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Hypoxia Does Not Contribute to High Pulmonary Artery Pressure in Exercising Horses

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ABSTRACT. Mean pulmonary artery pressure (P_{PA}) during exercise is higher in horses ($\geq$80 torr) than in humans and other mammals ($\leq$30 torr). The mechanisms are unknown. To see if hypoxic pulmonary vasoconstriction (HPV) was involved, we compared P_{PA}-flow ($\dot{Q}$) curves when inspired O_2 fraction (F_IO_2) was 0.16, 0.21, and 0.30, in 5 normal Thoroughbred horses standing quietly and after 2 and 2.5 min galloping at 10 and 14 m s^{-1} on a level treadmill. We measured P_{PA}, O_2 content of systemic and pulmonary arterial blood, and respired gas composition and flow, and calculated O_2 consumption ($\dot{V}O_2$) and then $\dot{Q}$ with the Fick method. There was no apparent effect of F_IO_2 on slopes and intercepts of $P_{PA}/\dot{Q}$ curves or on $\dot{V}O_2$ at any speed. We think it unlikely that HPV is an important mechanism in the high P_{PA} of exercising horses.

Key words Acute hypoxia; hypoxic pulmonary vasoconstriction; pulmonary vascular resistance; pulmonary hemodynamics; horses.

INTRODUCTION

During near-maximal exercise, mean pressure in the pulmonary artery (P_{PA}) reaches 80 torr or more in horses[7,13] compared to about 30 torr in humans.[11,12,19] We wondered what mechanisms might be responsible for these high values. Hypoxic pulmonary vasoconstriction (HPV) is one possible active mechanism. Horses are capable of a pulmonary pressor response to hypoxia,[4,25,26] and hypoxia occurs in horses during heavy exercise. That is, not only does systemic arterial and central venous hypoxemia occur,[1,14,21,23] but also there may be alveolar hypoxia in distal regions of the horse's long acinus when O_2 flux is high[24] and hypoventilation occurs.[1,14] To see if HPV contributed significantly to high P_{PA} in exercising horses, we compared $P_{PA}/\dot{Q}$ curves constructed from data taken at rest and while galloping at 10 and 14 m s^{-1} in horses breathing 16, 21 and 30% O_2.

METHODS

We studied five healthy Thoroughbred geldings aged 2 to 6 years and weighing 516 ± 42 kg (mean ± SD).

Animal preparation

At least six months before the beginning of the study, each horse had its left common carotid artery surgically relocated beneath the skin. The horses were trained for 2–3 months to run on a horizontal treadmill (SATO Inc, Uppsala, Sweden) at speeds up to 14 m s^{-1} for 3 min, and were accustomed to a face mask and associated equipment.

Measurements and calculations

P_{PA} was measured with a catheter-tip pressure transducer (Mikro-tip model PC 471A, Millar Instruments Inc., Houston, TX). It was inserted into the right jugular vein through a 7 French introducer. We moni-

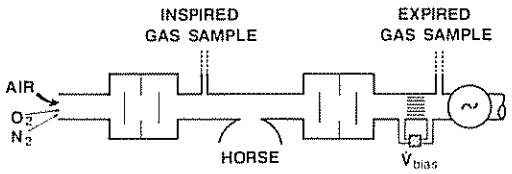

Fig 1. Diagram of experimental system. A bias flow (Vbias) is provided by pumps at the outlet and measured by a pneumotachograph. See text.

