration rate showed no significant difference between pre and post values for any treatment (Table 12). There was no significant difference seen between exposures; however, exercise tended to produce a greater increase in vasopressin excretion than control or thermal exposures. The percent changes in vasopressin excretion were 23, 79, and 17%, for control, exercise, and thermal exposures, respectively. Exercise produced an increase in six of the seven subjects, while a trend was not observed in either of the other exposures.

Summary: Exercise produced a decrease in urine flow and sodium excretion significantly less than control values. Passive elevation of rectal temperature resulted in a similar decrease in sodium excretion with no significant difference in urine flow. Mean arterial pressure was elevated during exercise, but not during thermal exposure. Vasopressin excretion showed a trend to increase following exercise, with no difference seen for either control or passive temperature elevation.

TABLE 12: Vasopressin excretion during the various exposures corrected for filtration rate

	CONTROL		EXERCISE		THERMAL	
	PRE	POST	PRE	POST	PRE	POST
Urinary AVP/creatinine $\bar{X}$ ( $\mu\text{U}/\text{mg}$ )	42.0	45.6	34.0	52.0	67.2	70.0
SE	7.0	4.2	6.3	10.0	19.2	29.0

## DISCUSSION

Vasopressin: The plasma concentrations of vasopressin observed at rest (0.4 to 2.9  $\mu\text{U/ml}$ ) were within the range reported for normal individuals (Beardwell et al., 1975; Robertson et al., 1973; Baylis and Heath, 1977). Exercise produced an increase in plasma vasopressin with a high value of 5.8  $\mu\text{U/ml}$ . The values were within the observed physiological range as higher values are reported after surgical trauma (Moran and Zimmerman, 1967) and fluid deprivation (Czazckes et al., 1964). The elevation of plasma vasopressin appeared to be related to work intensity and duration. Beardwell et al. (1975) reported no change in vasopressin levels following exercise at approximately 70% for 15 min. This agrees with our findings, but after 60 min at this workload our data indicated that a significant increase occurred. Baylis and Heath (1977) found vasopressin to be elevated after 5 min of heavy work. The change in vasopressin was independent of the amount of work performed, and the increase in vasopressin, 303%, suggests maximal exercise. The independence of vasopressin and workload conflicts with our findings and may be explained by the lack of gradation of the workload. It is possible maximal exercise may have been performed in all instances in their studies as the workload was defined as "vigorous" and was 5 min in duration.

Vasopressin was stimulated during exercise, and its regulation may change during the course of exercise as an increase was noted from 20 to 60 min at 70%. The return of plasma concentrations of vasopressin to control values during recovery in the absence of rehydration suggests a direct effect of exercise on the regulation of vasopressin release

independent of the dehydration resulting from fluid losses due to perspiration or insensible water losses.

Renal function: The antidiuresis seen with exercise has been reported by other investigators (Smith, 1951; Raisz et al., 1959; Castenfors, 1967, 1978; Refsum and Strömme, 1975, 1978). Kachadorian and Johnson (1972) found the decrease in urine flow to be workload dependent, although flow was not significantly different between workloads. We found no relationship between urine flow and work intensity, but the maximal workload was only of 20 min duration while others lasted 60 min. The difference in work duration may have affected the degree of anti-diuresis observed.

Glomerular filtration rate, as indicated by creatinine clearance, was reduced during exercise and was workload dependent. This finding has been noted previously by Kachadorian and Johnson (1972) and Castenfors (1978). The reduction in filtration has been used to explain the anti-diuresis (Kachadorian and Johnson, 1972; Brod, 1973; Castenfors, 1978), yet the antidiuresis persisted through recovery while creatinine clearance had returned to control levels. The performance of maximal exercise while hydrated produced a reduction in creatinine clearance, but urine flow was not significantly reduced. Therefore, a reduction in glomerular filtration rate cannot fully explain the observed changes in urine flow.

