Changes in respiratory control during and after 48 h of isocapnic and poikilocapnic hypoxia in humans

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Changes in respiratory control during and after 48 h of isocapnic and poikilocapnic hypoxia in humans. J. Appl. Physiol. 85(6): 2125–2134, 1998.—Ventilatory acclimatization to hypoxia is associated with an increase in ventilation under conditions of acute hyperoxia ($V_{E\text{hyperoxia}}$) and an increase in acute hypoxic ventilatory response (AHVR). This study compares 48-h exposures to isocapnic hypoxia (protocol I) with 48-h exposures to poikilocapnic hypoxia (protocol P) in 10 subjects to assess the importance of hypoxic alkalosis in generating the changes observed in ventilatory acclimatization to hypoxia. During both hypoxic exposures, end-tidal $P_{O_2}$ was maintained at 60 Torr, with end-tidal $P_{CO_2}$ held at the subject’s prehypoxic level (protocol I) or uncontrolled (protocol P). $V_{E\text{hyperoxia}}$ and AHVR were assessed regularly throughout the exposures. $V_{E\text{hyperoxia}}$ ($P < 0.001$, ANOVA) and AHVR ($P < 0.001$) increased during the hypoxic exposures, with no significant differences between protocols I and P. The increase in $V_{E\text{hyperoxia}}$ was associated with an increase in slope of the ventilation-end-tidal $P_{CO_2}$ response ($P < 0.001$) with no significant change in intercept. These results suggest that changes in respiratory control early in ventilatory acclimatization to hypoxia result from the effects of hypoxia per se and not the alkalosis normally accompanying hypoxia.

IN HUMANS, VENTILATORY ACCLIMATIZATION TO HYPOXIA (VAH) IS A PROGRESSIVE INCREASE IN VENTILATION ($V_E$) OVER HOURS/DAYS ACCOMPANIED BY A PROGRESSIVE DECREASE IN THE END-TIDAL $P_{CO_2}$ ($PET_{CO_2}$). THERE APPEAR TO BE AT LEAST TWO PROCESSES CONTRIBUTING TO THIS INCREASE IN VENTILATION: 1) A LEFTWARD SHIFT OF THE VENTILATORY RESPONSE TO AN INCREASE IN $PET_{CO_2}$ TOGETHER WITH AN INCREASE IN THE SLOPE OF THIS RELATIONSHIP (DETERMINED UNDER CONDITIONS OF ACUTE EUOxia/HYPOxia) (4, 12, 19, 20) AND 2) AN INCREASE IN ACUTE HYPOXIC VENTILATORY RESPONSE (AHVR) (12, 13, 22, 26).

One question surrounding these processes is to what degree they develop because of the hypoxia per se vs. to what degree they develop because of the concomitant alkalosis. One approach to answering this question has been to compare the effects of poikilocapnic hypoxia with those of isocapnic hypoxia. A comparison of 8 h of poikilocapnic hypoxia with 8 h of isocapnic hypoxia has suggested that the changes in $V_E$ under acute hypoxic conditions ($V_{E\text{hyperoxia}}$) (24) and AHVR (15) do not depend for their development on the presence of a respiratory alkalosis.

A criticism of these studies is that 8 h of hypoxia did not provide sufficient time for what is regarded classically as VAH in humans. Typically, the process takes several days, although substantial changes are seen by days 1 and 2. The purpose of this study was to extend the experiment comparing isocapnic and poikilocapnic hypoxia from 8 to 48 h so that the time course of the study would match more closely that normally associated with VAH in humans.

The particular questions to be addressed in this study were as follows: 1) For a 48-h conditioning period, were there significant differences in the progressive increase in $V_{E\text{hyperoxia}}$ between isocapnic and poikilocapnic hypoxic conditioning? 2) For a 48-h period of hypoxia, could the progressive increase in $V_{E\text{hyperoxia}}$ be attributed to an increase in slope of the hypoxic $V_E$-$PET_{CO_2}$ relationship and/or a shift in the intercept of this relationship? 3) For a 48-h conditioning period, were there significant differences in the progressive increase in AHVR between isocapnic and poikilocapnic hypoxic conditioning?

