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Ventilatory Response to Exercise in Horses with Exercise-Induced Hypoxemia

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Summary

Experiments were conducted to investigate the ventilatory response to strenuous exercise in six Thoroughbred horses. The horses performed 4 standard exercise tests (SET) on a treadmill at +10%. On 3 occasions they wore respiratory masks and breathed room air. On the other occasion $F_I O_2$ was increased in the range of 0.242 to 0.252. The SET consisted of a 2 min warm-up followed by 1 min galloping at each of 8, 9, and 10 m/sec. Arterial and mixed venous blood gas tensions, alveolar oxygen tensions ($P_A O_2$), alveolar-arterial oxygen differences $[(A - a)DO_2]$, minute ventilation (\dot{V}_E), and tidal volume were determined at each speed. The $P_A O_2$ increased by about 10 torr with the onset of exercise, but did not increase further despite increasing workload, \dot{V}_E , \dot{V}_A , and $P_a CO_2$, and decreasing pH. The $P_a O_2$ decreased and $[(A - a)DO_2]$ increased at each speed, the latter under normal conditions being 41.2 ± 2.9 torr (mean \pm SD) at 10 m/sec. The $[(A - a)DO_2]$ was not different under hyperoxic conditions, although $P_A O_2$ increased by 24.1 ± 1.0 torr and hypoxemia was largely abolished. The results of the studies suggest that exercise-induced hypoxemia is partially due to an inadequate ventilatory response. The possibility that diffusion disequilibrium and local \dot{V}_A : perfusion inequalities play a role cannot be discounted, whereas the existence of major pulmonary shunts seems unlikely.

Index terms: Blood gases, oxygen consumption, hyperoxia, hypercapnia

Introduction

Although hypoxemia frequently occurs in Thoroughbred and Standardbred horses during heavy exercise (Bayly *et al.*, 1983; Thornton *et al.*, 1983; Bayly and Grant, 1986), its origin is unknown. Elucidation of the mechanism involved in this exercise-induced hypoxemia has not been forthcoming and its resolution will probably require estimates or measures of alveolar ventilation (\dot{V}_A), alveolar-pulmonary capillary oxygen differences $[(A - a)DO_2]$, studies with multiple inert gases and isotopically labeled gases,

and studies under artificial conditions where inspired gas differs from atmospheric air. This problem is further clouded by the fact that these studies require wearing a gas collection mask, a condition that does not represent normal exercise (unpublished data).

This paper documents changes in blood gases, alveolar oxygen tension ($P_{A}O_2$), and $[(A - a)DO_2]$ of horses during high intensity exercise under normoxic and hyperoxic conditions. As a result of these studies it appears unlikely that shunting of blood is a major cause of exercise-induced hypoxemia in the horse. In contrast, the lack of an adequate or appropriate ventilatory response to exercise appears to be a factor in the genesis of this aberration in PaO_2 , with additional contributions coming from impairment of gas diffusion or from a lack of homogeneity in $\dot{V}_A : \dot{Q}_c$ ratios, or both.

Materials and Methods

Six healthy castrated male Thoroughbred horses performed a standard exercise test (SET) on four occasions. None of the animals had a history of pulmonary or cardiovascular disease. The first test was conducted with the animals wearing a conventional respiratory mask in which airflow was generated by the subject and expired air collected in a 600 l capacity spirometer. The direction of airflow was controlled by four 10 cm diameter unidirectional valves (Fig. 1). In the second exercise test, ventilatory measurements were made using a flow through system. In this system a funnel shaped mask was suspended from the horse's head and air was drawn at a rate of 3840 l/min down over the head, past the nares, and out a port located at the end of the funnel and into a 10 cm diameter hose. This mask was constructed of a frame covered with a flexible material that could expand to accept the expired air without producing a back pressure. Airflow was metered with a hotwire anemometer (TSI, Inc., Series 2210) located within this hose. The flow meter was calibrated from voltage changes produced by known flow rates. In this system airflow was generated by exhaust fans which were arranged in parallel within an airtight box that was connected to the end of the expiratory channel. The airflow was controlled by adjusting the rates of the exhaust fans with rheostats. A portion of the effluent air was collected in a 600 l spirometer and analyzed for oxygen and carbon dioxide (CO_2) concentrations with Applied Electrochemistry S-3A and Beckman LB-2 analyzers, respectively.

