Ventilatory response to 8 h of isocapnic and poikilocapnic hypoxia in humans

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Howard, L. S. G. E., and P. A. Robbins. Ventilatory response to 8 h of isocapnic and poikilocapnic hypoxia in humans. *J. Appl. Physiol.* 78(3): 1092–1097, 1995.—Almost all studies of the effects of prolonged hypoxia on ventilation ($\dot{V}E$) in humans have been performed with the end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) left uncontrolled. The purpose of this study was to compare the effects of 8 h of hypoxia with $P_{ET_{CO_2}}$ held constant with 8 h of hypoxia with $P_{ET_{CO_2}}$ left uncontrolled. Ten subjects completed the study. Each was seated inside a chamber in which the inspired gas could be controlled so as to maintain the desired partial pressures of end-tidal gases (sampled via nasal catheter) constant (see L. S. G. E. Howard et al. *J. Appl. Physiol.* 78: 1088–1091, 1995.). Three 8-h protocols were employed: *1*) isocapnic hypoxia, at an end-tidal P_{O_2} of 55 Torr with $P_{ET_{CO_2}}$ held at the subject's resting value; *2*) poikilocapnic hypoxia, at the same end-tidal P_{O_2}; and *3*) control, where the inspired gas was air. $\dot{V}E$ was measured (over 3 min) at 0 and 20 min and at hourly intervals between 1.5 and 7.5 h. There was a rise in $\dot{V}E$ during isocapnic hypoxia [from an initial $\dot{V}E$ of 16.2 ± 1.3 (SE) l/min to a final $\dot{V}E$ of 24.8 ± 1.6 l/min], which was significant compared with poikilocapnic hypoxia and control values ($P < 0.001$, analysis of variance). There was no significant progressive rise in $\dot{V}E$ during poikilocapnic hypoxia compared with control values. These results show that isocapnic hypoxia produces a progressive increase in $\dot{V}E$ when sustained over an 8-h period. The onset of this response is faster than has been noted in studies of the progressive rise in $\dot{V}E$ associated with the poikilocapnic hypoxia of altitude.

hypocapnia; alkalosis; altitude; acclimatization; hyperpnea

THE VENTILATORY RESPONSE in adult humans to sustained isocapnic hypoxia is biphasic (25). Ventilation ($\dot{V}E$) rises initially and then falls off over a period of 15–20 min to a level above the euoxic baseline. This phenomenon has been termed hypoxic ventilatory decline (HVD). On exposure to longer-term hypoxia at altitude (10) and at simulated altitude using hypobaric chambers (2), there is a progressive increase in $\dot{V}E$ over a period of days to weeks that is known as ventilatory acclimatization to hypoxia. HVD is seen under isocapnic conditions and so can be said to occur as a result of pure hypoxia, whereas the process of acclimatization takes place with an associated hypocapnic alkalosis that develops due to an initial hyperventilation caused by hypoxic stimulation of the peripheral chemoreceptors.

The aim of this study was to examine the ventilatory response to hypoxia over the little-studied time course between HVD and ventilatory acclimatization to hypoxia in both isocapnic and hypocapnic conditions. We chose to examine the first 8 h of the response. To overcome the problems of controlling the end-tidal gases for this length of time, we used a specially built chamber in which a subject could be seated comfortably for long periods of time with good control of end-tidal gases through frequent adjustments of the inspired gas composition (14).

METHODS

Subjects. Eleven subjects (6 females, 5 males) aged between 18 and 24 yr were studied. Their individual characteristics are listed in Table 1. All were healthy, and none gave a history of respiratory symptoms or illnesses. All were nonsmokers except for one subject (*subject 939*), who smoked ~5 cigarettes/day. The subjects had the basic experimental procedure explained to them but were naive as to the precise purpose of the experiment and to the particular protocol employed on the day. The experimental procedure was approved by the Central Oxford Research Ethics Committee, and all the subjects gave informed consent to the study.

Experimental technique. For the first 20 min of exposure to hypoxia, a fast gas-mixing system was used with the subject attached to a mouthpiece with the nose occluded. This was done to record $\dot{V}E$ during a period in which it is known to vary (25) and it also enabled the chamber composition to be set to an initial correct level for each individual subject. The chamber system was used for the remainder of the hypoxic exposure.