Sodium excretion ( $U_{Na}\dot{V}$ ) has been used to represent sodium reabsorption (Costill et al., 1976). Following the 70% workload, there was an increased sodium reabsorption with no change in excretion, while the opposite occurred at the 100% workload. The conflict is caused by

changes in urine flow independent of sodium reabsorption. The 0.14% reduction in sodium reabsorption following recovery from maximal exercise is similar to the 0.2% seen by Castenfor (1978) after an 85 km cross-country ski race. The increase in sodium reabsorption may be due to an elevated aldosterone. Plasma aldosterone has been correlated with plasma renin activity during exercise (Maher et al., 1975; Costill et al., 1976; Kosunen and Pakarinen, 1976). Plasma renin activity in the present study was elevated with exercise. However, after the recovery period PRA was not significantly elevated when the increase in sodium reabsorption was observed. The urine sample represents an integration of function over 60 min, while the blood sample represents less than 8 min. Therefore, PRA at the end of the recovery period may not be indicative of its effect on renal sodium reabsorption through the 60 min. An increase in sodium reabsorption may contribute to the antidiuresis; however, a change in reabsorption was not always present during a reduction in urine flow.

Potassium excretion decreased with urine flow, but no difference was seen in the percent of the filtered load excreted. Therefore, changes in the handling of potassium by the kidney may not explain the decreased plasma concentrations. Plasma potassium has been noted by others to be elevated during exercise, but returns to pre-exercise values within 1.5 min postexercise (van Beaumont et al., 1973; Greenleaf et al., 1979). Blood in the present study was drawn 3 min postexercise and may explain the lack of an increase in plasma potassium in response to exercise. The decrease during recovery may be due to potassium influx into the cells in exchange for hydrogen ions which was generated

during exercise and buffered within the cell (Rose, 1977). Also, post-exercise insulin levels rise and promote the entry of potassium into skeletal muscle and the liver (Pruett, 1970; Rose, 1977). Thus, there was no change in the renal handling of potassium with exercise, but movement of potassium between body fluid compartments may have resulted in a reduced plasma concentration.

The decrease in glomerular filtration and increased sodium reabsorption contributed to a reduction in osmotic clearance during exercise. The decreased osmotic clearance was accompanied by an increase in free water clearance. The osmotic clearance observed at all workloads under the various conditions was linearly related to urine flow ( $r = 0.89$ ,  $P < 0.001$ ) (Fig 13). This line represents a constant concentrating ability with the  $U_{OSM}/P_{OSM}$  ratio held constant. This ratio, 2.88, is well below that of maximal concentration ability, 4.0 (Smith, 1951). This conflicts with the findings of Refsum and Strömme (1975, 1978) who reported a decrease in the urine to serum osmolality ratio following a cross-country ski race. The skiers were allowed fluid during the race which was 4-6 hr in duration. The difference in fluid intake and exercise duration may account for the decrease in the ratio; however, their value of 2.84 postexercise is similar to that of the present study, 2.88. The difference between the line generated relating  $C_{OSM}$  to urine flow rate using the data from various workloads and the isosmotic line, where  $U_{OSM}$  is equal to  $P_{OSM}$ , is equivalent to tubular water reabsorption ( $T_{CH_2O}$ ). Tubular water reabsorption is the negative counterpart of free water clearance ( $C_{H_2O} = -T_{CH_2O}$  and  $T_{CH_2O} = -C_{H_2O}$ ). Therefore, as urine flow is reduced at a constant concentrating ability, osmotic clearance,  $C_{OSM}$ ,

