H₁-receptor antagonist, tripelennamine, does not affect arterial hypoxemia in exercising Thoroughbreds

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Manohar, Murli, Thomas E. Goetz, Sarah Humphrey, and Tracy Depuy. H₁-receptor antagonist, tripelennamine, does not affect arterial hypoxemia in exercising Thoroughbreds. J Appl Physiol 92: 1515–1523, 2002. First published December 21, 2001; 10.1152/japplphysiol.00925.2001.—It has been suggested that pulmonary injury and inflammation-induced histamine release from airway mast cells may contribute to exercise-induced arterial hypoxemia (EIAH). Because stress failure of pulmonary capillaries and EIAH are routinely observed in exercising horses, we examined whether preexercise administration of an H₁-receptor antagonist may mitigate EIAH. Two sets of experiments, placebo (saline) and antihistaminic (tripelennamine HCl at 1.10 mg/kg iv, 15 min preexercise) studies, were carried out on seven healthy, exercise-trained Thoroughbred horses in random order 7 days apart. Arterial and mixed venous blood-gas and pH measurements were made at rest before and after saline or drug administration and during incremental exercise leading to maximal exertion at 14 m/s on 3.5% uphill grade for 120 s. Galloping at this workload elicited maximal heart rate and induced exercise-induced pulmonary hemorrhage in all horses in both treatments, thereby indicating that capillary stress failure-related pulmonary injury had occurred. In both treatments, EIAH, desaturation of hemoglobin, hypercapnia, and acidosis of a similar magnitude developed during maximal exertion, and statistically significant differences between the placebo and antihistaminic studies could not be demonstrated. The failure of the H₁-receptor antagonist to modify EIAH significantly suggests that pulmonary injury–induced histamine release may not play a major role in bringing about EIAH in Thoroughbred horses.

STRENUOUSLY EXERCISING THOROUGHBREDS routinely exhibit arterial hypoxemia and desaturation of hemoglobin (2, 3, 10, 13, 15, 20, 21, 32–34). Whereas it is recognized that the development of arterial hypoxemia limits athletic performance of racehorses (13, 33), the mechanism(s) responsible for the development and severity of exercise-induced arterial hypoxemia continues to be debated (8, 15, 27). Exercise-induced arterial hypoxemia is also observed in human subjects, in whom it limits exercise performance as well (8, 27). The commonly mentioned causes of exercise-induced arterial hypoxemia in racehorses include the so-called “relative” alveolar hypoventilation (as evidenced by significant arterial hypercapnia in exercising horses, despite increased alveolar ventilation), ventilation-to-perfusion inhomogeneity, and diffusion limitation related to the significantly shortened transit time for blood in the pulmonary capillaries as cardiac output increases dramatically (3, 10, 13, 15, 20, 21, 33, 34). Strenuously exercising horses also exhibit significant pulmonary arterial, capillary, and venous hypertension (16–19, 22), and the ensuing high transmural (intracapillary-perivascular [alveolar]) pulmonary capillary pressures contribute to the stress failure of pulmonary capillaries (4, 36), resulting in exercise-induced pulmonary hemorrhage (EIPH). There is considerable speculation as to whether structural changes in the blood-gas barrier associated with stress failure of pulmonary capillaries (4, 12, 28, 36) contribute to the phenomenon of exercise-induced arterial hypoxemia. In the latter context, similar to the observations in human subjects (5, 11, 29), it was recently demonstrated in Thoroughbred horses that a successive bout of strenuous exercise, performed 6 min after the first high-intensity exercise bout (which induced EIPH), failed to accentuate the arterial hypoxemia (20). Inference from these studies (5, 11, 20, 29) is that the exercise-induced arterial hypoxemia, which manifests quite early during heavy exertion and does not become accentuated as exercise duration progresses, more likely has a functional basis rather than a structural basis related to the exercise-induced changes in the thickness and integrity of the blood-gas barrier, which would be expected to intensify with increasing exercise duration.

