

cating that the increase seen during exercise was not caused by upward drift in response to some perturbation not associated with exertion. Studies involving humans have not had parallel control trials; thus, interspecies comparisons regarding drift cannot be made.

On a practical level, ANP may be involved in accommodating the exercise related shifts of blood volume in the horse. This fluid shift may play a role in the onset of exercise-induced pulmonary hemorrhage (EIPH),<sup>9</sup> a pathological problem which affects many horses in competition.<sup>10</sup>

A fragment of the ANP molecule has been tested in humans for the treatment of hypertension, ascites associated with heart failure, and renal disorders. Atrial natriuretic peptide lowers vascular fluid volume and decreases vascular resistance—actions similar to those caused by furosemide, a drug currently used to treat humans with the aforementioned conditions and horses with EIPH. Atrial natriuretic peptide is a naturally occurring agent which may be useful for the treatment of epistaxis in racehorses. Future research should correlate hemodynamic changes and ANP during exercise.

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## Effects of Exercise on Plasma Concentrations of Prostaglandins and Thromboxane B<sub>2</sub>

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**ABSTRACT.** Plasma concentrations of prostaglandins (6-keto-PGF<sub>1 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> , PGE) and thromboxane (TXB<sub>2</sub>) were measured in 5 Thoroughbred horses running on a level treadmill. The exercise protocol was a 3 min warm up (4 m s<sup>-1</sup>), a 3 min rest, 2 min at 4 m s<sup>-1</sup>, 2 min at 7 m s<sup>-1</sup>, and 3 min at a speed eliciting a maximum rate of O<sub>2</sub> consumption ( $\dot{V}_{O_2,max}$ ) (14–16 m s<sup>-1</sup>). Horses walked (1.5 m s<sup>-1</sup>) for 30 min at the end of the exercise period. Blood samples were drawn from the pulmonary artery prior to the warm up, at the ends of the 7 m s<sup>-1</sup> and  $\dot{V}_{O_2,max}$  runs, and 15 min into the post-exercise period. Prostanoid concentrations in these blood samples were measured by radioimmunoassay. Concentrations of 6-keto-PGF<sub>1 $\alpha$</sub>  were elevated above resting values in all samples. The concentration of TXB<sub>2</sub> was significantly greater at the end of the post-exercise period than at all other sample times, while PGE and PGF<sub>2 $\alpha$</sub>  concentrations were unchanged throughout the experiment. The effects that these changes in the concentrations of prostanoids during exercise may have on cardiovascular function remains to be elucidated.

*Key words:* Horses; prostaglandins; thromboxane; exercise.

### INTRODUCTION

Arachidonic acid (AA) derivatives exert a number of important biological effects. Leukotrienes, products of the action of lipoxygenase on AA, affect primarily the immune system,<sup>24</sup> particularly by acting as chemotactic agents for leukocytes and causing increased vascular permeability.<sup>3</sup> The latter action may be important in inflammation by enhancing the potential for movement of compounds into and out of capillaries. The present study concentrated solely upon the prostanoids, AA products resulting from the action of cyclo-oxygenase.

In addition to well documented effects on the reproductive system<sup>16</sup> and platelet aggregation,<sup>2</sup> prostanoid actions on various portions of the cardiovascular system have received much attention.<sup>1,15</sup> It has been demonstrated that prostaglandins (PG) of the E series, especially PGE<sub>2</sub>, and PGI<sub>2</sub> (prostacyclin) can act as vasodilators.<sup>9</sup> These actions

have been observed on arterioles, as well as post-capillary venules. Conversely, PGF compounds have been shown to cause constriction of venules and veins.<sup>24</sup> Thromboxane compounds act in platelet aggregation, and can also cause vasoconstriction.<sup>6,9</sup> Studies using specific inhibitors of cyclo-oxygenase have demonstrated only slight changes in the resting blood pressures of normotensive or hypertensive humans.<sup>24</sup> In hypotensive states, however, these inhibitors tend to improve circulation and survival.<sup>8</sup> While these observations lead to much speculation, the exact role that these effects have upon the regulation of blood pressure and regional blood flow has yet to be elucidated.