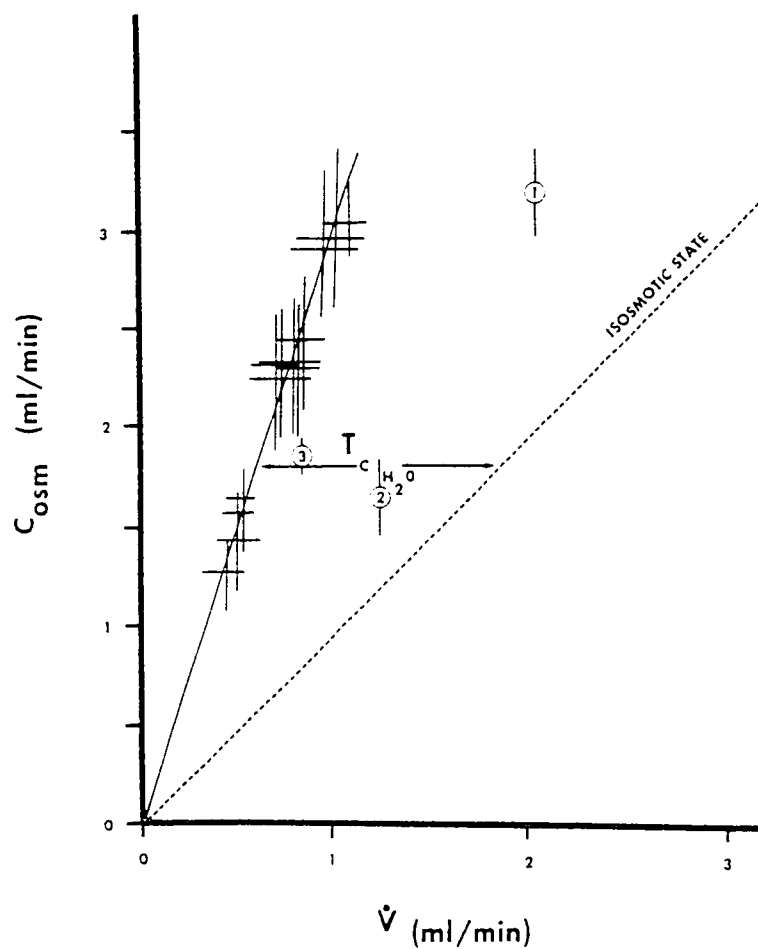


Figure 13: Presented here is osmotic clearance ( $C_{OSM}$ ) plotted against urine flow ( $\dot{V}$ ). The isosmotic state represents a urine osmolality equal to plasma osmolality. A shift to the left of this line represents a concentrating of the urine. Values for pre-exercise, postexercise, and recovery for the various workloads result in a linear relationship,  $2.33 \dot{V} + 0.53 = C_{OSM}$  ( $r = 0.89$ ,  $P < 0.01$ ). The hydrated maximal exercise is plotted as (1) pre-exercise, (2) post-exercise, and (3) recovery. The difference between the concentration line and the isosmotic line is equivalent to tubular water reabsorption,  $T_{CH_2O}$ .

and tubular water reabsorption are proportionally reduced and free water clearance is increased. The increase in free water clearance observed during exercise was a function of urine flow rate and not a decrease in plasma vasopressin as suggested by Kachadorian and Johnson (1972). Although plasma vasopressin was elevated, there appeared to be a lack of functional significance as there was no change in concentrating ability. Barclay et al. (1959) noted that exercise annulled the effect of injected Pituitrin determined by the time after the ingestion of 800 cc of water for urine flow to return to normal and the time for 800 cc to be voided. Recent work by Zambraski and Dunn (1979) noted the elevated excretion of renal PGE<sub>2</sub> and PGF<sub>2α</sub> in dogs following exercise. Renal prostaglandins are suggested to be important in the modulation of the renal effects of vasopressin (Olin, 1979; Share et al., 1978). Thus it is possible that the elevated plasma vasopressin observed during exercise does not affect concentrating ability because of the concurrent increase in prostaglandins.

Hydration caused a deviation toward the isosmotic line from the concentration line with a  $U_{Osm}/P_{Osm}$  ratio of 2.09. This ratio was maintained through exercise. The rightward shift of the concentration line may be due to a decrease in plasma vasopressin, though no difference was seen at rest. Following exercise, there was a significant difference compared to dehydrated maximal exercise. The observed lower plasma vasopressin concentrations would contribute to the shift. Following recovery from hydrated maximal exercise, there was a shift back to the concentration line with  $U_{Osm}/P_{Osm}$  equal to 2.54 which may be due to vasopressin. Dehydration after the water load may also explain this shift, as a control experiment with a water load without exercise was not performed.

In summary, an antidiuresis occurs during exercise at workloads equal to or greater than 70%. This antidiuresis may not occur in the presence of sufficient hydration. The decrease in urine flow is in part due to a decrease in glomerular filtration rate and an increase in sodium reabsorption. These factors result in a reduction in osmotic clearance with an accompanying increase in free water clearance. The increase in free water clearance is due to physical factors, glomerular filtration rate and sodium reabsorption, rather than a decrease in plasma vasopressin concentration.