Recently, it was demonstrated in human subjects performing heavy exertion that the reduction in arterial O₂ tension is concomitantly attended by significant histamine release (1, 25), possibly from airway mast cells in response to pulmonary injury and inflammation (1, 26, 27) associated with high transmural forces

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exerted onto the thin blood-gas barrier, which cause stress failure of pulmonary capillaries and EIPH (12). Further work has revealed that the stabilization of airway inflammatory and mast cells to prevent the release of histamine with inhaled nedocromil sodium, a known inflammatory and mast cell stabilizer (6) used for management of asthma, significantly attenuated (9, 26) or ameliorated (7) exercise-induced arterial hypoxemia in human subjects. Whereas these observations suggested a role for pulmonary injury-induced histamine release in bringing about exercise-induced arterial hypoxemia (1, 25–27), a causal relationship has not been established (26, 27, 37). However, recent demonstration that administration of an H1-receptor antagonist, diphenhydramine HCl, also ameliorated exercise-induced arterial hypoxemia in human subjects (7) has been more definitive in establishing histamine release as a culprit in bringing about exercise-induced arterial hypoxemia. Although the precise mechanism(s) by which released histamine brings about exercise-induced arterial hypoxemia is uncertain, it was suggested that histamine, being a potent capillary permeability promotant (via stimulation of H1 receptors), may cause interstitial pulmonary edema and affect the distribution of ventilation-to-perfusion inhomogeneity within the lungs, which in turn contributes to the observed exercise-induced arterial hypoxemia (1, 25–27).

The above observations in human subjects are quite pertinent to racehorses in that the transmural pulmonary capillary forces exerted onto the thin (0.3–0.5 μm in thickness) blood-gas barrier of exercising horses (16–19, 22) far exceed that in exercising human subjects, resulting in a rather high incidence (>75%) of capillary stress failure-induced EIPH (14, 31, 36). Thus the severity of lung injury and interstitial pulmonary edema may be more pronounced in racehorses. However, it is not known whether, similar to humans, airway histamine release in response to capillary stress failure-related pulmonary injury contributes to the phenomenon of exercise-induced arterial hypoxemia in horses. Therefore, in the present study, we examined the effects of an intravenously administered H1-receptor antagonist, tripeledennamine HCl, on exercise-induced arterial hypoxemia in Thoroughbred horses performing short-term, high-intensity exercise, which induced EIPH. Our hypothesis was that preexercise antihistaminic administration may prevent histamine (released from airway mast cells during exercise) from exerting its effects on pulmonary capillary permeability and, thereby, attenuate and/or alleviate the exercise-induced arterial hypoxemia.

MATERIALS AND METHODS

Horses. Experiments were carried out on seven healthy, sound Thoroughbred horses (3 fillies, 4 geldings), 3–6 yr old and weighing 460 ± 18 kg. They were exercised trained for a period of 7 wk before undertaking the blood-gas studies. 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 the horses were familiarized with walking, trotting, cantering, and galloping on the high-speed treadmill for 1 wk, all horses were exercised 3 days/wk in the following manner with the treadmill set on the flat, i.e., 0% grade. Beginning with a walk at 2 m/s for 120 s, belt speed was increased at the rate of 1 m/s every 60 s until the horse had trotted at 6 m/s for 60 s. Treadmill speed was then raised to 8 m/s, and the horses were cantered for 60 s. Cantering was followed by galloping at 10 m/s for 60 s and at 14 m/s for 120 s. Belt speed was then decreased, first to 5 m/s for 60 s and then to 2 m/s for 300 s before the treadmill was stopped. After initial exercise training for 4 wk in this manner, for the next 3 wk this incremental exercise regimen was performed 3 days/wk with the treadmill set at a 3.5% uphill grade.

Work intensity eliciting EIPH. It should be noted at the outset that, because occurrence of EIPH demonstrates that capillary stress failure-related pulmonary injury has indeed occurred (4, 12, 36), for the present study we intended to use a workload capable of eliciting EIPH consistently. Trials to ascertain work intensity needed to elicit maximal heart rate and EIPH were undertaken on completion of the above-described exercise training. In agreement with our laboratory’s previous work (10, 18, 20, 21), it was observed that galloping at 14 m/s on a 3.5% uphill grade not only elicited maximal heart rate, but also induced EIPH in all horses, as demonstrated by the presence of fresh blood in the trachea on postexercise airway endoscopic examination (14, 31). It was also observed in these trials that these horses could not sustain galloping at 14 m/s on a 3.5% uphill grade for >120 s, despite vigorous, humane encouragement. Thus this workload, i.e., 14 m/s on a 3.5% uphill grade, was selected for further experimentation as it represented a strenuous effort eliciting maximal heart rate and EIPH in the experimental horses.

