Intravenous pentoxifylline does not affect the exercise-induced pulmonary arterial, capillary or venous hypertension in Thoroughbred horses

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The present study was carried out to examine whether intravenously administered pentoxifylline—a phosphodiesterase inhibitor which increases red blood cell deformability and decreases blood viscosity—would attenuate the magnitude of exercise-induced pulmonary capillary hypertension in healthy, fit Thoroughbred horses and in turn, diminish the occurrence of exercise-induced pulmonary hemorrhage (EIPH). Experiments were carried out on six healthy, sound, exercise-trained Thoroughbred horses. Hemodynamic data were collected at rest, and during exercise performed at 8 and 14 m/sec on 3.5% uphill grade in the control (no medications) and the pentoxifylline (8.5 mg/kg, i.v.) experiments. The sequence of treatments was randomized for every horse and 7 days were allowed between treatments. Galloping at 14 m/sec on 3.5% uphill grade elicited maximal heart rate. In both treatments, simultaneous measurements of phasic and mean right atrial and pulmonary arterial, capillary and wedge pressures were made using catheter-tip-manometers whose signals were carefully referenced at the point of the left shoulder. In the control study, exercise resulted in progressive significant increments in heart rate, right atrial and pulmonary arterial, capillary and venous pressures; thereby, confirming that exercising Thoroughbreds develop significant pulmonary hypertension. All horses experienced exercise-induced pulmonary hemorrhage (EIPH) in the control experiments. Pentoxifylline administration to standing horses caused anxiety, tachycardia, muscular fasciculations/tremors and mild sweating, but statistically significant changes in right atrial and pulmonary arterial, capillary and venous pressures were not detected. Exercise in the pentoxifylline treatment also resulted in progressive significant increments in heart rate and right atrial as well as pulmonary vascular pressures, but these data were not statistically significantly different from those in the control study and the incidence of EIPH remained unchanged. Thus, it was concluded that i.v. pentoxifylline is ineffective in attenuating the exercise-induced pulmonary arterial, capillary and venous hypertension in healthy, fit Thoroughbred horses.

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INTRODUCTION

Exercise-induced pulmonary hemorrhage (EIPH) is frequently observed in racehorses. It has been reported that >75% of racing Thoroughbred and Standardbred horses experience EIPH (Sweeney, 1991; LaPointe *et al.*, 1994). Recent work has demonstrated that pulmonary arterial, capillary and venous blood pressures of exercising horses increase dramatically. The resulting high transmural (intracapillary minus perivascular/alveolar) pulmonary capillary pressure contributes to the stress failure of pulmonary capillaries, resulting in EIPH (Manohar, 1993; Manohar *et al.*, 1993; West *et al.*, 1993; Manohar, 1994, 1995; Manohar & Goetz, 1996, 1998, 1999a,b). Although the increment in pulmonary vascular pressures of exercising horses is largely attributable to the increased cardiac output, (Manohar *et al.*, 1993; West *et al.*, 1993; Manohar & Goetz, 1999b), recently, it has been argued that increased blood viscosity may play a role as well (Weiss & Smith, 1998).

