Thermal drive contributes to hyperventilation during exercise in sheep

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Entin, Pauline L., David Robertshaw, and Richard E. Rawson. Thermal drive contributes to hyperventilation during exercise in sheep. J. Appl. Physiol. 85(1): 318–325, 1998.—The etiology of exercise hypocapnia is unknown. The contributions of exercise intensity (ExInt), lactic acid, environmental temperature, rectal temperature (Tre), and physical conditioning to the variance in arterial CO2 tension (PaCO2) in the exercising sheep were quantified. We hypothesized that thermal drive contributes to hyperventilation. Four unshorn sheep were exercised at ~30, 50, and 70% of maximal O2 consumption for 30 min, or until exhaustion, both before and after 5 wk of physical conditioning. In addition, two of the sheep were shorn and exercised at each intensity in a cold (~15°C) environment. Tre and O2 consumption were measured continuously. Lactic acid and PaCO2 were measured at 5- to 10-min intervals. Data were analyzed by multiple regression on PaCO2. During exercise, Tre rose and PaCO2 fell, except at the lowest ExInt in the cold environment. Tre explained 77% of the variance in PaCO2, and ExInt explained 5%. All other variables were insignificant. We conclude that, in sheep, thermal drive contributes to hyperventilation during exercise.

hyocapnia; respiratory alkalosis; blood gases; hyperthermia; thermoregulation; respiratory control

HYPOCAPNIA during exercise has been observed in species spanning three classes of vertebrates, including mammals (2, 3, 9, 11, 15, 21, 22, 24, 25, 28, 31), birds (5, 18), and reptiles (20). The hypocapnia is characteristic of not only high-intensity exercise but of moderate-intensity exercise (≤50% of maximal oxygen consumption (VO2max)) as well. In some species, such as dogs (9, 15, 31) and sheep (3, 25), the hypocapnia is progressive and can result in a reduction of arterial CO2 tension (PaCO2) of >10 Torr. Despite multiple reports of exercise-induced respiratory alkalosis, the physiological imputus for exercise hyperventilation is uncertain.

Several facets of exercise could contribute to the reduced PaCO2. These include the following factors.

Exercise Intensity (ExInt)

In exercising ponies, the reduction of PaCO2 is proportional to the ExInt (21). This relationship may indicate that the central respiratory drive inherently oversteps metabolic demand (6, 10). A centrally driven respiratory alkalosis would be expected to stimulate negative feedback, but progressive hypocapnia suggests that any inhibitory feedback is overridden by other factors.

Blood Lactate Concentration ([Lac])

Ventilatory suppression caused by the low PaCO2 could be counterbalanced at the peripheral chemoreceptors by an exercise-induced lactic acidosis. Tradition-
individually in pens (1.8 m²) in a room maintained at 20 ± 2°C. All sheep were fed ~600 g of hay and 250 g of grain daily (Early Market Lamb Pellets; Agway, Syracuse, NY). A minimum of 15 h separated feeding and the start of an experimental trial. Water was provided ad libitum.

Surgical Preparation

Each sheep was prepared with an exteriorized carotid artery by using the method described by Hales and Webster (13). The sheep were allowed at least 2 wk to recover from surgery before the first catheterization of the carotid artery. Two of the animals were also instrumented with a catheter (Tygon microbore tubing, 1.78 mm OD) implanted in the right circumflex iliac artery. The catheter was flushed daily with heparinized physiological saline and was kept filled with heparin sodium (1,000 U/ml).

On the morning of an experiment, unless the sheep had a patent circumflex iliac catheter, the carotid artery was acutely catheterized with a 16-gauge 6.35-cm plastic catheter (IV Cath; Becton-Dickenson, Rutherford, NJ). This catheter was removed at the end of the experimental trial.

Experimental Protocol

Experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals [DHEW Publication No. (NIH) 86-23, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20892]. The research protocol was approved by the Institutional Animal Care and Use Committee of Cornell University.

