

Cardiorespiratory and Metabolic Effects of Propranolol during Maximal Exercise

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ABSTRACT. In a cross-over experiment, a standardized exercise test on a treadmill was used to examine the effects of propranolol and saline in Thoroughbred horses during exercise to fatigue. This test involved a warm up followed by acceleration to a speed that corresponded to 105% $\dot{V}O_2$ max, maintained until fatigue. Expired gas samples, mixed venous and arterial blood samples were collected and blood temperature was recorded during the test. Muscle biopsies were collected before and after each bout of exercise. Following propranolol, heart rate and cardiac output were lower during warm up. Throughout exercise venous oxygen saturation and content, and plasma lactate concentrations were lower after propranolol. Blood potassium concentrations were higher after propranolol treatment. Post-run muscle lactate and glucose-6-phosphate levels were significantly lower following treatment. Performance was diminished with propranolol treatment, as measured by a 31% decrease in the time to fatigue. These results highlight the importance of beta-blockade, by propranolol, in diminishing maximum performance.

Key words. Metabolites; oxygen uptake; performance; fatigue; muscle; horses.

INTRODUCTION

While regulatory authorities throughout the world spend large sums of money on drug detection, to prevent the possibility of race-horses' performance being modified, little is known about the effects of various drugs on performance. Racetrack tests have been used in both Thoroughbred^{18,19} and Standard-bred^{4,5} horses. However, such testing is very difficult given the problems in standardising racetrack conditions and the influence of the rider or driver.

The development of high speed treadmills has made it possible to standardize the amount of exercise each horse performs and to reproduce an exercise test reliably on many occasions. In addition, treadmill exercise facilitates the collection of blood and expired respiratory gas samples during exercise, even when the horse is moving at maximum speed. Thus, treadmill exercise can provide a valuable tool for assessing the effects of drugs on maximum performance and

allowing various physiological and biochemical variables to be assessed.

The aim of this study was to use a high intensity treadmill exercise test to extend previous work on propranolol used in field tests¹⁸ and in ponies during submaximal treadmill exercise.¹⁶

MATERIALS AND METHODS

Six Thoroughbred geldings aged from 6 to 10 years and weighing between 424 and 492 kg (454 ± 23 kg, mean \pm SD) were used. One common carotid artery was surgically elevated to a subcutaneous position,²⁰ at least 6 weeks prior to the commencement of the study. The horses were exercised on a treadmill (Beltalong, Euroa, Australia) inclined at a slope of 6°, while wearing an open flow gas collection mask, once or twice per week for 6 weeks before the start of the experiments, but were not in training. The horses were

assigned at random to either a control (saline) or treatment (propranolol) group for the first experimental day, and the treatments reversed one week later.

DL-propranolol hydrochloride (ICI, Melbourne, Australia) was prepared as a 5 mg ml⁻¹ solution in 0.9% (0.15 M) NaCl. The solution was sterilized by passage through a 0.2 micron millipore filter (Acrodisc, Gelman Sciences, Ann Arbor, MI). A fresh quantity of solution was prepared 12 hours before each experiment and stored at 4°C in a light proof container. Propranolol (0.2 mg kg⁻¹), or an equivalent volume of 0.9% NaCl, was given by slow intravenous injection 20 min before each exercise bout.

Prior to exercise, the carotid and pulmonary arteries were catheterised as previously described³ to permit sampling of arterial and mixed venous blood, respectively.

To examine the effects of propranolol on maximum performance a "run to fatigue" exercise test was used. The test consisted of a 3 min warm up at 4 m s⁻¹ followed by an increase in speed to the value that corresponded, using linear regression, to 105% of the previously established maximum oxygen uptake ($\dot{V}O_2$ max) for each horse using an incremental exercise test.³ $\dot{V}O_2$ max was identified as a plateau in oxygen uptake ($\dot{V}O_2$) despite an increase in treadmill speed.

The length of each run to fatigue was timed from when the horses first reached their set maximum speed until they were unable to maintain their position on the treadmill and were carried to the back bar. The run time to fatigue was recorded on three separate occasions for each horse. There were no statistically significant differences in the time taken to reach fatigue by each horse ($p > 0.05$ when analysed using a univariate analysis of variance test). The mean coefficient of variation (\pm SEM) for the run time to fatigue was $9.6 \pm 2.4\%$.