tored the vascular pressure on a strip chart (Beckman Dynograph recorder model R611) and advanced the catheter 10–15 cm beyond the point at which it entered the pulmonary artery. Inspired gas composition was varied by adding O_2 or N_2 to the inspired air (Fig. 1), which then passed through a mixing chamber made of 1 (for resting measurements) or 3 (in parallel, during exercise) 220 liter drums with internal baffles. Two centrifugal blowers in series drew a bias flow of gas through the horse's mask via a system of conduits (15 cm I.D.) and then through a second mixing chamber including 1 (rest) or 6 (in parallel, exercise) baffled drums. The plastic mask fitted the horse's muzzle loosely and was sealed around the face with an inflatable inner tube. Gas flow rate through the system (Vbias) was measured with a Fleisch type pneumotachograph (Meriam Instruments, Cleveland, OH) downstream of the second mixing chamber. The pressure drop across a 15 cm diameter flowmeter at rest ($\dot{V}bias \simeq 7\ l\ s^{-1}$) or a 25 cm diameter flowmeter during exercise ($\dot{V}bias \simeq 120$ and 160 $l\ s^{-1}$) was measured with a differential pressure transducer (PX163-005BD 5V, Omega Engineering Inc., Stamford, CT). Composition of inspired and mixed expired gases was analyzed with a mass spectrometer (Model 1100, Perkin-Elmer, Pomona, CA). Two-point calibrations were made daily with gas mixtures obtained by mixing pure N_2, O_2 and CO_2, using gas mixing pumps (model 301a-F, H. Woesthooff oHG Instruments, Bochum, FRG) with a 0.03% accuracy. The FO_2 calibration mixtures were close to the upper and lower values expected during the experiment. FCO_2 calibration mixtures were zero and a value near the highest expected FCO_2. Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and the respiratory exchange ratio (R) for air-breathing experiments were calculated using standard respiratory equations from values of $\dot{V}bias$, F_IO_2, F_ICO_2, F_EO_2, and F_ECO_2, and the temperature and relative humidity of the bias flow measured downstream of the flowmeter (Model 880 temperature and humidity sensor, General Eastern, Watertown, MA, calibrated in an environmental chamber against a dew point sensor M1 1111H, General Eastern, accuracy ± 2%).

When the inspired gas was other than room air, inward leaks of room air ($\dot{V}_{RA}$) into the system could cause errors in the calculated $\dot{V}O_2$ by creating errors in calculated $\dot{V}(x)$ (where x is O_2, CO_2, N_2) when $F_I(x) \neq F_{RA}(x)$. Thus errors in $\dot{V}O_2$, but not $\dot{V}CO_2$, were a concern. Errors in $\dot{V}O_2$ will lead to errors in $\dot{Q}$. We estimated $\dot{V}_{RA}$ and made corrections as follows:

1. For each x, calculate total outflow from the system:

   $$\dot{V}bias(x) = \dot{V}bias\ (STPD) \cdot Fbias(x).$$

2. Assume an inward leak $\dot{V}_{RA}$ (STPD) and, for each x, calculate

   $$\dot{V}_{RA}(x) = \dot{V}_{RA} \cdot F_{RA}(x).$$

3. For each x, calculate
   $\dot{V}true(x) = \dot{V}bias(x) - \dot{V}_{RA}(x)$.
4. For each x, calculate
   $F_E(x) = \dot{V}true(x)/(\dot{V}bias - \dot{V}_{RA})$.
5. For each x, substitute $F_E(x)$ in standard equations for open circuit gas exchange and calculate $\dot{V}CO_2$, $\dot{V}O_2$, and R.
6. Compare the calculated R with R measured in that animal at the same speed breathing air. If they are not equal, return to step 2 above, assume another value for $\dot{V}_{RA}$, and repeat the calculations until by successive approximation a value of $\dot{V}_{RA}$ is found at which the calculated and the previously observed Rs are equal. $\dot{V}_{RA}$ was generally less than 5% of $\dot{V}bias$.

The assumption is crucial that R at any speed is invariant with F_IO_2.

Samples of mixed venous blood were drawn through the transducer catheter's lumen and samples of arterial blood were drawn through a 16 gauge catheter (Abbocath, Abbott Hospitals Inc., North Chicago, IL) inserted in the left common carotid artery. Arterial and mixed venous blood samples were drawn simultaneously in heparinized plastic syringes and placed on ice until measurement of pH and partial pressures of O_2 and CO_2 (Instrumentation Laboratory model 213, Lexington, MA) and of oxygen content (Lex-O_2-Con, Lexington Instrument, Waltham, MA). The blood gas results were corrected to the temperature measured in the pulmonary artery (T_{PA}) with a thermistor catheter (Columbus Instruments, Columbus, OH).

Partial pressure of oxygen in alveolar gas (P_AO_2) was calculated with the alveolar gas equation, which implicitly defines P_ACO_2 by $PaCO_2$ and assumes steady state gas exchange. Cardiac output ($\dot{Q}$) was calculated as $\dot{V}O_2$ divided by the arteriovenous difference in O_2 content, $C(a\text{-}\bar{v})O_2$, according to the Fick principle.

