

# Renal Responses to High Intensity Exercise

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**ABSTRACT.** Renal blood flow (RBF), glomerular filtration rate (GFR), urine flow, and excretion of selected electrolytes were measured in 6 mares for 30 min at rest, during fatiguing exercise at  $VO_{2max}$ , and for 2 hours post-exercise. Cardiac output increased from 40.9 lmin<sup>-1</sup> at rest to 290.2 lmin<sup>-1</sup> during exercise, while RBF decreased from 9.0 lmin<sup>-1</sup> at rest to 2.6 lmin<sup>-1</sup> during exercise. GFR decreased from 1.88 mlmin<sup>-1</sup>kg<sup>-1</sup> at rest to 0.50 mlmin<sup>-1</sup>kg<sup>-1</sup> during exercise. Filtration fraction increased from 15.8% at rest to 23.2% during exercise. Urine flow decreased abruptly with the onset of high intensity exercise and increased transiently post-exercise. The increase in urine production post-exercise was accompanied by a decrease in urine specific gravity. Excretion of sodium and potassium were transiently increased and decreased, respectively, post-exercise but no change in chloride excretion was observed. These results demonstrate that renal hemodynamics and renal function are transiently altered during and following high intensity exercise. This is consistent with a major shunting of blood flow away from the kidneys.

*Key words* Horses; exercise; kidneys; renal blood flow; glomerular filtration rate; electrolytes.

## INTRODUCTION

The onset of high intensity exercise in the horse is accompanied by dramatic increases in cardiac output and oxygen consumption. Blood flow to skeletal muscle may increase 70- to 80-fold and cutaneous blood flow will increase to dissipate heat.<sup>17</sup> With this hemodynamic response to strenuous exercise, blood flow to renal and splanchnic tissues has been reported to decrease.<sup>8</sup> Such a distribution of cardiac output during intense exercise could lead to alterations in function of these less well perfused tissues during and following bouts of high intensity exercise.

Changes in renal blood flow (RBF) during high intensity exercise have not been reported for the horse, but in man,<sup>4,12</sup> miniature swine,<sup>19</sup> and the pony,<sup>8,10</sup> RBF decreased substantially (to 20–30% of the resting value). In contrast, blood flow to the kidneys

was unchanged during strenuous exercise in dogs.<sup>2,20,24</sup>

Decreases in glomerular filtration rate (GFR), urine flow, and urinary excretion of electrolytes have been reported with a variety of exercise protocols in man.<sup>12</sup> These renal responses to exercise are suggested to be a homeostatic mechanism to conserve sodium for the maintenance of plasma volume and cardiac output.<sup>1,3</sup> Despite a decrease in GFR, filtration fraction (FF) and excretion of urinary sediments (cells, casts, and protein) increase with exercise.<sup>12</sup> Since there are no apparent advantages for these latter renal responses, such changes may reflect impaired function rather than a homeostatic response to exercise.

We investigated the hypothesis that strenuous exercise causes a decrease in RBF and alterations in renal function in the horse.

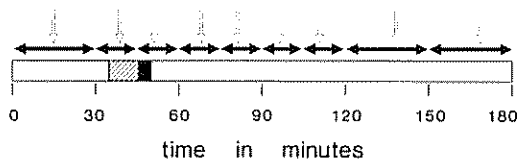


Fig. 1. Experimental protocol. Cross-hatched area in timeline represents warm-up period and filled area represents high intensity exercise. Urine collection periods (filled double arrows) and blood collection times (open arrows) are shown.

Using a technique of ureteral catheterization,<sup>21</sup> we were able to assess rapid changes in urine flow and urine composition that accompany a single bout of high intensity exercise.

## MATERIALS AND METHODS

**Horses.** Six mares (3 Thoroughbreds and 3 crossbreds) aged 3–7 years and weighing 394–497 kg were studied. All had the left carotid artery surgically relocated to a subcutaneous location and were accustomed to instrumentation and exercise on a high speed treadmill. The mares were housed in outside pens, were fed alfalfa hay twice daily and water *ad libitum*, and had free access to a trace mineral salt block. They were exercised on the treadmill for  $\approx 20$  min a day for a minimum of 30 days prior to study and maximal oxygen consumption ( $\dot{V}O_{2\max}$ ) was determined prior to experimentation.<sup>18</sup> Each mare was studied on two occasions with an interval between studies of no more than two weeks.

