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Effect of Airway Disease on Blood Gas Exchange in Racehorses

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Inflammatory Airway Disease (IAD), exercise-induced pulmonary hemorrhage (EIPH), and upper airway obstruction (UAO) are common respiratory tract diseases that can decrease performance. The purpose of this retrospective study was to compare bronchoalveolar lavage fluid cytology and arterial blood gas analysis during a treadmill test by poorly performing racehorses presented to Purdue University. One hundred thirty-two horses with a history of poor performance were included in this study. Ten horses with no history or diagnosis of EIPH, IAD, or UAO served as controls. Horses were evaluated by rhinolaryngoscopy for upper airway abnormalities and underwent a standardized treadmill test, and samples were collected for blood gas analysis. Horses with IAD or EIPH had a more severe exercise-induced hypoxemia, (mean $\pm$ SD; 84.8 $\pm$ 1.5 and 86.0 $\pm$ 1.7 mm Hg average Pa_{O_2}, respectively), than horses in the control group (92.8 $\pm$ 2.1 mm Hg). The average Pa_{O_2} of horses with only UAO (88.3 $\pm$ 3.3 mm Hg) was not significantly different from control horses. Gas exchanges were the most severely impaired in horses affected with both EIPH and UAO because they exhibited the lowest Pa_{O_2} and highest Pa_{CO_2} values (66.5 $\pm$ 15.2 and 52.2 $\pm$ 6.3 mm Hg, respectively).

Key words: Hemorrhage; Inflammation; Lung; Obstruction; Respiration; Ventilation.

Various diseases involving upper and lower airways have been associated with poor performance by racehorses. Inflammatory airway disease (IAD) is a common respiratory disease in young performance horses and is characterized by exercise intolerance, cough, and evidence of various amounts of mucus in the airways on endoscopic evaluation.[1,2] An initial diagnosis of IAD can be made on the basis of the horse's history, physical examination, and clinical signs. However, the diagnosis of IAD can be missed because clinical parameters of affected horses are usually within normal limits and there is no evidence of increased respiratory effort at rest. To confirm the diagnosis, additional diagnostic tests, including endoscopic evaluation, cytologic evaluation of the tracheal wash, and bronchoalveolar lavage fluid (BALF), and lung function tests may be performed.[1]

Horses affected with exercise-induced pulmonary hemorrhage (EIPH) might have evidence of blood in the trachea when evaluated endoscopically. The presence of blood in the trachea has been implicated in decreased performance[2]; however, studies have not been able to identify a relationship between the amount of blood present in the trachea and a horse's finishing position in a race.[3,4] Bleeding originates from the caudodorsal area of the lung and results from stress failure of pulmonary capillaries.[5] An endoscopically guided BALF aspiration enables collection of a sample from the region of interest. A BALF cytologic evaluation accurately reflects the cell population in the terminal airways and alveolar spaces, which aids in the diagnosis of the disease.[6,7] The presence of hemosiderophages in the BALF and tracheal wash fluid is diagnostic of EIPH if no other cause of pulmonary hemorrhage can be identified. Hemosiderophages will remain present in the BALF and tracheal wash for up to 3 weeks and possibly longer after an episode of EIPH.[8]

Upper respiratory tract obstruction (UAO) in racehorses is another common cause of exercise intolerance or decreased performance. The most common UAO are laryngeal paralysis, dorsal displacement of the soft palate, epiglottic entrapment, and dorsal pharyngeal collapse. Other causes that have been implicated are arytenoid chondritis, vocal fold collapse, granulomas, epiglottic hypoplasia, subepiglottic cysts, and nasopharyngeal masses.[9] Diagnosis of UAO is based on endoscopic examination.

Endoscopic evaluations reveal a high prevalence of diseases such as IAD, EIPH, and UAO in racehorses. The objective is to determine whether the findings are responsible for the abnormal performance reported by an owner or trainer. These respiratory diseases negatively affect performance primarily by obstructing airways and impairing gas exchanges and their effects are maximal during strenuous exercise.[10–12] Our hypothesis was that horses with upper and lower airway diseases would have impaired gas exchanges during high-speed treadmill exercise, which would result in more severe exercise-induced arterial hypoxemia, hypercapnia, or both when compared with a control group of healthy racehorses.

The purpose of this study was to compare BALF cytology and arterial blood gas analysis during a standardized treadmill test (STT) in racehorses diagnosed with IAD, EIPH, and UAO with values obtained in healthy racehorses.