A gas collection system as described by Rose et al.,¹⁴ was used to collect expired gases for determination of the concentrations of expired oxygen (Servomex; 570 A Sybron-Taylor UK) and carbon dioxide (CD

102 Datex, Finland). Standard equations were employed for the determination of $\dot{V}O_2$ and carbon dioxide output ($\dot{V}CO_2$) 15 s before the completion of the 180 s warm up and every 30 s during the run. Arterial and mixed venous blood samples were collected, and blood temperature recorded at rest and 5 s before the end of the warm up and every 30 s during the run. Final arterial and venous blood samples were collected just prior to the completion of the run, regardless of the time.

Using the needle biopsy technique,¹² muscle biopsies were taken prior to each run, 15 min after the administration of the propranolol or saline treatment, and again as soon as the horses came to a standstill on the treadmill after their exercise tests. After collection of the muscle biopsies, the muscle was immediately frozen in liquid nitrogen.

Arterial and mixed venous blood samples were collected into blood gas syringes (Preza-Pak II, Terumo, Tokyo, Japan) and all samples were analyzed within 60 min of collection, using an automated blood gas analyser (ABL 3 Blood Gas Laboratory, Radiometer, Copenhagen, Denmark), for oxygen and carbon dioxide tensions (pO_2 , pCO_2), pH and haemoglobin. Using the instrument's in-built computer, the following values were also derived: the saturation of oxyhaemoglobin, oxygen content and standard bicarbonate (SBC). Correction for the difference in temperature between that at which its electrodes operated (37°C) and the horse's blood temperature as measured by thermistor (Series 400, Model 528 Yellow Springs Instruments, Columbus, OH) placed at the level of the right atrium at the time of the sample collection was made automatically. Plasma Na and K concentrations were determined from the venous blood samples using a sodium and potassium analyser (KNA, 1, Radiometer, Copenhagen).

Mixed venous samples for plasma lactate concentrations were collected into tubes containing fluoride and oxalate immediately after the blood-gas samples. Plasma lactate concentrations were determined using auto-

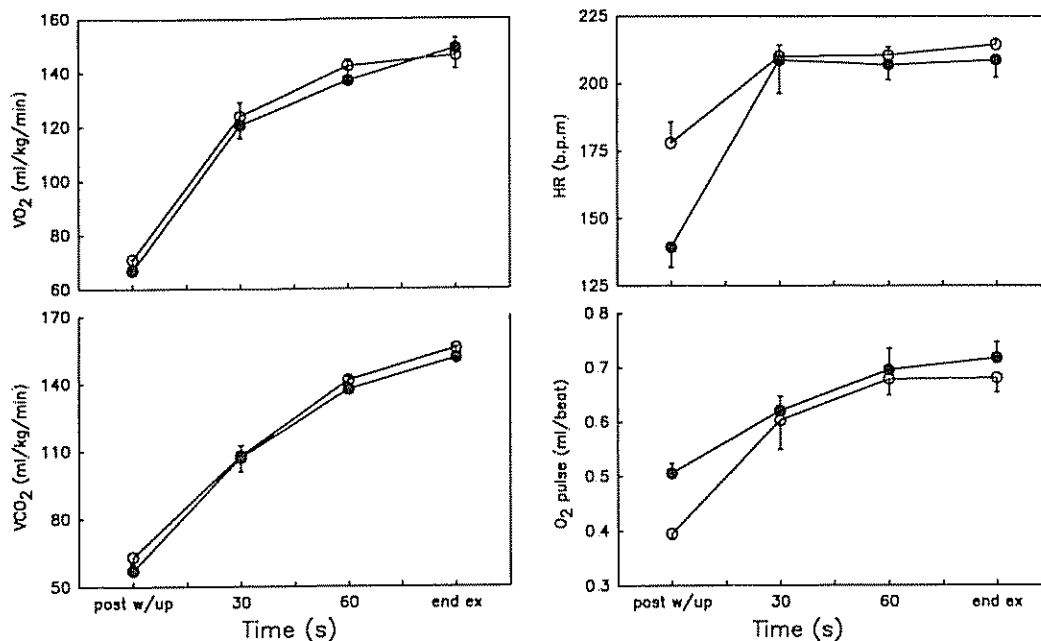


Fig. 1 Oxygen uptake (VO_2), carbon dioxide production (VCO_2), heart rate (HR) and oxygen pulse values (mean \pm SEM) from 6 Thoroughbred horses undergoing treadmill exercise at a speed

equivalent to 105% VO_{2max} until fatigue, following either 0.2 mg kg^{-1} propranolol (●) or saline (○) given intravenously.

mated lactate analysis (YSI-23LM Yellow Springs, OH).