**Part 1—Renal function study.** Mares were fed as usual on the morning of each experiment but water was withheld for the 2 hours prior to exercise (i.e. during instrumentation and collection of the resting samples). After insertion of bilateral intravenous catheters (jugular veins) and bilateral indwelling ureteral catheters (18 French silicone Foley catheters, Bard Urological, modified as described),<sup>21</sup> mares were led onto the treadmill and a solution containing inulin (IN, 2.5% solution) and p-aminohippurate (PAH, 1%

solution) was administered intravenously (bolus of  $1 \text{ ml kg}^{-1}$ , followed by constant infusion of  $0.01 \text{ ml kg}^{-1} \text{ min}^{-1}$ ). After a 30 min period for stabilization of plasma IN and PAH concentrations, nine volumetric urine collections (via gravity flow from the ureteral catheters) were performed. An initial 30 min collection was used to determine resting (control) values. This was followed by six 15 min collections and two 30 min collections (Fig. 1). Since urine production during high intensity exercise was low, 15 min was considered the minimum collection interval that could be used to accurately calculate clearances. The 3rd urine collection period started at the onset of high intensity exercise (after the warm-up period) and continued until 10 min after the end of exercise.

The exercise bout consisted of a warm-up period of 5 min at  $1.7 \text{ m s}^{-1}$  followed by 5 min at  $4 \text{ m s}^{-1}$  and continued with high intensity exercise ( $100\% \text{ VO}_{2\max}$ ) to fatigue. Fatigue was defined as the point where the mares failed to maintain the speed of the treadmill belt despite verbal encouragement. All exercise bouts were performed in a temperature controlled room ( $21.0^\circ\text{C}$ ) on a high speed treadmill (Säto, Sweden) set at a 10% slope.

Venous blood was collected into heparinized tubes near the midpoint of each urine collection period (Fig. 1) via the venous catheter contralateral to the infusion. A total of  $\approx 2.5$  l of the PAH/IN solution was administered during the study while  $\approx 1.0$  l of blood was collected resulting in a positive fluid balance of  $\approx 1.5$  l. This small fluid load was assumed to be inconsequential as a greater volume of fluid likely was lost as sweat during and after the exercise bout. Since even greater fluid shifts were anticipated to accompany the exercise bout (leading to an elevation in plasma PAH and IN concentrations), blood samples were collected every 5 min for the urine collections spanning the exercise bout (i.e. 2nd and 3rd collection periods) and mean IN and PAH concentrations were used in clearance calculations. 1 ml of plasma was deproteinized with

2 ml of 8% TCA and IN concentration of the supernatant fluid was determined.<sup>7</sup> PAH concentration of supernatant fluid was determined after deproteinization of 1 ml of plasma with 2 ml of 3 N NaOH and 2 ml of 3 N ZnSO<sub>4</sub>.<sup>6</sup> Urine IN and PAH concentrations were measured without deproteinization on samples diluted 1:500 to 1:2000. Urinalysis (specific gravity by refractometry and reagent strip analysis, Ames Multistix, Miles Inc., to assess changes in urine pH and glucose concentration) and measurement of urine IN, PAH, and electrolyte concentrations (sodium and potassium with Instrumentation Laboratory Model 143 Flame Photometer and chloride with Radiometer CMT 10 Chloride Titrator) were performed on aliquots of urine collected from each ureter. Effective renal plasma flow (ERPF), GFR, and FF were calculated.<sup>22</sup>

*Part 2—Cardiac output study.* After insertion of catheters into the carotid and pulmonary (confirmed by waveform) arteries, mares were led onto the treadmill and resting samples collected for measurement of arterial and mixed venous O<sub>2</sub> content (Instrumentation Laboratory 282 Oximeter). Oxygen consumption was determined by analysis of expired gases<sup>18</sup> and cardiac output ( $\dot{Q}$ ) determined by the direct Fick principle. Hematocrit (Hct) was measured in duplicate on samples of mixed venous blood. RBF (both the absolute value and as a percentage of  $\dot{Q}$ ) was calculated using a PAH extraction ratio of 0.91 as:

$$\text{RBF} = (\text{ERPF}/0.91)/(1-\text{Hct}).^{22}$$

After collection of resting samples, the mares performed an identical exercise bout as in Part 1 of the experiment. All parameters were measured at similar times during exercise and for 2 hours post-exercise as in the renal function study.