Plasma osmolality: Plasma osmolality is a major factor influencing transvascular shifts of fluid during exercise (Greenleaf et al., 1979). The changes in plasma osmolality with exercise in our study were similar to those reported by other investigators (van Beaumont et al., 1973; Costill et al., 1976; Refsum and Strömme, 1978; Greenleaf et al., 1979). At the 70% workload, plasma osmolality was constant between the 20 to 60 min samples, although a significant rise in vasopressin was observed between these time periods. Plasma osmolality during recovery from this workload was not significantly elevated above pre-exercise; however, plasma vasopressin was significantly increased. Maximal exercise with hydration or dehydration showed similar osmolality changes, yet the response of vasopressin was significantly different. Thus the response to osmotic changes appears to be altered by the state of hydration, possibly due to the interrelationship of plasma osmolality and volume. An increase in volume elevates the osmotic threshold for vasopressin release (Miller and Moses, 1971). This may occur during hydration and contribute to the observed differences in the response of vasopressin to

osmotic shifts during maximal exercise. Robertson et al. (1973) have presented a linear regression relating plasma vasopressin in  $\mu\text{U/ml}$  to plasma osmolality in  $\text{mOsm/kg}$ ,  $y = 0.152 (x - 280)$ . The calculated changes in vasopressin at the 35, 70, and 100% workloads were 0.2, 0.8, and 1.2  $\mu\text{U/ml}$  compared to the measured differences of 0.2, 1.2, and 1.8  $\mu\text{U/ml}$ . Maximal exercise with hydration results in a 0.6  $\mu\text{U/ml}$  change in plasma vasopressin well below the predicted value of 1.4  $\mu\text{U/ml}$ . These findings suggest that changes in plasma osmolality at low workloads with dehydration may explain the elevation of plasma vasopressin, while at higher workloads there appears to be a regulation other than that attributable to osmolality. Plasma sodium, which is the major osmotically active component in plasma, did not change during exercise, while plasma osmolality was significantly elevated. Greenleaf et al. (1979) found no change in plasma sodium with an increase of osmolality during exercise and attributed the increase to an elevation of calcium. Lactate has also been shown to contribute to hyperosmolemia (Greenleaf et al., 1978). In the present study, maximal exercise resulted in an 8  $\text{mOsm/kg}$  increase in plasma osmolality, while lactate was elevated 5  $\text{mM}$  accounting for part of the increase in osmolality. An increase in urea, although not physiologically an osmotic component, may contribute to the elevation of measured osmolality during exercise. Although  $\text{Ca}^{++}$ , lactate, and urea may alter measured osmolality, they do not comprise part of the physiological effective osmolality regulating vasopressin. Plasma sodium has been reported to be elevated following maximal exercise if the sample is taken immediately postexercise; however, no difference is noted 3 min

postexercise (van Beaumont et al., 1973; van Beaumont, 1973). Our data showed no change post maximal exercise, but this finding was suspect as the plasma sodium levels, 129-133 mEq/l, were below those normally observed, 136-145 mEq/l (Ganon, 1975). Andersson and Olsson (1973) postulated the osmoreceptor responsible for vasopressin regulation to be primarily mediated by changes in cerebral spinal fluid sodium concentration. Although plasma sodium may only be indicative of cerebral spinal fluid sodium, the lack of change during exercise appears to raise questions as to this hypothesis.

Plasma osmolality was elevated during exercise in the absence of a change in sodium. Plasma osmolality appeared to contribute to the stimulation of vasopressin. The effective osmolality during exercise may be less than the measured value due to elevations of urea, calcium, and lactate. Therefore, the quantitative contribution of osmolality to the elevation of vasopressin during exercise cannot be fully evaluated. However, the lack of alteration of vasopressin to osmolality and response without a change in osmolality suggest factors other than osmolality are important in regulating vasopressin during exercise. The hydration state of the subject, possibly due to resulting changes in plasma volume, may also vary the responses of plasma vasopressin to osmotic changes during exercise.