The apparatus associated with the fast gas-mixing system consisted of a turbine volume-measuring device (15) to measure respiratory volumes and a pneumotachograph to record respiratory flows and timing information. Gas was sampled continuously from a port close to the mouth at a rate of 80 ml/min and analyzed by mass spectrometry for P_{O_2} and P_{CO_2}. An IBM PC-AT computer was used to pick out the ends of inspiratory and expiratory phases from the flow data to determine inspiratory and expiratory timing and volumes and values of end-tidal P_{O_2} ($P_{ET_{O_2}}$) and P_{CO_2} ($P_{ET_{CO_2}}$). A second IBM PC-AT computer compared the end-tidal gas composition with the desired composition and calculated the new inspired gas mixture that should generate the desired composition for the following breath. The inspired gas mixture was produced through a series of outlet valves connected to a gas supply. This controlling system has been described elsewhere in greater detail (16, 19).

The apparatus associated with the rest of the hypoxic exposure employed a chamber that enabled the subjects to be seated comfortably without a mouthpiece. The subjects wore a pulse oximeter attached to one of the fingers to monitor arterial O_2 saturation and a fine catheter at the opening of one of the nostrils, through which tidal gas was sampled at 80 ml/min and analyzed by mass spectrometry for P_{O_2} and P_{CO_2}. An Elonex 286SX-12 PC monitored the data at a sampling rate of 50 Hz and picked out the ends of inspiratory and expiratory phases from the P_{CO_2} data. End-tidal and inspired gas tensions and arterial blood saturation were stored in a breath-by-breath file.

The estimated inspired composition that would generate the desired end-tidal partial pressures was set manually before the subject entered the chamber. Then, at 5-min or manually overidden intervals, the inspired gas composition was altered to minimize the error between the actual and desired

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TABLE 1. *Physical characteristics of subjects*

Subject No.	Sex	Height, m	Weight, kg	Age, yr
884	M	1.87	75	24
894	F	1.58	51	20
910	F	1.70	62	21
927	F	1.68	64	21
930	F	1.80	70	22
932	F	1.73	62	21
934	M	1.83	75	19
935	M	1.82	75	21
939	F	1.68	62	21
945	M	1.78	69	23
*947**	M	1.85	70	18

* Subject did not complete the study.

end-tidal gases. This system has been described separately in greater detail (14).

For measurements of $\dot{V}E$ inside the chamber, subjects breathed through a mouthpiece fixed in series with a turbine volume-measuring device with the nose occluded, and respiratory volumes, flows, and durations were obtained as above.

Protocols. Subjects were exposed to three different protocols on 3 different days (in random order with each protocol separated by ≥1 wk from the others), each lasting 8 h: *1*) isocapnic hypoxia (*protocol I*), where $P_{ET_{O_2}}$ was held at 55 Torr and P_{CO_2} was held at the subject's resting value; *2*) poikilocapnic hypoxia (*protocol P*), where $P_{ET_{O_2}}$ was held at 55 Torr and $P_{ET_{CO_2}}$ was uncontrolled; and *3*) control (*protocol C*), where the inspired gas was air. Subjects spent the first 20 min of exposure breathing from the fast gas-mixing system and were placed in the chamber after a 15-min test of the ventilatory response to acute hypoxia, again using the fast gas-mixing system, for use in another study.

$\dot{V}E$ was measured over a 3-min period at the beginning of the exposure, after 20 min of exposure, and then at hourly intervals from 1.5 to 7.5 h. The subjects remained inside the chamber for the entire period, except for 15 min at the end of 4 h of exposure to hypoxia (or control) when they were again assessed for ventilatory response to acute hypoxia outside the chamber using the fast gas-mixing system.

Subjects were not allowed caffeinated drinks such as coffee, tea, and certain canned drinks, and all ate lunch after 4.5 h.

Analysis. The last 15 breaths of each 3-min period of ventilatory measurement were used to calculate the subjects' $\dot{V}E$ at each point of measurement.

Analysis of variance (ANOVA) was used to test for possible differences in the ventilatory response to the three protocols. With the notation defined by Armitage (1), the linear model for $\dot{V}E$ for the ith subject (S_i) at the jth time (T_j) of measurement and for the kth protocol (P_k) together with interaction terms used was

$$\dot{V}E_{ijk} = \mu + S_i + T_j + P_k + (TP)_{jk} + (ST)_{ij} + (SP)_{ik} + (STP)_{ijk} + e_{ijk} \quad (1)$$

where μ is mean value and e is error.