Muscle lactate (La), adenosine triphosphate (ATP), creatine phosphate (CrP), and glucose-6-phosphate (G-6-P) were measured fluorimetrically¹³ following freeze drying and dissection of the muscle samples.

Muscle glycogen content was measured fluorimetrically after the muscle samples had been heated for 1 h at 60°C in 2 M NaOH, boiled for 2 h in 2 M HCL and finally neutralized with 2 M NaOH.² Muscle pH was determined using the method described by Hodgson et al.⁹

RESULTS

VO_2 and VCO_2 both increased during the runs, but there were no differences between the treated or control groups (Fig. 1). There was no significant effects of treatment on any of the cardiovascular values at rest. Following propranolol treatment there was a

significant ($p < 0.01$) decrease in the heart rate (HR) of the horses, during submaximal exercise. At the end of warm up, the mean HR of the treated horses was 139 compared with 178 in the control group. The end-of-run mean HR for the treated and control groups were 208 and 214 respectively (Fig. 1) and were not significantly different. Cardiac output increased with exercise in both groups but was significantly less ($p < 0.05$) in the treated group (Fig. 2) at the end of warm up. Stroke volume increased with exercise, however, there was no significant difference between the two groups (Fig. 2).

Na and K concentrations increased with exercise, but only the K showed a significantly ($p < 0.001$) greater increase in the treated group compared to the control group (Fig. 3). The mean K concentration for the treated group and the control group at the end of the warm up were 5.5 and 4.9 mmol l^{-1} respectively and at the end of the run were 8.4 and 7.9 mmol l^{-1} respectively.

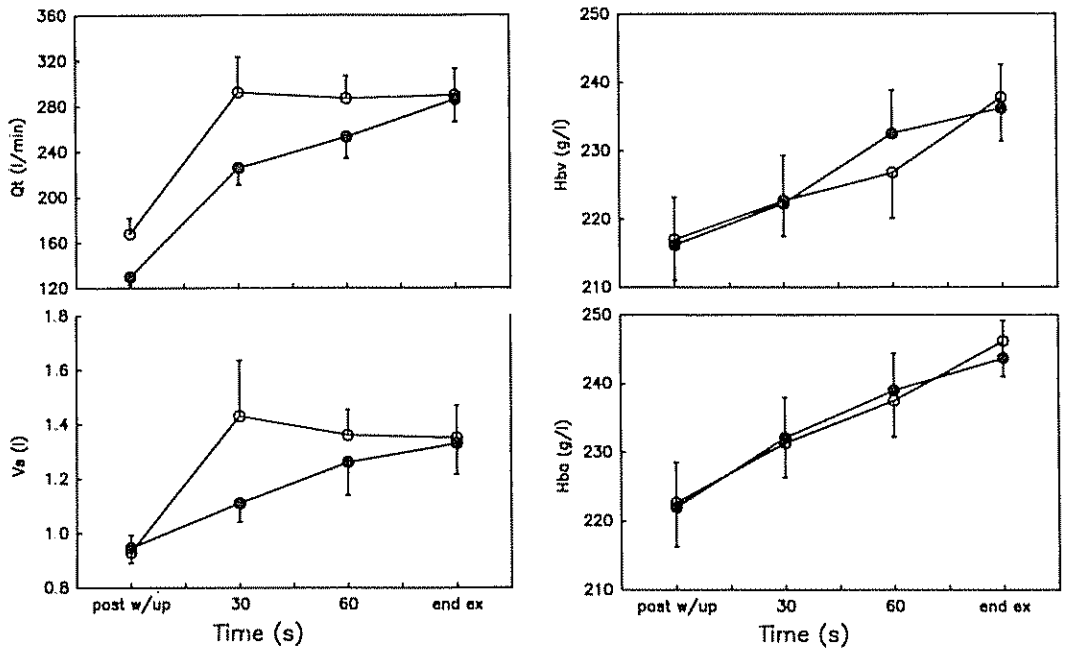


Fig. 2. Cardiac output (Q), stroke volume (Vs) and mixed venous (Hbv) and arterial (Hba) haemoglobin values (mean \pm SEM) from 6 Thoroughbred horses undergoing treadmill exercise at a speed

equivalent to 105% $\dot{V}O_{2\max}$ until fatigue, following either 0.2 mg kg⁻¹ propranolol (●) or saline (○) given intravenously.