In addition to the study of 48 h of hypoxia, the 48-h period after the relief of hypoxia was also investigated to compare the recovery processes from the isocapnic and poikilocapnic hypoxic exposures.

METHODS

Subjects. Ten healthy subjects (7 men, 3 women), 18–27 yr of age, volunteered to take part in the study. The requirements of the study were fully explained in writing and verbally in such a way that the subjects were aware of the exact purpose of the experiment. Subjects gave informed consent before participation in the study. Each subject was required to make one or two preliminary visits to the laboratory, during which control measurements of $PET_{CO_2}$ and estimates of hypoxic sensitivity were made and subjects were familiarized with the apparatus. The research had been approved by the Central Oxford Research Ethics Committee.

Hypoxic exposure. Two 48-h hypoxic exposures were used: 1) an isocapnic protocol (protocol I), where end-tidal $P_{O_2}$ ($PET_{O_2}$) was held at 60 Torr and $PET_{CO_2}$ was held at the subject’s prehypoxic control value, and 2) a poikilocapnic protocol (protocol P), where $PET_{O_2}$ was held at 60 Torr and $PET_{CO_2}$ was uncontrolled. Hypoxic exposures were separated by $\geq 1$ wk and carried out in a randomly determined order. After each hypoxic exposure the subjects were allowed to go home but were required to return to the laboratory at intervals over the subsequent 48 h for further testing.

During the hypoxic exposure, individual subjects lived inside a specially built chamber that was large enough to allow them to be seated comfortably or move around if they wished and to accommodate a bed. Respiratory gas was sampled via fine catheters held at the opening of each nostril by a nasal $O_2$-therapy mask. The gas was analyzed continuously for $P_{O_2}$ and $P_{CO_2}$ by mass spectrometry, and the signals were sampled by computer at a rate of 50 Hz. Inspiratory and end-tidal values for $P_{O_2}$ and $P_{CO_2}$ were identified for each breath by computer and recorded together with arterial $O_2$.
saturation, which was monitored by a pulse oximeter attached to a finger. At the start of the experiment the inspired gas composition necessary to produce the desired end-tidal partial pressures was estimated and set manually before the subject entered the chamber. Once the subject had entered the chamber, the inspired composition was altered automatically every 5 min or at manually overridden intervals to minimize the error between the actual and desired end-tidal gases. This system has been described in detail elsewhere (14).

\[ V_E \]

\[ V_E \] was measured before the chamber exposures were started and then at 30 min into the hypoxic exposure, 90 min into the hypoxic exposure, and every 2 h during wakefulness for the remainder of the 48-h protocol. Each measurement of \[ V_E \] took 5 min, and the last 2 min of this period were used to calculate the \[ V_E \] for that time point. The measurements were made using inductance plethysmography. The inductance plethysmograph was calibrated at the end of each 5-min measurement period by asking the subject to breathe through a mouthpiece for a further 5 min. This gave accurate values for the subject's pulmonary volume.

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Fig. 1. Timing of measurements undertaken during each protocol. AHVR, acute hypoxic ventilatory response; \( V_{E_{\text{hyperoxia}}} \), ventilation under acute hyperoxia; AHCVR, acute hypercapnic ventilatory response.

Fig. 2. Ventilatory data collected in chamber during 48-h isocapnic (protocol I, left) and poikilocapnic (protocol P, right) hypoxic exposures. End-tidal \( P_O_2 \) (\( P_{ET_2} \)), end-tidal \( P_CO_2 \) (\( P_{ETCO_2} \)), and \( O_2 \) saturation are 5-min averages for individual subjects. For ventilation (\( V_E \)), thin lines represent individual values and heavy lines represent mean values. Rise in \( V_E \) in protocol I is significantly different (\( P < 0.001 \)) from \( V_E \) in protocol P.
for tidal volume using a turbine flowmeter (17) while data collection continued with the inductance plethysmograph.