To compare *protocol I* with the other two protocols and then *protocol P* with *protocol C*, the protocol term was split into *protocol I* vs. other $(I\text{-}PC)_k$ and *protocol P* vs. *protocol C* $(P\text{-}C)_l$. Thus, the new model used was

$$\dot{V}E_{ijkl} = \mu + S_i + T_j + (I\text{-}PC)_k + (P\text{-}C)_l + [T(I\text{-}PC)]_{jk} + [T(P\text{-}C)]_{jl} + ST_{ij} + [S(I\text{-}PC)]_{ik} + [S(P\text{-}C)]_{il} + [ST(I\text{-}PC)]_{ijk} + [ST(P\text{-}C)]_{ijl} + e_{ijkl} \quad (2)$$

The terms in this model act as individual sources of variance that contribute to the total error. Their significance as sources of variance was examined using two types of variance ratio tests. In the first test, sources of variance were removed from the error sequentially from left to right in the model and each source of variance was tested for its significance by dividing it by the remaining mean square error to give the first F ratio. In the second test, the mean square error from the source of variance being tested was divided by the mean square error from the interaction between the subject term and the source of variance to give a second F ratio. The analysis was performed with GLIM statistical software.

RESULTS

The subjects generally spent their time in the chamber reading, watching television or videos, playing computer games, or listening to the radio. Some subjects reported mild headaches and nausea during each of the three protocols but more so during the protocols involving hypoxia. One subject (*subject 947*) had to be withdrawn from the study after more severe sensations of light-headedness. Two subjects did not remain in the chamber for the full 8-h duration of every protocol because of time constraints, but none left the chamber before ≥7 h had been completed.

End-tidal gases. Figure 1 shows the end-tidal gases, averaged every 5 min, recorded in each subject while in the chamber. These plots illustrate the quality of control of both $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ [held at 56.87 ± 0.08 (SE) and 38.36 ± 0.09 Torr, respectively, throughout] during *protocol I* and of $P_{ET_{O_2}}$ (held at 57.47 ± 0.08 Torr throughout) during *protocol P*. Within the first 1 min of exposure to poikilocapnic hypoxia in *protocol P*, $P_{ET_{CO_2}}$ dropped from the control value of 38.85 ± 0.73 to 35.65 ± 0.78 Torr and, as $\dot{V}E$ tailed off over the first 20 min, $P_{ET_{CO_2}}$ rose to 36.38 ± 0.73 Torr. Over the course of the remaining exposure, $P_{ET_{CO_2}}$ dropped to 34.1 ± 0.71 Torr, dipping to 33.51 ± 0.91 Torr in the fourth hour. A reduction in $P_{ET_{CO_2}}$ from the initial control reading (38.85 ± 0.73 Torr) was also detected in *protocol C*. The lowest reading detected was 35.75 ± 0.24 Torr at 1.5 h, and at the end of 8 h $P_{ET_{CO_2}}$ was 36.01 ± 0.34 Torr. The mean value of measured $P_{ET_{O_2}}$ during *protocol C* was 110.61 ± 0.22 Torr. The average $P_{ET_{CO_2}}$ for all subjects in each protocol is shown in Fig. 2*B*.

In two subjects, we failed to get adequate signals for arterial O_2 saturation from the pulse oximeter throughout the whole 8-h period. The reasons for this are unclear. In the subjects in which satisfactory records were obtained, there were no significant changes in saturation during *protocol I* [90.79 ± 0.16 (SE) and 89.86 ± 0.20% for the 1st and 8th h, respectively; n = 8; P = NS, paired t-test], *protocol P* (90.42 ± 0.24 and 89.72 ± 0.14% for the 1st and 8th h, respectively; P = NS, paired t-test), or *protocol C* (98.50 ± 0.29%, whole experiment).

