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# Alleviation of Exercise-induced Hypoxemia Utilizing Inspired 79% Helium 20.95% Oxygen

B. K. ERICKSON, R. L. PIESCHL and H. H. ERICKSON

*College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA*

ABSTRACT. We investigated the effect of reducing gas density on arterial and mixed venous $PO_2$ and $PCO_2$, pulmonary artery (PAP) and esophageal pressures (ESP), and ventilatory and cardiac frequencies (fR, HR) during treadmill exercise in the horse. Four horses were exercised for 4 min on separate occasions at 10 m $s^{-1}$ and 11–13 m $s^{-1}$ while breathing ambient air (time 0–2 min) and then when gas density was reduced by substituting helium ($He–O_2$) for nitrogen in the inspirate (time 2–4 min). At 10 m $s^{-1}$ and 11–13 m $s^{-1}$ $He–O_2$ produced increases in $PaO_2$ from 63.1 (8.41) to 86.5 (11.53) mm Hg (kPa) and from 62.2 (8.29) to 75.7 (10.09) mmHg (kPa). At both work rates, $He–O_2$ induced a 6 mmHg (0.79 kPa) decrease in $PaCO_2$ and a 11–14 mmHg (1.46–1.86 kPa) decrease in peak inspiratory to expiratory ESP difference. Mean PAP, HR, and mixed venous $PO_2$ and $PCO_2$ did not change with $He–O_2$. The data show that the hyperventilation produced by $He–O_2$ could not explain the increased $PaO_2$.

*Key words* Horses; blood gases; ventilation; esophageal; pulmonary artery.

## INTRODUCTION

Strenuously exercised horses routinely develop hypoxemia and hypercapnia concurrent with severe acidosis.[2–5,8,10,11] Accordingly, hypotheses have been advanced suggesting that ventilation is mechanically restricted, because of the 1:1 phase locking of breath to stride frequency.[5,8] At a locked breath frequency (single breath time of approximately 200–250 ms), tidal volume and, therefore, alveolar ventilation are inadequate to maintain arterial blood gas homeostasis.[5] Consequently, hypoventilation produces hypercapnia and hypoxemia, despite the increased ventilatory stimulation of acidosis. However, extending exercise time reduced the $PaCO_2$ to hypocapnic values yet $PaO_2$ remained unchanged.[5] This means that despite increased alveolar ventilation ($\dot{V}A$) either ventilation-perfusion ($\dot{V}/\dot{Q}$) worsened or diffusion impairment increased. Recent studies demonstrated during heavy exercise that $\dot{V}/\dot{Q}$ mismatch and hypoventilation accounted for approximately 25% of the hypoxemia; shunt, 1%; and diffusion limitation, nearly 70%.[11] The question of relative contributions to hypoxemia by either hypoventilation or $\dot{V}/\dot{Q}$ mismatch remains unresolved.

To gain insight into the contribution of the hypoventilation to hypoxemia, we have alleviated the hypoventilation by reducing airway resistance using low density He instead of $N_2$ in the inspired gas.

## METHODS

Three Quarterhorses and one Thoroughbred (495 ± 32 kg SEM, age 4–8 years) free of any known disease were studied. These animals were experienced in running on a high speed treadmill and in appropriate physical condition to complete the exercise protocol.

### *Exercise protocols and gas administration*

Each horse exercised on the treadmill (3° incline) at 2 m $s^{-1}$ for 2 min followed by 4 min at 10 m $s^{-1}$ and on a separate occasion

at 2 m $s^{-1}$ for 2 min followed by 4 min at 11–13 m $s^{-1}$, the latter speed dependent on exercise tolerance. The horses inspired ambient air during exercise at 2 m $s^{-1}$ and for the first 2 min at either 10 or 11–13 m $s^{-1}$. For the final 2 min each horse inspired 20.95±0.02% $O_2$-balance He gas mixture at 10 m $s^{-1}$ and 11–13 m $s^{-1}$.

Each horse wore a bias-flow mask sealed around the muzzle and with two 12.7 cm diameter side ports for delivery of air or He–$O_2$ gas. The gas mixture and expired air were vented to the room through a 25 cm hole extending approximately 15 cm from the nostrils. The He–$O_2$ was added and continuously mixed with a fan in a large, flexible, plastic bag of sufficient thickness to prevent diffusion of He, $N_2$, and $O_2$. The gas mixture was pumped by a centrifugal fan through a 15 cm diameter plastic pipe to two 12.7 cm flexible tubes connected to the side ports of the mask. Ambient air and He–$O_2$ were pumped at 90 l $s^{-1}$ to the mask, which was sufficient flow to prevent inspiration of ambient air through the expired gas port, as verified with the $N_2$ sensor of a mass spectrometer.