Materials and Methods

One hundred thirty-two horses were examined during treadmill exercise between January 1, 1996, and December 31, 2001, and were included in this study. Of these, 122 horses were diagnosed with respiratory disease. Ten horses with no history or diagnosis of EIPH, IAD, or UAO were used as controls. All horses were evaluated on the basis of CBC, serum biochemistry profile, airway endoscopic evaluation, STT, BALF cytology, measurement of blood lactate, blood gas (BG) analysis (Pa_{O_2}, Pa_{CO_2}), and serum creatine phosphokinase (CPK) activity before and 6 hours after exercise.

The testing protocol has been previously described[10] and included blood work, BALF cytologic evaluation, and treadmill training on day 1 and additional training, treadmill test (dynamic upper airway endoscopy, BG, blood lactate), tracheobronchial endoscopy 1 hour after ex-

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ercise, and CPK 6 hours after exercise on day 2. An institutional animal care and use committee approved all procedures. A client consent form was signed by the owner at the time of enrollment in the study.

Control horses were clinically normal on the basis of physical examination; lameness evaluation; respiratory tract endoscopy before, during, and 1 hour after treadmill exercise; CBC; and serum biochemistry profile. According to their trainer, these horses were racing satisfactorily and finishing in the top 4 during their last 4 races.

Horses with EIPH had endoscopic evidence of blood in the trachea 1 hour after treadmill exercise. Horses with IAD had moderate to large amounts of mucopurulent secretions present in the trachea 1 hour after treadmill exercise. Upper airway obstruction was detected by endoscopic examination during exercise tests.

BALF Cytology Procedure

The animals were sedated with xylazine hydrochloride (0.4–0.6 mg/kg of body weight) or detomidine (0.02 mg/kg IV) and butorphanol (0.05 mg/kg IV). Lidocaine 0.2% solution was instilled in the airways as the endoscope was advanced into the caudodorsal lung area. A volume of 250 mL of warm 0.9% sterile saline solution was administered. The BALF recovered by suction was placed in a container on ice. All samples were processed within 20 minutes of collection. Specimens were prepared for cytology by cytocentrifugation and stained with Wright's stain. Cells were counted manually.

Standardized Treadmill Test

The treadmill test consisted of a warm-up period of 4 minutes of walking at 2 m/s and 4 minutes at 4 m/s. The treadmill was then stopped, and a videoendoscope was passed through the right nostril and positioned to visualize the caudal nasopharynx and larynx. The treadmill was started and a preprogrammed test was initiated. This test consisted of 120 seconds at 4 m/s, followed by five 1-minute incremental speed steps at 6, 8, 10, 11, and 12 m/s. The incline was set at 10% for Thoroughbreds and 5% for Standardbreds. The treadmill was stopped when the horse showed signs of fatigue and could not keep up with the treadmill speed.

Blood Gas Analysis

The transverse facial artery was catheterized and an arterial blood sample was collected in a heparinized syringe in the last 15 seconds of each step of the STT. Blood temperature was measured by a thermocouple probe inserted ~5 cm from the catheter hub and used for temperature correction of gas tensions by the analyzer.[10,a] A 2-mL aliquot of blood was placed in a dry tube for lactate measurement by a spectrophotometric method. The syringes were then capped and placed on crushed ice for blood gas analysis within 15 minutes of collection.

Statistical Analysis

Normal distribution of cytology, blood gas, and blood biochemistry variables was assessed by the Wilks-Shapiro test.[b] Most BALF cytology variables were nonnormally distributed, so between-group comparisons were assessed by the Kruskal-Wallis analysis of variance tests. All CBC, blood gas, and biochemistry data were normally distributed. For each horse, the minimum PaO_2; the maximum $PaCO_2$; and the average PaO_2, $PaCO_2$, and blood lactate concentration during the 1st 4 steps of the STT were compared between groups by analysis of variance.[c] Blood gas values at each step of the STT were compared between groups by repeated-measures analysis of variance. When significant main group effects were detected, least significant difference post hoc tests were performed to determine specific group differences. Results were expressed as median (1st–3rd quartiles) for BALF data and mean ± SD for the other data. The significance level was established at $P \leq .05$.