In a third test the horses exercised while breathing air in which the F_1O_2 was between 0.242 and 0.252. As it is essential to have a complete seal of the respiratory mask around the head when conducting this type of study, it was necessary to design a third gas collection system (Fig. 1). In this system, mixed hyperoxic gas was drawn into the sealed mask through a single inspiratory port and out dual expiratory ports in the same fashion as that described for the funnel-like system. The rate of airflow was 3800 l/min. The inspiratory hose was 10 cm in diameter and 10 m long. Air was blown into the system by fans placed at the end of the inspiration hose. The input flow was adjusted to create as close to a neutral pressure as possible within the mask. Oxygen was bled into the open end of this hose at a constant rate. A mixing chamber was inserted between the input fans and the respiratory mask. Samples of the mixed inspiratory gas were continuously drawn from a point in the inspiratory hose between the mixing chamber and respiratory mask to determine the oxygen content. Neutralization of the pressure changes within the respiratory mask was further aided by inserting a bellows between the mixing chamber and the site of sampling of inspired air. Flow of oxygen into the

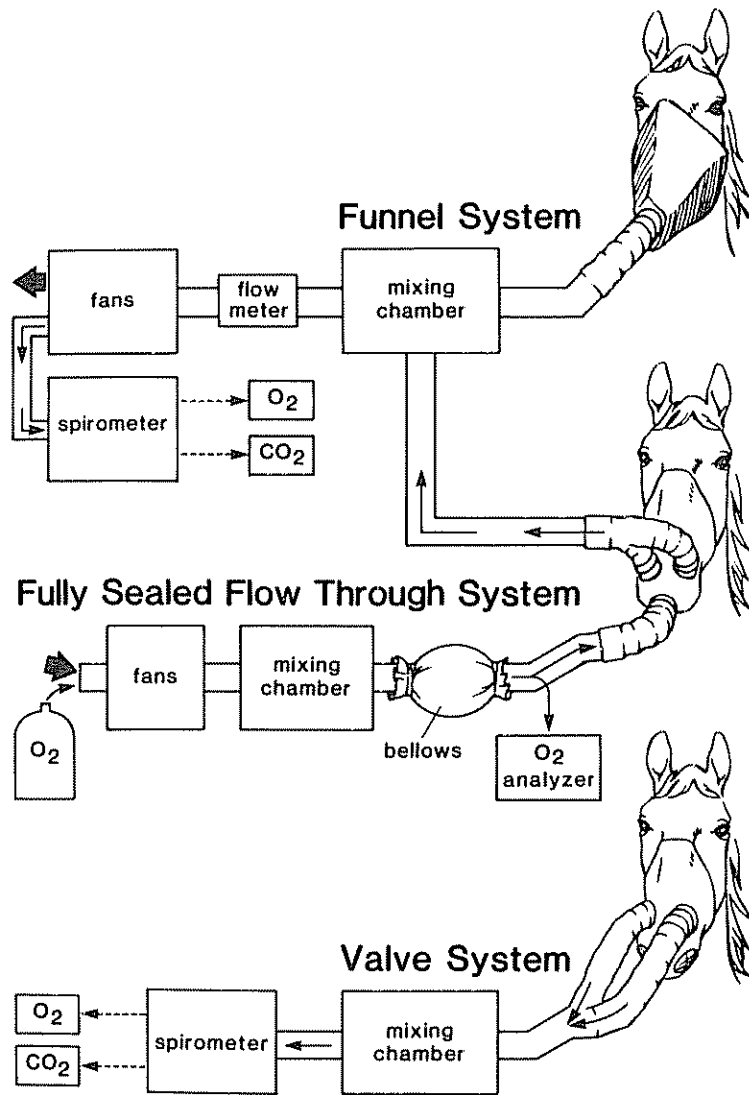


FIGURE 1 Schematic representation of the gas collection systems and respiratory masks used to evaluate the ventilatory response to the standardized exercise test.

system was adjusted to maintain $F_I O_2$ between 0.242 and 0.252, the actual value being recorded in the last 20 sec of exercise at each speed. The exercise test was repeated a fourth time, with the horses wearing the same system, but breathing room air ($F_I O_2 = 0.2093$).