The potential for direct relationships existing between prostanoid concentrations and alterations in various cardiovascular parameters raises a question as to the role of these interactions during exercise, when changes in the cardiovascular parameters

from the resting state are maximized.<sup>20</sup> While the literature is replete with studies detailing the biological activities of the various prostanoids in both humans and animals, few have examined the relationships between prostanoids and exercise. Conflicting results have been reported from the few studies that measured prostanoid concentrations during exercise in humans. Following a marathon run, plasma concentrations of PGE<sub>2</sub>, PGF<sub>2α</sub>, and 6-keto-PGF<sub>1α</sub>, a stable derivative of PGI<sub>2</sub>, were found to have increased.<sup>5</sup> Treadmill<sup>17</sup> and cycle<sup>14</sup> ergometer exercise also cause an increase in the plasma concentration of 6-keto-PGF<sub>1α</sub>. However, other studies involving treadmill and cycle ergometer exercise have shown either only a transient increase, or a decrease, in plasma 6-keto-PGF<sub>1α</sub> concentrations.<sup>22,23</sup> Additionally, in studies involving human patients with coronary artery disease, no appreciable changes in plasma PGI<sub>2</sub> concentrations were detected even during maximal treadmill exercise.<sup>17</sup>

Exercise studies examining changes in prostanoid concentrations in non-human animals are rare.<sup>18</sup> This paper describes the effects of exercise in horses on plasma concentrations of the prostanoids PGF<sub>2α</sub>, PGE (PGE<sub>1</sub> + PGE<sub>2</sub>), 6-keto-PGF<sub>1α</sub> and thromboxane B<sub>2</sub> (TXB<sub>2</sub>), a stable derivative of thromboxane A<sub>2</sub>.

## METHODS AND MATERIALS

Five Thoroughbred geldings ( $5.8 \pm 0.8$  (SD) year old, weighing  $462 \pm 19$  (SD) kg) were trained to run on a motorized treadmill while wearing a mask over their muzzles. The mask was utilized to collect expiratory gases for the determination of  $\dot{V}_{O_2}$  with an open-flow system previously described.<sup>1,7</sup> At the end of a 3 month treadmill conditioning program, running 3 times per week, a reproducible  $\dot{V}_{O_2\max}$  was obtained for each horse.<sup>1</sup>  $\dot{V}_{O_2\max}$  was defined in these studies as occurring when  $\dot{V}_{O_2}$  did not increase with increased running speed and anaerobic glycolysis could account for the additional ener-

gy (ATP production) needed to run at the increased speed. Plasma lactic acid accumulation rates were utilized to estimate the energetic contribution from anaerobic glycolysis. For this procedure, two blood samples taken at a timed interval are used to determine the rate at which lactic acid entry into the blood exceeds its removal.<sup>1</sup> The horses ran on the treadmill according to the following protocol: (1) pre-run samples were collected; (2) a 3 min warm-up trot at  $4 \text{ m s}^{-1}$ ; (3) 3 min rest standing on the treadmill, during which the gas collection mask was attached to the horse's muzzle; (4) 2 min at  $4 \text{ m s}^{-1}$ ; (5) 2 min at  $7 \text{ m s}^{-1}$ ; (6) 3 min at a running speed previously determined for each horse, as described below; (7) 30 min of recovery at a slow walk ( $1.5 \text{ m s}^{-1}$ ). Because the running speed that elicited  $\dot{V}_{O_2\max}$  differed for each of the 5 horses, as did the magnitude of  $\dot{V}_{O_2\max}$ , the maximum speed at which each horse ran was  $1 \text{ m s}^{-1}$  faster than the speed that elicited  $\dot{V}_{O_2\max}$  for that horse, to ensure that  $\dot{V}_{O_2\max}$  was achieved on each run.