It is well known that the packed cell volume of exercising horses increases dramatically as the splenic erythrocyte reservoir is released into the circulation. This autologous blood doping increases aerobic capacity and contributes to the increased blood viscosity (von Engelhardt, 1977; Coyne *et al.*, 1990). It has also been suggested (Boucher, 1984) that erythrocytes released from the spleen may be smaller and have an irregular surface/shape (echinocytes). Although disagreement exists (Smith *et al.*, 1989), the hyperviscosity of blood in exercising horses may also be attributable, in part, to the diminished red blood cell (RBC) deformability (McClay *et al.*, 1992; Geor *et al.*, 1994; Weiss *et al.*, 1996a). Because individual capillaries have internal diameters smaller than the RBC diameter, resistance to blood flow posed by diminished RBC deformability may become significant as their ability to squeeze through narrow capillaries is reduced. The high pulmonary capillary blood pressure observed in strenuously exercising horses (Manohar, 1993, 1994, 1995; Manohar & Goetz, 1996, 1998, 1999a,b) may thus, in part, be a result of the exercise-induced increase in rigidity of the RBC membrane (Weiss & Smith, 1998). Recent work has indicated that the pentoxifylline—a phosphodiesterase inhibitor which enhances RBC deformability and decreases blood viscosity (Beermann *et al.*, 1985; Ward & Crisold, 1987; Ambus *et al.*, 1990; Clemens & Ruess, 1991; Crisman *et al.*, 1993)—improves equine hemorheologic properties. For example the ability of erythrocytes to filter through microfilters without affecting their size and decreased blood viscosity (Weiss *et al.*, 1994; Weiss *et al.*, 1996b). Based on these observations, Weiss and Smith (1998) suggested that increased RBC deformability resulting from pentoxifylline treatment may reduce the exercise-associated shear stress in pulmonary capillaries, thereby attenuating EIPH. Despite this reasoning, to our knowledge, studies examining the pulmonary hemodynamic effects of pentoxifylline in exercising horses have not been reported as yet. Therefore, our primary objective in the present study was to ascertain whether an i.v. pentoxifylline administration would affect the pulmonary arterial, capillary and venous hypertension in strenuously exercising horses, and thereby, affect the occurrence of EIPH. The absorption of pentoxifylline from the equine gastrointestinal tract is poor and highly erratic (Crisman *et al.*, 1993). Although the drug is rapidly metabolized upon i.v. administration, its metabolites are reported to possess hemorheologic properties as well (Ambus *et al.*, 1990; Geor *et al.*, 1992; Crisman *et al.*, 1993).

MATERIALS AND METHODS

Horses

Experiments were carried out on six healthy, sound Thoroughbred horses (one filly and five geldings), 3–6 years old, and weighing between 382 and 511 kg. They were exercise trained for a period of 7 weeks before hemodynamic studies were undertaken. The horses were housed in an air-conditioned building, and were accustomed to being handled by people. They were fed a diet of alfalfa hay and oats, and free access to water was provided. The horses were dewormed periodically and were inoculated with tetanus toxoid and strangles vaccine. Our protocols and procedures were approved by the Institutional Laboratory Animal Care and Use Committees.

Exercise training

After initial familiarization with walking, trotting, cantering and galloping on the high speed treadmill, the horses were exercised for 4 weeks (3 days/week) in the following manner with the treadmill set on the flat (0% grade). Starting with a walk at 2 m/sec for 60 sec, belt speed was increased at 1 m/sec every 60 sec until the horse had trotted at 6 m/sec for 60 sec. The treadmill speed was then raised to 8 m/sec and the horses were cantered for 60 sec. The horses were then galloped, first at 10 m/sec for 60 sec and thereafter, at 14 m/sec for 120 sec. Belt speed was then decreased; first to 5 m/sec for 60 sec and then to 2 m/sec for 5 min before stopping the treadmill. Upon completing 4 weeks of exercise training in this manner, for the next 3 weeks this incremental exercise regimen was performed 3 days/week with the treadmill set at a 3.5% uphill grade.

In separate trials carried out after completing 7 weeks of exercise training, it was observed that galloping at 14 m/sec on 3.5% uphill grade not only elicited maximal heart rate, but also induced EIPH in all horses.

Experimental design and protocol

All horses were studied in the control as well as pentoxifylline experiments. The sequence of control and pentoxifylline treatments was randomized for every horse, and 7 days were allowed between experiments. Ambient temperature in the laboratory was maintained at 19–20 °C, and all exercise was performed with the treadmill set at 3.5% uphill grade.