Experimental procedures. Our procedures for blood-gas and hemodynamic studies have been described in detail previously (10, 16–21); therefore, only a brief description is given here. On the day of the study, after local anesthesia in the 17th intercostal space, the abdominal aorta was percutaneously catheterized (10, 20, 21). Thereafter, using local infiltration of 2% lidocaine HCl, cardiac catheters (8 F) equipped with a tip-manometer (Millar Instruments, Houston, TX), fluid-filled lumen, and a thermistor (Edward Laboratories, Santa Clara, CA) were advanced into the pulmonary artery via introducers inserted into the left jugular vein. The locations of various catheters were confirmed by monitoring the characteristic phasic blood pressure waveforms on an oscillographic recorder (E for M, Lanexa, KS). Besides blood pressure monitoring, these catheters permitted simultaneous sampling of the aortic and pulmonary arterial (mixed venous) blood, as well as continuous monitoring of the pulmonary arterial blood (core) temperature during the experiments. After catheter placement, horses stood quietly on the treadmill for ~45–50 min before blood-gas and pH studies were undertaken.

Blood-gas tensions, pH, hemoglobin concentration, hemoglobin-O2 saturation, and O2 content were determined using a carefully calibrated blood-gas analyzer and CO-oximeter (ABL520 system, Radiometer, Copenhagen, Denmark), and all blood-gas tensions and pH data were corrected to the simultaneously measured pulmonary arterial blood temperature. The calibration of our blood-gas and pH analyzer and CO-oximeter was checked frequently and was verified using tonometered solutions of known blood-gas tensions, pH, he-
moglobin concentration, and O₂ saturation. In the present study, the O₂ extraction (%) was calculated as (arterial-to-mixed venous blood O₂ content gradient/arterial O₂ content) × 100.

Experimental design and protocol. All horses were studied in the placebo (saline control) and the antihistaminic (tripelennamine HCl, an H₁-receptor antagonist) studies, which were carried out in random order, 7 days apart. All experimentation was carried out in an air-conditioned laboratory, where the ambient temperature was maintained at 20–21°C.

In both treatments, at first, blood-gas and pH measurements were made in duplicate on quietly standing horses (without any medications) when heart rate and pulmonary vascular pressures had been stable for 10–15 min; hereafter, these data are referred to as predrug rest. Then H₁-receptor antagonist tripelennamine HCl (RE-COV, Fort Dodge Animal Health, Fort Dodge, IA), at 1.10 mg/kg body wt dissolved in 250 ml of physiological saline or an equivalent volume of physiological saline (placebo control), was administered into the left jugular vein via the side port of the introducer used for advancing the cardiac catheter into the pulmonary artery. About 12–14 min after intravenous (IV) placebo or tripelennamine HCl injection, resting blood-gas and pH measurements were made (in duplicate) on standing horses; hereafter, these data are referred to as postdrug rest. The efficacy of systemic tripelennamine HCl administered at 0.44 mg/kg in reversing the histamine-induced bronchoconstriction, increased transpulmonary pressure, increased pulmonary vascular resistance, and diminished dynamic compliance has been demonstrated in horses (23).