Plasma volume and blood pressure: The trend of change in plasma volume after 20 min of exercise was similar to that seen by Wilkerson et al. (1977). Their observed change in plasma volume was a linear function of work intensity from rest through about 60%. A break occurred at this point, and there was a rapid decrease in volume in relation to work

intensity. However, our reduction of 4.3-12.8% following maximal exercise was below the 14% seen by others (Costill and Fink, 1974; Wilkerson et al., 1977). This difference does not appear to be due to the initial state of dehydration since during studies of dehydration and hydration the change in plasma volume in response to exercise was similar. The mode of exercise has been shown to alter the response of plasma volume to exercise (Senay, 1979). Wilkerson et al. (1977) performed this work on a treadmill in a fashion similar to the present study. Further, the tendency of plasma volume to increase above control values with 60 min of exercise in our study was not consistent with the literature. At submaximal workloads, plasma volume is noted to be reduced after 20 min and to remain lowered throughout exercise (Costill and Fink, 1974). This reduction is noted to persist through recovery (Costill and Fink, 1974; Harrison et al., 1975). During the 1 hr of recovery in the present study, plasma volume increased. Recent work by Colt et al. (1978) found extracellular water to increase by 3.5% after a 10-mile run in the presence of a 2.3% weight loss. The measurement taken over 3 hr post-exercise occurred with a 2.6% increase in plasma volume. The difference in the change in plasma volume response was suggested to be due to the fitness level of the subjects. Thus, trained subjects appear not to have as great a reduction in plasma volume during exercise and may increase plasma volume during a recovery period. The subjects in our study were physically active males who took part in some form of athletic training. Vasopressin infused at concentrations which do not elicit a pressure response increases plasma volume at the expense of extravascular spaces (Khokhär et al., 1976). The influx which increased plasma volume

at 60 min of exercise and during recovery may be explained by the elevated plasma vasopressin; however, no direct evidence is available.

During exercise, an elevation of plasma vasopressin may contribute to the maintenance of the effective blood volume. With training, repeated bouts of exercise, there is an increase in plasma volume (Dill et al., 1974). This increase could be due to an elevated plasma vasopressin as training is performed at workloads of 70 to 80%, which resulted in an elevation of plasma vasopressin through the recovery period in the present study. Repeated injections of Pitressin over 5-10 days have been shown to result in an increase in plasma volume, even though fluid intake was restricted (Goodwin et al., 1970). Thus, the elevation of vasopressin during exercise may contribute to the maintenance of the effective blood volume and, over long periods with repeated exercise, the elevation of plasma volume.

The changes in plasma volume early in exercise would stimulate vasopressin release, yet blood pressure is elevated negating the effect of a decrease in volume. The change in blood pressure was due to an elevation of systolic pressure during exercise. Exercise also increases heart rate which would increase left atrial baroreceptors activity (Henery et al., 1963) and increase pulse pressure, altering carotid baroreceptor activity (Share, 1974; Boykin et al., 1975). These factors would suppress vasopressin release. At 60 min of 70% exercise, there was no significant change in plasma volume or osmolality as compared to 20 min, but there was a significant reduction in blood pressure during this time. This reduction of blood pressure may explain the rise in

plasma vasopressin. However, this pressure was still greater than pre-exercise, indicating a negative input to vasopressin release during exercise. The quick return of blood pressure to resting values during recovery would be expected to further stimulate vasopressin release, but a decrease in plasma vasopressin concentration is seen. Therefore, while changes in blood pressure during exercise may alter vasopressin release, these changes would appear to suppress some other dominant stimulation of vasopressin release.

The reduction in plasma volume during exercise appears to have no effect on vasopressin release since the receptors sensitive changes in plasma volume seem to be stimulated. Indeed, plasma volume may itself be altered by vasopressin. The increased systolic blood pressure offers a suppressive effect on vasopressin release. Blood pressure and change in plasma volume during exercise cannot explain the elevation of vasopressin.

Plasma renin activity: Plasma renin activity appears to be dependent on work intensity and duration. Other investigators have demonstrated a linear relationship of PRA to workload (Maher et al., 1975; Kosunen and Pakarinen, 1976). However, the relationship to work duration has not been investigated. Workloads of 70% produced a 350% increase after 10 min of bicycle exercise, while 60 min at 60% produced a similar increase (Kotchen et al., 1971; Costill et al., 1976).

Angiotensin II, which stimulates vasopressin, parallels the change in PRA during exercise (Kosunen and Pakarinen, 1976). In the present study, the change in PRA during exercise paralleled that of vasopressin. However, when all values were considered, a relationship was not present. This may be due to a postulated negative feedback of

vasopressin on renin release (Tagawa et al., 1971; Khokhär et al., 1976). The elevation of the renin-angiotensin system may contribute to the potentiation of the osmotic stimulation of vasopressin (Shimizu et al., 1973). Maximal exercise with dehydration produced a PRA slightly greater than hydration; however, there was no significant difference. Therefore, angiotensin II potentiation of vasopressin release cannot explain the observed difference between dehydration and hydration with the same osmotic stimulus present.