*Statistical analysis.* Values presented are means  $\pm$  SD. Since differences in urine volume and urine PAH, IN, and electrolyte concentrations between samples collected from the right and left ureteral catheters were

minimal, the results for each kidney were combined. A repeated measures analysis of variance was used to compare differences between means across time. When significant F ratios were found, a Dunnett's post-hoc test was used to compare treatment means (collection periods 2 to 9) to control means (collection period 1). Unless otherwise indicated,  $p < 0.05$  was considered significant.

## RESULTS

*Metabolic responses to exercise.* Time to fatigue after onset of high intensity exercise (treadmill speed 8.0 to 11.4 m s<sup>-1</sup>) was  $4.46 \pm 1.4$  min. Peak VO<sub>2</sub> ( $119.1 \pm 21.0$  ml min<sup>-1</sup> kg<sup>-1</sup>) was achieved between the 3rd and 5th min of high intensity exercise.  $\dot{Q}$  increased from  $40.9 \pm 8.6$  l min<sup>-1</sup> at rest to  $290.2 \pm 38.4$  l min<sup>-1</sup> during high intensity exercise.

*Renal responses to exercise.* ERPF decreased from  $11.9 \pm 2.7$  ml min<sup>-1</sup> kg<sup>-1</sup> at rest to  $2.4 \pm 1.5$  ml min<sup>-1</sup> kg<sup>-1</sup> (20% of rest) ( $p < 0.01$ ) during high intensity exercise (Fig. 2). Absolute RBF decreased from  $9.0 \pm 1.9$  l min<sup>-1</sup> at rest to  $2.6 \pm 1.6$  l min<sup>-1</sup>. This represented a decrease in RBF from 22% of  $\dot{Q}$  at rest to 0.09% of  $\dot{Q}$  during high intensity exercise. GFR decreased to 27% of control value during exercise (from  $1.88 \pm 0.67$  ml min<sup>-1</sup> kg<sup>-1</sup> at rest to  $0.50 \pm 0.25$  ml min<sup>-1</sup> kg<sup>-1</sup>,  $p < 0.01$ ). FF increased from  $15.8 \pm 4.8\%$  at rest to  $23.2 \pm 6.3\%$  during exercise.

Urine flow stopped shortly after the onset of high intensity exercise and was absent for the remainder of the exercise bout. Further, as urine production resumed post-exercise, the rate progressively increased (to greater than the resting value) during the 20–30 min following the exercise bout. Although all mares demonstrated this cessation of urine flow during high intensity exercise and had a post-exercise period of diuresis, the total volume of urine collected during the 3rd collection period (and thus the calculated urine flow rate) was not different from the resting

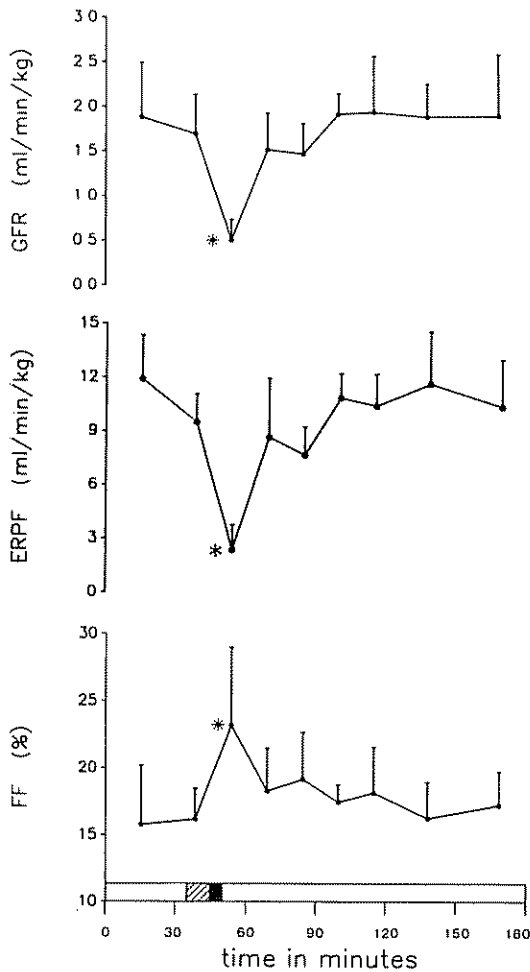


Fig 2 Effective renal plasma flow (ERPF), glomerular filtration rate (GFR), and filtration fraction (FF) during and following high intensity exercise. Cross-hatched area in timeline represents warm-up period and filled area represents high intensity exercise. Data points (means  $\pm$  SD bar) are plotted at the midpoint of each collection period. \*  $p < 0.05$ .