1. *Control study*: In these experiments, horses received no medication(s). Measurements were first made on quietly

standing horses when heart rate and pulmonary vascular pressures had been stable for 10–15 min (resting data). Thereafter, exercise was performed in the following manner with the high-speed treadmill set at 3.5% uphill grade. Exercise began with a walk at 2 m/sec for 60 sec. Belt speed was raised in increments of 1 m/sec every 60 sec until the speed was 6 m/sec. Having trotted for 60 sec at 6 m/sec, belt speed was raised to 8 m/sec (canter) for 60 sec and then to 14.0 m/sec. Horses galloped at 14 m/sec on 3.5% uphill grade for 90 s. Thereafter, belt speed was reduced to 5 m/sec for 60 sec, and then, to 2 m/sec for 5 min before stopping the treadmill.

2. *Pentoxifylline study*: In these experiments, measurements were first made on quietly standing horses when heart rate and pulmonary vascular pressures had been stable for 10–15 min (pre-pentoxifylline rest). Thereafter, a freshly prepared solution of pentoxifylline (8.5 mg/kg; Sigma Chemical Co., St Louis, MO, USA) was administered intravenously. Pulmonary hemodynamic measurements were made in standing horses in the 10th and 15th minute after pentoxifylline administration, and immediately thereafter, exercise was started. Exercise was performed on the treadmill set at 3.5% uphill grade, exactly in the same manner as described above for the control study.

Post-exercise airway endoscopy

In both treatments, careful examination of the nasopharynx, larynx and trachea (up to the carina) was undertaken 45–50 min post-exercise, using a flexible fiberoptic endoscope (Pentax Fiberscopes, Orangeburg, NY, USA). The presence of fresh blood in the trachea was regarded as evidence for the occurrence of EIPH.

Experimental procedures

Our procedures for measurement of pulmonary vascular pressures in standing and exercising horses have been described in considerable detail previously (Manohar, 1993, 1994, 1995; Manohar & Goetz, 1996, 1998, 1999a,b); therefore, only a brief description is given here. On the day of the study, after local infiltration of 2% lidocaine HCl, cardiac catheters (8F) equipped with tip-manometers and fluid-filled lumens (Millar Instruments, Houston, TX, USA) were advanced via introducers inserted in the left jugular vein so as to simultaneously record phasic right atrial, right ventricular, pulmonary arterial and pulmonary artery wedge pressures. The *in vivo* catheter-manometer signals were matched with corresponding fluid-filled pressure signals obtained using conventional transducers (Statham/Gould, Oxnard, CA, USA) zeroed at the level of the point of the left shoulder. The data were continuously displayed on an oscillographic recorder and mean pressures were obtained by electronic integration of the phasic pressure signals (E for M Corp., Lanexa, KS, USA).

Hemodynamic measurements and statistical analysis

In both treatments, hemodynamic data were collected at rest and during exercise performed on 3.5% uphill grade at 8 and 14 m/sec. Measurements were made over all consecutive cardiac cycles recorded during 15–45 sec of exercise at 8 m/sec, and during 15–60 sec of exercise at 14 m/sec. Based on the work of Bhattacharya *et al*. (1982) and as suggested by West *et al*. (1993), the mean pulmonary capillary blood pressure was calculated as 1/2(mean pulmonary artery pressure + mean pulmonary artery wedge pressure). The pulmonary perfusion pressure gradient was determined as the difference between mean pulmonary artery pressure and the mean pulmonary artery wedge pressure. Heart rate was determined from the continuously recorded phasic right ventricular pressure.

The hemodynamic data were subjected to repeated measures analysis of variance (SAS statistical software version 6.12, SAS Institute, Cary, NC, USA), and the treatment comparisons were made using the least squares significant difference method (Steel & Torrie, 1960). The effects of work intensity within each treatment were also determined with the Newman–Keuls' multiple range test (Steel & Torrie, 1960). For all statistical analyses, a probability level of $P < 0.05$ was regarded as being statistically significant, and the data are presented as mean $\pm$ 1 SEM.