The mean plasma [La] increased from a mean of 3.0 mmol l⁻¹ at the end of the warm up to 24.7 and 17.1 mmol l⁻¹ at the end of the run in the control treated groups, respectively (Fig. 3). This increase was significantly greater ($p < 0.001$) than the rise in the plasma [La] of the propranolol treated group of 1.4 mmol l⁻¹ at the end of the warm up to 17.1 mmol l⁻¹ at the end of the run. Associated with the increase in plasma [La] was a fall in arterial and venous pH, although, there was no significant difference between the treated or control groups (Fig. 4). Standard bicarbonate concentrations fell during exercise in both the arterial and venous samples (Fig. 4). At the end of the warm up and the end of the run, SBC values were significantly lower ($p < 0.001$) for the propranolol treated group.

Blood temperature, although elevated during the exercise test, was not significantly different between the treated or control

groups (Fig. 3). The treated horses appeared to sweat less than the control group both before and at the completion of the exercise tests.

Muscle [La] increased with exercise but was significantly lower in the treated group ($p < 0.05$) compared to the controls (Table 1). The mean muscle concentration of G-6-P in the pre-run samples of the control group was 5.4 $\mu\text{mol l}^{-1}$, at the end of the run this had risen to 19.3 $\mu\text{mol l}^{-1}$. In the treatment group the mean pre- and post-run [G-6-P] were 5.5 and 8.7 $\mu\text{mol l}^{-1}$, respectively. Thus, treatment had a significant effect ($p < 0.001$) in decreasing the post-run [G-6-P] (Table 1). There was no significant effect of treatment on pre- or post-run muscle pH (Table 1). Muscle glycogen levels post-exercise decreased ($p < 0.05$) compared to the pre-exercise values in both the treated and control groups but were not significantly different between the two groups (Table 1).

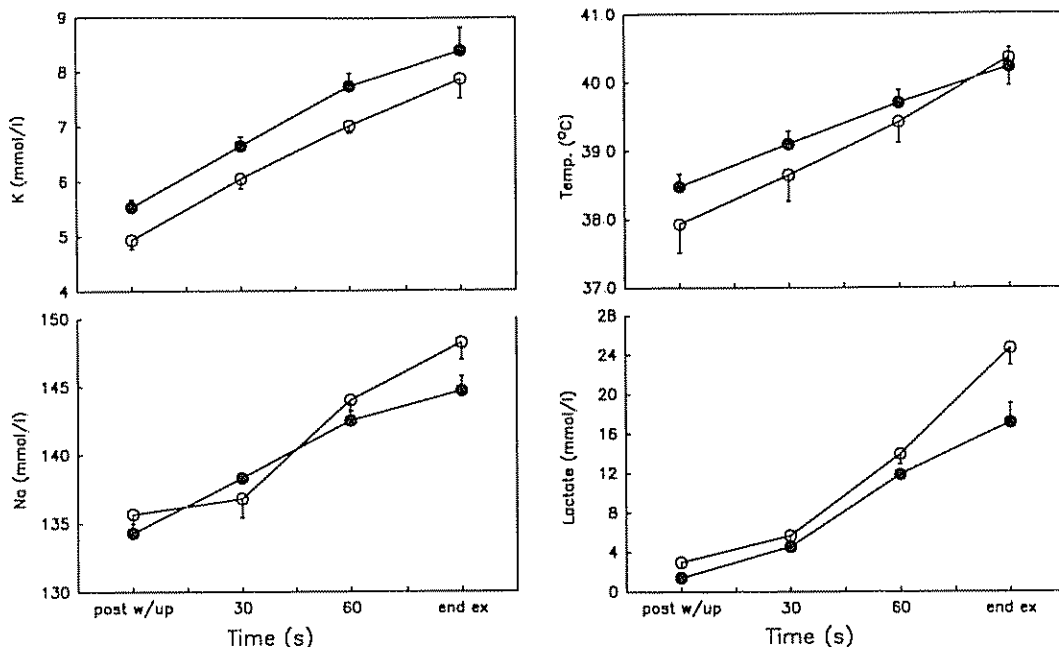


Fig. 3. Plasma sodium (Na), potassium (K) and lactate values and central venous blood temperature values (mean \pm SEM) from 6 Thoroughbred horses undergoing treadmill exercise at a speed

equivalent to 105% $\dot{V}O_2$ max until fatigue, following either 0.2 mg kg⁻¹ propranolol (●) or saline (○) given intravenously.