Exercise was performed on a +10% slope and consisted of a brief period of walking followed by a warm-up of 3.5 m/sec for 30 sec and 5 m/sec for 90 sec. Each horse subsequently galloped for 60 sec each at speeds of 8, 9, and 10 m/sec. Prior to starting the exercise test, catheters were placed into the pulmonary and carotid arteries. Samples

of blood were drawn from each catheter for blood gas analysis pre-exercise, during the final stage of the warm-up period, and during the last 5 sec while galloping at 8, 9, and 10 m/sec. The blood samples were analyzed for PO₂, PCO₂, and pH with a tonometer calibrated Instrumentation Laboratories 813 blood gas analyzer. Correction for temperature difference was based on a recording made from a flexible rectal probe which was inserted 30 to 40 cm into the rectum and connected to a Bailey Instruments BAT 8 digital temperature monitor. Heart rate (HR) and respiratory frequency was recorded at each speed. A cardiometer (Polar Electro, PEH100) was used for the former, while the latter was determined over the last 20 sec of running speed. Gas was collected in the spirometer during the last 20 sec of exercise at 5, 8, 9, and 10 m/sec. Alveolar oxygen tensions were calculated for each mask system using the ideal gas equation. Measures of minute ventilation (\dot{V}_E), tidal volume (V_T), physiological dead air space (V_D), and alveolar ventilation (\dot{V}_A) were determined from samples collected via the respiratory mask system that incorporated valves and relied on a subject-generated airflow.

Results

An increasingly marked hypoxemia was noted as the workload became more strenuous. The magnitude of the decrease was greater ($P < 0.01$) when the self-generated flow system incorporating valves was used, going from 87.0 ± 0.3 torr at rest to 52.3 ± 0.4 torr at 10 m/sec as compared to values of 91.5 ± 3.0 and 66.3 ± 4.2 torr, respectively, when the flow through system was used (Table 1, Fig. 2). Corresponding values for P_aCO₂ were 43.7 ± 0.5 and 57.6 ± 1.3 torr for the mask containing the valves, and 40.4 ± 2.3 and 46.6 ± 1.3 torr with the funnel-like system. P_aCO₂ mea-

TABLE 1 Arterial gas tensions (P_sO₂, P_sCO₂), alveolar oxygen tension (P_AO₂), and alveolar-arterial oxygen tension differences [(A - a)DO₂] during each of the exercise tests

Condition		Rest	5 m/sec	8 m/sec	9 m/sec	10 m/sec
P _A O ₂	Funnel	94.9 ± 4.9	105.2 ± 2.0	103.9 ± 3.6	105.0 ± 1.6	105.4 ± 1.6
	Valve	90.9 ± 0.9	92.9 ± 1.3	86.6 ± 1.0	94.0 ± 4.2	97.9 ± 2.5
	Hyperoxia	112.2 ± 3.5	119.7 ± 3.5	121.7 ± 1.9	122.7 ± 1.6	121.8 ± 1.3
	Normoxia	89.5 ± 1.6	95.0 ± 0.6	95.6 ± 1.0	97.6 ± 1.0	100.6 ± 0.9
(A - a)DO ₂	Funnel	3.6 ± 2.1	16.0 ± 2.9	29.8 ± 2.4	36.7 ± 3.7	39.1 ± 3.9
	Valve	4.4 ± 1.2	19.8 ± 2.1	34.5 ± 1.7	44.1 ± 2.6	45.6 ± 1.4
	Hyperoxia	9.2 ± 1.7	17.3 ± 2.2	24.8 ± 2.9	34.1 ± 2.3	42.3 ± 2.4
	Normoxia	3.4 ± 0.2	12.5 ± 1.9	29.1 ± 4.4	34.0 ± 2.7	38.9 ± 1.6
P _s O ₂	Funnel	91.5 ± 3.0	88.8 ± 3.9	72.6 ± 3.9	68.3 ± 4.4	66.3 ± 4.2
	Valve	87.0 ± 0.3	73.1 ± 2.9	52.1 ± 1.8	49.9 ± 2.3	52.3 ± 0.4
	Hyperoxia	103.6 ± 4.1	103.9 ± 3.8	94.1 ± 3.6	88.6 ± 3.2	79.5 ± 3.0
	Normoxia	86.1 ± 1.7	84.3 ± 1.6	72.1 ± 3.8	63.6 ± 3.1	62.1 ± 1.9
P _s CO ₂	Funnel	40.4 ± 2.3	41.2 ± 1.1	45.4 ± 6.6	47.8 ± 2.4	46.6 ± 1.3
	Valve	43.7 ± 0.5	48.4 ± 1.6	57.0 ± 1.4	56.9 ± 3.3	57.6 ± 1.3
	Hyperoxia	50.3 ± 1.4	46.6 ± 1.2	49.4 ± 0.8	50.1 ± 1.6	50.7 ± 1.4
	Normoxia	44.9 ± 1.3	44.5 ± 0.4	47.6 ± 1.6	47.6 ± 1.1	45.9 ± 0.7