Extreme care was taken to verify that 20.95±0.02% $O_2$ was present in the He–$O_2$ gas mixture. Two gas analyzers (Beckman OM-11 & McGaw Mass Spectrometer) were calibrated with commercially prepared tanks of 20.9% and 15.5% $O_2$-balance He gas mixtures. The $O_2$ fractions of these tanks were independently verified by the Scholander method. He and $O_2$ were mixed immediately after calibration and exercise followed.

*Instrumentation*

Prior to exercise, the jugular vein was catheterized for measurement of pulmonary artery pressure (PAP) (Millar pressure transducer), blood temperature, and mixed venous blood sampling. A previously elevated carotid artery was also catheterized with a 16 gauge angiocath for collection of arterial blood. Heart rate was determined from electrocardiograph electrodes. Esophageal pressures (ESP) and ventilatory frequency (fR) were measured using a 240 cm Millar pressure transducer placed via the nostril and externalized through the mask[7]. Pressure and airflow data were recorded on a Beckman recorder. Arterial and mixed venous blood samples were collected every 30 s during exercise and analyzed for $PCO_2$ and $PO_2$ (IL 213 electrodes tonometered with each horse's blood). All blood gases were corrected for changes in pulmonary artery blood temperature, as described previously.[11] All horses were examined with an endoscope within 1 hour of exercise for evidence of pulmonary hemorrhage.

*Statistics*

All variables were analyzed using a one-way analysis of variance (ANOVA) with time as the factor. The Newman-Keuls multiple range test detected specific differences when significant F ratios ($p<0.05$) were detected with the ANOVA.

## RESULTS

Following warm-up exercise (2 m $s^{-1}$), exercise at 10 m $s^{-1}$ on ambient air caused $PaCO_2$ to transiently decrease but then return to values observed at 2 m $s^{-1}$ (Fig. 1). When horses breathed ambient air for the entire exercise run, $PaCO_2$ remained at these values (Table 1). Within 30 seconds of the switch to He–$O_2$, $PaCO_2$ decreased 6 mmHg (0.79 kPa) ($p<0.05$) and it remained at this value for the duration of He–$O_2$ breathing. $PaCO_2$ changes during exercise at 11–13 m $s^{-1}$ were similar but were not significantly different ($p>0.10$) from values at rest or during exercise breathing ambient air.

During ambient air breathing $PaO_2$ declined significantly from rest by 21.2 (2.82) and 25.0 (3.33) mmHg (kPa) at 10 m $s^{-1}$ and 11–13 m $s^{-1}$ exercise respectively (Fig. 1). Switching inspired gas to He–$O_2$ during exercise produced an increase in $PaO_2$ from 63.1 (8.41) at 10 m $s^{-1}$ and 62.2 (8.29) mmHg (kPa) at 11–13 m $s^{-1}$ to 86.5 (11.53) and 75.7 (10.09) mmHg (kPa), respectively,

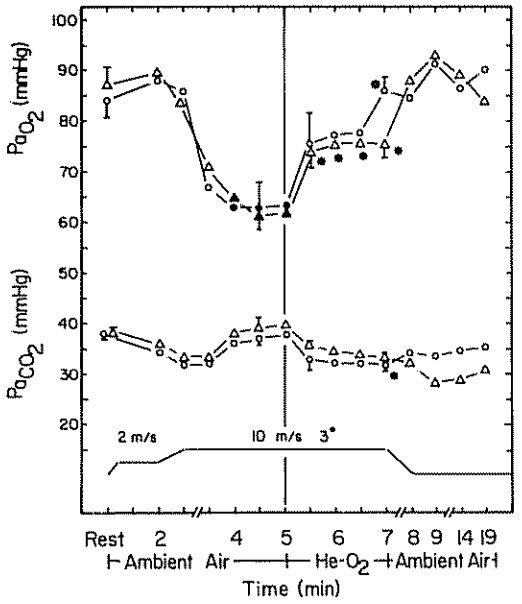


*Fig. 1* Mean values ± SE of arterial $PO_2$ and $PCO_2$ of 4 horses breathing ambient air and 79% helium—20.95% oxygen gas during treadmill exercise ○=10 m s$^{-1}$; △=11–13 m s$^{-1}$; ●, ▲=significantly different from rest; *=significantly different from ambient air at min 5.

measured during the final 30 seconds of $He–O_2$ breathing (Fig. 1).

PAP and HR increased from rest to exercise but did not change with the switch to $He–O_2$ at either speed (Table 1). The peak inspiratory to expiratory ESP difference increased from rest to exercise and then declined during $He–O_2$ breathing (Table 1). Mixed venous $PCO_2$ and $PO_2$ did not change at either speed when ambient air was replaced by $He–O_2$ (Table 1). No evidence of pulmonary hemorrhage was detected in any horse following exercise.

