Respiratory effects in humans of a 5-day elevation of end-tidal P\textsubscript{CO\textsubscript{2}} by 8 Torr

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Crosby, Alexi, Nick P. Talbot, George M. Balanos, Simon Donoghue, Marzieh Fatemian, and Peter A. Robbins. Respiratory effects in humans of a 5-day elevation of end-tidal P\textsubscript{CO\textsubscript{2}} by 8 Torr. J Appl Physiol 95: 1947–1954, 2003; 10.1152/japplphysiol.00548.2003.—The aims of this study were to determine 1) whether ventilatory adaptation occurred over a 5-day exposure to a constant elevation in end-tidal P\textsubscript{CO\textsubscript{2}} and 2) whether such an exposure altered the sensitivity of the chemoreflexes to acute hypoxia and hypercapnia. Ten healthy human subjects were studied over a period of 13 days. Their ventilation, chemoreflex sensitivities, and acid-base status were measured daily before, during, and after 5 days of elevated end-tidal P\textsubscript{CO\textsubscript{2}} at 8 Torr above normal. There was no major adaptation of ventilation during the 5 days of hypercapnic exposure. There was an increase in ventilatory chemosensitivity to acute hypoxia from 1.35 ± 0.08 to 1.70 ± 0.07 l/min/%; \(P < 0.01\) but no change in ventilatory chemosensitivity to acute hypercapnia. There was a degree of compensatory metabolic alkalosis. The results do not support the hypothesis that the ventilatory adaptation to chronic hypercapnia would be much greater with constant elevation of alveolar P\textsubscript{CO\textsubscript{2}} than with constant elevation of inspired P\textsubscript{CO\textsubscript{2}}, as has been used in previous studies and in which the feedback loop between ventilation and alveolar P\textsubscript{CO\textsubscript{2}} is left intact.

MINUTE VENTILATION (V\textsubscript{E}) rises in response to increased levels of CO\textsubscript{2}. The primary mechanism through which this occurs is stimulation of the peripheral and central chemoreflexes, which have time constants in the order of ~15 and ~130 s, respectively (2, 26). In addition to these responses, there is also a slower rise in V\textsubscript{E} with a time constant of ~1 h (36). This slower response generally manifests itself as a trend toward higher V\textsubscript{E} over time in short-term experiments employing hypercapnia.

For exposures to CO\textsubscript{2} that are of longer duration, it is not clear whether V\textsubscript{E} remains constant or whether it adapts back toward a lower value. In an authoritative review of the subject, Dempsey and Forster (11) concluded that “Pulmonary and alveolar ventilation remains [above control and] at or above levels during acute CO\textsubscript{2} breathing throughout 5–42 days of breathing 1–4% CO\textsubscript{2}.” However, a number of studies have found adaptation toward lower levels of V\textsubscript{E} in subjects exposed to an increase in inspired P\textsubscript{CO\textsubscript{2}} for a period of days (9, 27, 33). One possible reason for the uncertainty is that all such studies have exposed volunteers to a fixed increase in the percentage of CO\textsubscript{2} in the inspired gas. This leaves the feedback loop between V\textsubscript{E} and alveolar (or arterial) P\textsubscript{CO\textsubscript{2}} intact. Thus, should some adaptation toward a lower V\textsubscript{E} occur, it will give rise to an increase in alveolar P\textsubscript{CO\textsubscript{2}}, which would stimulate breathing and limit the fall in V\textsubscript{E}. The first aim of this study was to determine whether there was a large reduction in V\textsubscript{E} from its initial value when alveolar, rather than inspired, P\textsubscript{CO\textsubscript{2}} was held at a constant elevated value over a 5-day period.

Stimulation of the respiratory system by sustained hypoxia results in an increased acute ventilatory sensitivity to hypoxia (17, 31) and an increased acute hypercapnic ventilatory sensitivity to hypercapnia (12, 25). It seems likely that at least part of this response is due to the specific effects of hypoxia (3, 4), but part of it may be due to a general increase in respiratory stimulation. If so, then a sustained exposure to hypercapnia should also result in increases in the acute ventilatory sensitivity to hypoxia and hypercapnia. A second aim of this study was to determine whether such an exposure had any effects on the sensitivity of the chemoreflexes to acute changes in the level of CO\textsubscript{2} and hypoxia.