Values are torr with means ± SEM. See text for description of the respiratory gas collections systems and methods for producing hyperoxia

measurements were different ($P < 0.01$) for these two masks at each speed (Table 1, Fig. 2). Mixed venous blood gas values were similar at each speed with respect to gas collection systems with the exception that $P_{\bar{v}}\text{CO}_2$ at 10 m/sec was greater when the valve system was used (126.9 ± 6.70 versus 98.7 ± 5.6 torr, $P < 0.01$). The pH of

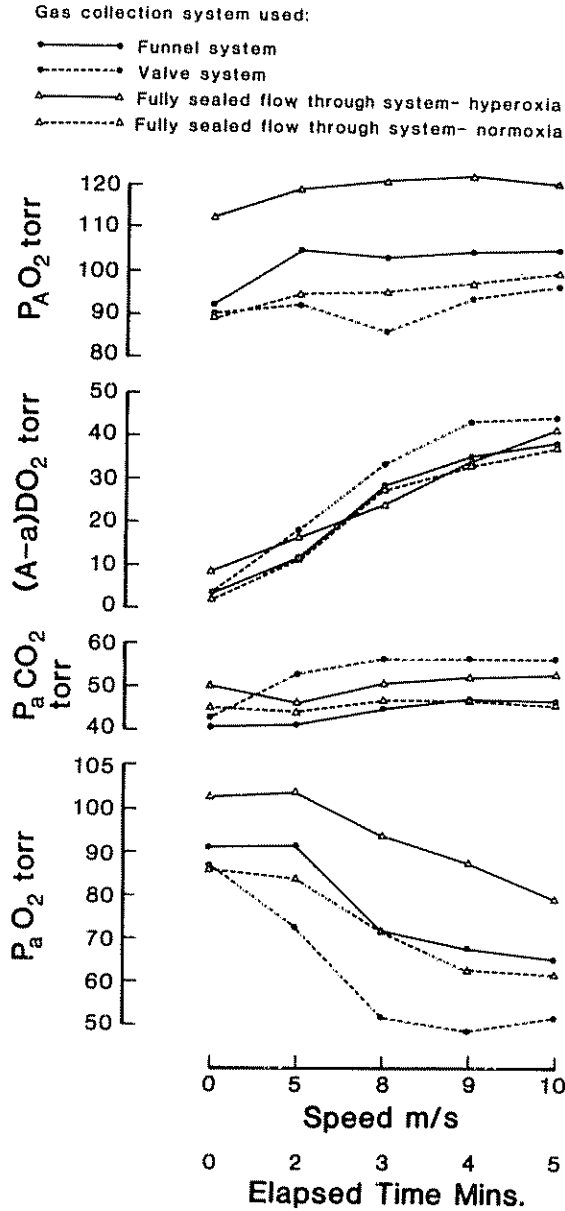


FIGURE 2 Arterial gas tensions (P_aO_2 , P_aCO_2), alveolar oxygen tensions (P_AO_2), and alveolar-arterial oxygen differences [(A - a)DO₂] during each of the exercise tests and their relationship to speed.

arterial blood at rest averaged 7.42 and declined to 7.24 and 7.22 during exercise at 10 m/sec with the funnel mask, and valve mask conditions, respectively.