value ( $9.9 \pm 6.3 \mu\text{l min}^{-1} \text{kg}^{-1}$  during exercise compared to  $21.4 \pm 10.0 \mu\text{l min}^{-1} \text{kg}^{-1}$  at rest). During the 4th collection period (10–25 min post-exercise) urine production increased ( $49.3 \pm 34.0 \mu\text{l min}^{-1} \text{kg}^{-1}$ ). A decrease in urine specific gravity accompanied this increase in urine flow rate; however, specific gravity actually reached its mini-

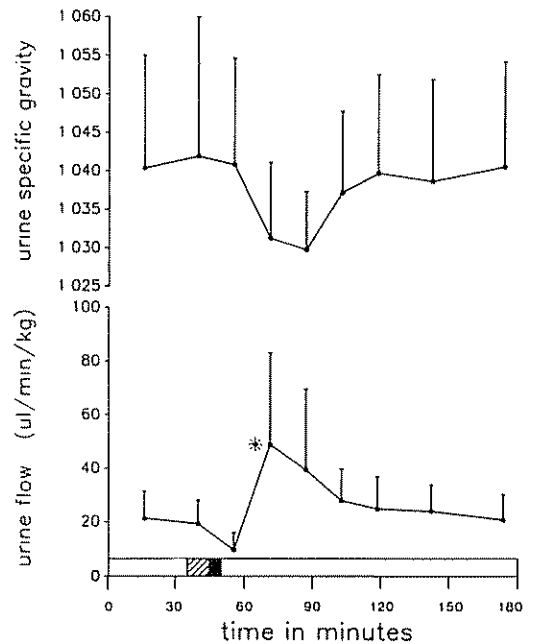


Fig 3 Urine flow rate and urine specific gravity during and following high intensity exercise. Cross-hatched area in timeline represents warm-up period and filled area represents high intensity exercise. Data points (means  $\pm$  SD bar) are plotted at the midpoint of each collection period. \*  $p < 0.05$ .

mum value during the 5th collection period (Fig. 3).

High intensity exercise resulted in a transient increase and decrease in the urinary excretion of sodium and potassium, respectively (Fig. 4). There was no change in chloride excretion. From 15 to 60 min post-exercise, urine pH decreased (from a resting value of 8.5 in all mares) to 6.0–8.0. Transient post-exercise glucosuria was also noted in the 3 crossbred mares.

## DISCUSSION

High intensity exercise resulted in a substantial reduction in RBF and GFR in horses. The decrease in RBF was similar to what has been described in man,<sup>4,12</sup> miniature swine,<sup>19</sup> and the pony.<sup>8,10</sup> In man, RBF decreases linearly with increasing exercise in-

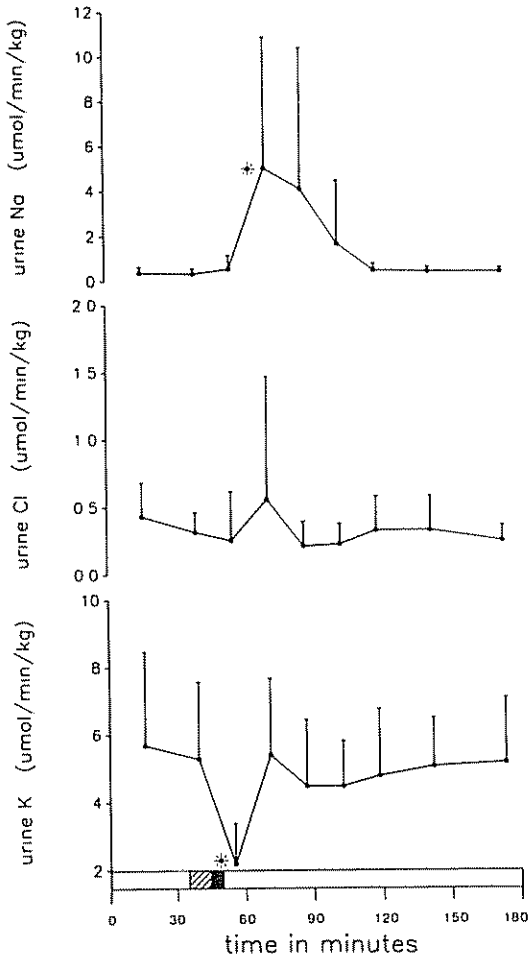


Fig. 4. Urinary excretion of electrolytes during and following high intensity exercise. Cross-hatched area in timeline represents warm-up period and filled area represents high intensity exercise. Data points (means  $\pm$  SD bar) are plotted at the midpoint of each collection period. \*  $p < 0.05$ .