For an experiment, a horse breathed either hypoxic gas ("N_2"; $F_IO_2=0.16$), normoxic gas ("air"; $F_IO_2=0.2095$) or hyperoxic gas ("O_2"; $F_IO_2=0.3$) assigned randomly in a Latin-square design. We were able to set F_IO_2 and F_IN_2 within 0.2% of the desired values.

Procedures

Before each experiment, the pressure transducers were calibrated using a mercury (for the PA catheter) or a water U-tube manometer (for the pneumotachograph) and the catheters and introducers were then inserted under local anesthesia. The flowmeters were calibrated by a nitrogen dilution technique.[9] A one-point calibration of the Lex-O_2-Con was carried out according to the manufacturer's instructions. The IL 213 was calibrated daily with commercial certified standard gases (accuracy 0.01%) and standard buffers (Instrumentation Laboratory Lexington, MA). These two-point calibrations were compared with values measured by the IL 213 on blood tonometered for 30 min with the calibration gases (Instrumentation Laboratory model 237, Lexington, MA). If the value measured in tonometered blood, considered as the "truth", differed from that in the gas used for tonometry, a correction factor (C.F., ratio of true partial pressure in gas to measured value in blood) was applied to the experimental measurements. C.F. values ranged from 0.98 to 1.02.

The signals of $\dot{V}$bias, P_{PA}, T_{PA}, and respired gas fractional concentrations were recorded by a digital data collection module (DCM, MRG Aspects Inc., Windham, ME) and displayed on the monitor of a host micro-computer (Zenith Data Systems, Deerfield, IL) for adjustment of gains of the computer-based data acquisition system.

Experimental protocol

At rest, data were recorded and blood was sampled 2 min or more after the desired inspired gas composition was set. The exercise protocol was started at least 1 hour after the resting measurements. It consisted of a 2 min warm-up at 3.5 m s^{-1} after which the treadmill speed was increased to either 10 or 14 m s^{-1} (approximately 60 and 90% of $\dot{V}O_2$ max respectively, in our laboratory) for 3 min. Measurements were made and blood was drawn 2 and 2.5 min after the treadmill reached the appropriate speed. Horses rested at least 30 min between runs.

Data processing and analysis

At the end of each run the data were downloaded to the micro-computer and processed with a digital worksheet program (DADISP Development Corporation, Cambridge, MA) and the values of each variable were read. P_{PA} was plotted against $\dot{Q}$ for each gas mixture, at rest and at each exercise intensity. Straight regression lines were fitted to the data and their slopes and intercepts were compared by analysis of covariance. The effects of gas composition and exercise were

Table 1. *Effect of altering P_IO_2 on P_AO_2, PaO_2 and $P\bar{v}O_2$ in exercising horses*

	O_2		AIR		N_2	
P_IO_2	207±0.5		144±0.3		105±0.4	
P_AO_2						
Rest	158±1.3	NS	99±0.8	NS	66±0.9	NS
10 m s^{-1}	159±2.5		96±3.0		68±3.3	
14 m s^{-1}	149±1.1		93±1.3		65±1.2	
PaO_2						
Rest	124±3.3	NS	88±0.9		65±1.1	
10 m s^{-1}	118±6.6		69±4.6		46±3.8	
14 m s^{-1}	103±5.5		56±2.2		38±1.1	
$P\bar{v}O_2$						
Rest	40±2.3		36±1.5		37±1.3	
10 m s^{-1}	23±1.3		22±1.4		19±1.5	
14 m s^{-1}	21±0.7		15±1.4		9±1.4	

Values in torr, are expressed as mean ± SEM. Values of each variable are significantly different between speeds except as noted. NS: not significantly different. Values of each variable, except $P\bar{v}O_2$, are significantly different between gases.

evaluated by a two-way analysis of variance. When an F value was significant ($p<0.05$), a Fisher's least significant difference (LSD) test was performed to determine with which gas and at which exercise level the difference was significant.

RESULTS

Inspired, alveolar and arterial PO_2 fell with F_IO_2 under all conditions (Table 1), but $P\bar{v}O_2$ did not. At each F_IO_2, P_AO_2, PaO_2 and $P\bar{v}O_2$ fell with increasing speed, except as noted in Table 1. However, varying F_IO_2 did not change $P\bar{v}O_2$ significantly.