Table 1. *Hemodynamic, esophageal pressure, and blood gas data*

| | | 10 m s$^{-1}$ | | 11–13 m s$^{-1}$ | |
|---|---|---|---|---|---|
| Variable | Rest | Air | $He–O_2$ | Air | $He–O_2$ |
| PAP | | | | | |
| (mmHg) | 25 | 63 | 59 | 74 | 69 |
| (kPa) | 3.33 | 8.39 | 7.86 | 9.86 | 9.19 |
| | (2) | (7) | (11) | (8) | (6) |
| ESP | | | | | |
| (mmHg) | 4 | 46 | 35* | 59 | 45* |
| (kPa) | 0.53 | 6.13 | 4.66 | 7.86 | 5.99 |
| | (0.3) | (4) | (3) | (3) | (6) |
| HR | | | | | |
| (beats | 39 | 183 | 186 | 205# | 208# |
| min$^{-1}$) | (6) | (3) | (3) | (10) | (11) |
| $PO_2$ | | | | | |
| (mmHg) | – | 12.1 | 12.0 | 13.0 | 14.0 |
| (kPa) | – | 1.61 | 1.59 | 1.73 | 1.86 |
| | – | (2.4) | (1.7) | (0.8) | (0.7) |
| $PCO_2$ | | | | | |
| (mmHg) | – | 63.3 | 65.5 | 79.5# | 74.8# |
| (kPa) | – | 8.43 | 8.73 | 10.59 | 9.97 |
| | | (4.7) | (2.4) | (8.0) | (7.3) |
| | | Air-2 | Air-4 | Air-2 | Air-4 |
| $PaO_2$ | | | | | |
| (mmHg) | – | 63.2 | 61.8 | 65.1 | 66.7 |
| (kPa) | – | 8.42 | 8.23 | 8.67 | 8.89 |
| | | (2.8) | (3.6) | (4.1) | (2.5) |
| $PaCO_2$ | | | | | |
| (mmHg) | – | 38.2 | 37.0 | 39.7 | 37.9 |
| (kPa) | – | 5.09 | 4.93 | 5.29 | 5.05 |
| | | (2.0) | (1.9) | (3.3) | (3.6) |

All variables increased ($p<0.05$) from rest to exercise. #=significantly different from 10 m s$^{-1}$, *=significantly different from ambient air. $n=2$ for $PO_2$ and $PCO_2$ at 10 m s$^{-1}$. (#)=± standard error. The values during exercise represent min 2 on ambient air and min 4 on helium-oxygen. $PaO_2$ and $PaCO_2$ values represent min 2 and 4 on ambient air.

## DISCUSSION

### *Technical considerations*

All blood samples were analyzed on carefully calibrated blood gas electrodes, as described previously.[11] Obviousy, small changes in inspired fractional $O_2$ concentration could account for the increase in $PaO_2$ observed during this study. Extreme care was taken to ensure that hyperoxic inspired gas did not alleviate hypoxemia during exercise. We were satisfied that, by using independently analyzed calibrating gases and techniques

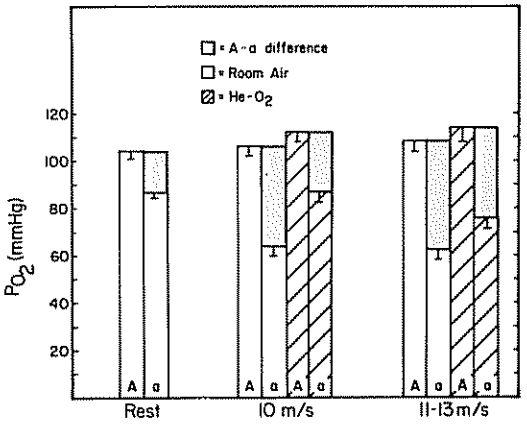


*Fig. 2* Values ± SE of alveolar (A), arterial (a), and alveolar-arterial $PO_2$ difference from rest to 10 m $s^{-1}$ and 11–13 m $s^{-1}$ in horses breathing ambient air and 79% helium–20 95% oxygen. Alveolar $PO_2$ calculated from the alveolar air equation.

described in the Methods, inspired $O_2$ concentration was 20.95 ± 0.02%.

*Potential factors contributing to hypoxemia*

Exercise at 10 m $s^{-1}$ and 11–13 m $s^{-1}$ produced decreases in $PaO_2$ by 21.2 (2.82) and 25.0 (3.33) mmHg (kPa), respectively. Breathing He–$O_2$ increased $PaO_2$ by 23.4 (3.11) and 13.5 (1.79) mmHg (kPa), respectively, at 10 m $s^{-1}$ and 11–13 m $s^{-1}$. Because $PaCO_2$ decreased nearly 6 mmHg (0.79 kPa) during He–$O_2$ breathing, presumably due to increased VA, then relative hypoventilation *per se* accounts for at most 6 mmHg (0.79 kPa) of the decrease in $PaO_2$ during ambient air breathing. Fig. 2 depicts the change in alveolar-arterial $O_2$ gradient (A-a $DO_2$) when changed from ambient air to He–$O_2$.