Alveolar oxygen tensions increased from pre-exercise values (increments 9.5 ± 3.7 torr for the funnel system, 7.8 ± 3.3 torr for the valve system) in response to exercise but there were no differences between results determined at individual exercise loads with a given system (Table 1, Fig. 2). Calculated values for P_AO_2 were higher when the flow through system rather than valve system was used. The $[(A - a)DO_2]$ increased with each exercise level, ranging from 16.0 ± 2.9 torr at 5 m/sec to 39.1 ± 3.9 torr at 10 m/sec for the flow through mask (Table 1, Fig. 2). The type of gas collection system used had no influence on $[(A - a)DO_2]$. This was also the case when the sealed mask was used under normoxic and hyperoxic conditions. Increasing the PO_2 of inspired air by 26.5 ± 0.6 torr resulted in a consistent increase in P_AO_2 regardless of whether the horses were exercising or at rest. The mean increment in P_AO_2 for all measurement times was 24.1 ± 1.0 torr, when compared to values generated with the sealed mask under normoxic conditions. When breathing hyperoxygenated air, the horses were only hypoxemic at 10 m/sec ($P_aO_2 = 79.5 \pm 3.0$ torr) although this was within 10 torr of the normal resting P_aO_2 . Arterial oxygen tensions were 20.3 ± 1.6 torr greater than their corresponding values generated under normoxic conditions and changed in proportion to P_AO_2 with each measurement.

Minute ventilation and V_T increased from pre-exercise values of 42 ± 7.1 l/min and 2.1 ± 0.7 l (BTPS) to 1253 ± 35.7 l/min and 10.6 ± 0.6 l, respectively, when the mask incorporating valves was used (Fig. 3). V_D/V_T decreased from 0.63 ± 0.02 pre-exercise to 0.15 ± 0.02 at 10 m/sec. Physiological dead space varied from 1.32 l/breath at rest to 3.51 l/breath at 5 m/sec, but subsequently decreased progressively as workload increased, to 1.70 l/breath at 10 m/sec (Fig. 3).

Neither heart rates nor breathing frequencies varied between exercise tests at any speed. Highest mean respiratory frequency was 118 ± 2.1 at 10 m/sec. Mean HR during work ranged from 169.2 ± 2.1 at 5 m/sec to 213.5 ± 2.3 at 10 m/sec. Despite the similarity in HR and P_iO_2 values for the valve-mask and funnel collection systems, $\dot{V}O_2$ was greater ($P < 0.01$) at all speeds when using the latter system (Fig. 4). There was no difference in $\dot{V}O_2$ at any speed when figures for the funnel system were compared to those for the sealed mask generated under hyperoxic and normoxic conditions. Measurements at 10 m/sec were 131.5 ± 5.9 ml/kg/min for the funnel, 146.2 ± 9.7 ml/kg/min ($F_iO_2 = 0.2471 \pm 0.06$) and 146.0 ± 16.2 ml/kg/min ($F_iO_2 = .2093$).

Discussion

Three possible causes of exercise-induced hypoxemia are: 1) an inadequate ventilatory response to exercise, 2) impaired diffusion due to an increased diffusion distance, reduced erythrocyte transit times through the pulmonary capillaries or an altered slope of the alveolar-blood diffusion gradient, and 3) right-to-left vascular shunts or inter- or intra-regional inhomogeneities in ventilation-perfusion ratios. Although the present study did not assess the contributions of these factors to the observed hypoxemia, an inadequate ventilatory response and the progressive widening of the $[(A - a)DO_2]$ appear as the most likely causes for the inability of the horses to maintain PaO_2 at or near resting levels.