METHODS

Subjects

All subjects were nonsmokers and had no history of cardiovascular or respiratory disease. The experiment was explained both verbally and in writing, but in such a way that the subjects remained naive as to the exact purposes of the experiment.

Subjects were familiarized with the equipment before undertaking the experiment. For each subject, this included spending a trial night in the laboratory, during which their end-tidal P\textsubscript{CO\textsubscript{2}} (PET\textsubscript{CO\textsubscript{2}}) was maintained at 8 Torr above their normal air-breathing value. The study had the approval of the Central Oxfordshire Research Ethics Committee.
The main experiment lasted 13 days. On the first 2 days (days –2 and –1), the subject attended the laboratory for control measurements. On the morning of the following day (day 1), a further set of control measurements was made. The subject then entered a purpose-built chamber to undertake the hypercapnic exposure. Except for brief periods, the subject remained in this chamber for 5 days and nights (days 1–5). The following morning (day 6), the subject left the chamber, and a further set of measurements was made. The subject then attended the laboratory for a further 5 days for follow-up measurements (days 7–11).

For the 2 days before chamber exposure (days –2 and –1), subjects came to the laboratory at 8:30 AM. Subjects rested quietly for 30 min, and then capsaicin cream was put on the earlobe to arterialized the capillary blood. Half an hour later, PetCO2 and end-tidal PO2 (PetO2) were measured for a period of 10 min by using a fine nasal catheter to sample the respired gases. An arterialized capillary blood sample was then taken from the earlobe. The recording of the end-tidal values continued while these samples were drawn. The blood samples were then analyzed for PCO2, PO2, pH, and HCO3– concentration ([HCO3–]). (These variables are subsequently noted with the modifier “ac” when the values have been obtained from arterialized capillary blood.) Standard bicarbonate and standard base excess were calculated (7). After this, the subjects’ air-breathing Ve arterial O2 saturation. Inspired and expired volumes, end-inspiratory and end-expiratory gas tensions, and saturation were detected in real time by a computer and logged breath by breath. A dynamic end-tidal forcing system (18, 29) was used to control the end-tidal gases in the manner required for the determination of both AHVR and AHCVR. Before the start of each experiment, a cardiopulmonary model was used to construct a forcing function that contained the breath-by-breath values for inspiratory PCO2 and PO2 predicted to produce the desired end-tidal sequences. During the experiment, a computer-controlled gas-mixing system was used to generate this sequence in a modified manner. The modifications resulted from feedback control based on the deviations of the measured values for PetCO2 and PetO2 from their desired values.

For the measurement of AHVR, PetCO2 was held constant at 8 Torr above the subject’s control air-breathing value for PetCO2 as determined at the start of the overall experiment. PetO2 was held at 100 Torr. After this, PetO2 was alternated between 100 Torr for 60 s and 50 Torr for 60 s.

For the measurement of AHCVR, a multifrequency binary sequence in PetCO2 was used. PetO2 was held at 200 Torr throughout. For the first 5 min, PetCO2 was held at 2 Torr above the subject’s air-breathing PetCO2 (as measured on that day). After this, PetCO2 followed the pattern of stimulation associated with the Van den Bos Octave (13), switching repeatedly between a low value of 2 Torr above and a high value of 10 Torr above the subject’s air-breathing PetCO2. Overall, the binary sequence lasted for a period of 1,408 s.

**Data Analysis**

**Modeling of the hypoxic and hypercapnic ventilatory responses.** To quantify the ventilatory responses to acute variations in hypoxia and hypercapnia, dynamic models relating Ve to the end-tidal gas profiles were fitted to the
data. For the measurements of AHVR, model 3 of Clement and Robbins (10) was employed. This is a single-compartment model in which parameter GpO2 reflects the ventilatory sensitivity to hypoxia and parameter Ve reflects residual V̇E in the absence of hypoxia. For the measurements of AHCVR, the model of Pedersen et al. (26) was used. This is a two-compartment model in which the individual compartments describe separate peripheral and central chemoreflex contributions to V̇E. In this model, parameter GpCO2 reflects the ventilatory sensitivity of the peripheral chemoreflex to CO2, and parameter GcCO2 reflects the sensitivity of the central chemoreflex to CO2. Parameter B is the calculated P ETCO2 for which V̇E/H11005l/min. Both models were fit in conjunction with a stochastic model based on a Kalman filter to describe the correlation that is present between successive breaths (24).