ExInt and Physical Conditioning

Three exercise intensities were selected to represent ~30, 50, and 70% of V˙O₂max, assuming the average V˙O₂max of sheep to be 57 ml·kg⁻¹·min⁻¹ (17). For each ExInt, the treadmill speed and incline were set according to the linear relationship between these factors and the O₂ consumption (V˙O₂) of sheep (17). Treadmill settings for each of the three intensities (hereafter referred to as low-, medium-, and high-intensity exercise) are shown in Table 1.

The experiment was divided into two parts on the basis of environmental condition.

Part 1. The warm condition. A moderate environmental heat load was imposed. The average room temperature was 22.4 ± 2.5°C, and each sheep bore a fleece coat at least 2 cm thick. The sheep were habituated to the experimental procedures but were not physically conditioned before the start of experimental trials. Each sheep exercised for 30 min at low and medium intensity and until exhaustion (average 20.6 ± 3.7 min) at high intensity. The trials were ordered randomly with respect to exercise intensity. After these trials, each sheep was physically conditioned for 5 wk. Conditioning consisted of five 30-min exercise bouts/wk and was progressive. For the first week of conditioning, the sheep were exercised for 30 min at low intensity. Over the next 4 wk, the exercise intensity was increased gradually, so that in the final week, the sheep were exercised for 20 min at high intensity plus 10 min at medium intensity. After conditioning, experimental trials were conducted in which each animal again exercised for 30 min at low and medium intensity and to exhaustion at high intensity (average 26.7 ± 2.2 min).

Part 2. The cold condition. The environmental heat load was reduced by lowering the Ta to 12.8 ± 0.5°C and shearing the wool to a thickness of <0.5 cm. Two of the four sheep used in part 1 were randomly selected for participation in part 2. The two sheep completed the experimental trials only in the physically conditioned state. Technical problems with reducing the laboratory temperature prevented completion of the trials with the other two sheep.

During all trials, a window fan was placed behind the sheep. A minimum of 24 h separated any two experimental trials on an individual ewe.

Data Collection

T re (an index of body core temperature) and temperature of the skin of the ear (T sk; an indicator of peripheral vasomotor constriction or vasodilation) were measured continuously from 5 min preexercise through the end of exercise. T re was monitored with a copper-constantan thermocouple encased in a sealed plastic tube and inserted ~12 cm into the rectum. T sk was monitored by using a copper-constantan thermocouple glued to the sheep’s ear on the morning of an experimental trial. V O₂ was also measured continuously by using an open-flow system described previously (17). Data were stored on computer discs.

Arterial blood samples were drawn between 1 and 5 min preexercise and at 2, 5, 10, 20, and 30 min during exercise. During high-intensity trials, blood was also collected at 15 and 25 min of the duration of the exercise. The blood samples were collected anaerobically into 1-ml syringes, which were capped and immediately placed on ice. Analyses for pH, arterial oxygen tension (P aO₂), and P aCO₂ were performed, generally within 2 h, with the use of a self-calibrating acid-base analyzer (Radiometer ABL-30; Copenhagen, Denmark). The analysis temperature was adjusted to the T re of the sheep at the time the sample was taken. The accuracy of the acid-base analyzer was occasionally checked against tonometered sheep or horse blood.

At all blood-gas sampling points, except at 2 min of exercise, an additional 1 ml of arterial blood was collected for analysis of blood [Lac]. Blood was drawn into heparinized plastic syringes and immediately dispensed into microcentrifuge tubes and placed on ice. [Lac] was measured typically within 15 min by using a lactate-glucose analyzer (model 2300 Stat; Yellow Springs Instruments, Yellow Springs, OH). The accuracy of the lactate analyzer was checked against known standards on the day of each experimental trial. [Lac] was not measured in two low-intensity trials.

Table 1. Treadmill inclines and speeds used to produce low-, medium-, and high-intensity exercise

<table>
<thead>
<tr>
<th>Exercise Intensity</th>
<th>%V O₂max (approximate)</th>
<th>TM Incline, °</th>
<th>TM Speed, m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>30</td>
<td>0</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Medium</td>
<td>50</td>
<td>3</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>High</td>
<td>70</td>
<td>5</td>
<td>1.9 ± 0.2</td>
</tr>
</tbody>
</table>

Values for treadmill (TM) speed are given as means ± SD of 10 trials at each intensity. %V O₂max, percentage of maximal O₂ consumption.