$\dot{V}O_2$ increased from 3.8 ml min^{-1} kg^{-1} at rest to 73.4 and 130.2 ml min^{-1} kg^{-1} at 10 and 14 m s^{-1} respectively. At a given speed, $\dot{V}O_2$ did not change with F_IO_2.

There was no significant difference among

Table 2. *Effect of inspired gas composition on the slopes and intercepts of $P_{\bar{v}A}/\dot{Q}$ curves in 5 Thoroughbred horses*

F_IO_2	Slope (torr min kg l^{-1})	Intercept (torr)
0.30	88±13	21±5
0.21	108±5	14±3
0.16	75±8	24±5

$\dot{Q}$ scaled to body mass. Values are expressed as mean ± SEM. There are no significant differences ($p>0.05$).

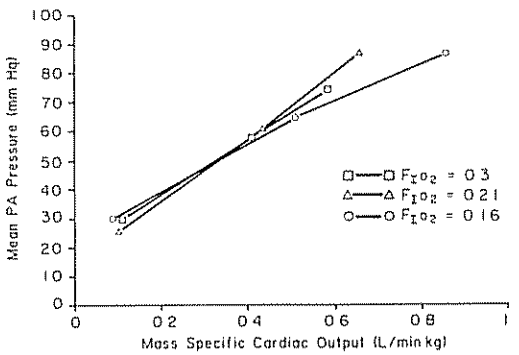

Fig. 2. Effect of F_IO_2 on the pulmonary artery pressure-flow curves of 5 Thoroughbred horses. Varying F_IO_2 had no significant effect on slopes or intercepts of the pulmonary artery pressure-flow curves (Table 2).

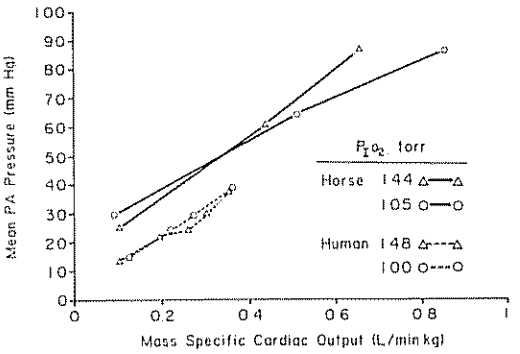

Fig. 3. Effect of hypoxia on $P_{PA}/\dot{Q}$ curves in horses and humans. Human data from Wagner et al.[22]

slopes or intercepts of $P_{PA}/\dot{Q}$ curves of horses breathing hyperoxic, normoxic and hypoxic gases (Fig. 2, Table 2).

DISCUSSION

Breathing air

The $\dot{V}O_2$ values obtained in this study were about the same as those reported by others for horses at rest and galloping at near maximal speeds.[1,2,8,14,23] Cardiac output and P_{PA} also increased (Fig. 2) as previously reported.[13,14,23] Like others,[7,13] we found mean P_{PA} around 30 torr in horses breathing air at rest, which is higher than values reported in man (about 15 torr)[11,12,19,22] and other mammals;[4,5,15,26] the reasons for these differences are unknown. We find that mean P_{PA} ranges upward of 80 torr in horses during heavy exercise, again higher than values reported in other mammals. We found only three other studies of P_{PA} in exercising horses. Two of them were comparable with ours, and reported similar values of P_{PA}.[7,13] In the third report,[20] P_{PA} during swimming exercise ranged from 60 to 100 torr at the highest exercise intensity and was quite variable for a given workload. We are uncertain what effects the hydrostatic pressure of immersion has on the magnitude and variation of intrathoracic vascular pressures referenced to atmospheric pressure during exercise.