**Statistical analysis.** Repeated-measures ANOVA was used as the principal method for assessing the statistical significance of the observations made in this study. For the variables that were studied just within the chamber (e.g., V̇E in hypercapnia), values for each day were included in the ANOVA to address the question of whether their values changed over time. For other variables that were studied over the whole time course of the experiment (e.g., GpO2), the statistical question to be addressed was whether the hypercapnic exposure had any effect on their value. In these cases, measurements during the first 2 days of hypercapnic exposure and return to air were considered transitional and were not included in the analysis. This left a balanced design with 3 days of data grouped into each of these main sections, before hypercapnic exposure (days 2, 1, and 1), during hypercapnic exposure (days 4–6), and after hypercapnic exposure (days 9–11). The SPSS statistical package was used for all statistical analysis. Statistical significance was assumed at P < 0.05.

**RESULTS**

**Subjects**

The average age for the subjects was 22.3 ± 4.2 (SD) yr. Their average height was 177.9 ± 9.4 cm, and average weight was 74.5 ± 6.0 kg.

**Control of End-Tidal Gases in Chamber**

Figure 1 shows the breath-by-breath end-tidal gases averaged every 5 min for the 10 subjects during their time in the chamber. Good control over both PETCO2 and PETO2 was achieved. Also shown are the inspired P CO2 and PO2. There is a clear diurnal pattern to the data, with inspired PO2 rising and inspired P CO2 falling at night to compensate for the fall in V̇E. Standard deviations for the 5-min averages for PETCO2 and PETO2 for each subject are given in Table 1.

**Ventilation, Inspired and End-Tidal Gas Tensions and Arterialized Capillary Blood-Gas Data During the Hypercapnic Exposure**

Figure 2 illustrates the mean values for V̇E, inspired gas tensions, end-tidal gas tensions, and arterialized capillary blood-gas data measured in the chamber during the hypercapnic exposure.

On initial exposure to hypercapnia, there was a large increase in V̇E, reaching ~3.5 times air-breathing V̇E on day 1. The subsequent changes observed in V̇E throughout the hypercapnic exposure did not quite reach statistical significance (0.05 < P < 0.06). These took the form of a decline in V̇E over the first 3 days in the chamber, followed by a rise in V̇E over the final 2 days.
in the chamber. The changes in \( V \dot{E} \) were associated with nonsignificant changes in inspired \( P\text{CO}_2 \) and \( P\text{O}_2 \) (\( P \leq 0.09 \) and \( P \leq 0.08 \), respectively), which mirrored the changes in \( V \dot{E} \) during the hypercapnic exposure.

The arterialized capillary blood-gas data indicate that a metabolic alkalosis was induced in response to the sustained hypercapnic exposure. \( \text{pH}_{ac} \), \([\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]\) \(_{ac}\), standard bicarbonate, and standard base excess all changed significantly over the 5-day exposure to hypercapnia (\( P \leq 0.02 \), \( P \leq 0.001 \), \( P \leq 0.001 \), and \( P \leq 0.001 \), respectively). Inspection of Fig. 2 indicates that much of the change occurred over the first 24–48 h of exposure to hypercapnia. The pattern of induction and maintenance of the metabolic alkalosis does not provide an obvious explanation for the pattern of change observed in \( \dot{V}E \) recorded in the chamber.

### Ventilation, End-Tidal Gas Tensions, and Arterialized Capillary Blood-Gas Data While Breathing Air

Figure 3 illustrates the mean values for \( \dot{V}E \), end-tidal gas tensions, and arterialized capillary blood-gas data measured while breathing air outside the chamber before, during, and after the sustained hypercapnic exposure.