$\dot{V}E$. Figure 1 shows the ventilatory responses of each subject and the mean ventilatory response of all the subjects combined during the whole 8-h experiment. Figure 2*A* shows these mean responses superimposed on the same plot. Table 2 gives the results of ANOVA

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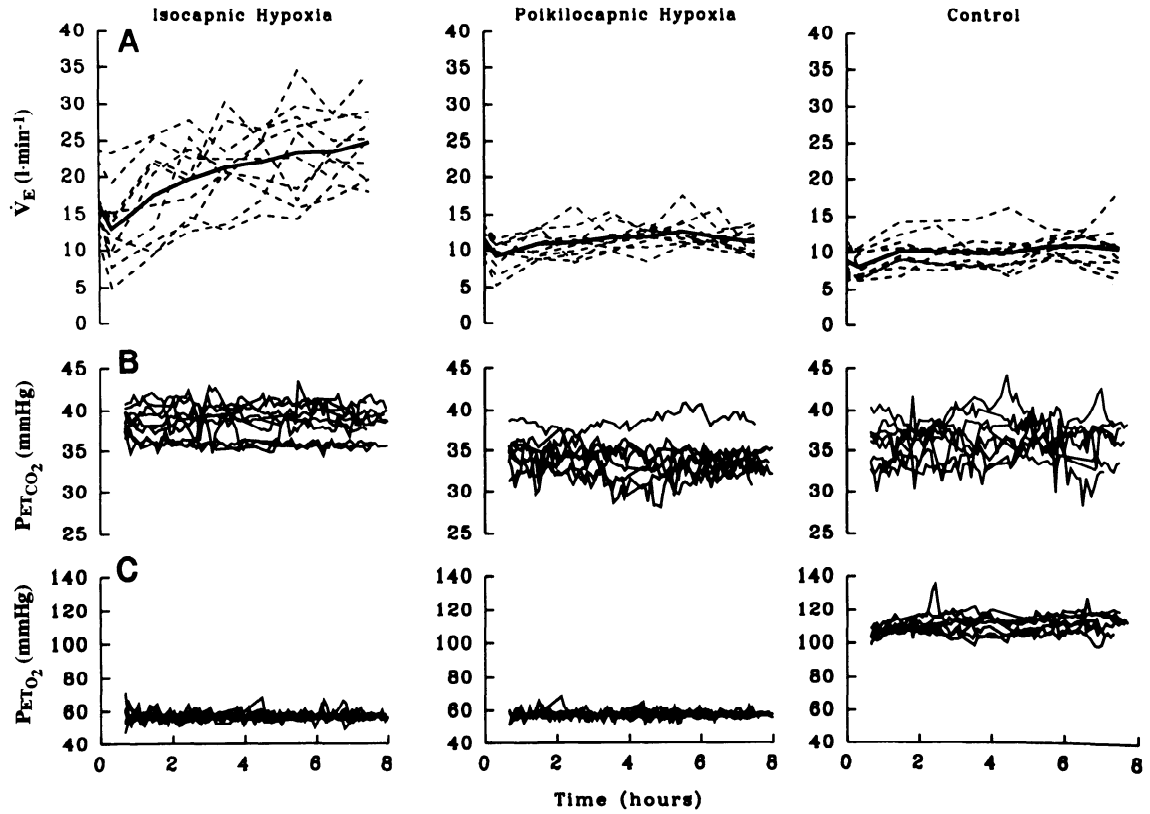

FIG. 1. *A*: individual (dashed lines) and mean (solid line) ventilatory responses ($\dot{V}E$) during each protocol. *B* and *C*: end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) and P_{O_2} ($P_{ET_{O_2}}$) averaged every 5 min for each individual while in chamber.

for $\dot{V}E$. $\dot{V}E$ fell significantly during the first 20 min in all subjects in both *protocol I* [from 16.20 ± 1.3 (SE) to 12.96 ± 1.7 l/min; $P < 0.005$, paired *t*-test] and *protocol P* (from 11.46 ± 0.7 to 9.22 ± 0.6 l/min; $P < 0.001$, paired *t*-test) but not during *protocol C*. In all subjects, $\dot{V}E$ rose steadily during *protocol I* (exposure to isocapnic hypoxia from 16.2 ± 1.3 to 24.8 ± 1.6 l/min) vs. *protocol P* and *protocol C* ($P < 0.001$, ANOVA), but *protocol P* did not elicit a progressive rise in $\dot{V}E$ compared with *protocol C*. However, in *protocol P*, $\dot{V}E$ was greater than values during *protocol C* ($P < 0.01$, ANOVA, first *F* ratio; $P < 0.025$, ANOVA, second *F* ratio), and $\dot{V}E$ during *protocol I* was also greater than values during *protocols P* and *C* ($P < 0.001$, ANOVA).