Exactly 15 min after placebo or tripelennamine HCl injection, exercise began on the high-speed treadmill set at a 3.5% uphill grade in the following manner. The horses began with a walk at 2 m/s for 300 s before the treadmill was stopped. In this exercise protocol, along with continuous core temperature measurement, simultaneous arterial and mixed venous blood samples were obtained for determining blood-gas tensions, pH, hemoglobin concentration, hemoglobin-O₂ saturation, and O₂ content at 55 s of trotting at 6 m/s, at 55 s of exercise at 8 m/s, at 30, 60, 90, and 120 s of galloping at 14 m/s on a 3.5% uphill grade, the belt speed was decreased, first to 5 m/s (trot) for 60 s and then to 2 m/s. Horses walked at 2 m/s for 300 s before the treadmill was stopped. In this exercise protocol, along with continuous core temperature measurement, simultaneous arterial and mixed venous blood samples were obtained for determining blood-gas tensions, pH, hemoglobin concentration, hemoglobin-O₂ saturation, and O₂ content at 55 s of trotting at 6 m/s, at 55 s of exercise at 8 m/s, at 30, 60, 90, and 120 s of galloping at 14 m/s on a 3.5% uphill grade, and at 120 s of walk at 2 m/s.

Postexercise airway endoscopic examination. In both treatments, with the use of a flexible fiber-optic endoscope (Pentax Fiberscopes, Orangeburg, NY), careful examination of the nasopharynx, larynx, and trachea (up to the carina) was undertaken 45–50 min postexercise (14, 16, 31). The presence of fresh blood in the airway(s) was regarded as indicative of the occurrence of EIPH (14, 16, 31).

Data analysis. All data were subjected to repeated-measures, split-plot design analysis of variance using the SAS statistical software package (SAS version 8.1, SAS Institute, Cary, NC), and the treatment comparisons were made using the least squares significant difference method (30). Data for the placebo (control) as well as tripelennamine HCl experiments were also individually subjected to analysis of variance followed by Newman-Keuls multiple-range test (30) (SAS version 8.1, SAS Institute) to determine the significant effects of work intensity and duration within each treatment.

RESULTS

General observations. IV administration of tripelennamine HCl to standing horses caused central nervous system (CNS) excitement, and the horses became very alert, agitated, and uncomfortable, as indicated by their raising the head and tightening the neck muscles, excessive rapid movements of eyes and ears, biting, snorting, briskly swishing the tail, and stomping and pawing with front feet. Concomitantly, a sharp increase in hemoglobin concentration was also observed, presumably due to splenic contraction caused on sympathoadrenal activation associated with CNS excitement; from its predrug resting value of 12.7 ± 0.5 g/dl (in both the placebo and tripelennamine HCl treatments), hemoglobin concentration of standing horses increased significantly (P < 0.0001) to reach 17.7 ± 0.6 g/dl in the tripelennamine HCl experiments. The latter was accompanied by significantly increased mixed venous blood O₂ tension and hemoglobin-O₂ saturation (Fig. 1), as well as arterial and mixed-venous blood O₂ contents (Fig. 2), but the arterial-to-mixed-venous O₂ content gradient of standing horses was not significantly affected (Fig. 2).

CNS excitement in resting horses caused on tripelennamine HCl administration was also attended by significant tachycardia (a doubling of the predrug heart rate values), as well as systemic and pulmonary hypertension. However, during exercise, heart rate and pulmonary and systemic blood pressure values were not different between the placebo and tripelennamine HCl experiments.

Changes in core temperature. Preexercise values of core temperature [37.4 ± 0.1 and 37.5 ± 0.1°C in the placebo (control) and tripelennamine HCl treatments, respectively] were not significantly different from each other. Although core temperature increased progressively with increasing work intensity in both treatments, the increment was found to be significantly greater (P < 0.0001) in the tripelennamine HCl study. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and tripelennamine HCl experiments, core temperature had reached 40.7 ± 0.1 and 41.2 ± 0.1°C (P < 0.0001), respectively.

Changes in arterial O₂ tension and hemoglobin-O₂ saturation. See Fig. 1. Predrug resting data for these variables were similar in both treatments, and the administration of tripelennamine HCl did not cause significant changes in standing horses. During submaximal exercise at 6 and 8 m/s, arterial O₂ tension and hemoglobin-O₂ saturation were well maintained in both treatments.