There were no obvious changes in air-breathing \( \dot{V}E \), as measured by using a mouthpiece, over the course of the study. However, values for \( \dot{P}\text{ETCO}_2 \) measured with a nasal catheter and values obtained for \( \dot{P}\text{aco}_2 \) indicated that the \( \dot{P}\text{CO}_2 \) associated with resting \( \dot{V}E \) had been reset by the hypercapnic exposure to a value that was \( \sim 2 \) Torr higher (\( P < 0.001 \) for both variables). The lower values for air-breathing \( \dot{P}\text{aco}_2 \) during the period associated with the hypercapnic exposure (\( P < 0.02 \)) were consistent with this notion, although for some reason no significant change in \( \dot{P}\text{ETO}_2 \) was observed.

The increases in \( \dot{P}\text{ETCO}_2 \) and \( \dot{P}\text{aco}_2 \) were associated with significant increases in \( \text{[HCO}_3^-]/[\text{H}_2\text{CO}_3]_{ac} \), standard bicarbonate, and standard base excess (\( P < 0.001 \) for all 3 variables). This indicates that the rise in air-breathing \( \dot{P}\text{ETCO}_2 \) and \( \dot{P}\text{aco}_2 \) was associated with the presence of a compensatory metabolic alkalosis induced by the sustained hypercapnic exposure. Any changes in \( \text{pH}_{ac} \) were not significant.

### Table 1. Standard deviations of the 5-min averages for \( \dot{P}\text{ETCO}_2 \) and \( \dot{P}\text{ETO}_2 \) for each subject during the 5-day exposure to hypercapnia

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>SD ( \dot{P}\text{ETCO}_2 ), Torr</th>
<th>SD ( \dot{P}\text{ETO}_2 ), Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,136</td>
<td>1.41</td>
<td>0.65</td>
</tr>
<tr>
<td>1,175</td>
<td>1.88</td>
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<td>1,200</td>
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<td>1,209</td>
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<tr>
<td>1,253</td>
<td>1.06</td>
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<td>1,300</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>1.33 ± 0.43</td>
<td>1.84 ± 0.51</td>
</tr>
</tbody>
</table>

SD, standard deviation; \( \dot{P}\text{ETCO}_2 \), end-tidal \( \dot{P}\text{CO}_2 \); \( \dot{P}\text{ETO}_2 \), end-tidal \( \dot{P}\text{O}_2 \).

![Fig. 2. Ventilation, inspired and end-tidal gas tensions, and arterialized capillary blood-gas data during the hypercapnic exposure. Left: ventilation (top); \( \dot{P}\text{ETCO}_2 \) (●), arterIALIZED capillary \( P\text{CO}_2 \) (\( \text{Paco}_2 \)); and \( \dot{P}\text{ETO}_2 \) (●) (middle); and \( \dot{P}\text{ETO}_2 \) (●), arterIALIZED capillary \( P\text{O}_2 \) (\( \text{Paco}_2 \)); and \( \dot{P}\text{ETO}_2 \) (●) (bottom). Right: arterialized capillary \text{pH} (\text{pH}_ac; top); arterIALIZED capillary \text{HCO}_3^- \text{concentration} ([\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]_{ac}; ●) and standard bicarbonate (SBC; ●) (middle); and standard base excess (SBE; bottom). Air-breathing data were collected on day 1 (open symbols in each panel). Values are means ± SE.](http://jap.physiology.org/ by 10.220.32.246 on October 23, 2017)
Measurement of AHVR and AHCVR

Figure 4 illustrates an example of the breath-by-breath data obtained during a measurement of AHVR and AHCVR from an individual subject on a single day of the study. During the measurement of AHVR, PETO₂ switched regularly between 100 and 50 Torr, whereas PETCO₂ was maintained at 8 Torr above the subject’s air-breathing control value. During the measurement of AHCVR, PETO₂ was held constant at 200 Torr, whereas PETCO₂ alternated between 2 and 10 Torr above the subject’s air-breathing PETCO₂ for that day, as prescribed by the particular multifrequency binary sequence employed. VE clearly responded to both the hypoxic and hypercapnic stimuli. The line through the data points for VE shows the fit of the respiratory models to the data. The line illustrates the fit in the absence of the stochastic component of the models, indicating that the deterministic component of the models describes the data well.