During both *protocols P* and *C*, there is a noticeable bulge in $\dot{V}E$ at 5.5 h. However, this measurement was consistently made 0.5 h after lunch when a rise in $\dot{V}E$ is expected because of an increased metabolic rate.

DISCUSSION

The major finding of this study is that $\dot{V}E$ rose steadily over 8 h of isocapnic hypoxia in *protocol I* once the phenomenon of HVD was completed. Although $P_{ET_{CO_2}}$ in the *protocol I* was 1.8 Torr higher than that actually determined over the 8-h of *protocol C*, we are satisfied that $P_{ET_{CO_2}}$ during *protocol I* was held close to the subject's natural value, as the $\dot{V}E$ and $P_{ET_{O_2}}$ data for *protocol C* suggest a mild hyperventilation. The cause of this hyperventilation is not known but may be due to the unfamiliar environment of the chamber. Even though we did not detect any significant time-dependent change in $\dot{V}E$ during *protocol P*, we observed a drop in $P_{ET_{CO_2}}$ throughout the 8-h exposure to hypoxia. If we assume no change in metabolic rate or dead space, this would suggest an increase in $\dot{V}E$ (13).

Studies of sustained isocapnic hypoxia in humans. There have been previous attempts to look at sustained isocapnic hypoxia in humans (8, 11), but the authors of these studies did not take any direct measurements of $\dot{V}E$ over the time course employed in the present study. Eger et al. (11) used a face mask and rebreathing arrangement to expose subjects to 8 h of hypoxia with and without hypocapnia. They did not report on changes in $\dot{V}E$, since in some cases a respirator was used to lower alveolar P_{CO_2}, but instead examined changes in the relationship between $\dot{V}E$ and P_{CO_2} in hyperoxia (the CO_2 response). They showed that there was an increase in the slope of the CO_2 response after exposure to isocapnic, hypercapnic, and hypocapnic hypoxia but not after euoxic exposure with any condition of alveolar P_{CO_2}. They also demonstrated that a left shift of the CO_2 response curve occurred during exposure to hypocapnic hypoxia, which was reduced, but not eliminated, when the subject was kept isocapnic during exposure to hypoxia to prevent the hypocapnic alkalosis from developing. These results seem consistent with our observation that isocapnic hypoxia causes a rise in $\dot{V}E$ over 8 h and are not inconsistent with the notion that this rise would be masked by the associated alkalosis in poikilocapnic hypoxia. However, Eger et al. did caution that the observed increase in slope of the CO_2 response in hypoxia was questionable,

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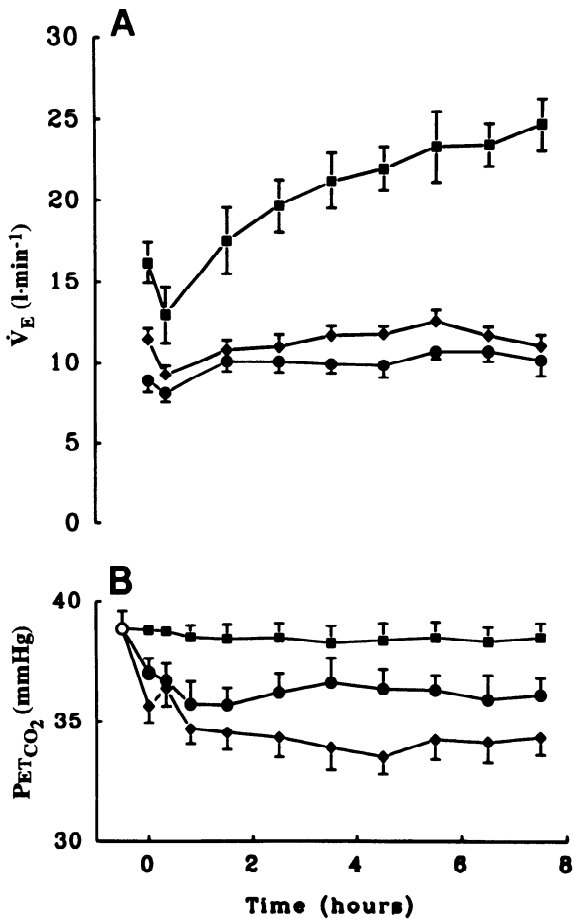

FIG. 2. Values are means ± SE. *A*: ventilatory responses of all subjects for each protocol. ■, Isocapnic hypoxia; ♦, poikilocapnic hypoxia; ●, control. *B*: $P_{ET_{CO_2}}$ of all subjects for each protocol. ○, Mean resting value of $P_{ET_{CO_2}}$.

as the slope of the CO_2 response preceding the hypoxic studies was significantly less than that preceding the euoxic studies. Furthermore, the method of controlling gas tensions suffered drawbacks; in particular, the subjects found it stressful (R. H. Kellogg, personal communication to P. A. Robbins) and had taken breaks of 10–30 min every 2 h to eat, drink, and attend to other necessities.