Blood samples. Venous blood samples were taken at the times indicated in Fig. 1. The samples were taken inside the chamber under hypoxic conditions during the hypoxic exposures and outside the chamber with the subject breathing room air at other times. Before each sample was taken, the hand and lower arm were warmed for 5 min using an electric heating pad in an attempt to arterialize the blood sample. A venous sample was then taken from the cubital fossa or the dorsum of the hand. The sample was analyzed for \( \text{pH} \), \( \text{PCO}_2 \), \( \text{Hb} \), and \( \text{HCO}_3^- \) concentrations, and \( \text{O}_2 \) saturation. Simultaneous measurements of \( \text{PETO}_2 \) and \( \text{PETCO}_2 \) were also made, and this end-tidal gas composition was used to estimate arterial values for \( \text{pH} \).

Measurement of AHVR, \( \dot{V}_{\text{E}} \text{hyperoxia} \), and the acute hypercapnic ventilatory response. Measurements of these respiratory responses were undertaken at the times indicated in Fig. 1. Apart from the \( \text{pH} \)-matched measurements (see below), measurements of AHVR and \( \dot{V}_{\text{E}} \text{hyperoxia} \) were undertaken at all times with the \( \text{PETCO}_2 \) held at a \( 1.5-2 \) Torr above the subject’s initial air-breathing value before the start of the chamber exposure (\( \text{PCO}_2 \)-matched measurements). The procedure for measuring AHVR consisted of an initial 5 min of steady \( \text{PETO}_2 \) (100 Torr) followed by six square waves in \( \text{PETO}_2 \), each period of 120 s, stepping between 50 and 100 Torr. Numerical values for AHVR were obtained by fitting a model of the ventilatory response to hypoxia to these data (see below).

Immediately after measurement of AHVR, \( \dot{V}_{\text{E}} \text{hyperoxia} \) was measured by elevating the \( \text{PETO}_2 \) to \( \sim300 \) Torr for 5 min. The last 2 min of this period were used to determine \( \dot{V}_{\text{E}} \text{hyperoxia} \).

The acute hypercapnic ventilatory response (AHCVR) was measured at the beginning of each day, and followed on directly from the determination of \( \dot{V}_{\text{E}} \text{hyperoxia} \). \( \text{PETCO}_2 \) was elevated by 7.5 Torr above the value for the \( \text{PCO}_2 \)-matched tests for 5 min. \( \text{PETCO}_2 \) was kept constant at 300 Torr, the value associated with the measurement of \( \dot{V}_{\text{E}} \text{hyperoxia} \). The final 2 min of data were used for calculating AHCVR along with the results from the measurement of \( \dot{V}_{\text{E}} \text{hyperoxia} \).

AHVR, \( \dot{V}_{\text{E}} \text{hyperoxia} \), and AHCVR were measured outside the chamber using a dynamic end-tidal forcing system. The subject sat in an upright position and breathed through a mouthpiece with the nose occluded with a clip. Respiratory volumes were measured using a turbine volume-measuring device fixed in series with the mouthpiece; flows and timing information were obtained using a pneumotachograph.
arterial pH that occurred in the first test (0 h). The level of PETCO₂ required was calculated from the pH, PCO₂, Hb content, and saturation of the venous blood samples using the relationships described by Michel et al. (18). These measurements are termed “pH matched.”

Modeling of hypoxic responses. To obtain numerical estimates for AHVR from the data collected, the six square waves of each of the AHVR tests were fit by a single-compartment model of the peripheral chemoreflex (model 3) as described by Clement and Robbins (5). Parameter Gp of this model reflects the ventilatory sensitivity to hypoxia, and parameter V˙c reflects the residual ventilation when no hypoxia is present. The two other parameters of the model, which are not of such immediate interest to this study but are provided as part of the fitting process, are the time constant (τ) and the time delay (T δ) for the peripheral chemoreflex.