Though PRA is indicative of angiotensin II during exercise and mirrored the elevation of vasopressin, a direct effect on the release of vasopressin cannot be identified. A potentiation of the osmotic stimulus during exercise also cannot be clarified. Thus, the role of angiotensin II in the regulation of vasopressin during exercise is not clear.

Stress: Although the role of stress upon vasopressin release is presently unclear, the subjects were familiarized with all procedures to eliminate possible "emotional" stress. The lack of response of cortisol to exercise at all workloads suggests ACTH is not elevated. Cortisol is elevated upon waking and falls over the next 2 hr (Clayton et al., 1963; Williams, 1974). Our studies were performed in the early morning, 0700-1100. This decrease in cortisol during the morning may mask the response of cortisol to exercise and explain the observed variability in the literature (Tharp, 1974; Sutton, 1978). However, in the present study no significant difference was noted in the control experiment which was performed at the same time. The lack of a response of cortisol to exercise would tend to negate stress as a stimulus of vasopressin and eliminate a possible direct effect of cortisol on renal function.

However, studies of the diurnal variation of cortisol show a fall in concentration during this period; therefore, some stress may have been present.

Temperature: Body temperature was elevated during exercise and throughout recovery. Maximal exercise produced an  $0.9^{\circ}$  C. increase in oral temperature. This magnitude of change in body temperature has been reported to elevate plasma vasopressin significantly in the rat (Szczepanska-Sadowska, 1974). The highest temperatures in this study were seen during recovery when vasopressin was decreasing. Maximal exercise during dehydration exhibited a greater change in temperature than with hydration and also had a greater change in vasopressin. However, the change in vasopressin was not related to the change in temperature. Temperature regulation is postulated to be governed by an osmoreceptor similar to that of vasopressin (Greenleaf, 1974). Therefore, the change in both parameters in this experiment may be due to central mediation. During recovery, however, temperature continued to rise while vasopressin and plasma osmolality decreased. Passive elevation of body temperature in a manner similar to that observed during exercise showed no significant difference in vasopressin excretion compared to compared to control or exercise experiments. Exercise tended to result in a higher excretion; however, more time was spent in an upright position which would elevate vasopressin (Moore, 1971; Davies and Forsling, 1975). The lack of difference may be due to the long sampling period, 5 hr, which included a 2-hr equilibration period. The heart rate observed during exercise,  $147 \pm 6$ , would be equivalent to a 72% workload. Vasopressin would be elevated with this workload;

therefore, when a Wilcoxon signed rank test was used to compare pre and postexercise vasopressin excretion, a significant difference was noted with exercise ( $P < 0.01$ ).

The response of vasopressin to exercise appears to be independent from temperature, as at the highest temperatures which were seen during recovery, vasopressin was decreasing from the elevated values seen postexercise.

Vasopressin metabolism: Renal and liver blood flow are reduced during exercise (Rowell, 1973; Castenfors, 1978). A reduction in renal blood flow is indicated by the decrease in glomerular filtration rate and, therefore, creatinine clearance (Castenfors, 1978). Vasopressin metabolism is a function of hepatic and renal blood flow (Lauson, 1974). Therefore, during exercise vasopressin renal metabolism was decreased in our study as creatinine clearance was significantly reduced. The change in creatinine clearance, however, was not significantly related to the elevation of vasopressin. The decrease in vasopressin renal metabolism may contribute to the elevation of plasma vasopressin during exercise, but it was not a singular effect.

Summary: Exercise produces an increase in plasma vasopressin concentration which is varied by work intensity and duration (Fig 14). The hydration state of an individual alters the response to exercise with a greater increase in plasma vasopressin observed in response to maximal exercise with dehydration. An elevated plasma osmolality and decreased glomerular filtration rate may contribute to an elevated plasma vasopressin during exercise; however, a singular factor cannot be

identified. Plasma renin activity indicative of angiotensin II concentration during exercise is elevated, but the role of this system and its effects on vasopressin are not clear.