Prior to each experiment, catheters were placed percutaneously into the right carotid artery (CA), which had previously been transposed to a subcutaneous position, and into the pulmonary artery (PA) via the left jugular vein. Positioning of the PA catheter was verified by monitoring blood pressure at the tip of the catheter during advancement. During the experiment, these catheters were used to collect blood samples for determination of concentrations of prostanoids and lactic acid. At times when blood samples were not being collected, these same catheters were connected via saline-filled tubing to pressure transducers (Statham P23Db, Gould Inc., Cleveland, OH) to monitor mean blood pressure, determined electronically by the transducer amplifier as the time-weighted average of the blood pressure waveform. The transducers, calibrated daily with a Hg manometer, were placed at heart level utilizing the caudal point of the olecranon process of the forelimb as the external landmark. Gel electrodes were securely at-

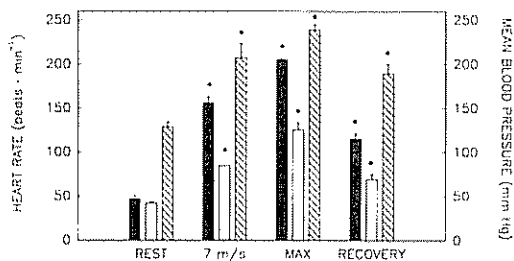


Fig 1 Heart rate (solid box), mean pulmonary arterial (PA) pressure (open box), and mean carotid arterial (CA) pressure (left diagonal box) at various exercise intensities. Values are means  $\pm$  SEM of samples from 5 horses. \*indicates significantly different from resting values,  $p < 0.0001$ .

tached with cyanoacrylate cement (Quick Gel, Loctite Corp., Cleveland, OH) to shaved areas on the neck and flank for collection of ECG signals. These signals, recorded with the output of the pressure transducers on a chart recorder (Brush 2400, Gould Inc., Cleveland, OH), were used to determine heart rate.

Blood samples to be analyzed for prostanoid concentrations were drawn from the PA at 4 time periods: immediately prior to running (REST), after 2 min of running at 7 m  $s^{-1}$  (7 m  $s^{-1}$ ), after 3 min at the maximum running speed for each horse (MAX), and 15 min following the run at maximum speed (RECOVERY). PA blood was utilized to minimize the influence of rapid pulmonary degradation of many of the eicosanoids.<sup>9</sup> For prostanoid analyses, 70–80 ml of heparinized blood were placed in tubes containing 10 mg nordihydroguaiaretic acid, an inhibitor of both lipoygenase and cyclo-oxygenase, and 10 mg indomethacin, an inhibitor of cyclo-oxygenase. These tubes were kept on ice until plasma was separated by centrifuging at 1500 G (4°C) for 20 min. Plasma aliquots of 5 ml each received 0.5 ml 6 N HCl and 100  $\mu$ l of either [<sup>3</sup>H]-6-keto-PGF<sub>1 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub> , PGE<sub>2</sub>, or TXB<sub>2</sub> (approximately 2000 cpm). The spiked samples were extracted 3 times with chloroform (40 ml combined total volume). Chloroform extracts were dried under N<sub>2</sub> and stored at  $-20^{\circ}$ C until assayed

by RIA using techniques previously described in detail.<sup>10</sup> Recoveries of the different prostanoids were 61–67% for 6-keto-PGF<sub>1 $\alpha$</sub> , 39–47% for TXB<sub>2</sub>, 40–49% for PGF<sub>2 $\alpha$</sub> , and 39–41% for PGE. The prostanoid concentrations reported represent the immunoreactive fraction in plasma of the indicated compound corrected for the percentage recovery. Because the catheters served a dual purpose, the sampling times for blood pressures differed from those for blood. For the resting sample, as well as those at 7 m  $s^{-1}$  and maximum running speed, the blood pressure/heart rate values were collected during the final minute of the particular time period. For the post-exercise sample, blood pressure/heart rate values were taken 6 min into the recovery period.