Muscle [ATP] did not differ significantly before or after exercise in either the treated or control groups (Table 1).

decreased ($p < 0.01$) by pre-treatment with propranolol. The mean run time to fatigue (\pm SEM) in the control group was 118.6 \pm 7.7 s, and in the treated group 81.7 \pm 11.1 s.

The run time to fatigue was significantly

Table 1. Effects of propranolol on muscle metabolite values (mean \pm SEM) before and after maximum exercise in Thoroughbred horses

All measurements, except pH, were made using freeze dried muscle samples

Metabolite	Control		Propranolol	
	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
ATP ($\mu\text{mol g}^{-1}$)	25.1 \pm 1.0	24.0 \pm 2.5	23.8 \pm 2.1	22.2 \pm 1.0
G-6-P ($\mu\text{mol g}^{-1}$)	5.4 \pm 0.9	19.1 \pm 2.0	5.5 \pm 1.0	8.7 \pm 0.8**
Lactate ($\mu\text{mol g}^{-1}$)	11.8 \pm 1.7	104.7 \pm 7.4	7.6 \pm 0.6	80.6 \pm 9.0*
pH	7.05 \pm 0.02	6.60 \pm 0.05	7.01 \pm 0.02	6.65 \pm 0.05
Glycogen ($\mu\text{mol g}^{-1}$)	604.0 \pm 28.0	430.7 \pm 38.3	634.6 \pm 38.9	472.7 \pm 45.4

* $p < 0.05$, ** $p < 0.01$. Significant differences when control and propranolol values compared.

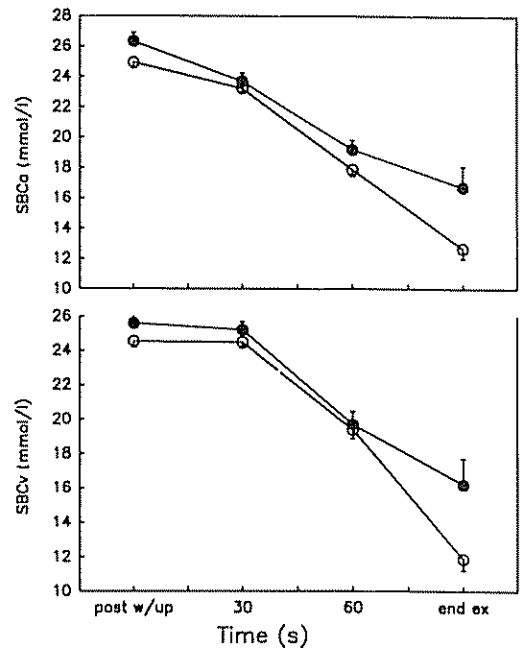
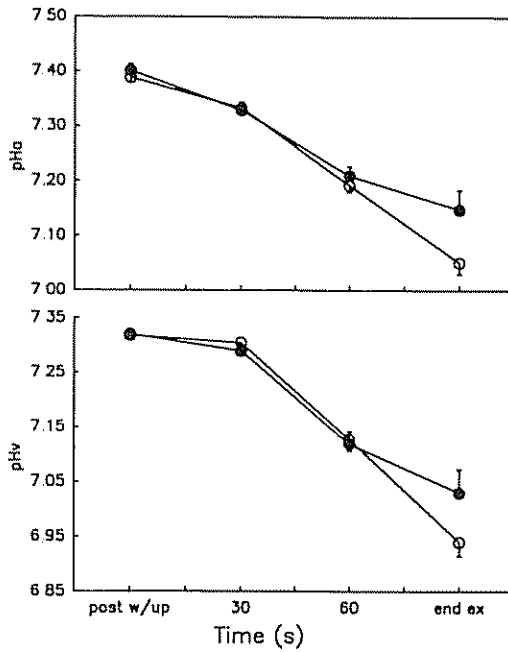


Fig. 4 Arterial (pHa) and mixed venous (pHv) pH and arterial (SBCa) and mixed venous (SBCv) standard bicarbonate values (mean \pm SEM) from 6 Thoroughbred horses undergoing treadmill exer-

cise at a speed equivalent to 105% $\dot{V}O_{2max}$ until fatigue, following either 0.2 mg kg^{-1} propranolol (●) or saline (○) given intravenously.