Statistical Analysis

Multiple-regression analysis was used to form a model of P aCO₂ based on ExInt, T re, T a, [Lac], Cond, and individual ewe (Sheep). For the multiple regression, T a and Cond were coded as zero (warm or unconditioned) or one (cold or conditioned). ExInt was represented by the mean V O₂ during each exercise bout. The variables measured repeatedly (T re, [Lac], and P aCO₂) were summarized within each experimental trial to eliminate autocorrelation.

Summarization process for T re, [Lac], and P aCO₂. For each exercise bout completed by each sheep, T re, [Lac], and P aCO₂
were regressed against time during exercise. Each variable was modeled separately. A regression equation of order 0, 1, 2, or 3 was applied to the data within each plot. If there was no change in the variable over time, the mean value was used (0 order); otherwise, a first-order equation was tested first. The regression order was then increased until the resulting improvement in the correlation coefficient was $>0.05$. As a result, $>90\%$ of the final correlation coefficients were at least 0.90, excepting the cases in which a zero-order equation was appropriate. The regression equations were then used to calculate the theoretical $T_{re}$, $[\text{Lac}]$, and $P_{aCO_2}$ at minute 25 ($t_{25}$) of the exercise period of each experimental trial. The statistical analysis was performed on these index numbers ($T_{re25}$, $[\text{Lac}]_{25}$, and $P_{aCO_225}$), not on the original data points.

The variables were entered into the multiple regression shown in Eq. 1.

$$P_{aCO_225} = \mu + T_{re25} + T_{a} + ExInt + [\text{Lac}]_{25} + Cond + \text{Sheep} + \text{all 2-way interactions} + \text{Error}$$

(1)

where $\mu$ signifies the grand mean and Error refers to the residual error.

Because the primary goal was to rank order the main effects, interactions of third, fourth, fifth, and sixth order were excluded from the model.

The variables were entered into Eq. 1 by using the stepwise form of multiple regression (Minitab 11 for Windows); thus the order of the variables shown in Eq. 1 is unimportant. In addition, the best subsets function was used to compare the model produced by stepwise regression with other possible models having the same or a smaller number of regressors.

Values are means $\pm$ SD; no. of sheep is given in parentheses. Values for low- and medium-intensity exercise were taken at 30 min of exercise; values for high-intensity exercise were taken at 20 min of exercise, except 1 preconditioning value which was taken at 15 min. Statistical comparisons were made between pre- and postraining by using a paired $t$-test. *$P < 0.01$; **$P < 0.02$.

### RESULTS

Neither $T_a$ nor Cond had a significant effect on $\dot{V}O_2$ during exercise. The $\dot{V}O_2$ values for low-, medium-, and high-intensity exercise were 18.0 $\pm$ 1.3, 30.8 $\pm$ 0.3, and 44.9 $\pm$ 0.9 ($\pm SE$) ml$\cdot$kg$^{-1}\cdot$min$^{-1}$, respectively.

Physical conditioning reduced the $[\text{Lac}]$ response to medium- and high-intensity exercise ($P < 0.01$ and $P < 0.02$, respectively; Table 2). During low-intensity exercise, $[\text{Lac}]$ did not exceed 1 mM in either the unconditioned or the conditioned state.

$T_a$ affected $T_{re}$ and $T_{sk}$. Before exercise in the warm environment (part 1), the mean $T_{re}$ was 38.9 $\pm$ 0.3°C ($n = 24$); in the cold environment (part 2), the mean $T_{re}$ was 38.2 $\pm$ 0.3°C ($n = 6$). $T_{re}$ rose during all exercise trials, although in the cold environment, low-intensity exercise failed to raise $T_{re}$ above 39.1°C, which is within the control range (Fig. 1). The average rate of rise of $T_{re}$ was proportional to the ExInt (Fig. 1). The highest $T_{re}$ reached was 41.7°C after 25 min of high-intensity exercise.