The impression that ventilation may be insufficient stems from the observation that V_E , V_A , and P_AO_2 change little in response to potent ventilatory stimuli of increased

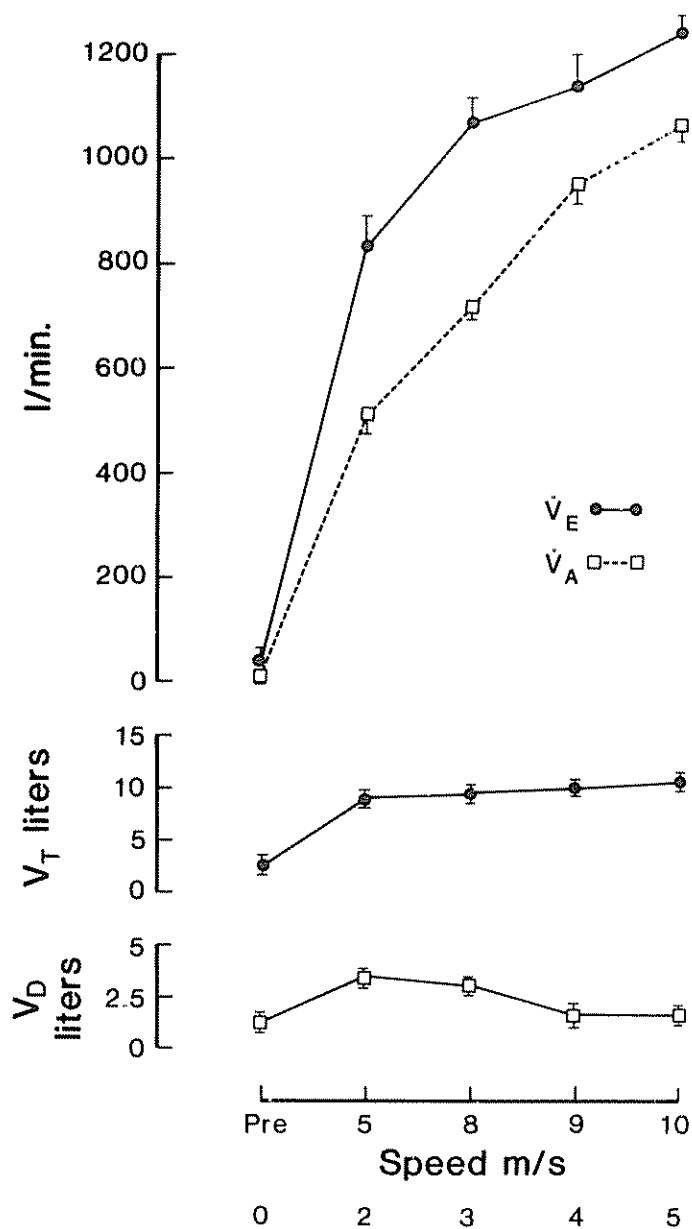


FIGURE 3. Ventilatory response (\dot{V}_E , \dot{V}_A , V_T , V_D) to increased running speeds in horses wearing a respiratory mask containing unidirectional valves.

P_aCO_2 , decreasing pH, and increasing workload. In man there is an exponential rise in ventilation between light and heavy work loads (Åstrand and Rodahl, 1977) rather than the hyperbolic rise observed in the present studies (Fig. 3). Furthermore, in the present study when P_AO_2 increased by 20–25 torr under hyperoxic conditions, P_bO_2 increased