Studies using the multiple inert gas technique on these same horses at similar exercise intensities[11] concluded that exercise-induced hypoxemia is mainly a result of 1) $\dot{V}/\dot{Q}$ mismatch and relative hypoventilation, accounting for 25% of the A-a$DO_2$ 2) shunt, accounting for 1% and 3) diffusion limitation, accounting for approximately, 70%. The hyperventilatory response to exercise observed in other studies[5] accounts for nearly the same magnitude of hypoxemia (6 mmHg, 0.79 kPa) as that measured using the multiple inert gas technique.[11] However, the observed increase in $PaO_2$ during He–$O_2$ breathing at 10 m $s^{-1}$ and less at 11–13 m $s^{-1}$, was greater than that attributable to increased $\dot{V}A$ (5.8 of 23.4, and 5.8 of 13.5 mmHg, respectively). Assuming that shunt was negligible, then He–$O_2$ breathing must have improved $\dot{V}/\dot{Q}$ ratio and/or diffusive gas exchange. If these horses responded to exercise similarly as in a previous study[11] (i.e. no exercise-induced pulmonary hemorrhage), then the $\dot{V}/\dot{Q}$ ratio could not be improved significantly at 10 m $s^{-1}$ and 11–3 m $s^{-1}$. Accordingly, He–$O_2$ breathing during heavy exercise may reduce gas exchange impairment because of either alveolar/capillary or gas phase convection and diffusion.[6] Gas phase diffusion and convection may be altered relative to ambient air because of differing physical diffusivity properties between He–$O_2$ and $N_2$–$O_2$. The theoretical role of diffusion and convection while breathing He–$O_2$ is unclear, particularly because of the large range of ventilation, high ventilatory frequency, and unknown alveolar perfusion characteristics[9] in the horse.

*Potential factors contributing to hypocapnia*

Airflow resistance partitioning studies[1] demonstrated that, in trotting ponies, airflow resistance was significantly elevated. It was predominantly upper airway resistance during inspiration, but more equally upper and lower airway resistance during expiration. Airflow resistance has not been measured, to our knowledge, in galloping horses, but we assumed airflow resistance increased from rest to 10 m $s^{-1}$ and 11–13 m $s^{-1}$ exercise in this study.

In this study, given that fR and mixed venous $PCO_2$ remained constant when horses were switched to He–$O_2$, and peak inspiratory to expiratory ESP difference was reduced (Table 1), tidal volume must have increased because of reduced airflow resist-

ance. Accordingly, $\dot{V}A$ must have increased, because $PaCO_2$ declined nearly 6 mmHg (0.79 kPa) at 10 m $s^{-1}$ and 11–13 m $s^{-1}$. Alternatively, $\dot{V}A$ could remain constant, and the ESP difference and $PaCO_2$ could have been reduced simply because of the lower density of He and associated binary diffusion resistance of He.

Why does the horse not hyperventilate to maintain a normal $PaO_2$ during maximal exercise? One possibility is that, given elevated airflow resistance and constant fR, the additional pleural pressure excursions required to increase tidal volume may be energetically unfavorable, despite some exercising horses having added ventilatory stimulation due to hypercapnia and metabolic acidosis.

The potential reduction in airflow resistance observed during $He–O_2$ breathing accounts for only 6 mmHg (0.79 kPa) of the hypoxemia observed during ambient air breathing, despite an increase in $PaO_2$ of 23.4 mmHg (3.11 kPa) at 10 m $s^{-1}$ and 13.5 mmHg (1.79 kPa) at 11–13 m $s^{-1}$. The lack of a hyperventilatory response to heavy exercise during ambient air breathing may be related to airflow resistance, because $PaCO_2$ of these horses did not decrease when ambient air breathing was continued throughout exercise. This suggests that the increased ventilation due to $He–O_2$ (>6 mmHg, 0.79 kPa) was not adequate to achieve normoxemia and that $He–O_2$ could improve $\dot{V}/\dot{Q}$ and gas-phase diffusion limitation at 10 m $s^{-1}$, but not at 11–13 m $s^{-1}$. If the above is true, then $\dot{V}/\dot{Q}$ mismatch and diffusion limitation may have been worse at 11–13 m $s^{-1}$ and not adequately improved by $He–O_2$, which could explain the smaller increase in $PaO_2$ during $He–O_2$ breathing.

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