During warm trials (part 1), $T_{sk}$ invariably indicated that the sheep were vasodilated within 5 min of the onset of exercise, and the sheep remained vasodilated throughout exercise. Before exercise in the cold (part 2), $T_{sk}$ was in all cases $<25°C$; in five of six cases, $T_{sk}$ was $<20°C$, indicating that the sheep were vasoconstricted before exercise. $T_{sk}$ remained $<25°C$ for the duration of low-intensity exercise. In contrast, at medium- and high-intensity exercise in the cold, $T_{sk}$ rose by at least 10°C to 25–33°C within 10 min of the onset of exercise, indicating vasodilation.

Before exercise, the mean $P_{aO_2}$ was higher in the warm environment than in the cold environment (115.1 $\pm$ 7.7 vs. 102.3 $\pm$ 6.4 Torr). In both environments, $P_{aO_2}$ tended to rise during exercise (Fig. 2). At
the end of medium- and high-intensity exercise in the warm environment, the mean $P_aO_2$ was >135 Torr (Fig. 2). At each intensity, the mean $P_aO_2$ remained higher in the warm environment than in the cold environment (Fig. 2).

The mean preexercise $P_aCO_2$ was slightly lower in the warm environment than in the cold environment (33.8 ± 1.7 vs. 35.5 ± 1.2 Torr). In the warm environment, $P_aCO_2$ decreased progressively during exercise at all three intensities (Fig. 3). The rate at which $P_aCO_2$ fell was proportional to the exercise intensity (Fig. 3). The lowest $P_aCO_2$ recorded was 13.0 Torr, measured in one sheep after 30 min of medium-intensity exercise. In the cold environment, low-intensity exercise failed to depress $P_aCO_2$ below the control range (Figs. 3 and 4). During medium- and high-intensity exercise in the cold, $P_aCO_2$ fell, but not to as great an extent as in the warm environment (Fig. 3).

Arterial pH tended to rise during exercise, except when the unconditioned sheep exercised at high intensity (Fig. 5). When the sheep were physically conditioned, pH rose more during medium- and high-intensity exercise in the warm environment than it did at the same intensities in the cold environment (Fig. 5). The highest pH observed was 7.72, measured in one unconditioned sheep after 30 min of medium-intensity exercise in the warm environment. The lowest pH recorded was 7.32, measured in one unconditioned sheep after 10 min of high-intensity exercise in the warm environment.

The regression analysis produced two two-regressor equations of equal predictive value

$$P_aCO_2 = -5.93T_re - 0.22ExInt + 269$$

$$R^2 = 0.82$$ (2)

$$P_aCO_2 = -5.74T_re - 0.01(Tre · ExInt) + 261$$

$$R^2 = 0.82$$ (3)

Because the purpose of the multiple regression was to rank order the main effects for influence on $P_aCO_2$, Eq. 2 was preferred over Eq. 3 and will be used for purposes of discussion. In either case, $T_re$ alone accounted for 77% of the variance in $P_aCO_2$ during exercise ($P < 0.0002$; Table 3). ExInt (or the interaction between ExInt and $T_re$) explained an additional 5% of the variance in $P_aCO_2$ ($P < 0.02$). All other variables, i.e., [Lac], Cond, $T_a$, and individual ewe (Sheep), did not contribute significantly ($P > 0.025$) to the variance in $P_aCO_2$ (Table 3).

The negative correlation between $P_aCO_2$ and $T_re$ during exercise is evident in the primary data (Fig. 6). Each data point represents a single sampling point within a particular trial on an individual ewe; 124 data points originating from 30 trials are shown.
The correlation matrix for the five independent variables and \( \text{PaCO}_2 \) during exercise is given in Table 4. Correlations between indicator variables (i.e., \( T_a \) and Cond) are meaningless and therefore are omitted. \( T_r \), ExInt, and \([\text{Lac}]\) were significantly correlated with \( \text{PaCO}_2 \). Both \( T_r \) and \([\text{Lac}]\) were positively correlated with ExInt; higher exercise intensity produced greater hyperthermia and \([\text{Lac}]\). \([\text{Lac}]\) was positively correlated with \( T_r \), indicating that \([\text{Lac}]\) and hyperthermia progressed with a similar time course. In addition, \( T_r \) was correlated with \( T_a \), indicating that \( T_r \) tended to be lower during cold trials.