Galloping at 14 m/s on a 3.5% uphill grade was attended by a significant (P < 0.0001) reduction in arterial O₂ tension at 30 s in both treatments, but further statistically significant changes did not occur.
as exercise duration progressed to 120 s. At 120 s of
galloping at 14 m/s on a 3.5% uphill grade in the
placebo and tripelennamine HCl experiments, the
arterial O₂ tension values were 71.3 ± 2.8 and 71.3 ± 2.2
Torr, respectively. Statistically significant differences
between the placebo and the tripelennamine HCl
experiments could not be discerned at any point during the protocol. Work intensity-related reductions in mixed
venous blood O₂ tension and hemoglobin-O₂ saturation
were observed in both treatments, and statistically
significant differences between the treatments were not found. Predrug rest and postdrug rest refer to measure-
ments made in standing horses before and after placebo (saline) or tripelennamine HCl administration, respec-
tively. Statistically significant differences: * from pre- and postdrug rest data, as well as data for exercise at 6 and
8 m/s in the same study; † from pre- and postdrug resting data in the same study; ‡ from predrug rest in the same
study; § from corresponding values in the placebo study; ‖ from data for 30 s of galloping at 14 m/s on a 3.5% uphill
grade in the same study; ¶ from data for 60 s of galloping at 14 m/s on a 3.5% uphill grade in the same study; † from
data for all drug and exercise in the same study, P < 0.05.

as exercise duration progressed to 120 s. At 120 s of
galloping at 14 m/s on a 3.5% uphill grade in the
placebo and tripelennamine HCl experiments, the
arterial O₂ tension values were 71.3 ± 2.8 and 71.3 ± 2.2
Torr, respectively. Statistically significant differences
between the placebo and the tripelennamine HCl
experiments were not discerned during the exercise protocol.

In both treatments, statistically significant desatura-
tion of hemoglobin in the arterial blood was observed
at 30 s of galloping at 14 m/s on a 3.5% uphill grade. As
exercise duration progressed to 120 s, the desaturation
of hemoglobin intensified (Fig. 1), but statistically
significant differences between the placebo and the tri-
pelemamine HCl studies were not found. The increasing
desaturation of arterial hemoglobin observed in
going from 30 to 120 s of galloping at 14 m/s on a 3.5%
uphill grade probably resulted from the rightward shift
of the hemoglobin-O₂ dissociation curve as hypercap-
nia (Fig. 3), acidosis (Fig. 4), and hyperthermia (from
39.1 ± 0.1 and 39.7 ± 0.2°C, respectively, at 30 s of
galloping in the placebo and tripelennamine HCl ex-
periments to 40.7 ± 0.1 and 41.2 ± 0.1°C, respectively,
at 120 s; both $P < 0.0001$) intensified with increasing exercise duration. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and tripelennamine HCl experiments, arterial hemoglobin-O$_2$ saturation values were 83.8 ± 2.7 and 80.6 ± 2.3%, respectively, and statistically significant differences between the treatments were not discerned.

Changes in mixed venous blood O$_2$ tension and hemoglobin-O$_2$ saturation. See Fig. 1. Whereas predrug values of these variables were similar in the two treatments, after tripelennamine HCl administration, a statistically significant ($P < 0.001$) rise in mixed venous blood O$_2$ tension as well as hemoglobin-O$_2$ saturation was observed. During exercise, significant work intensity-related reductions in these variables were observed in both treatments, but statistically significant differences between the placebo and the tripelennamine HCl experiments were not found.

Changes in arterial CO$_2$ tension. See Fig. 3. Administration of tripelennamine HCl to standing horses did not significantly affect the arterial CO$_2$ tension. Whereas submaximal exercise at 6 and 8 m/s in both treatments was attended by hyperventilation, during galloping at 14 m/s on a 3.5% uphill grade, a significant hypercapnia developed. The extent of exercise-induced arterial hypercapnia in galloping Thoroughbreds was found to be similar between the placebo and the tripelennamine HCl experiments. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and the tripelennamine HCl treatments, arterial CO$_2$ tension values were 56.2 ± 2.9 and 60.1 ± 3.0 Torr, respectively.