RESULTS

Control study

In standing horses, the respective pre-exercise values of heart rate, mean right atrial pressure and mean pulmonary arterial, capillary and wedge pressures were 39 ± 3 beats/min, 7 ± 1, 32 ± 2, 26.8 ± 1.4 and 22 ± 1 mmHg. Incremental exercise resulted in progressive significant ($P < 0.05$) increments in each of these variables (Figs 1–5). The pulmonary perfusion pressure also widened significantly ($P < 0.05$) with exercise. During galloping at 14 m/sec on 3.5% uphill grade, the respective values of heart rate, mean right atrial and mean pulmonary arterial, capillary and wedge pressures approached 220 ± 3 beats/min, 55 ± 6, 98 ± 5, 86.2 ± 5.0 and 75 ± 5 mmHg. All horses experienced EIPH as demonstrated by the presence of fresh blood in the trachea on post-exercise airway endoscopic examination.

Pentoxifylline study

In standing horses, pentoxifylline administration caused anxiety/nervousness, tachycardia, generalized muscular fasciculations/tremors, and mild sweating on the neck, shoulders and brisket region. Except for tachycardia (Fig. 1), these signs had largely abated by 15 min post-pentoxifylline administration, and significant changes in the right atrial and pulmonary vascular pressures were not observed (Figs 2–5).

Incremental exercise in the pentoxifylline experiments also caused progressive significant increments in heart rate as well as the right atrial and pulmonary vascular pressures (Figs 1–5),

but the values achieved during sub-maximal (8 m/sec) as well as strenuous (14 m/sec on 3.5% uphill grade) exercise in the pentoxifylline treatment were not significantly different from respective data in the control study. All horses experienced EIPH in the pentoxifylline experiments as well.

DISCUSSION

These experiments (Figs 2–5) confirmed earlier observations (Manohar, 1993, 1994, 1995; Manohar & Goetz, 1996, 1998,

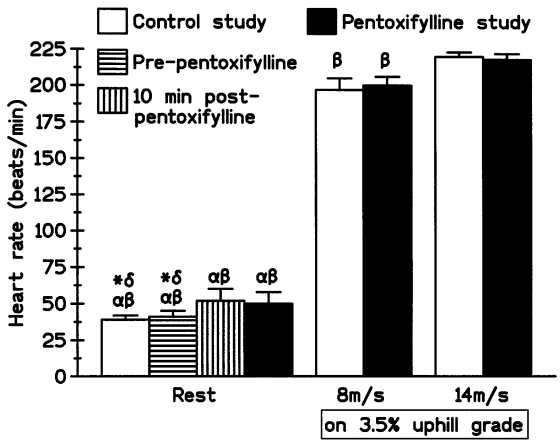

Fig. 1. Heart rate of horses increased progressively with incremental exercise in the control and the pentoxifylline experiments. The solid bar for resting data in the pentoxifylline study represents values collected during the 15th minute after administration of the drug in standing horses. α, Statistically significant difference from values for exercise at 8 m/sec. β, Statistically significant difference from values for exercise at 14 m/sec. *, Statistically significant difference from values at 10 min post-pentoxifylline dose in standing horses. δ, Statistically significant difference from values at 15 min post-pentoxifylline dose in standing horses.

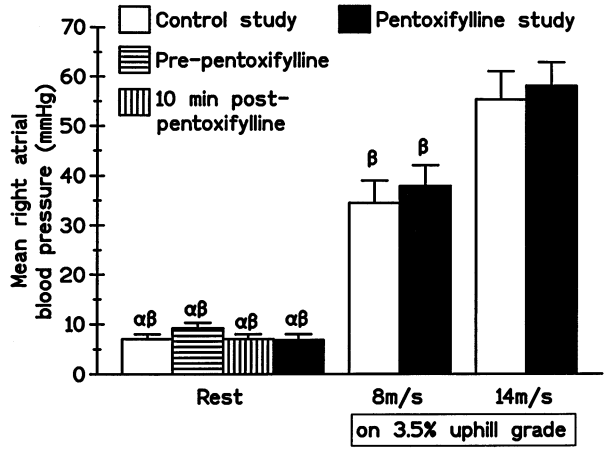

Fig. 2. Changes caused by pentoxifylline administration in the mean right atrial blood pressure of standing and exercising horses were not found to be statistically significant. For key to the symbols, refer to Fig. 1.