Statistical analysis. For statistical analysis the data were split into two parts: the first relates to the 48-h hypoxic period and the second to the 48 h after the relief of hypoxia. All statistical analysis was undertaken using ANOVA. In most cases a repeated-measures analysis was undertaken with protocol and time as within-subject factors. In a few cases where there appeared to be a closely linear relationship for the variable with time, a regression model was used with time as a covariate, protocol as a fixed factor, and subject as a random factor. Where time has been treated as a covariate, this is indicated.

All statistical analysis was undertaken using the SPSS software package.

RESULTS

Subjects. Of the 10 subjects studied, 9 provided data that were suitable for analysis. The remaining subject withdrew from the study during the poikilocapnic protocol suffering from headache, nausea, and general discomfort, which could be interpreted as symptoms of acute mountain sickness. While in the chamber, other subjects were generally comfortable, spending their days reading, watching television, or playing computer games. Some did report mild headaches and, during isocapnic hypoxia, some discomfort from the high levels of V˙E experienced toward the end of the exposure. However, no others sought to withdraw from the study. All subjects managed to sleep satisfactorily during both protocols, although some had episodes of periodic breathing in protocol P. During such periods the in-
spired gas composition within the chamber was held constant until regular breathing returned.

Hypoxic exposure. Figure 2 shows values for the end-tidal gas tensions and arterial O₂ saturation averaged every 5 min for each of the nine subjects while in the chamber for protocols I and P. These plots illustrate the quality of control achieved over the end-tidal gases. PETO₂ was maintained very close to desired values throughout the exposure for both protocols. For protocol I, PETCO₂ was controlled accurately during the day but tended to rise at night when the subjects were asleep. For protocol P, PETCO₂ tended to fall during the 48 h, although the diurnal variation was again evident, with higher values of PETCO₂ at night. Mean values over 12-h periods for PETO₂, PETCO₂, and arterial O₂ saturation are given in Table 1.

Figure 2 also shows values for VE recorded in the chamber using inductance plethysmography at 2-h intervals while the subjects were awake. There appears to have been a progressive increase in VE with time over the 48-h hypoxic exposure during protocol I that was not apparent in protocol P. This difference was significant (P < 0.001, time treated as a covariate).

Blood samples. Mean values relating to blood samples are given in Table 2. There was a significant rise in Hb concentration over the 48-h exposure to hypoxia in both protocols (P < 0.001), with no significant difference between them. The mean value for venous saturation [53.8 ± 1.4% (SD)] indicated that the procedure of warming the hand to obtain arterialized samples was not particularly successful; consequently, the venous values for PCO₂ and pH were difficult to interpret on their own. Two derived variables were calculated and are shown in Table 2. The first, standard HCO₃⁻ ([HCO₃⁻]std, i.e., calculated HCO₃⁻ concentration at 40 Torr PCO₂ in fully saturated blood) showed little change in either protocol, and statistical analysis of the values from the start of each day revealed no significant effects of time or protocol. The second derived variable was the calculated arterial pH, where it was assumed that PETCO₂ and PETO₂ could be used as a measure of the PCO₂ and P O₂ of arterial blood. With use of time as a covariate, for protocol I there was no significant change in calculated arterial pH over the 48-h period of hypoxia, whereas for protocol P there was a significant rise (P < 0.005).

Measurements of VEhyperoxia. An experimental determination of VEhyperoxia is shown in Fig. 3. Mean values for VEhyperoxia measured at various stages through each protocol are illustrated in Fig. 4. There was an increase in VEhyperoxia over time during the hypoxic period of both protocols (P < 0.001). This increase did not differ significantly between the two protocols.