Fig. 4. Intravenous administration of tripelennamine HCl failed to significantly affect the arterial blood pH at rest or during exercise in horses. In both treatments, although arterial blood pH did not exhibit statistically significant changes during submaximal exercise, a progressive, significant acidosis was evident during galloping at 14 m/s on a 3.5% uphill grade as exercise duration increased to 120 s. Statistically significant differences: * from pre- and postdrug rest, as well as from all exercise data in the same study; # from pre- and postdrug rest in the same study; $\Phi$ from values for exercise at 6 and 8 m/s in the same study; + from data for 30 s of galloping at 14 m/s on a 3.5% uphill grade in the same study, $P < 0.05$.
Changes in arterial blood pH. See Fig. 4. In quietly standing horses, arterial pH values before and after placebo or tripelennamine HCl administration were not significantly different. In either treatment, arterial pH did not change significantly with exercise performed at 6 and 8 m/s. During galloping at 14 m/s on a 3.5% uphill grade, a progressive, significant acidosis of a similar magnitude was observed in both treatments. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and the tripelennamine HCl experiments, the arterial pH values were 7.090 ± 0.044 and 7.040 ± 0.030, respectively.

Changes in arterial and mixed venous blood O₂ content. See Fig. 2. Predrug resting values of arterial and mixed venous blood O₂ content were similar in the placebo and the tripelennamine HCl experiments. Because of the excitement-related increment in hemoglobin concentration in standing horses after tripelennamine HCl administration, a significant (P < 0.0001) increase in arterial as well as mixed venous blood O₂ content of standing horses was also observed (see postdrug rest in Fig. 2). However, the arterial-to-mixed venous O₂ content gradient (4.9 ± 0.3 ml O₂/dl blood) of standing horses after tripelennamine HCl administration was not found to be significantly different from that in the placebo study (4.4 ± 0.3 ml O₂/dl blood).

As expected, with exercise, hemoglobin concentration of horses increased significantly (P < 0.0001 vs. predrug rest) in both treatments, and statistically significant differences between the placebo and the tripelennamine HCl experiments could not be discerned. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and the tripelennamine HCl experiments, the arterial hemoglobin concentration was 22.2 ± 0.5 and 22.5 ± 0.5 g/dl, respectively.

In both experiments, a significant (P < 0.0001 vs. predrug rest) increment of a similar magnitude in arterial blood O₂ content was observed during exercise as hemoglobin concentration increased significantly. Concomitantly, a work intensity-related reduction of a similar magnitude in the mixed venous blood O₂ content was also observed. Consequently, arterial-to-mixed venous O₂ content gradient of exercising horses increased significantly (P < 0.0001 vs. rest) to reach similar values in both treatments. At 120 s of galloping at 14 m/s on a 3.5% uphill grade in the placebo and tripelennamine HCl experiments, arterial-to-mixed venous blood O₂ content gradient had reached 23.2 ± 0.7 and 22.8 ± 0.8 ml O₂/dl of blood, respectively, as O₂ extraction approached 91.5 ± 1.0 and 92.2 ± 0.6%, respectively. Statistically significant differences between the placebo and tripelennamine HCl treatments were not observed in these variables during exertion.

Airway endoscopic observations. All horses were found to have experienced EIPH in the placebo as well as the tripelennamine HCl experiments, as demonstrated by the presence of fresh blood in the trachea (14, 16, 31).