All data were analyzed using 2-way ANOVA. When differences were detected with a significance of  $p \leq 0.05$ , Tukey's HSD post-test was utilized to identify specific differences.<sup>4</sup>

## RESULTS

To ensure that the horses were exercising at maximum aerobic capacity, each horse ran at 1 m  $s^{-1}$  faster than the minimum speed required to elicit  $\dot{V}_{O_2,max}$ . The procedure utilized to identify this speed has been previously reported.<sup>1</sup> For these 5 horses,  $\dot{V}_{O_2,max}$  ranged from 2.54 to 3.01 ml O<sub>2</sub> [STPD]  $s^{-1}$  kg<sup>-1</sup>. Mean  $\dot{V}_{O_2,max}$  ( $\pm$ SEM) was  $2.73 \pm 0.07$  ml O<sub>2</sub> [STPD]  $s^{-1}$  kg<sup>-1</sup>.

Heart rate, mean PA and mean CA pressures all increased with exercise (Fig. 1). Average heart rates were 47 and 205 bpm for the REST and MAX samples, respectively. The heart rates observed at each sample time differed significantly from every other sample period ( $p < 0.0001$ ). Mean CA and PA pressures at REST were significantly lower than pressures measured at all other sampling times ( $p < 0.0001$ ). The lowest mean PA pressures were at REST (42 mmHg), while the highest mean pressures (125 mmHg) were measured at MAX. Mean CA

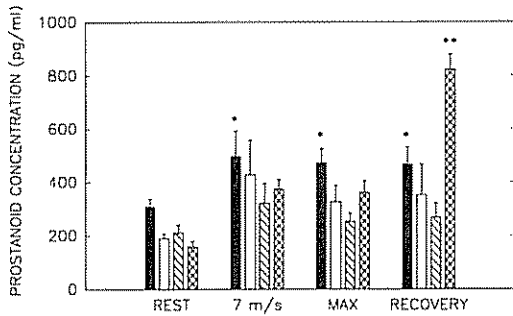


Fig. 2 Apparent prostanoid concentrations at various exercise intensities. Solid box, 6-keto-PGF<sub>1α</sub>; open box, PGE; left diagonal box, PGF<sub>2α</sub>; hatched box, TXB<sub>2</sub>. Values are means  $\pm$  SEM for samples from 5 horses. \* indicates significantly different from resting concentration,  $p < 0.05$ . \*\* indicates significantly different from resting concentration,  $p < 0.01$ .

pressures for these horses were 129 mmHg and 239 mmHg for the REST and MAX samples, respectively. Mean pressures for both the CA and PA were significantly higher at MAX than those observed at 7 m s<sup>-1</sup> or during RECOVERY ( $p < 0.01$ ). However, the pressures at 7 m s<sup>-1</sup> and at the 6 min RECOVERY sample were not significantly different from each other. While still significantly elevated above resting values at the 6 min post-exercise sampling time, all of the measured cardiovascular parameters had decreased toward resting values from the maxima observed while the horses ran at MAX.

Of the prostanoids measured, only plasma concentrations of 6-keto-PGF<sub>1α</sub> and TXB<sub>2</sub> changed from resting concentrations during the exercise protocol (Fig. 2). Plasma 6-keto-PGF<sub>1α</sub> concentrations were significantly elevated above resting values at all later sample times ( $p = 0.03$ ), while the only significant change in TXB<sub>2</sub> concentration was an increase observed at RECOVERY ( $p = 0.002$ ). Although both PGF<sub>2α</sub> and PGE plasma concentrations tended to increase transiently with exercise, no significant changes occurred either in PGF<sub>2α</sub> concentration ( $p = 0.20$ , analysis had the power to detect a 58% difference at the 0.05 $\alpha$ -level with 90% probability) or PGE concentration ( $p = 0.12$ ,

analysis had the power to detect a 66% difference at the 0.05 $\alpha$ -level with 90% probability).