Fig. 5. Mean PETO₂, PETCO₂, and VE during PCO₂-matched assessments of AHVR at 0–48 h during protocols I (left) and P (right). Numbers on VE traces represent hours.
Measurements of AHCVR. Ventilatory responses to hypercapnia were measured under conditions of hyperoxia every 24 h throughout the 96-h protocol (Fig. 3). Mean values for the slope and intercept of the responses are illustrated in Fig. 4. For both protocols, the slope appeared to increase during the 48 h of hypoxia and then to decrease during the subsequent 48 h of euoxia. The increase and the decrease in slope were significant ($P < 0.05$), with no differences being detected between the responses for protocols I and P.

Inspection of the data for the intercept of the mean $\dot{V}E$-$\text{PETCO}_2$ responses with the x-axis for each time period suggested that there was little change in this value over the 48-h period of hypoxia, and indeed no significant changes were detected.

Measurements of AHVR. Figure 3 illustrates an example of $\text{PETO}_2$, $\text{PETCO}_2$, and $\dot{V}E$ measured breath by breath during an experimental determination of AHVR. The $\text{PO}_2$ record shows that the $\text{PETO}_2$ profile followed the required pattern accurately, with only slight inaccuracies at the transitions between the two levels of $\text{PETO}_2$. The $\text{PCO}_2$ record shows that $\text{PETCO}_2$ values were maintained close to the desired level throughout the test. Average end-tidal gas tensions and ventilatory responses for the six hypoxic square waves averaged across all subjects are shown in Figs. 5 and 6. For both protocols, $\text{PETCO}_2$ appears to have been well controlled throughout. For $\text{PETO}_2$, the transitions between the two levels of $\text{PO}_2$ were generally fairly sharp, although there was some overshoot at the release of hypoxia.

For both protocols, the records for $\dot{V}E$ suggested an increase in the amplitude of response to the hypoxic stimulus over the 48-h period of hypoxia that was gradually reversed during the subsequent 48 h of euoxia. There also appears to have been an increase in the baseline ventilation in euoxia. To quantify these appearances, a dynamic model (see METHODS) was fit to the individual responses to the hypoxic square waves to obtain estimates for hypoxic sensitivity ($G_p$) and baseline (calculated hyperoxic) ventilation ($V_c$). As part of this process, values for the pure delay ($T_d$) and $\tau$ associated with the acute hypoxic chemoreflex were also obtained. Mean values for $G_p$ and $V_c$ are summarized for both protocols in Fig. 7. In general, for both protocols the values for $G_p$ and $V_c$ showed an increase over the 48 h of hypoxia and then a decrease over the ensuing 48 h of euoxia. There was little change in $T_d$ ($7.65 \pm 5.01 \text{ (SD) s, } n = 9 \text{ subjects}$) or $T_d$ ($4.23 \pm 0.63 \text{ s}$).

The above appearances were tested statistically. There was a significant effect of time on $G_p$ and $V_c$ during the 48 h of hypoxia ($P < 0.001$), with no significant difference detected between the protocols. In the 48 h after the relief of hypoxia there was a decrease in $G_p$ and $V_c$ with time ($P < 0.001$), again with no
Average end-tidal gas tensions and ventilatory responses for the six hypoxic square waves for the pH-matched data averaged across all subjects are shown in Fig. 8. Again, PETCO₂ appears to have been well controlled throughout both protocols.

Values for Gp and Vc are summarized in Fig. 9. In general, for both protocols the values for Gp and Vc appeared to increase over the 48 h of hypoxia and then to decrease over the ensuing 48 h of euoxia. Again, these appearances were tested statistically. There was a significant effect of time for both Gp and Vc during the 48 h of hypoxia (P < 0.001) but no significant difference in this process between the two protocols. There were similar statistical observations for the 48 h after hypoxia for Gp (P < 0.001) and Vc (P < 0.005). ANOVA also showed no significant changes over time during the 48 h of hypoxia for τ (6.75 ± 4.79 s) or Tₐ (4.61 ± 0.74 s) or any significant differences between the protocols. These results were consistent with the observations for the PCO₂-matched tests.