**DISCUSSION**

Of the variance in \( \text{PaCO}_2 \) during exercise in the sheep, 82% was accounted for by a linear model dependent on only \( T_r \) and ExInt (Eq. 2). \( T_r \) alone accounted for 77% of the variance in \( \text{PaCO}_2 \) during exercise. These results suggest that the need to increase respiratory evaporation and dissipate metabolic heat during exercise contributes to the development of alveolar hyperventilation and hypocapnia. Thermal drive appears to arise principally from core receptors, because \( T_a \) exerted no statistically significant effect on the magnitude of the hypocapnia.

A similar relationship between \( T_r \) and \( \text{PaCO}_2 \) during exercise was found previously in the dog (31). Wagner et al. (31) exercised dogs for 30 min at 32 and 50% of \( \text{VO}_2\text{max} \) and observed progressive hypocapnia concomitant with a gradual rise in \( T_r \). They reported a correlation between \( T_r \) and \( \text{PaCO}_2 \) in the dog (Eq. 4), which was remarkably similar to that found in the present experiment on sheep (Eq. 5).

\[
\text{PaCO}_2 = -7.26T_r + 318.6
\]

\[ R^2 = 0.79 \text{ (dog, preexercise and exercise data pooled; Ref. 31)} \]  

\[
\text{PaCO}_2 = -8.18T_r + 352.6
\]

\[ R^2 = 0.77 \text{ (sheep, present experiment)} \]

Thermal drive to increase respiratory evaporative heat loss appeared to be the primary ventilatory stimulant during exercise in the dog (31). A negative correlation between \( T_r \) and \( \text{PaCO}_2 \) also appears to be present in the results of previous experiments on goats (28) and sheep (3, 25). In addition,
decreased during a step-up in intensity and increased between Tre and PaCO2 has not been definitively shown in temperature during exercise (24), a relationship be-

hypocapnia (7–11 Torr below rest) and increasing body exercising rat. Although ponies do exhibit both mild independent variable and PaCO2 during exercise between independent variables and between each Correlation matrix showing correlations Table 4.

For a causal relationship between ExInt and PaCO2 is

The latter authors attributed the increased venti-
lation to thermoregulatory drive that particularly served to cool the brain.

A relationship between Tre and PaCO2 during exercise has not been documented in all species studied, how-

ever. Fregosi and Dempsey (11) found no relationship between Tre and the magnitude of hypocapnia in association with progressive hyperthermia. Similarly, White and Cabanac (33) found that, once a threshold core temperature was reached, minute ventilation in exercising humans increased in proportion to increases in body core temperature. The latter authors attributed the increased ventilation to thermoregulatory drive that particularly served to cool the brain.

although exercise in humans is generally considered to be isocapnic, Hanson et al. (14) found that, during endurance exercise (at least 60 min), runners experienced progressive hypocapnia in association with progressive hyperthermia. Similarly, White and Cabanac (33) found that, once a threshold core temperature was reached, minute ventilation in exercising humans increased in proportion to increases in body core temperature. The latter authors attributed the increased ventilation to thermoregulatory drive that particularly served to cool the brain.

A relationship between Tre and PaCO2 during exercise has not been documented in all species studied, how-

ever. Fregosi and Dempsey (11) found no relationship between Tre and the magnitude of hypocapnia in the exercising rat. Although ponies do exhibit both mild hypocapnia (7–11 Torr below rest) and increasing body temperature during exercise (24), a relationship between Tre and PaCO2 has not been definitively shown in ponies. Instead, Pan et al. (21) suggested that PaCO2 may be inversely related to ExInt in the pony. The case for a causal relationship between ExInt and PaCO2 is supported by the observation that the PaCO2 of ponies decreased during a step-up in intensity and increased during a step-down in intensity (21). The rapidity of these changes in PaCO2, corresponding to work-to-work transitions, excludes the possibility that the PaCO2 of the ponies was altered in response to ExInt-related changes in core temperature per se. A negative correlation between ExInt and PaCO2 has also been reported previously in the dog (31), goat (28), and sheep (25).