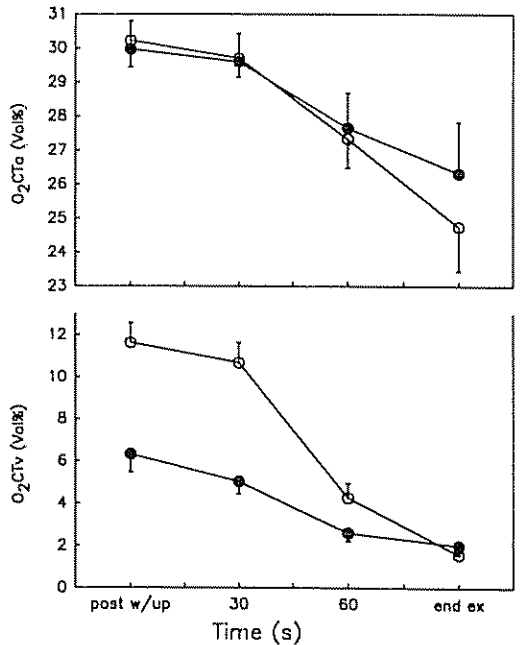
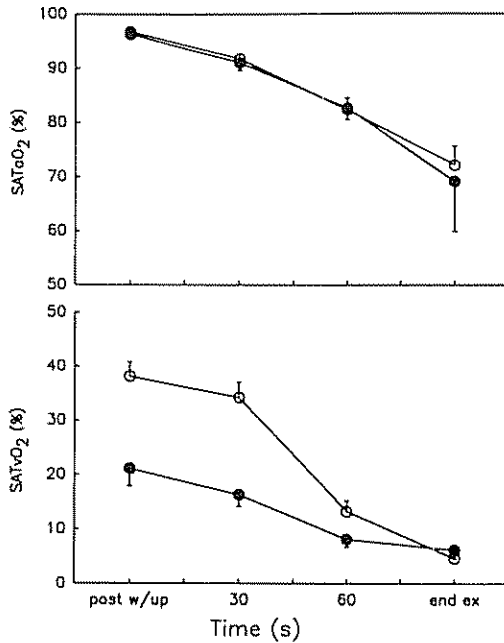


Fig. 5. Arterial (SATaO₂) and mixed venous (SATvO₂) oxygen saturation and arterial (O₂CTa) and mixed venous (O₂CTv) oxygen content values (mean \pm SEM) from 6 Thoroughbred horses un-

dergoing treadmill exercise at a speed equivalent to 105% $\dot{V}O_{2max}$ until fatigue, following either 0.2 mg kg^{-1} propranolol (●) or saline (○) given intravenously.