Cruz et al. (8) used a hypobaric chamber to study $\dot{V}_E$ over 100 h. Subjects were studied using both isocapnic and poikilocapnic protocols. To try to attain isocapnia, a fixed proportion of 3.77% CO_2 was added to the chamber inspirate, and a lower pressure was used to try to match $P_{ET_{O_2}}$ between the two hypoxic protocols. They observed a sharp rise in $\dot{V}_E$ after 3 h of exposure to isocapnic hypoxia and then a steady level of $\dot{V}_E$ over the remaining period. In subjects exposed to poikilocapnic hypoxia, they saw a gradual rise in $\dot{V}_E$ toward levels of $\dot{V}_E$ produced in the isocapnic protocol. However, during the first 24 h of exposure, they only measured $\dot{V}_E$ once at 3 h and may have missed the progressive increase in $\dot{V}_E$ occurring over 8 h of isocapnic hypoxia reported in *protocol I* of the present study. Furthermore, their control of the alveolar gases was relatively poor; after 27 h of exposure, $P_{ET_{O_2}}$ had drifted from 55 to 62 Torr and $P_{ET_{CO_2}}$ had drifted from 39 to 43 Torr.

Studies of sustained isocapnic hypoxia in animals. The ventilatory response to prolonged hypoxia has been studied in some detail using a carotid body perfusion model in awake goats, in which one of the carotid bodies is perfused separately from the systemic arterial circulation (and central nervous system) with the opposite carotid body denervated. The investigators showed that perfusion of the carotid body with isocapnic hypoxic blood with the animal breathing air produced a progressive increase in $\dot{V}_E$ (7). When the systemic circulation was maintained euoxic and eucapnic by addition of CO_2 to the inspired gas, a rise in $\dot{V}_E$ was still seen (4). It was thus concluded that neither brain hypoxia nor brain hypocapnia was required for an increase in $\dot{V}_E$ to occur. This model was used further to demonstrate that when the carotid body stimulus is changed from hypoxia to hypercapnia, there is a steady hyperventilation but no time-dependent rise as with hypoxia (3). This established carotid body hypoxia as the essential stimulus in producing this phenomenon and that the changes in $\dot{V}_E$ were not the result of central nervous system conditioning by carotid body afferent activity.

TABLE 2. *Statistical analysis of ventilatory data using analysis of variance*

Source of Variance	Degrees of Freedom	Sum of Squares, (l/min)^2	Degrees of Freedom of Error	Error, (l/min)^2	1st *F* Ratio	2nd *F* Ratio
No factor			269	9,978.7		
S_i	9	858.2	260	9,120.4		
T_j	8	793.8	252	8,326.6		
$(I\text{-}PC)_k$	1	5,547.8	251	2,778.8	501.1‡	53.7‡
$(P\text{-}C)_l$	1	89.9	250	2,688.9	8.4†	8.9*
$T_j\,(I\text{-}PC)_k$	8	555.5	242	2,133.4	7.9†	9.5‡
$T_j\,(P\text{-}C)_l$	8	16.5	234	2,116.9	0.2	0.8
$S_i\,T_j$	72	387.1	162	1,729.8		
$S_i\,(I\text{-}PC)_k$	9	929.2	153	800.7		
$S_i\,(P\text{-}C)_l$	9	90.5	144	710.2		
$S_i\,T_j\,(I\text{-}PC)_k$	72	523.9	72	186.3		
$S_i\,T_j\,(P\text{-}C)_l$	72	186.3	0	0.00		

First *F* ratio is determined from ratio of error from source of variance being considered (*column 3*) to remaining error (*column 5*). Second *F* ratio is determined from ratio of error from source of variance being considered to error from the interaction term between source of variance and subjects. S_i, ith subject; T_j, jth time; $(I\text{-}PC)_k$, isocapnic vs. other protocols; $(P\text{-}C)_l$, poikilocapnic vs. control protocol. Significantly different at: * $P < 0.025$; † $P < 0.01$; ‡ $P < 0.001$.