DISCUSSION

The main findings from this study were an increase in V̇Ehyperoxia and an increase in AHVR over a 48-h exposure to hypoxia. This time scale is one over which the early phases of VAH are known to occur. Importantly, these observations did not differ significantly between the isocapnic and poikilocapnic hypoxic exposures, which suggests that the changes were a product of hypoxia alone and did not require the hypocapnia and alkalosis that normally accompany VAH. These findings were entirely consistent with previous findings from our laboratory using 8-h exposures to hypoxia (15, 24), and the importance of the present work is that it has extended the results into the time frame normally associated with VAH in humans.

Control of hypoxic stimulus within the chamber. The records for PETO₂ indicated that this variable was well controlled throughout the 48 h that the subjects spent in the chamber. Nevertheless, inspection of the data obtained for arterial saturation by pulse oximetry indicated that there may have been some drop in mean saturation during sleep. One possible explanation for this drop in saturation is that there was poorer ventilation-perfusion matching during sleep in the supine position under these conditions. Another possibility is that the end-tidal O₂ overestimated “alveolar” O₂ during sleep, and so overall alveolar O₂ was lower than the regulated end-tidal value, thus causing a lower saturation. Against this possibility is the observation that the increase in PETCO₂ during sleep was well recorded, and, as we used a mass spectrometer, the dynamic characteristics for the measurements of CO₂ and O₂ would have been identical.

In addition to the apparent modest change in mean saturation during sleep, there were some values that appeared to indicate a much greater transient fall in saturation. These low values appeared mostly, but not exclusively, during sleep. Our impression is that these values were artifacts arising during periods when there was a poor signal from the pulse oximeter. They
occurred more commonly during sleep, as, during periods of sleep, we were unable to ask the subject to reposition the finger probe. It is also possible that shorter periods of poor signal could underlie the small changes in mean saturation during sleep referred to above.

Acid-base status during protocol P. Although there was a change in calculated arterial pH in protocol P, no compensation for this change was detected in the acid-base status of the blood. This lack of change in the standard HCO₃⁻ concentration 48 h after the induction of hypoxia is consistent with previous observations by others (23). It is also consistent with the notion that the early stages of VAH occur without the need for compensatory changes in blood acid-base status generated by renal excretion of HCO₃⁻. However, this does not rule out effects of renal compensation later in VAH. Nor does it have any bearing on changes in cerebrospinal fluid HCO₃⁻ concentration.

Persistent hyperventilation after relief of hypoxia. The observation that hyperventilation persists for some considerable time after return from high altitude is long standing (8), and some of this effect almost certainly is related to a slow reversal of the acid-base changes induced by residence at altitude. However, the results from the present study suggest that acid-base adjustment cannot be the sole mechanism that underlies this slow return, since the return to baseline was also slow after the isocapnic exposure. Indeed, the isocapnic and poikilocapnic exposures did not differ in this respect, a finding consistent with an earlier report from our laboratory in relation to shorter (8-h) periods of exposure and recovery from hypoxia (24).

In the present study the persistent hyperventilation was generated by an increase in the slope of the V̇E-PETCO₂ relationship without any concurrent leftward shift of the intercept of this relationship with the PETCO₂ axis. However, from studies at altitude, it has generally been accepted that there is an increase in the slope of the hyperoxic/euoxic V̇E-PETCO₂ relationship and a leftward shift of the intercept (4, 12, 19, 20). One possible interpretation of these two sets of findings is that the increase in slope begins early in VAH and does not require alkalosis (although this does not rule out further changes later in VAH) but that the changes in intercept require a longer duration of hypoxia, a more intense level of hypoxia, or a shift in the acid-base status of the blood.