Results

Eighty-three of the 132 horses (62.9%) were Standardbreds, 42 of 132 (31.8%) were Thoroughbreds, and 7 of 132 (5.3%) were from other breeds. Forty-eight out of 132 horses (36.4%) were <3 years old, 44 of 132 were 3–6 years of age (33.3%), and 40 of 132 were >6 years of age (30.3%). All horses enrolled in this study completed at least the 1st 4 steps of the STT (4, 6, 8, and 10 m/s). Eight groups were identified: 28 of 132 (21.2%) had IAD; 20 of 132 (15.2%) had EIPH; 12 of 132 (9.1%) had IAD and EIPH; 10 of 132 (7.5%) had IAD and some type of UAO; 12 of 132 (9.1%) had EIPH and some type of UAO; 38 of 132 (28.8%) had only a diagnosis of upper respiratory tract obstruction; 2 of 132 (1.5%) were diagnosed with a combination of IAD, EIPH, and UAO; and 10 of 132 (7.5%) horses were healthy (control group). Analyses of BALF and blood gas data revealed no significant differences between horses diagnosed with IAD only and horses with IAD and upper respiratory tract obstruction; therefore, data from these 2 groups were pooled. Data from horses with IAD and EIPH and horses with IAD, EIPH, and UAO were also pooled for the same reason. Pooling of data did not change results of the analyses. Adjusting for age did not change the outcomes of the study.

BALF Cytology

Total nucleated cell counts and percentage of hemosiderophages were not significantly different between groups (Table 1).

Lymphocyte percentage and absolute number were significantly ($P \leq .05$) higher in horses with IAD than in control animals.

Alveolar macrophage percentage was significantly higher in control horses and horses with a combination of EIPH and UAO than in horses with IAD ($P < .03$). Alveolar macrophage cell counts were not significantly different between groups.

Four horses from the IAD group had a high percentage of eosinophils (>1%, n = 2) or mast cells (>2%, n = 2). However, percentage or absolute numbers of eosinophils, mast cells, and epithelial cells were not different between groups.

Blood Gas Tensions

PaO_2 decreased significantly as speed increased ($P < .0001$). There were no difference in PaO_2 at each step of the STT ($P = .062$). The average PaO_2 and minimum PaO_2 during the 1st 4 steps of the STT were significantly lower in horses with IAD (84.8 ± 1.5, 71.7 ± 6.7 mm Hg), EIPH (86.0 ± 1.7, 74.3 ± 5.0 mm Hg), IAD and EIPH (86.6 ± 2.5, 68.9 ± 4.9 mm Hg), and EIPH in combination with UAO (82.4 ± 2.3, 66.5 ± 15.2 mm Hg) when compared with control horses (92.8 ± 2.1, 83.2 ± 8.5 mm Hg; $P = .026$ and $P = .001$, respectively). However, the average PaO_2 of horses with only UAO (88.3 ± 3.3 mm Hg) was not significantly different from control horses. Horses diagnosed with IAD or EIPH had a more severe exercise-induced hypoxemia than other horses (Fig 1).

$PaCO_2$ increased significantly ($P < .001$) with each ad-

Table 1. Bronchoalveolar lavage fluid cytology analyses from racehorses diagnosed with various respiratory conditions. Results are expressed as median (1st quartile–3rd quartile).

	Cell Count (cells/μL)					
	Control (n = 10)	IAD (n = 25)	EIPH (n = 14)	IAD + EIPH (n = 10)	EIPH + UAO (n = 9)	UAO (n = 10)
Total nucleated cells	436 (326–536)	491 (394–634)	741 (449–1,002)	584 (269–646)	514 (348–620)	425 (277–519)
Neutrophils	8 (4–18)	34 (8–82)	28 (22–56)	24 (7–45)	13 (9–24)	17 (8–24)
Lymphocytes	97[a] (63–156)	185[b] (125–228)	217 (113–351)	154 (104–221)	132 (87–164)	151 (59–192)
Macrophages	294 (246–349)	279 (192–347)	474 (217–572)	286 (245–425)	350 (279–415)	321 (254–343)
Neutrophil %	2.0 (1.0–4.0)	5.0 (3.0–13.0)	4.5 (3.0–6.0)	4.0 (1.7–8.0)	2.0 (2.0–4.5)	3.5 (2.0–5.2)
Lymphocyte %	25.0[a] (15.0–29.2)	37.0[b] (30.8–48.5)	36.0 (28.0–48.0)	34.5 (21.2–39.0)	26.0 (19.5–30.2)	29.5 (17.7–36.2)
Macrophage %	65.0[a] (63.0–76.7)	54.0[b] (44.0–58.0)	49.0 (49.0–67.0)	60.0 (50.5–68.2)	72.0[a] (63.0–78.0)	66.5 (50.2–75.5)
Hemosiderophage %	13.5 (4.7–17.2)	8.0 (1.0–28.0)	48.0 (27.0–52.0)	28.5 (7.5–50.0)	34.6 (19.0–60.0)	2.0 (1.5–20.5)