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A progressive rise in $\dot{V}E$ over 4 h of isocapnic hypoxia has also been demonstrated in the conscious intact goat (12, 20). In both of these studies and in the study of systemic eucapnia with carotid body hypoxia (4), $\dot{V}E$ returned to baseline on relief of hypoxia. Furthermore, with the observation that no time-dependent rise in $\dot{V}E$ was seen during carotid body hypercapnia (3), the progressive rise in $\dot{V}E$ can be attributed to a time-dependent increase in ventilatory sensitivity to hypoxia.

However, there are some substantial differences between the results from goats and those from conscious humans. There is a significant progressive fall and subsequent stabilization in $P_{ET_{CO_2}}$ in goats after 4–8 h of poikilocapnic hypoxia (6, 12, 13, 22) that is not observed in the present study. This pattern of change in $P_{ET_{CO_2}}$ is characteristic of near-complete acclimatization to high altitude in the goat (6, 12, 13, 22), and so it is reasonable to consider that the concomitant increased carotid body response to sustained hypoxia seen in the above experiments may be the primary mechanism in ventilatory acclimatization in these animals. Moreover, it is probable that acclimatization can take place in goats without any changes in pH. However, as the acclimatization process takes days to weeks in humans, the mechanisms proposed to account for acclimatization in the goat cannot simply be extended without caution.

Possible mechanisms for rise in $\dot{V}E$ during isocapnic hypoxia. Clearly, one possible mechanism for the rise in $\dot{V}E$ during isocapnic hypoxia is that it is a progressive effect of hypoxia on the carotid body, analogous to that described in the goat. If so, the failure to observe any rise in $\dot{V}E$ during *protocol P* (despite observing a progressive decline in $P_{ET_{CO_2}}$) could be attributed to the concurrent hypocapnic alkalosis masking the change in carotid body sensitivity. Alternatively, the progressive rise of $\dot{V}E$ in *protocol I* might arise from the higher initial level of $\dot{V}E$ compared with *protocol P*. For example, Smith et al. (23, 24) showed that in partially paralyzed individuals, 24 h of altered $\dot{V}E$ or ventilatory pattern imposed by a respirator persisted after removal of the respirator. They demonstrated this effect when subjects were maintained isocapnic through altered dead space. The phenomenon has been termed hyperventilation-induced hyperpnea.

Another possibility is that the phenomenon is caused by some central effect of hypoxia. It has been established that hypoxia per se causes an acidification of the ventral medullary surface above the postulated sites of the central chemoreceptors in anesthetized cats and newborn pigs (5, 9, 18, 27) and in awake goats (28). Topical application of H^+ or CO_2 at these sites elicits an increase in $\dot{V}E$ (17, 21). However, Weizhen et al. (26) demonstrated that in awake goats, isocapnic brain hypoxia with carotid body euoxia did not elicit any slow time-dependent rise in $\dot{V}E$, although it did cause a small steady elevation of $\dot{V}E$ (maximal after 30 min), which persisted for the 4-h duration of the experiment. Xu et al. (27, 28) found no hyperventilation in response to acidification of the ventral medullary surface caused directly by a 5-min period of either isocapnic or poikilocapnic hypoxia (with arterial saturation in the range of 40–90%). However, it remains just possible that in the present study, hypoxia is causing an increase in $\dot{V}E$ through lactic acidosis, which is masked during poikilocapnic hypoxia because of the associated hypocapnic alkalosis.

Conclusion. We observed a progressive time-dependent rise in $\dot{V}E$ during exposure to 8 h of isocapnic, but not poikilocapnic, hypoxia. We postulate that this phenomenon may result from a progressive effect of hypoxia per se, probably on the carotid body, but other explanations remain possible.

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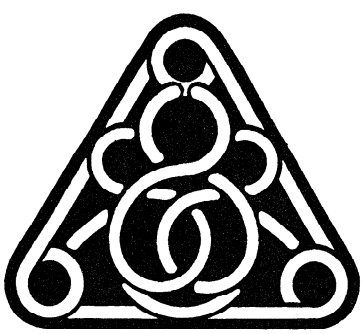

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