Temperature was elevated during exercise but did not appear to contribute to the stimulation of vasopressin release. A significant "stress" probably did not occur during exercise, as cortisol did not increase, and therefore did not appear to participate in the elevation of plasma vasopressin. The change in plasma volume probably did not contribute to the stimulation of vasopressin release as blood pressure was elevated. The elevation of blood pressure appeared to be effective in suppressing the release of vasopressin, but was overridden by stimulatory factors.

The antidiuresis postexercise in subjects with 10 hr of dehydration was not due to the increase in vasopressin and an increase in tubular water reabsorption, but to alterations in glomerular filtration rate and sodium reabsorption. Vasopressin appeared to be ineffective in altering renal concentrating mechanism during exercise in dehydrated subjects.

## THE RESPONSE AND REGULATION OF VASOPRESSIN DURING EXERCISE

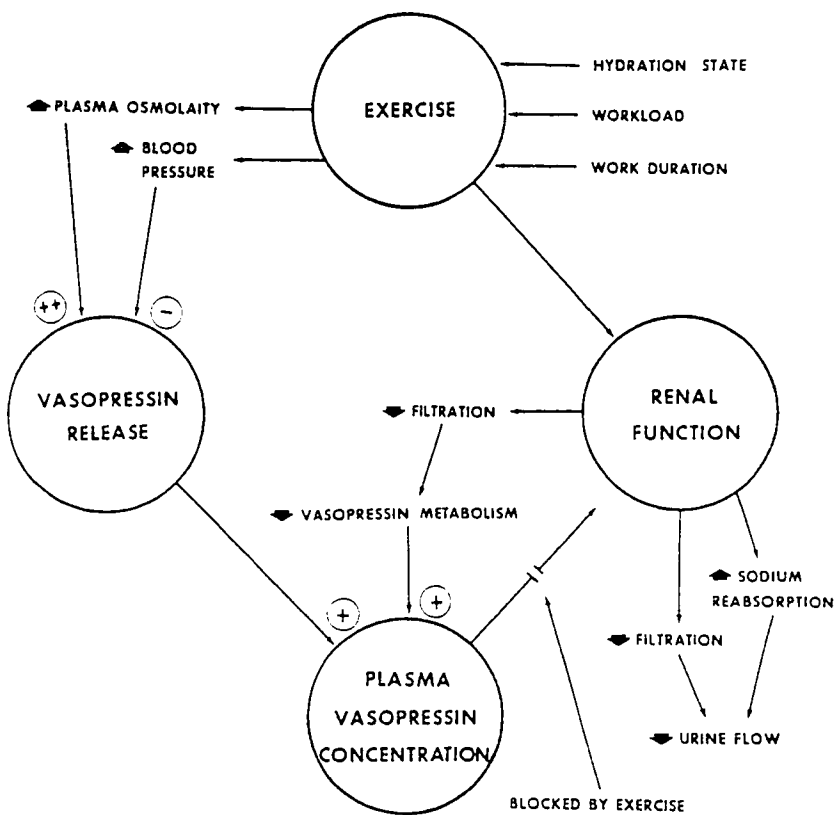


Figure 14: This figure summarizes the response and regulation of vasopressin during exercise. Stimulation is represented as a + and suppression as -. The arrows represent an increase or decrease in the corresponding parameter.

## CONCLUSIONS

(1) Plasma vasopressin concentrations were elevated in response to exercise depending upon the duration and intensity of the exercise. The return of plasma concentrations of vasopressin to control values during recovery in the absence of rehydration suggests a direct effect of exercise in the regulation of vasopressin release independent of the dehydration occurring during exercise.

(2) The elevation of plasma vasopressin may be altered by plasma osmolality or blood pressure; however, conditions negating these factors as regulators did occur. Therefore, exact roles of plasma osmolality and blood pressure in the regulation of vasopressin release during exercise are unclear. Vasopressin metabolism may be decreased during exercise contributing to the elevation of plasma concentrations.

(3) Body temperature, the change in plasma volume, and plasma cortisol appeared to play minor roles in the regulation of vasopressin release during exercise.

(4) The hydration state of an individual altered the response of vasopressin release to exercise.

(5) The elevation of vasopressin during exercise was ineffective in altering the concentrating ability of the kidney in dehydrated individuals. Therefore, vasopressin did not contribute to the antidiuresis associated with the exercise.

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