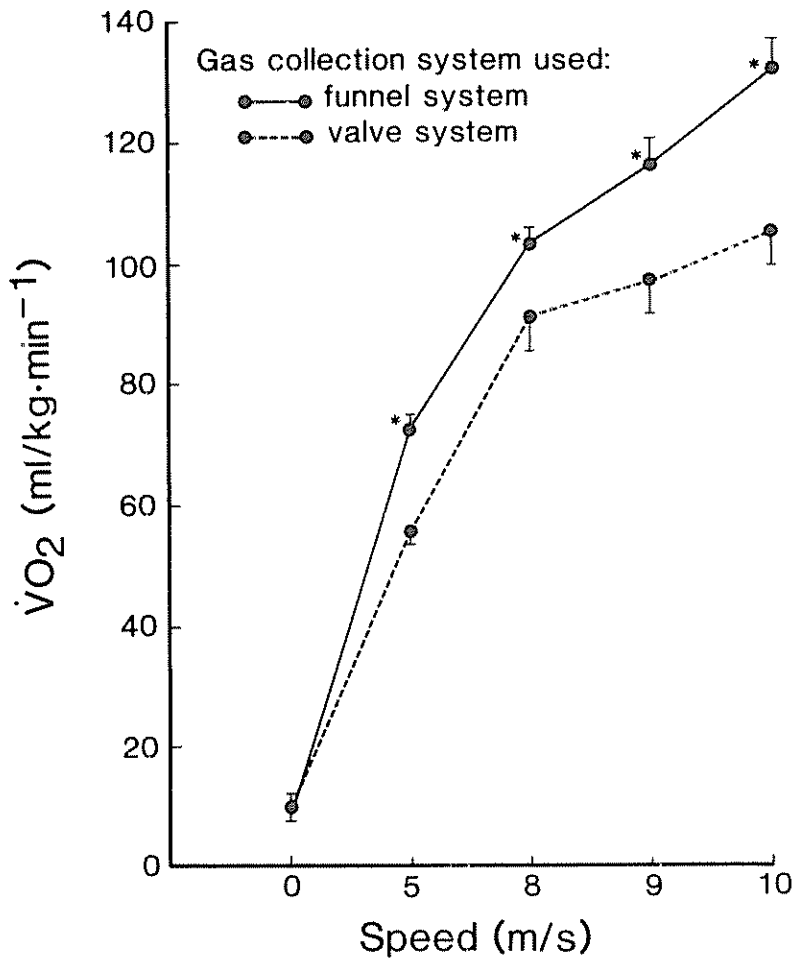


FIGURE 4. Ventilatory response (V_E , V_A , V_T , V_D) in relationship to oxygen consumption ($\dot{V}O_2$) in horses wearing a respiratory mask containing unidirectional valves

a proportional amount and hypoxemia was abolished or considerably reduced, evidence that hypoxemia is due, at least in part, to ventilatory impairment.

Values of \dot{V}_A and $P_{A}O_2$ have not been previously reported in the horse during strenuous work. Minute ventilation, however, was similar to that reported in the horse while galloping (Hönicke *et al.*, 1983). Although $P_{A}O_2$ increased at the onset of exercise, it subsequently changed little and values were below those reported for human athletes exercising at comparable relative intensities (Dempsey *et al.*, 1980). The reason for this apparent inability to increase $P_{A}O_2$ is unclear. Mechanical restrictions causing flow limitations and chest wall constraints may be important factors. At breathing frequencies observed in these studies, it may be impossible to generate flow rates necessary for optimum ventilation without severe respiratory muscle fatigue, or diversion of blood from skeletal to respiratory muscles and therefore, in the short-term, a reduction in performance. This idea is supported by the observations that V_T changed little following

the onset of exercise despite a doubling of the workload. Breathing frequency, however, increased by 30% for the 2 gas collection systems (funnel and valve masks). It seems clear that the animals were capable of greater ventilatory response than occurred during the exercise as V_T rose to 15.6 l and P_AO_2 to 118.4 torr in the first minute post-exercise.

Although there was only a slight increase in V_T at each workload, \dot{V}_A increased in a linear fashion. This was due not only to the greater respiratory frequency, but also the marked decrease in V_D/V_T . This observation was similar to that in man (Wasserman *et al.*, 1967).

Elite athletes who become hypoxemic during stressful exercise develop $[(A - a)DO_2]$ similar to those which existed in the horses in the present experiment (Dempsey *et al.*, 1984). Although there is no reference base for comparing data from man to the horse, the results from the elite athletes were different from those seen in less capable subjects. Why the $[(A - a)DO_2]$ widened to such an extent in our horses is unclear from the experiments reported here. Failure of $[(A - a)DO_2]$ to increase when the horses exercised under hyperoxic conditions, suggests that shunting of markedly desaturated mixed venous blood plays an unimportant role in widening the $[(A - a)DO_2]$.