DISCUSSION

Our observations regarding development of arterial hypoxemia, desaturation of hemoglobin, hypercapnia, acidosis, hemococoncentration, increased O₂ extraction, and arterial-to-mixed venous blood O₂ content gradient (Figs. 1–4), as well as significant hyperthermia in horses performing short-term, high-intensity exercise in the placebo study are similar to those reported previously (2–4, 10, 13, 15, 20, 21, 32–34). In view of the reports in human subjects that exercise-induced arterial hypoxemia may be associated with pulmonary injury-induced airway histamine release (1, 25–27) and that administration of an H₁-receptor antagonist, diphenhydramine HCl, ameliorated exercise-induced arterial hypoxemia (7), our primary objective in the present study was to ascertain whether pulmonary injury-associated histamine release plays a role in bringing about exercise-induced arterial hypoxemia and desaturation of hemoglobin in Thoroughbred horses. Because histamine-induced increase in pulmonary capillary permeability (contributing to interstitial pulmonary edema and ventilation-to-perfusion inhomogeneity within lungs, a suggested mechanism for inducing exercise-induced arterial hypoxemia; Refs. 1, 25–27) is mediated via stimulation of H₁-receptor receptors, we examined the effects of a large dose of intravenously administered H₁-receptor antagonist tripelennamine HCl on arterial O₂ tension and hemoglobin-O₂ saturation in Thoroughbred horses performing short-term, high-intensity exercise, which induced capillary stress failure and EIPH. In this context, in contrast with observations in human subjects (7, 9, 26), our data did not demonstrate beneficial effects of intravenously administered tripelennamine HCl on the time course for development and/or severity of exercise-induced arterial hypoxemia and desaturation of hemoglobin in healthy Thoroughbred horses (Fig. 1). The failure of an intravenously administered H₁-receptor antagonist to significantly affect the exercise-induced arterial hypoxemia in our experiments suggests that pulmonary injury-induced histamine release may not play a major role in bringing about the phenomenon of exercise-induced arterial hypoxemia in Thoroughbred horses. Although the reasons for divergent findings of the present study, vis-à-vis reports in human studies (7, 9, 26), are difficult to discern, species differences cannot be ruled out.

Plasma histamine concentration was not determined in the present study because it is not an accurate measure of histamine released from airway mast cells (24, 37). In fact, circulating histamine to a much greater extent reflects basophil-released histamine rather than that released from airway mast cells (24). Also, there are significant methodological problems in obtaining accurate estimates of plasma histamine concentration because of its extremely short half-life and the possibility that even centrifugation of blood (to separate plasma) causes histamine release (24, 37).

Because we did not observe an improvement in arterial O₂ tension, hemoglobin-O₂ saturation, and O₂
content of horses exercising after tripeledennamine HCl administration (Figs. 1 and 2), the arterial-to-mixed venous blood \( O_2 \) content gradient and \( O_2 \) extraction during exercise performed at the same workload also remained unaffected. It is also noteworthy that the extent of exercise-induced hypercapnia as well as metabolic acidosis in our tripeledennamine HCl experiments was not significantly different from that in the placebo study (Figs. 3 and 4). These observations suggest that, during galloping at 14 m/s on a 3.5% uphill grade, the aerobic and anaerobic metabolic needs remained similar between the placebo and the tripeledennamine HCl studies.

In view of the negative findings of the present study, vis-à-vis human experiments in which diphenhydramine HCl and nedocromil sodium had a favorable effect on exercise-induced arterial hypoxemia and desaturation of hemoglobin (7, 9, 26), it must also be noted that a discrete causal relationship between the pulmonary injury-induced airway inflammatory and mast cell histamine (and possibly other chemical mediators as well) release and exercise-induced arterial hypoxemia remains to be established. In fact, recently, Wetter et al. (37) reported that, although plasma histamine increased throughout exercise in women, it was inversely correlated with the severity of exercise-induced arterial hypoxemia at end exercise. There are other contradictions in the human data as well; for example, the alleviation (7) and/or attenuation (26) of exercise-induced arterial hypoxemia with diphenhydramine HCl or nedocromil sodium in human subjects did not cause an augmentation of the maximal \( O_2 \) uptake (\( VO_2\text{max} \)). This is contrary to several reports in the literature demonstrating that alleviation of exercise-induced arterial hypoxemia augments \( VO_2\text{max} \) (8, 27, 33). However, in another report (9), significant gains in \( VO_2\text{max} \) were reported subsequent to improved arterial hemoglobin-\( O_2 \) saturation after nedocromil sodium inhalation. Another paradoxical observation in the work of Prefaut et al. (26) was that the improvement in arterial \( O_2 \) tension of maximally exercising human subjects after inhibition of histamine release was attended by a significant reduction in alveolar ventilation with an attendant reduction in alveolar \( O_2 \) tension, i.e., a diminished pressure head for \( O_2 \) diffusion across the blood-gas barrier.