In man, P_{PA} doubles when $\dot{Q}$ increases to four times the resting values during heavy exercise at sea level.[11,12,19,22] P_{PA} did not increase in sheep or cattle during exercise that respectively doubled[5] and tripled[15] $\dot{Q}$. The reasons for these apparent differences are not known. We do not know what happens to P_{PA} in other mammals capable of high mass specific $\dot{Q}$ and $\dot{V}O_2$ like the blue fox.[16]

Breathing O_2 or N_2

We expected that if HPV contributed to the high P_{PA} during exercise in horses breathing air, then $P_{PA}/\dot{Q}$ curves would vary with F_IO_2. We found that varying the F_IO_2 from 0.16 to 0.21 to 0.3 had no apparent effect on the slopes and intercepts of those curves over the range of $\dot{Q}$ studied (Fig. 2 and Table 2). An obvious interpretation is that HPV was not present during exercise on air, for if it had been, then the increase in P_AO_2 achieved with the hyperoxic gas mixture should have relieved it, resulting in a lower P_{PA} for the same $\dot{Q}$. For similar reasons, it appears that HPV was not elicited by N_2.

Before accepting those interpretations, we need to consider two other possibilities. First, perhaps HPV was present on air but our intervention did not alter PO_2 at the relevant site(s). We did change the calculated P_AO_2, and alveolar PO_2 is thought to be the dominant variable for stimulation of pulmonary hypoxic vasoconstriction.[10] We also varied PaO_2, but hardly affected $P\bar{v}O_2$ (Table 1). Although $P\bar{v}O_2$ has been shown to have an effect on HPV in dogs with atelectatic lungs,[3,6,10] the effect is not strong.[17] Therefore we think that our intervention did alter PO_2 at the dominant relevant site. Secondly, maybe HPV was present on air or elicited by N_2, but its effect was negligible, i.e. insufficient to change the $P_{PA}/\dot{Q}$ curves, for example because it was intrinsically weak, or because it was offset by other influences such as high vascular transmural pressures or chemoreceptor reflexes through which peripheral hypoxia inhibits HPV.[18] Such reflexes operate in anesthetized dogs[18] but, if present, they do not prevent acute HPV in other mammals at rest[5,10,11,25,26] including ponies.[4]

It is not known if they operate in horses. Thus, we think it acceptable to conclude that HPV does not contribute to the high pulmonary artery pressure in exercising horses, either because it is not present or because its effects are negligible.

In man at rest, as in our horses, mild acute hypoxia ($P_IO_2=100$ torr) did not produce any change in P_{PA} or $\dot{Q}$.[22] However, with severe acute hypoxia ($P_IO_2=63$ torr) an increase in P_{PA} (from 15 torr to 20 torr) and a slight increase in $\dot{Q}$ (from 6.7 to 8.1 l min^{-1}) has been observed in resting humans.[11] And, in exercising man as in our horses, mild acute hypoxia did not produce any change in slope or intercept of $P_{PA}/\dot{Q}$ curves (Fig. 3). In other species during exercise, however, more severe acute hypoxia does change those curves. For example in sheep exercising at $\dot{Q}$ twice the resting value, P_{PA} increases from 18 torr breathing air to 28 torr with severe hypoxia ($P_IO_2=80$ torr) maintained for 2 hours.[5] We do not know how exercising sheep respond to less severe hypoxia.

The hypoxic vasopressor response takes about 3 min to develop.[10] Our horses were exposed to hypoxia 4–5 min. A longer exposure might have had a different outcome, although exercising humans exposed to 10 min hypoxia of the same intensity showed no differences in P_{PA} or $\dot{Q}$ compared to exercise in air.[22]

Our correction of the $\dot{V}O_2$ values to account for inward leaks of room air into the system may not have eliminated errors in the determination of $\dot{V}O_2$ and thus in the calculation of $\dot{Q}$. A crucial assumption is used in those corrections, namely that R at any speed is invariant with F_IO_2. The justification is empirical. Observed $\dot{V}CO_2$ at any speed was invariant with F_IO_2; either the same was true of $\dot{V}O_2$ and R, or else they varied together in just such a way as to result in invariance of $\dot{V}CO_2$; we think that is unlikely. The invariance of $\dot{V}CO_2$ further implies that changes in F_IO_2 were not associated with big changes in dependence on anaerobic metabolism at any given speed.

In conclusion, we found no effect of changing F_IO_2 from 0.16 to 0.3 on the slope or position of $P_{PA}/\dot{Q}$ curves in horses over a wide range of $\dot{Q}$. We conclude that HPV is not an important mechanism for the high P_{PA} seen at rest and during exercise in horses compared to humans and other mammals.

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