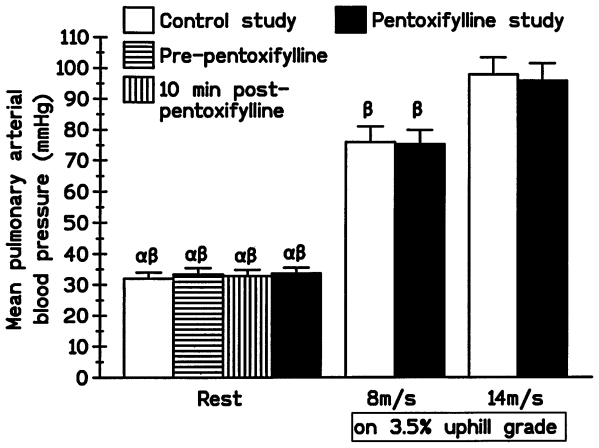

Fig. 3. Pentoxifylline administration in horses did not cause significant changes in the mean pulmonary arterial blood pressure at rest or during exercise. For key to the symbols, refer to Fig. 1.

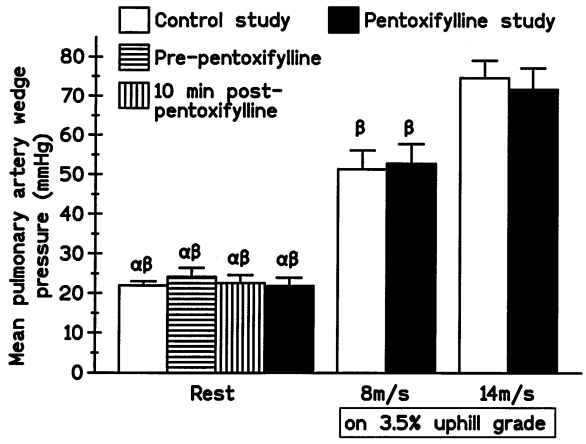

Fig. 4. Mean pulmonary artery wedge pressure of standing and exercising horses was not significantly affected by pentoxifylline administration. For key to the symbols, refer to Fig. 1.

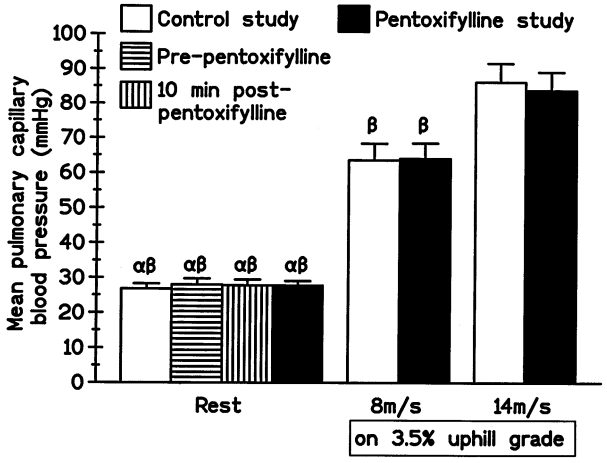

Fig. 5. After pentoxifylline administration, significant changes in the mean pulmonary capillary blood pressure were not observed in standing or exercising horses. For key to the symbols, refer to Fig. 1.

1999a,b) that exercising horses develop significant right atrial and pulmonary arterial, capillary and venous hypertension. The new finding in the present study is that i.v. pentoxifylline administration to healthy, exercise-trained Thoroughbred horses neither significantly altered their pulmonary vascular pressures at rest, nor did it significantly affect the magnitude of exercise-induced pulmonary capillary hypertension, and therefore, the incidence of EIPH remained unaffected as well.