In the present study, because all horses were observed to have experienced EIPH in both treatments, there can be no doubt that stress failure of pulmonary capillaries (4, 36) and pulmonary injury (26, 27) had indeed occurred, and yet intravenously administered \( H_1 \)-receptor antagonist, tripeledennamine HCl, was ineffective in significantly affecting the development and severity of exercise-induced arterial hypoxemia. Thus it appears unlikely that pulmonary injury-related airway inflammatory and mast cell histamine release plays a major role in bringing about the exercise-induced arterial hypoxemia in Thoroughbred horses. In the context of the time course for the development and severity of exercise-induced arterial hypoxemia, we observed in the placebo as well as the tripeledennamine HCl studies that hypoxemia was already well developed by 30 s of high-intensity exercise and that increasing exercise duration to 120 s did not cause further statistically significant changes in the arterial \( O_2 \) tension (Fig. 1). According to the pulmonary injury, airway histamine release, and interstitial pulmonary edema hypothesis (1, 25–27), one would expect that there would be an intensification of the exercise-induced arterial hypoxemia with increasing exercise duration, as interstitial pulmonary edema (due to the increased capillary permeability in response to airway mast cell-released histamine; Refs. 1, 25, 26) intensifies over time. The fact that this was not the case in the present study (Fig. 1) or in previous studies using a similar exercise protocol (10, 20, 21) argues against a significant role for pulmonary capillary stress failure and pulmonary injury-induced airway histamine release (1, 25–27) in bringing about the exercise-induced arterial hypoxemia in horses. Further support for this argument is provided by our laboratory’s observations (20) that, during a successive bout of strenuous exercise performed 6 min after the first high-intensity exercise bout, which caused stress failure of pulmonary capillaries and EIPH, an accentuation of the arterial hypoxemia could not be demonstrated.

In the present study, we used tripeledennamine HCl, at a dosage of 1.10 mg/kg IV, to cause \( H_1 \)-receptor blockade. Tripeledennamine HCl belongs to the ethylenediamine class of first-generation \( H_1 \)-receptor antagonists, and our choice of this drug was based on the findings that tripeledennamine HCl injection to horses at 0.44 mg/kg abolished the histamine-induced bronchoconstriction and the associated changes in pulmonary mechanics (i.e., increased transpulmonary pressure, increased pulmonary resistance, and decreased dynamic compliance), thereby revealing the involvement of \( H_1 \) receptors (23). Also, this agent is used to treat acute allergic [i.e., immediate (type I) hypersensitivity] reactions in horses mediated via H1 receptors, e.g., urticaria, hives, insect bites, and feed allergies (35). In the context of negative findings of our study (vis-à-vis human experiments; Refs. 7, 9, 26), although it may be suggested that the concentration of histamine released on capillary stress failure-induced pulmonary injury in horses may have been so massive as to competitively negate or overwhelm the effects of IV tripeledennamine HCl, the fact is that a rather large dose of the antihistaminic agent was used in our experiments, as demonstrated by the fact that all horses exhibited CNS excitement, becoming very alert and agitated after administration of the drug. The significant rise in hemoglobin concentration of standing horses after IV tripeledennamine HCl administration was most likely due to splenic contraction caused on sympathoadrenal activation associated with CNS excitement and agitation caused by the drug. It is our clinical judgment, based on behavioral observations of horses after tripeledennamine HCl administration at 1.10 mg/kg in the present study, that a larger dose(s) would have induced convulsions as a result of more pronounced CNS excitement; the latter is a known adverse reaction.
to tripeledennamine HCl overdose (see pamphlet provided with the drug by the manufacturer).

In conclusion, our data demonstrated that intravenously administered H₁-receptor antagonist tripeledennamine HCl failed to significantly affect arterial hypoxemia, desaturation of hemoglobin, and hypercapnia in horses performing short-term, high-intensity exercise, which caused stress failure of pulmonary capillaries and pulmonary injury leading to EIPH. Thus it appears unlikely that pulmonary injury-related histamine release plays a major role in bringing about exercise-induced arterial hypoxemia in Thoroughbred horses. The rapid development of exercise-induced arterial hypoxemia and the fact that its severity did not change with increasing exercise duration suggest that this phenomenon more likely has a functional basis, probably related to the significantly shortened transit time for blood in the pulmonary capillaries as cardiac output increases dramatically.

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