## DISCUSSION

Although abundant evidence demonstrates the effects that various eicosanoids have on vascular smooth muscle, studies investigating their role in hemodynamic control are inconclusive.<sup>15</sup> Attempts to define potential involvement of this class of compounds in cardiovascular homeostasis have taken two approaches: (1) using specific inhibitors of AA metabolism,<sup>6,8,13,19</sup> and (2) observing circulating or excreted eicosanoid concentrations during and following exercise.<sup>20,25</sup> The first approach has inadvertently been applied in equine medicine due to the mechanism of action of many non-steroidal anti-inflammatory (NSAI) agents used in horses. However, the anti-inflammatory and analgesic effects, rather than hemodynamic control, are usually the desired actions when NSAIs are utilized and are far better documented. Thus, in horses, a major source of information on the involvement of eicosanoids in the regulation of the cardiovascular system remains unexplored. In man, however, therapy for a variety of clinical manifestations involves modulation of adverse hemodynamic conditions. Of particular interest is the dynamic interaction of TXA<sub>2</sub> and PGI<sub>2</sub> in the regulation of coronary blood flow during ischemia caused by myocardial infarction. As noted earlier, TXA<sub>2</sub> has primarily vasoconstrictive effects on vascular smooth muscle, whereas PGI<sub>2</sub> has mainly vasodilatory effects. Inhibition of thromboxane synthetase, thereby increasing the ratio of PGI<sub>2</sub>/TXA<sub>2</sub>, causes vasodilation of coronary arteries.<sup>11</sup> However, infused PGI<sub>2</sub> substantially reduces mean arterial blood pressure, which could lead to reduced coronary blood flow.<sup>12</sup> This demonstrates that local synthesis, coupled with rapid degradation, is of prime importance if prostanoids are to serve in the regulation of regional blood flow.

During exercise, enhanced blood flow to the active skeletal muscle and diminished blood flow to organs not requiring it would obviously be beneficial. While particular prostanoids seem to have similar actions in various organ systems, considerable differences in sensitivity exist.<sup>6,15</sup> Additionally, the capacity for interaction of prostanoids with both neural and hormonal mechanisms of cardiovascular control varies among organ systems.<sup>15</sup> Even with these complexities, several intriguing effects of exercise on prostanoid concentrations have been observed.

Rates of thromboxane biosynthesis, as estimated from excreted TXB<sub>2</sub>, were unaffected in humans exercising submaximally on a cycle ergometer<sup>23</sup> or a treadmill.<sup>17</sup> Contradictory evidence has been reported, however, with findings of as much as a 150% increase in plasma TXB<sub>2</sub> concentration during exhaustive exercise.<sup>14</sup> The present study is in partial agreement with the latter study, with the exception that TXB<sub>2</sub> concentration only increased after the exercise bout had ended. Recently described platelet activation due to shear stress could help explain this observed increase in TXB<sub>2</sub> concentration.<sup>21</sup>

As with thromboxane, findings of the effects of exercise on the biosynthesis of PGI<sub>2</sub> are equivocal. Studies have shown a variety of alterations in circulating or excreted concentrations of 6-keto-PGF<sub>1α</sub>, the stable metabolite of PGI<sub>2</sub>, ranging from dramatic increases<sup>17</sup> and only transient increases<sup>14</sup> to no change,<sup>23</sup> and even decreases.<sup>22</sup> In this study, a moderate elevation in 6-keto-PGF<sub>1α</sub> concentration was observed both during and following treadmill exercise.