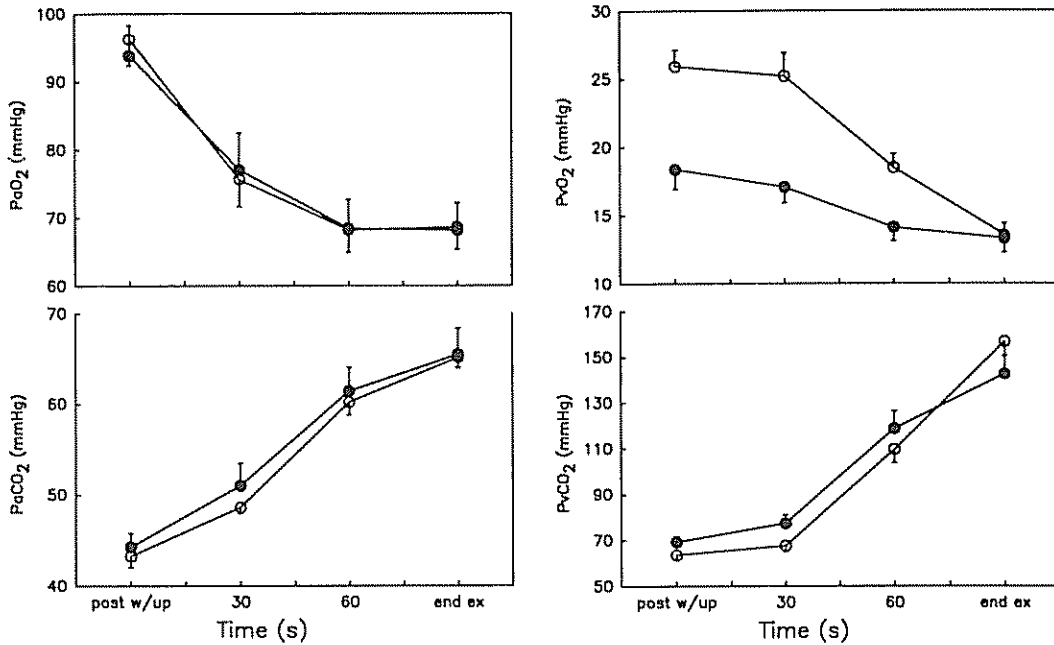


Fig 6 Arterial (PaO₂) and mixed venous (PvO₂) oxygen and arterial (PaCO₂) and mixed venous (PvCO₂) carbon dioxide partial pressure values (mean \pm SEM) from 6 Thoroughbred horses un-

dergoing treadmill exercise at a speed equivalent to 105% VO₂max until fatigue, following either 0.2 mg kg⁻¹ propranolol (●) or saline (○) given intravenously.

DISCUSSION

The object of the exercise test was to examine the effect of beta blockade on maximum performance, cardiorespiratory function and muscle metabolism, during and after maximum exercise under controlled conditions. The horses were exercised at 105% of their individual VO₂ max values, rather than a set speed, so that each horse would be working at the same relative intensity based on their individual aerobic capacities. Performance changes were assessed as alterations in the time taken to reach fatigue at this speed. In all cases the coefficient of variation for the run time to fatigue was less than 10%, indicating a reproducible test at high exercise intensities. Thus, the decrease in run time could be seen as an effect of the drug, providing all other variables were kept constant. Snow et al.¹⁸ reported reduced maximum performance in 4 Thoroughbred horses following non-selective beta blockade. A de-

crease in performance was measured by an increased time to perform a series of standardized track gallops. However, in their study only pre- and post-exercise data could be collected.

Reduced performance during maximum exercise has been reported in man following beta blockade.¹⁵ Schnabel et al.¹⁵ concluded that the single-dose administration of beta blockers reduced the capacity for maximum exercise and that this was most likely due to impaired glycolytic energy production. According to Tesch,²² during short-term exercise following beta-blockade, where the energy demand approaches or exceeds VO₂ max, the reduction in performance is primarily the result of decreased cardiac output diminishing O₂ supply to the exercising muscles. The metabolic effects of beta-blockers may also contribute to the fall in exercise performance.²³

The muscle metabolic alterations in our

experiment also suggest glycolytic inhibition, which may also contribute to the decreased run time in the treated group. This could have resulted in a lower O_2 deficit and therefore less demand for anaerobic energy production which will consequently lower plasma and muscle lactate concentrations.

The rapid metabolism of muscle glycogen, stimulated via beta adrenoreceptors during high intensity exercise results in the production of lactate. Glycogen metabolism is believed to be stimulated via beta adrenoreceptors in the horse.¹⁸ During high intensity exercise, the rate of production of pyruvate by glycolysis exceeds the rate of oxidation of pyruvate by the citric acid cycle. When this occurs, pyruvate is reduced to lactate via a mass action effect. However, glycolysis is dependant on the activation of the enzyme phosphorylase by cyclic adenosine monophosphate (cAMP). The formation of cAMP from ATP is decreased by beta-blockade and thus phosphorylase activity, glycolysis and subsequent lactate production are inhibited. Propranolol would therefore be expected to block beta adrenoreceptor mediated muscle glycogenolysis and so limit lactate production leading to lower blood lactate levels.