In a number of previous studies, PETO₂ and PETCO₂ have been manipulated together, and it may be useful to compare these with the present study. Eger et al. (9) investigated in four subjects the effects of holding PETCO₂ at various levels over an 8-h period with and

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**Fig. 8.** Mean PETO₂, PETCO₂, and V̇E during pH-matched assessments of AHVR at 0–96 h during protocols I (left) and P (right). Numbers on V̇E traces represent hours.
Involving hypoxia. Measurements were compared with those after experiments not involving hypoxia. However, the results are not entirely clear cut, inasmuch as the increase in slope did not involve hypoxia. This result is consistent with the present study. This increase did not occur in experiments that were employed to keep the carotid body euoxic and eucapnic. Without hypoxia. They detected a significant increase in the slope of the eucapnic VE-PETCO2 relationship after experiments involving hypoxia if these values were compared with measurements made before the hypoxic exposure. This result is consistent with the present study. This increase did not occur in experiments that did not involve hypoxia. However, the results are not entirely clear cut, inasmuch as the increase in slope was not significant if the slopes after hypoxic experiments were compared with those after experiments not involving hypoxia.

In addition to these results with respect to the slope of the VE-PETCO2 relationship, Eger et al. (9) also reported a leftward shift of the VE-PETCO2 relationship that was related to the degree of hypocapnia but was always greater if hypoxia was present rather than absent. This finding appears consistent with the result of a study by Dempsey et al. (7) of 26 h of hypocapnia in goats, which is isocapnic and poikilocapnic hypoxia in goats, which is persistent hyperventilation was observed after poikilocapnic hypoxia but not after isocapnic hypoxia. The hyperventilation was associated with a leftward shift of the intercept of the VE-PETCO2 response curve with the PETCO2 axis. Because these features did not occur after isocapnic hypoxia, the authors concluded that the effect was dependent on a respiratory alkalosis developing during the hypoxic exposure. These findings, when compared with ours, suggest that there may be qualitative differences between goats and humans with respect to this response. However, the authors did observe a significant increase in the slope of the VE-PETCO2 response after isocapnic hypoxia in keeping with the present study.

Weizhen et al. (25) studied isocapnic hypoxia in awake goats, where a separate perfusion system was employed to keep the carotid body euoxic and eucapnic. They did not find any persistent hyperventilation after the hypoxic exposure, nor did they find any change in the slope of the VE-PETCO2 relationship. These results, together with those of Engwall and Bisgard (10), suggest that in goats the increase in slope of the VE-PETCO2 relationship may require carotid body hypoxia and that it is not generated by central nervous system hypoxia.

Progressive increase in AHVR. Several investigators have reported that AHVR increases with exposure to high altitude (12, 13, 22, 26). The study of Howard and Robbins (15) demonstrated that 8 h of isocapnic hypoxia can cause a progressive increase in AHVR, and the present study has now extended this finding to 48 h, a time scale more commonly associated with VAH in humans.
These results are in some contrast to those of Cruz et al. [6], who found that, for hypoxic exposures with added inspired CO₂, there was no significant progressive effect of the exposure on AHVR. Interpretation of their results is difficult, inasmuch as only four subjects were studied and it is not entirely clear at which PETCO₂ the measurements of hypoxic sensitivity were made in the experiments in which CO₂ was added.

Experiments in awake goats have produced results that are broadly consistent with ours in humans [11] and, in addition, have provided good evidence to link the response to a process at the carotid body. In particular, an increase in hypoxic sensitivity has been observed in studies of sustained hypoxia isolated to a carotid body of goats maintained systemically euvoxic and isocapnic [3], whereas Weizhen et al. [25] observed no change in hypoxic sensitivity with sustained central nervous system hypoxia. Hypercapnia isolated to a carotid body of goats maintained systemically euoxic and isocapnic [4], whereas Weizhen et al. [25] observed no change in hypoxic sensitivity with sustained central nervous system hypoxia. Hypercapnia isolated to a carotid body of goats maintained systemically euoxic and isocapnic [3], whereas Weizhen et al. [25] observed no change in hypoxic sensitivity with sustained central nervous system hypoxia.

Ventilatory responses to hypoxia during and after 48 h of hypoxia.

**REFERENCES**