That the horses in our experiments indeed performed strenuous exercise was demonstrated by the following observations. First, in separate trials before undertaking the hemodynamic studies we demonstrated that maximal heart rate was elicited during galloping at 14 m/sec on 3.5% uphill grade and that this value (Fig. 1) was comparable with the maximal heart rate values reported in previous studies (Manohar, 1993, 1994, 1995; Manohar & Goetz, 1996, 1998, 1999a,b). Second, our exercise protocol caused all horses to experience EIPH in both treatments.

In standing horses, pentoxifylline administration induced anxiety, muscular fasciculations, and tachycardia. These observations are similar to those reported previously and are probably a manifestation of the pentoxifylline-induced phosphodiesterase inhibition at various tissue sites (Barton *et al.*, 1997). The dosage/administration regimen of pentoxifylline in our experiments was based on previous work (Crisman *et al.*, 1993; Barton *et al.*, 1997) demonstrating that peak plasma concentrations of pentoxifylline and its metabolite I—which is rheologically active (Ambus *et al.*, 1990; Ward & Crisold, 1987)—occurred 15 min after bolus injection in horses. The *in vivo* concentration of pentoxifylline thus achieved is also believed to be effective in improving equine RBC deformability *in vitro* (Weiss *et al.*, 1994). Other considerations for the i.v. administration of pentoxifylline in our experiments were its known poor/erratic absorption from the equine gastrointestinal tract and the significantly lower plasma concentrations achieved after oral administration (Crisman *et al.*, 1993). Besides eliciting rheologic effects (Geor *et al.*, 1992; Weiss *et al.*, 1994; Weiss & Smith, 1998), pentoxifylline administration in horses increases circulating prostaglandin concentrations and suppresses formation of endotoxin-induced tumor-necrosis factor (Barton *et al.*, 1997). Although *in vitro* beneficial rheologic effects of pentoxifylline have been described (Geor *et al.*, 1992; Weiss *et al.*, 1994), the effective plasma concentration of the drug and its metabolite(s) as well as the precise duration for which the drug must be administered to achieve these effects remain unknown.

The professed *in vivo* beneficial effects of pentoxifylline on pulmonary hemodynamics (Weiss & Smith, 1998) are supposed to emanate from its ability to enhance RBC deformability which decreases blood viscosity (Ward & Crisold, 1987; Ambus *et al.*, 1990). Although diminished RBC deformability has been suggested to play a role in causing pulmonary hypertension in exercising horses (Weiss & Smith, 1998), the issue is far from being settled. This is because other investigators (Smith *et al.*, 1989) have been unable to detect diminished RBC deformability and significant numbers of echinocytes in exercising horses. Thus, our observation that i.v. pentoxifylline failed to affect the magnitude of exercise-induced pulmonary arterial, capillary and venous hypertension and the incidence of EIPH in Thoroughbreds (Figs 3–5), would suggest that the contribution of diminished RBC deformability and/or echinocytes to the exercise-induced pulmonary hypertension may be negligible. In addition, it is worth noting that the pulmonary vascular resistance of exercising horses decreases to its minimal value (and becomes a fixed variable) during moderate exercise (8 m/sec), thereby causing the pulmonary arterial blood pressure to become a direct function of the cardiac output as workload is increased to maximal exercise (Manohar & Goetz, 1999b).

In conclusion, these experiments demonstrated that pentoxifylline administration to healthy, fit Thoroughbred horses did not affect pulmonary vascular pressures at rest, or during moderate and strenuous exercise, and the incidence of EIPH remained unaffected. An implication of these findings is that diminished RBC deformability may be an insignificant component in bringing about the exercise-induced pulmonary arterial, capillary and venous hypertension in horses as suggested previously (Smith *et al.*, 1989; Manohar *et al.*, 1993).

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