tensity as activation of the sympathetic nervous system and circulating catecholamines lead to a progressive increase in renal vascular resistance.<sup>3,12</sup> In contrast, GFR does not decrease during exercise of low or moderate intensity and with heavy exercise, the reduction in GFR (to 50% of the resting value) is considerably less than that in RBF.<sup>4,12</sup> This sparing effect on GFR in man, reflected by an increase in FF from 20% at rest to 30–35% during strenuous exercise,<sup>12</sup> was not

observed in horses. This difference may reflect a species variation in the renal response to high intensity exercise, but further investigations at submaximal exercise intensities are required to detail the relative decreases in RBF and GFR in the exercising horse.

Urine flow from the ureteral catheters was observed to stop with the onset of high intensity exercise and as flow resumed post-exercise, the rate increased above the resting value. The antidiuretic effect of exercise is well described in man<sup>12,15,16,24</sup> but measurement of changes in urine flow has been largely limited to collection of urine samples voided prior to and at various times following exercise. In investigations employing indwelling bladder catheters, changes in urine flow were not significant (limited number of subjects)<sup>9</sup> or were not described.<sup>4</sup> However, trends in urine flow data similar to our observations in mares have been reported,<sup>9</sup> as have transient declines in renal concentrating ability post-exercise.<sup>15,16,24</sup> The use of ureteral catheters in these mares allowed assessment of rapid changes in urine flow such that our results may be the first to detail the time course of changes in urine production during strenuous exercise in any species.

Urinary excretion of sodium and potassium were increased and decreased, respectively, after high intensity exercise in horses. These results are in contrast to the renal conservation of sodium during exercise in man.<sup>1,12</sup> Equine urine normally contains more potassium and less sodium than human urine, which is largely due to differences in diet.<sup>23</sup> Further, equine sweat has a greater sodium and chloride content in comparison to man.<sup>23</sup> Considering these physiological differences, horses would be expected to conserve sodium to a greater extent during exercise than man, but our findings during high intensity exercise and that of others<sup>23</sup> during moderate exercise do not support this.

The mechanism for these alterations in urinary excretion of electrolytes in exercising horses is not known. Strenuous exercise in man is accompanied by a transient increase

in filtration fraction and impairment of tubular function, manifested by a post-exercise proteinuria of both glomerular and tubular origin.<sup>13</sup> If similar changes occur with high intensity exercise in the horse, the return of RBF post-exercise could lead to an increase in glomerular filtrate and more rapid fluid transport through the tubule. Tubular modification of glomerular filtrate may be diminished (due to more rapid transit or functional impairment) resulting in less sodium reabsorption and potassium excretion. Such a mechanism would be consistent with the almost parallel increase in urine production and sodium excretion observed in these mares. A difficulty with this explanation is that urine chloride would be expected to passively follow urine sodium and an increase in urinary chloride excretion was not observed. High intensity exercise, however, is associated with a dramatic increase in urine lactate concentration.<sup>9</sup> The large load of a more poorly resorbable anion (lactate) in tubular fluid may promote passive reabsorption of chloride.<sup>9</sup> Glucosuria was observed only in the crossbred mares. These mares manifested a higher peak plasma glucose concentration (all above 200 mg dl<sup>-1</sup>) in comparison to the Thoroughbred mares suggesting that the transport maximum was exceeded.

Exercise results in activation of the renin-angiotensin-aldosterone system.<sup>3</sup> Increases in plasma renin activity and elevations in aldosterone concentration have been reported after maximal exercise in horses.<sup>5,14</sup> The action of aldosterone on the distal tubule should result in complete sodium resorption and enhanced potassium excretion (again in contrast to our findings). A factor contributing to the observed decrease in potassium excretion may be diminished exchange with hydrogen ions in the distal tubule (consistent with the decrease in urine pH post-exercise).