Evidence for the inhibition of glycolysis following beta-blockade was the decreased accumulation of [G-6-P] in the post-exercise muscle samples of the treated group. The accumulation of [G-6-P] was suggested by Harris et al.⁸ to reflect glycolytic rate. Thus, lowered post-run [G-6-P] values following beta-blockade may indicate a reduced rate of glycolysis in the muscle and subsequently reduced lactate levels. Decreased [G-6-P] accumulation after propranolol administration has been reported in man following intense short term exercise and that these responses suggested a reduced rate of glycolysis during non-selective beta-blockade.^{1,7,10}

Muscle glycogen levels post-exercise decreased compared to the pre-exercise values in both the treated and control runs but were not different between the two groups. Thus, while glycolysis may have been inhibited by beta-blockade this was not reflected in the

muscle glycogen concentrations following maximum exercise. This finding may be partly due to the techniques employed in this study to measure glycogen concentrations in the muscle. The samples were analyzed using a homogenate of muscle which meant only the average fibre content of glycogen was recorded and there was no way of differentiating the relative change in glycogen content of different muscle fibre types. Snow et al.¹⁸ reported a decrease in glycogen utilisation following propranolol treatment in 2 horses. However, the muscle samples used by Snow and his co-workers were collected after four consecutive gallops, each at maximum speed for the individual horse. It is possible that the discrepancies between the muscle glycogen results in this study and those obtained by Snow et al.¹⁸ were due to the differences in the design of the two exercise tests there being a greater total glycogen utilisation in the study of Snow et al.¹⁸ In human subjects, Chasiotis et al.¹ demonstrated reduced utilization of muscle glycogen during maximum exercise of short duration after non-selective beta-blockade. However, decreased glycogen utilization has been reported following beta-blockade in maximally exercised rats.⁶

Muscle [ATP] did not differ before or after the exercise in either the treated or control groups. Previous work in horses has produced varying results on the effect of maximum exercise on muscle [ATP].^{9,12,13,17} There are no reports of the effects of beta-blockade on muscle [ATP] in horses and studies in man show no clear pattern with regard to [ATP] after beta-blockade.^{7,11,22}

Muscle pH showed a similar decline during exercise in both the treated and control groups. However, the treated horses reached the same pH values much more rapidly than the controls and so fatigue was associated with similar pH values in both groups. However, the muscle lactate concentrations were lower in the treated horses indicating that either another source of hydrogen ions contributed to the low pH or the buffering capacity of the muscle was reduced in these horses. Lovell et al.¹² found a similar decline

in the intramuscular pH during different durations of high intensity exercise to that found in the present study. It seems likely that the reduction in muscle pH during high intensity exercise could have a major influence on fatigue, by inhibition of various enzyme systems in skeletal muscle.²¹ The mechanism for the similarity in pH in the control and treated groups, despite the different muscle lactate concentrations could not be determined from the current study.

Despite similar $\dot{V}O_2$ values in the treated and control groups, there was an increase in the arterio-venous O_2 content difference $[C(a-v)O_2]$. This was due primarily to a decrease in the venous O_2 content. These alterations may reflect increased O_2 extraction by muscle which may be secondary to partial inhibition of glycolysis.

The venous and arterial blood pH values in both groups of horses declined during exercise. In both instances, the effect of treatment was a higher blood pH at the completion of the exercise test compared to the controls. At the same time, SBC in the arterial and venous samples was higher for the treated group at the completion of exercise. This reflects the lower blood lactate concentration associated with beta-blockade.

Blood temperatures recorded in the run-to-fatigue test were not different for treatment and control groups, despite the decreased run time for the treatment group. Lovell et al.¹² reported a positive correlation between exercise duration and muscle temperature in 5 Standardbred horses and indicated that high muscle and/or core temperatures during maximal exercise, may limit performance, by adverse effects on muscle metabolism or by effects on central homeostatic mechanisms involving neuromuscular control. Thus, it is possible that the more rapid elevation of blood temperature seen in the propranolol treated horses may have contributed to earlier onset of fatigue.

Heart rate was only decreased by beta-blockade during the submaximal warm up period, when horses were trotting at 4 m s^{-1} . During high intensity exercise the competi-

tive inhibition of cardiac beta-adrenoceptors by propranolol may be partly overcome due to the high levels of catecholamines that are released under these conditions.

In conclusion, beta-blockade resulted in a decrease in performance when the horses were exercised at an intensity equivalent to 105% $\dot{V}O_{2\text{max}}$. The mechanism for beta-blockade limitation to performance, appears to be related to the inhibition of muscle glycolysis. The cardiovascular adaptations to exercise following beta-blockade, such as an increase in $[C(a-v)O_2]$ would appear to compensate, at least partially for the small reduction in HR and cardiac output during maximal exercise. It is doubtful whether these effects *per se* have a limiting effect on short duration, maximum intensity exercise.

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