Effects of exercise on PGF<sub>2α</sub> and PGE biosynthesis have only rarely been reported, even in humans.<sup>5</sup> For both of these prostaglandins, the present study demonstrated no significant differences in plasma concentrations at any of the exercise intensities. PGE, like PGI<sub>2</sub>, has been shown to have primarily vasodilatory activity, and might have been expected to exhibit changes similar to those observed for PGI<sub>2</sub>. PGF<sub>2α</sub>, however, has vasoconstrictor activity in most species stud-

ied, with major effects being reported on the pulmonary circulation.<sup>13</sup> PGF<sub>2α</sub>-induced pulmonary vasoconstriction could help explain increased PA pressure during exercise. However, in this study, although PA pressure increased dramatically with exercise, PGF<sub>2α</sub> concentrations remained unchanged.

This study provides evidence that changes in the plasma concentrations of several prostanoids occur with maximal aerobic exercise in horses. Whether these changes result from, or are merely correlated with, exercise remains to be demonstrated. Regional blood flows were not studied in these experiments, consequently, the possible relationship between prostanoid activity and blood flow remains speculative. Closer examination of the kinetics, as well as the effects of specific inhibitors on the biosyntheses of prostanoids will be necessary to fully elucidate the mechanisms responsible for the observed changes in prostanoid concentrations with exercise.

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# Effects of Exercise and Metabolic Alkalosis on Selected Plasma Amino Acid Concentrations in Thoroughbred Racehorses

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**ABSTRACT.** The present study was undertaken to investigate: 1) changes in selected plasma amino acid concentrations during 1 000 m of high intensity exercise 2) the influence of pre-exercise metabolic alkalosis on these changes. Twenty-four Thoroughbred horses in training raced over a distance of 1 000 m on two occasions separated by 6–7 days. Four hours prior to exercise each horse was administered in randomised manner, a 2 l solution of sodium bicarbonate NaHCO<sub>3</sub>, (0.6 g kg<sup>-1</sup> body weight, test) or water (control) by nasogastric intubation. Venous blood samples were taken prior to exercise and 5 min after exercise. The concentration of 22 plasma amino acids were determined using an automatic amino acid analyser. At rest considerable variation was found between horses in individual amino acid concentrations. Exercise produced changes in plasma amino acid concentrations; some of them could be accounted for by the decrease of plasma volume. Marked increases (mean ± SE) were found in alanine (352.3 ± 24.7 to 509.7 ± 36.3 μmol l<sup>-1</sup>, *p* < 0.001) and glutamine (263.7 ± 16.0 to 304.2 ± 22.7 μmol l<sup>-1</sup>, *p* < 0.05). Significant increases were also recorded for leucine (*p* < 0.001) and the total amino acid content (*p* < 0.01). Tryptophan decreased from 75.1 ± 3.7 to 63.9 ± 3.8 μmol l<sup>-1</sup> (*p* < 0.01). Metabolic alkalosis, whilst affecting acid–base status, produced only minor changes in some of the amino acid concentrations between control and test group before and after exercise.

**Key words** Horses; plasma amino acids; exercise; metabolic alkalosis; alanine; glutamine.

## INTRODUCTION

Despite considerable recent research in the field of equine exercise physiology, there have been few investigations of changes in amino acids during high intensity exercise. Some studies have been done examining the alterations in alanine,<sup>15,19,21</sup> glutamate and glutamine<sup>15,21</sup> during exercise, which are correlated with their role as a transporter of ammonia produced by working muscles. However, there has been less interest in the role of branched chain amino acids—leucine, isoleucine and valine<sup>15,21</sup> and other free plasma amino acids during exercise.

The aim of the present study was to investigate: 1) the changes in selected plasma amino acids during 1 000 m of high intensity exercise, and 2) the influence of metabolic alkalosis on the plasma amino acid profile following submaximal exercise. One might expect a change to occur as a result of a pH induced alteration in amino acid efflux and/or production.

## MATERIAL AND METHODS

Twenty 2 year old Thoroughbred racehorses in training, but novices to competition, and