IAD, inflammatory airway disease; EIPH, exercise-induced pulmonary hemorrhage; UAO, upper airway obstruction.
[a,b] Data on a line with different superscripts are significantly different from each other ($P \leq .05$).

ditional step of the STT, but there were no significant differences between groups at each step of the test (Table 2). However, the maximum Pa_{CO_2} reached by horses with a combination of EIPH and UAO (52.2 ± 6.3 mm Hg) was significantly higher than the values reached by other groups (Table 2; $P = .03$)

Blood Lactate

Blood lactate concentration increased significantly during the 1st 4 steps of the STT in all groups (1.3 mmol/L at 4 m/s, 1.7 mmol/L at 6 m/s, 2.9 mmol/L at 8 m/s, 6.3 mmol/L at 10 m/s); however, there was no significant difference in blood lactate concentration between groups. Speed for a lactate concentration of 4 mmol/L and peak lactate achieved during STT were not statistically different between groups.

Discussion

Data from this study suggest that racehorses with IAD and EIPH have impaired lung function, as illustrated by the more pronounced degree of exercise-induced hypoxemia they experience during an STT.

BALF Cytology

Bronchoalveolar lavage was performed before, rather than after, exercise on the basis of previous findings that indicated a better ability to differentiate between control horses and horses with IAD.[10] Bronchoalveolar lavage fluid in horses with an endoscopic diagnosis of IAD was characterized by neutrophilia and lymphocytosis, as previously reported.[10,13] Others have reported that BALF from horses with IAD is characterized by an increase in total nucleated cell counts, with the predominant inflammatory cells being neutrophilic, eosinophilic, or mastocytic.[13,14] In this study, some horses with accumulation of mucus in the trachea had a high percentage of eosinophils (>1%, n = 2) or mast cells (>2%, n = 2). However, some horses with excess mucus visible by endoscopy had normal BALF (n = 8) and others, with no detectable mucus accumulation, had inflammatory BALF (n = 14). These findings suggest that a combination of BALF cytologic evaluation performed before exercise and endoscopy of the airways after exercise are helpful to identify horses with IAD.

Distinct pathophysiologic mechanisms could be responsible for the observed differences in BALF phenotypes. Predominance of mast cells and eosinophils in BALF suggest an allergic mechanism (type I hypersensitivity) as the cause of airway inflammation.[15,16] BALF neutrophilia and lymphocytosis might result from persistent viral respiratory tract infection or chronic inhalation of airborne particles.[13]

Exercise-induced pulmonary hemorrhage can be diagnosed by the presence of variable amounts of blood in the trachea after exercise, but a more sensitive indicator is the presence of hemosiderophages in respiratory secretions because quantification of the amount of blood visible in the trachea is subjective.[17] Quantification of red blood cells in a BALF sample is also helpful when there is no endoscopic evidence of bleeding in the trachea.[18] In this retrospective study, animals were classified into the EIPH group by the presence of blood in the trachea after exercise. It is important to remember that not all horses experiencing pulmonary hemorrhage will have evidence of blood in the trachea after strenuous exercise. Indeed, prior episodes of pulmonary hemorrhage in control and IAD horses were revealed by the presence of hemosiderophages in their BALF (13.5 and 8.0% median values, respectively). Our data suggest that racehorses with blood visible in the trachea within 1 hour of a STT have more severe EIPH than horses that do not have blood detectable by endoscopy. For this reason, the presence of hemosiderophages is probably a more sen-