The wide $[(A - a)DO_2]$ may have developed on the basis of the normal small shunt (due to thebesian and bronchial circulations) and relatively low $\dot{V}:Q_c$, stemming from the inadequate ventilatory response. These effects may be further compounded by the existence of intra-regional $\dot{V}_A:Q_c$ inhomogeneities of the type present in man during exercise (Gledhill *et al.*, 1978; Gale *et al.*, 1985). Although it is not known whether low $\dot{V}_A:Q_c$ regions exist in the galloping horse, the physiological relevance of their existence is worth considering. These low \dot{V}_A/Q_c regions have their greatest impact when P_vO_2 is drastically reduced, as occurred in our horses. The low P_AO_2 resulting from low \dot{V}_A/Q_c reduced the diffusion gradient, and thus the rate of O_2 equilibration in the pulmonary capillaries. The rate of equilibration of P_vO_2 with P_AO_2 is heavily dependent on the "effective slope" of the oxyhemoglobin dissociation curve between P_vO_2 and end pulmonary capillary PO_2 , which is assumed to equal P_AO_2 (Wagner, 1982). The nearer P_AO_2 to the steep part of the dissociation curve, and the lower the P_vO_2 , the slower the rate of diffusion equilibration, and the longer the pulmonary capillary transit time needed by an erythrocyte to reach equilibrium with alveolar gas. If one assumes that the oxygen-hemoglobin dissociation curve and rate of reaction of oxygen with hemoglobin in the horse are similar to those in man, then for a P_vO_2 of 10 torr, as P_AO_2 approaches the steep part of the curve, the longer the time needed for complete diffusion equilibration. Using Wagner's homogeneous lung model with normal diffusion capacity at $P_AO_2 = 100$ torr and $P_vO_2 = 10$ torr, diffusion equilibration is only about 80% complete after 400 msec. As the diffusion capacity of equine lung has not been determined, the extent to which this may affect gas exchange is unknown. Another advantage of improved ventilation is demonstrated by this model, in that a mixed venous blood with an oxygen tension of 30 torr will equilibrate faster with alveolar gas in which $PO_2 = 120$ torr, and therefore require a shorter transit time, when compared to when $P_vO_2 = 10$ torr and $P_AO_2 = 100$ torr, even though $P_AO_2 - P_vO_2$ is the same in each case.

Neither the minimum transit time needed for gas equilibration nor the actual transit time during high intensity exercise are known for horses. Based on the reasoning of Dempsey and Fregosi (1985), there is cause to believe that transit time may be shortened to the point where complete diffusion equilibrium is not possible. Given that transit

time reflects the relationship between pulmonary capillary blood volume (V_c) and pulmonary blood flow (Q_c), it can be estimated that mean transit time during maximal exercise is about 400 msec using the allometric equation $V_c(\text{ml}) = 3.2 \times \text{body weight (kg)}$ (Linstedt, 1984) and $Q_c = 250 \text{ l/min}$. Although this time would be ample for gas exchange, distribution of transit times around the mean may result in shorter times in some parts of the lung.

Additional factors which may interact with the diffusion of O_2 from alveoli to blood are the existence of stratified inhomogeneities (Adaro and Piiper, 1976; Weibel, 1983) and the increasing of diffusion distances secondary to the transient development of interstitial edema at heavy workloads. With respect to the latter, lymphatic drainage abilities may be exceeded should pulmonary microvascular pressures rise markedly during exercise and lead to an increased rate of fluid extravasation. However, these have not been measured in exercising horses.

Thus, although the origins of the exercise-associated hypoxemia remain unknown, we hypothesize that the effects of inadequate ventilation, local $\dot{V}_A:Q_c$ inequalities and diffusion disequilibrium combine to produce the reduction in PaO_2 . Although speculative, we hope that these ideas will be proven or disproven by results from future experiments.

The results from the present studies illustrate the difficulties associated with conducting ventilatory studies with horses exercising at high work loads. The valve type respiratory masks are clearly inadequate for such studies. Under all conditions where they were used to assess ventilatory volumes, the partial pressures of gases in arterial and venous blood were compromised. These data demonstrate that at the high flow rates that exist during strenuous exercise, the traditional type of respiratory mask imposes constraints upon the horse that alter the normal ventilatory adjustments to exercise. These constraints were far less when using the flow-through funnel-like system where the flow rate was high, as evidenced by the PaO_2 and $\dot{V}O_2$ values recorded at the same workloads and heart rates.

Another potential source of error in such studies is reliance upon the assumption that CO_2 equilibrates across the blood-gas barrier, with the result that alveolar CO_2 tension and $PaCO_2$ are equal. The calculations of P_{AO_2} , \dot{V}_A , and V_D/V_T are based on this premise. However, this is open to question (Piiper, 1986), particularly when CO_2 production is great (Piiper, *et al.*, 1980), as when horses exercise near maximal intensity.

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