Because ExInt has a direct effect on the rate of rise of body temperature (Fig. 1), it can be difficult to dissect the effects of body temperature on PaCO2 (in part an indirect effect of ExInt) from the direct effects of ExInt per se on PaCO2. Few studies have been designed to make this distinction. Feistkorn et al. (7) exercised goats instrumented with intravascular heat-exchange devices at the same ExInt at three different core temperatures. They found that PaCO2 during exercise varied inversely with body temperature. Similarly, Bell et al. (3) exercised sheep for 30 min at the same ExInt in a warm environment and in a cool environment. They found a significantly greater decline in PaCO2 in the warm environment, in concert with a significantly greater rise in Tre. In the present experiment, hypocapnia was not observed during low-intensity exercise in the cold environment, the only condition in which the sheep remained vasoconstricted and Tre remained in the normothermic range (Fig. 4).

The differences among species in the apparent influence of body temperature and ExInt on PaCO2, may stem from differences in thermoregulatory strategy and experimental conditions. Sheep, goats, and dogs are panting species and thus rely on the respiratory system for evaporative heat loss, whereas horses depend primarily on cutaneous evaporative heat loss during heat stress (16). Rats neither pant nor sweat but instead exhibit behavioral thermoregulation. Regardless of the thermoregulatory strategy, respiration does provide a potential avenue of heat loss; nonetheless, a panting species might logically demonstrate a stronger thermal drive to respiration than a nonpanting species.

Increased respiratory evaporative heat loss caused by hyperventilation provides a rationale for the inverse relationship between body temperature and PaCO2 observed in some animals during exercise. In contrast, the significance of the relationship between ExInt per se and PaCO2 is unclear. On the basis of data collected in the exercising pony, Forster and Pan (10) speculated that nonhuman mammals might exhibit fewer alveolar–capillary adjustments to exercise than do humans (who generally maintain isocapnia during low- and moderate-intensity exercise), thus rendering these nonhuman species dependent on an increased alveolar Po2 to maintain PaO2 homeostasis. Actual measurements of ventilation-perfusion inequality do not support the premise of this hypothesis. Galloping horses have better matching of ventilation to perfusion than do running humans (27). Nonetheless, hyperventilation may benefit PaO2 at severe exercise intensities (80–100% of VO2max), when the pulmonary transit time decreases toward the minimum time required for alveolar-arterial Po2 equilibration. An increase in alveolar

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**Table 4. Correlation matrix showing correlations between independent variables and between each independent variable and PaCO2 during exercise**

<table>
<thead>
<tr>
<th>ExInt</th>
<th>[Lac]</th>
<th>Tre</th>
<th>Ts</th>
<th>Cond</th>
<th>PaCO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExInt</td>
<td>1.00</td>
<td>0.62*</td>
<td>0.74*</td>
<td>0.00$</td>
<td>-0.02$</td>
</tr>
<tr>
<td>[Lac]</td>
<td>1.00</td>
<td>0.76*</td>
<td>-0.12$</td>
<td>-0.37$</td>
<td>-0.71*</td>
</tr>
<tr>
<td>Tre</td>
<td>1.00</td>
<td>0.00$</td>
<td>-0.51†</td>
<td>-0.49‡</td>
<td>-0.88*</td>
</tr>
<tr>
<td>Ts</td>
<td>1.00</td>
<td>0.38$</td>
<td>1.00</td>
<td>0.36$</td>
<td></td>
</tr>
<tr>
<td>Cond</td>
<td>1.00</td>
<td>0.36$</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Correlations between indicator variables (i.e., between Ts and Cond) are omitted. *P < 0.0001; †P < 0.005; ‡P < 0.01; $NS.
PO₂ could serve to prevent arterial oxygen desaturation (10, 22).

At moderate exercise intensities, however, arterial oxyhemoglobin desaturation is not likely. Bayly et al. (2) found that PO₂ homeostasis was maintained by horses exercising at 40% of VO₂max both before and after the horses began to hyperventilate. These authors concluded that thermal drive was the most likely impetus for the progressive hypocapnia exhibited by the horses after 25 min of exercise (2). In the exercising sheep, hyperventilation raises PO₂, (Fig. 2; see also Ref. 3), suggesting that sheep are not dependent on hyperventilation to maintain PO₂ at its resting level. Even if PO₂ were to fall in the absence of hyperventilation, at low altitudes, a very large fall in PO₂ (30–40 Torr) would be required for a significant decrease in arterial oxyhemoglobin saturation. In contrast, the thermoregulatory system is sensitive to small changes in body temperature, and thermal drive is a more tenable explanation for the hyperventilation observed in the exercising sheep. The inverse correlation observed between ExInt per se and PaCO₂ may reflect an inherently excessive feed-forward respiratory drive during exercise (6), rather than a causative relationship.