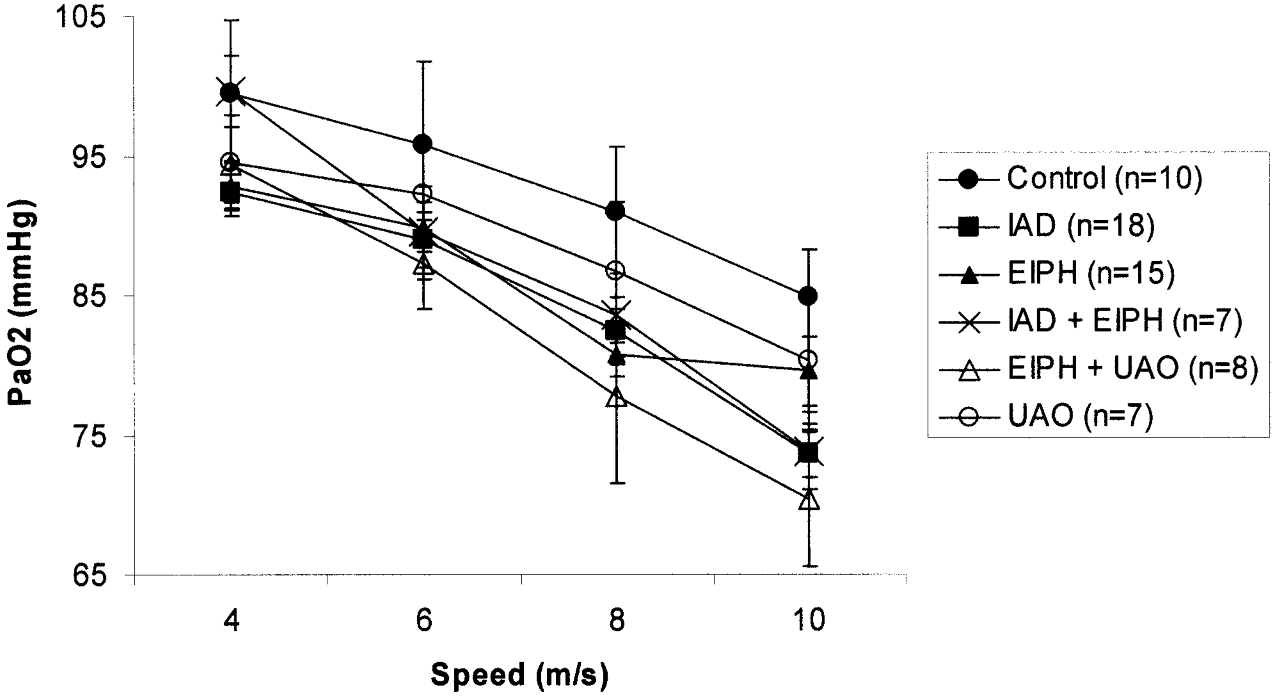

Fig 1. Pa_{O_2} values (mean ± SD) during the 1st 4 steps of the standardized treadmill test. EIPH, exercise-induced pulmonary hemorrhage; IAD, inflammatory airway disease; UAO, upper airway obstruction.

sitive means of determining the severity of EIPH in horses than is endoscopy. Exercise-induced pulmonary hemorrhage is not homogeneous throughout the lung, and with BALF cytology, just a small portion of the lung is being evaluated. For this reason, the endoscope used to perform the BALF cytologic evaluation was wedged in bronchi located in the caudodorsal portion of the lungs, where the bleeding originates. However, regional variation of the percentage of hemodiserophages in BALF is unknown. Such knowledge would improve our ability to diagnose and assess the severity of EIPH.

IAD and EIPH are highly prevalent in racehorses and have been identified as potential causes of impaired performance, especially in younger horses.[2,19] The relationship between airway inflammation and EIPH is a matter of debate. A previous study found an association between IAD and EIPH in young Thoroughbreds in training.[18] It is important to take into consideration that the presence of blood in the airways can in itself cause lung inflammation.[20] Others have proposed that lower airway inflammation plays a role in EIPH pathogenesis.[21] This study found that the majority of horses diagnosed endoscopically with EIPH did not exhibit signs of airway inflammation on the basis of BALF cytology. Further investigation is required to elucidate the relationship between these diseases and their effects on performance.

Blood Gases

In all horses, the degree of exercise-induced arterial hypoxemia worsened as treadmill speed increased throughout the STT, which is consistent with previous reports.[11,12] In addition, we observed that horses with IAD exhibited a significantly lower Pa_{O_2} than control horses during the 1st 4 steps of the STT as previously reported by Couetil et al.[10] Presumably, airway inflammation impaired ventilation-perfusion matching because Pa_{CO_2} was similar between groups. On the basis of these findings, we recommend treat-

Table 2. Pa_{CO_2} (mean ± SD) at 4, 6, 8, and 10 m/s during standardized treadmill test (STT).