Another mechanism for the post-exercise alterations in urinary electrolyte excretion that should be considered is the action of atrial natriuretic peptides (ANPs). ANPs, released in response to atrial distension, have

potent natriuretic, diuretic, and vasodilatory properties which are thought to modulate the neural and hormonal responses to exercise.<sup>11</sup> The significance of their role during exercise in humans is not well established although increased in ANPs have been reported during strenuous exercise.<sup>11</sup>

Our results demonstrate that RBF and renal function are transiently but markedly altered with high intensity exercise in the horse. The changes are consistent with a major shunting of blood flow away from the kidneys. Further investigation over a range of submaximal to maximal exercise intensities is needed to more completely define the changes in renal hemodynamics and renal function which accompany exercise in horses. Additionally, the systemic and intrarenal neuroendocrine responses to exercise in the horse warrant further definition in order to understand the mechanisms responsible for the renal responses which accompany exercise.

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# Atrial Natriuretic Peptide during Exercise in Horses

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**ABSTRACT.** Six unfit mares were subjected to maximal and steady state submaximal treadmill exercise to examine exercise-induced changes in the plasma concentration of atrial natriuretic peptide (ANP), a hormone with profound vasodilatory and renal effects, that is released by atrial stretch. In Experiment 1, ANP was measured at each step of an incremental maximal heart rate (HR) test. Exercise was started at 4 m s<sup>-1</sup>, and speed was increased 1 m s<sup>-1</sup> each min until HR reached a plateau. In Experiment 2, mares were randomly assigned to either an exercise (EX) or parallel control (CON) trial on day 1 and the alternate trial 1 week later. The horses ran on a treadmill, up a 6° slope, for 1 hour at 55–60% of HR<sub>max</sub>. Central venous blood was collected at 0, 20, 40, and 60 min during EX or CON. Plasma was stored at -80°C and later thawed, extracted with C18 columns and assayed for ANP by a RIA kit (Peninsula Laboratories, Inc.). Plasma ANP increased 600% ( $p < 0.05$ ) from  $9 \pm 1$  pg ml<sup>-1</sup> (mean  $\pm$  SE) at rest to  $63 \pm 14$  pg ml<sup>-1</sup> at HR<sub>max</sub> in Experiment 1, and from  $11 \pm 1$  pg ml<sup>-1</sup> at rest to a peak of  $40 \pm 9$  pg ml<sup>-1</sup> (264%,  $p < 0.05$ ) at 40 min of EX in Experiment 2. During CON, ANP did not change ( $p > 0.05$ ) from  $13 \pm 2$  pg ml<sup>-1</sup> at 0 min. There were no significant differences among the three baseline values, observed for the two experiments. Increases in ANP concentration were highly correlated with %HR<sub>max</sub> ( $r = 0.92$ ). These results suggest a potential role for increasing concentrations of ANP in the cardiovascular/renal responses to maximal and submaximal exercise in horses.

*Key words:* Atrial natriuretic peptide; exertion; horses.

## INTRODUCTION

Atrial natriuretic peptide (ANP) is a hormone produced by the heart which may be important in the regulation of blood flow distribution and blood pressure during exercise.<sup>3,5</sup> Granules of ANP are stored within the walls of the atria and are released during atrial stretch.<sup>3</sup> Receptor sites for ANP have been identified in the posterior pituitary, the kidneys, vascular smooth muscle, adrenal cortex, heart, and lung.<sup>2</sup> This hormone causes a rapid and profound vasodilation and a pronounced natriuresis.<sup>1,2,3,8</sup> Atrial natriuretic peptide inhibits vasopressin, renin, and aldosterone secretion and also inhibits the binding of aldosterone at the kidney tubule.<sup>2,8</sup> Specific receptors for ANP have been found in the glomeruli, the thick ascending

limb, and the collecting ducts of the kidney, and renal effects of ANP have been attributed to both changes in glomerular filtration rate and changes in tubular sodium reabsorption.<sup>1,2,3,8</sup> Cardiovascular effects of ANP are rapid (seconds) and include vasodilation, bradycardia, and hypotension.<sup>3,8</sup> The action of ANP on the posterior pituitary and the kidney takes minutes,<sup>3,8</sup> and the circulating half-life of ANP is 1–15 min.<sup>3,8</sup>

At the onset of exercise, there is a significant shift of blood volume from the venous vessels to the arterial side of the circulatory system.<sup>14,15</sup> This increase in venous return is accompanied by simultaneous increases in blood flow to the working muscles and to cutaneous vascular beds associated with thermoregulation.<sup>14,15</sup>