The lack of a significant independent effect of [Lac] on exercise PaCO₂ in the present study agrees with a previous report in sheep (25) and with a similar result in the exercising pony (22). Furthermore, the traditional hypothesis of H⁺ stimulation of hyperventilation during high-intensity exercise in humans has been questioned (6). The lack of an independent effect of Ta on PaCO₂ suggests that the influence of Tsk can be overridden or overwhelmed by core temperature. Physi- cal conditioning does not appear to modify the response of the respiratory controller to input from the other variables.

Limitations

In exercising ponies (23) and horses (16), the use of Tref instead of arterial temperature to correct arterial gas tensions has been shown to cause analytical error, because Tref increased more slowly than arterial temperature during exercise. The severity of the error in correction of PaCO₂ was found to depend on the ExInt and the duration of exercise, increasing with either factor (23). However, in a sheep exercising at ~50% of VO₂max, Tref lagged only transiently behind blood temperature in the right ventricle. By 20 min of exercise Tref surpassed right ventricular temperature (26). The maximum difference between Tref and right ventricular temperature during 30 min of exercise was 0.2°C (26). Bradley et al. (4) reported that a 1°C fall in blood temperature lowers the Pco₂ by 4.4%. Based on these findings, the error in PaCO₂ during exercise caused by correction by Tref should be <1 Torr. Thus, it is unlikely that error in estimation of PaCO₂ caused by using Tref for temperature adjustment has significantly biased the conclusions of this study.

The significant correlations among several of the independent variables, particularly among Tref, ExInt, and [Lac], obscure determination of which variable contributes most to the prediction of PaCO₂. Although physical conditioning achieved some dissociation between ExInt and [Lac], unfortunately removal of the fleece and cold Ta were not sufficient to uncouple ExInt and Tref. A univariable linear model for exercise PaCO₂, using only Tref, would have an R² of 0.77 (Eq. 5). A similar model, using only ExInt, would have an R² of 0.64 (square of the Pearson correlation coefficient given in Table 4). On post hoc statistical examination, the correlation coefficient between Tref and PaCO₂ was not significantly larger than that between ExInt and PaCO₂ (P > 0.025). Nonetheless, the interchangability of ExInt with the ExInt·Tref interaction (Eqs. 2 and 3) reduces the status of ExInt per se as a predictor of exercise PaCO₂. In contrast, Tref appears in both equations. Based on the relationship between Tref and PaCO₂ at each ExInt (Fig. 6), the significance of the ExInt·Tref interaction may indicate that Tref is particularly influential at medium and high intensities. The omission of [Lac] from the multiple-regression model is expected, given the relatively low independent correlation of [Lac] and PaCO₂ (0.51) and the fact that the correlations between [Lac] and both Tref and ExInt are greater than that between [Lac] and PaCO₂.

Implications

In the sheep, a panting species, thermal drive has a greater role in determining PaCO₂ during exercise than does either ExInt per se or [Lac]. Thus, during exercise, temperature regulation appears to be a higher homoeostatic priority than acid-base regulation. Experiments addressing respiratory control in panting species, especially those involving exercise, should be designed to account for thermal effects. Moreover, continued study of the mechanism by which hyperthermia affects hyperventilation is merited. Hyperthermia may increase chemoreceptor gain, leading to an enhanced respiratory response to a given CO₂ load. Alternatively, hyperthermia may lower the set point at which PaCO₂ is regulated. In the case of either increased gain or increased threshold, a direct effect of temperature on the hypothalamus and respiratory centers is a possible mechanism. However, panting animals can maintain brain temperature below that of the body (1). Consequently, any direct effect of temperature on the brain must be exerted by a smaller change in temperature than that experienced peripherally.

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