		Pa_{CO_2} (mm Hg)				
	n	4	6	8	10	Max[a]
Control	10	40.2 ± 2.66	39.8 ± 5.92	41.2 ± 4.78	44.6 ± 3.37	45.7 ± 2.6
EIPH	17	40.53 ± 2.72	40 ± 4.34	41.38 ± 6.16	43.94 ± 5.45	46.7 ± 4.1
IAD + EIPH	7	38.29 ± 6.23	41.93 ± 3.44	40.89 ± 6.77	43.67 ± 5.53	46.7 ± 2.7
EIPH + UAO	8	37.15 ± 7.44	42.05 ± 3.64	46.41 ± 6.35	48.6 ± 2.49	52.2 ± 6.3[b]
IAD	21	39.84 ± 10.86	40.56 ± 4.61	43.17 ± 3.58	42.61 ± 5.09	47.3 ± 4.4
UAO	6	33.27 ± 8.03	40.35 ± 1.63	37.72 ± 8.57	42.35 ± 5	46.0 ± 3.3

EIPH, exercise-induced pulmonary hemorrhage; IAD, inflammatory airway disease; UAO, upper airway obstruction.
[a] Maximum $PaCO_2$ reached during STT.
[b] Significantly different from other groups (P = .03).

ing racehorses with IAD; however, whether current therapies will restore normal gas exchange and performance level has not been demonstrated yet. Horses affected with both EIPH and UAO had a significantly lower Pa_{O_2} level, when compared with horses with EIPH or UAO alone (Fig 1). This lower Pa_{O_2} in horses with both conditions might have been secondary to a relative hypoventilation, as suggested by the significantly higher maximum Pa_{CO_2} reached by these animals during STT. Also, UAO results in higher pressure swings in alveolar spaces and across capillary beds.[22] Higher pressure swings are more likely to lead to stress failure of pulmonary capillaries and result in EIPH.[23] Therefore, worsening of EIPH in horses that also developed UAO during STT might have impaired gas exchanges further. Successful treatment of UAO is therefore paramount to the management of EIPH when both conditions are detected in a horse. Blood gas data in horses with UAO were not different from controls, and 90% of those horses had $<$20% of hemosiderophages present in BALF. Therefore, horses with lower airway disease and $\geq$20% hemosiderophages are likely to have impaired pulmonary gas exchanges, which might adversely affect their performance.

The degree of exercise-induced hypoxemia worsens as a horse's maximum oxygen consumption increases.[11] Other factors such as quality of the horse and level of training are known to affect maximum oxygen consumption and could have confounded our blood gas results.[24,25] However, there was no significant difference in blood lactate concentration and racing times between groups (data not shown), suggesting comparable fitness levels and intrinsic quality of horses between groups. Nevertheless, we cannot exclude the possibility that there could have been large differences in maximal oxygen uptake between the control group and other groups of horses with respiratory disease, which could have resulted in the observed differences in level of exercise-induced hypoxemia.

The finding that horses with UAO had blood gas values similar to control horses was unexpected. Laryngeal hemiplegia, for example, is known to impair ventilation during high-speed exercise and result in a worsening of exercise-induced hypoxemia and hypercapnia.[26] Horses with laryngeal hemiplegia tend to experience progressive worsening of gas exchanges as they exercise. Other types of UAO, such as dorsal displacement of the soft palate, develop more suddenly during high-speed exercise and result in rapid fatigue and stopping of the horse. Because blood samples in this study were collected during the last 15 seconds of each step of the STT, the lack of blood gas abnormalities is likely because horses developing sudden UAO stop quickly and do not complete the step. Therefore, blood is rarely collected while the horse exhibits UAO. This speculation is supported by the finding that, among the 40 horses diagnosed with UAO in this study, 14 exhibited laryngeal hemiplegia and 26 dorsal displacement of the soft palate.

Horses affected with IAD as defined by the presence of mucus in the trachea after exercise are characterized by a neutrophilic and lymphocytic inflammation of the airways, as demonstrated by examination of the BALF. Horses affected by EIPH, as defined by the presence of blood in the trachea after exercise, tend to have a higher percentage of hemosiderophages in the BALF than horses with other respiratory conditions, including UAO. This study also indicates that horses with IAD and EIPH can exhibit some degree of pulmonary gas exchange impairment. Horses affected with UAO and EIPH appear to have the most severe gas exchange impairment. The findings concerning gas exchanges will require further confirmation by studies examining the effect of both aerobic capacity and airway diseases on exercise-induced blood gas changes. Comprehensive evaluation of racehorses by BALF cytology and STT with dynamic airway endoscopy are valuable aids in the diagnosis of causes of decreased performance. Interpretation of arterial blood gas measurement must be used cautiously until future studies validate its use.

Footnotes

[a] Ciba-Corning 238 Blood Gas Analyzer, Norwood, MA
[b] Statistix version 8.0 Analytical Software, Tallahassee, FL
[c] SPSS version 11.5. SPSS Inc, Chicago, IL

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