The mean sensitivities obtained from the measurements of AHVR and AHCVR are illustrated in Fig. 5. The standard deviations within subjects for the between-day variability (after any effects of the chamber exposure were allowed for) were 0.3 l/min/% (21.7% of mean) for GpO₂ and 4.8 l/min (13.8% of mean) for Vc. There were significant differences in the values before, during, and after the chamber exposure for both GpO₂ and Vc (P < 0.01 and P < 0.001, respectively). Values for GpO₂ were greater from the measurements made during the period associated with sustained hypercap-
The main findings of the present study were as follows. 1) There was no major adaptation of \( V_E \) back toward normal air-breathing values during 5 days of hypercapnia with \( P_{E_{\text{TCO}_2}} \) maintained constant. 2) Five days of hypercapnia resulted in a modest, but significant, increase in the ventilatory chemoreflex sensitivity to hypoxia but no change in the ventilatory chemoreflex sensitivity to hypercapnia. 3) A degree of compensatory metabolic alkalosis developed during the 5-day period. This was associated with a rise in \( P_{E_{\text{TCO}_2}} \) during air breathing, a rise in the value of parameter \( B \) associated with the measurements of ventilatory chemoreflex sensitivity to hypercapnia, and a fall in parameter \( V_c \) associated with the measurements of chemoreflex sensitivity to hypoxia.

Comparison with Other Studies of Ventilation During Sustained Hypercapnia

There have been a number of studies investigating the effects of sustained alterations of inspired \( P_{\text{CO}_2} \) on the ventilatory responses in humans (8, 9, 14, 15, 27, 32, 33). The complication with all these studies has been that any change in \( V_E \) would also have changed the alveolar/arterial \( P_{\text{CO}_2} \) and consequently the stimulus at the chemoreceptors, e.g., a fall in \( V_E \) would have produced a rise in \( P_{\text{CO}_2} \) at the chemoreceptors and vice versa. Nevertheless, the majority of studies have concluded that there is some reduction in \( V_E \) with sustained hypercapnia compared with the response to acute hypercapnia (8, 9, 14, 27). Our original concern with such studies was that the scale of the reduction in \( V_E \) may have been underestimated because, with the fall in \( V_E \), there would have been a concomitant rise in \( P_{E_{\text{TCO}_2}} \). However, the results from the present study, where \( P_{E_{\text{TCO}_2}} \) has been held constant, are not especially dissimilar from previous studies where the inspiratory value for \( P_{\text{CO}_2} \) has been held constant. Although there was a relatively small fall in \( V_E \) over the first 3 days of the hypercapnic exposure, \( V_E \) actually rose during days 4 and 5 of exposure to end at a level very similar to the acute response. This rise in \( V_E \) was not correlated with any underlying shift in acid-base status.

Within these preexisting studies of sustained hypercapnia, the degree and duration of the sustained hypercapnic stimulus has varied substantially, with inspired concentrations for \( \text{CO}_2 \) varying from 1 to 4% and durations varying from 3 to 42 days. Within these variations, most studies suggest that there is a fairly rapid component of ventilatory acclimatization to \( \text{CO}_2 \), where \( V_E \) falls (and alveolar/arterial \( P_{\text{CO}_2} \) rises) over the first 24 h (8, 9, 14). The longer term responses are less consistent, possibly because these studies, in general, have been conducted with the lower levels of inspired \( \text{CO}_2 \). On the one hand, Schaefer et al. (33) found that \( V_E \) remained consistently elevated through-
out 42 days of breathing gas containing 1.5% CO₂, and Clark et al. (9) found that most of the fall in V̇E occurred in the first 24 h of exposure to 3% CO₂ for 30 days. On the other hand, Pingree (27) found that V̇E fell to below control values throughout 42 days of breathing gas containing 1% CO₂. The data of Guillerm and Radziszewski (14) also suggest some reduction of V̇E occurring later on in an experiment exposing volunteers to 30 days of breathing 2% CO₂.

Studies on experimental animals have permitted the use of higher levels of CO₂ for extended periods. In dogs, Schwartz et al. (34) reported that, for three dogs exposed to 6 wk of 10% inspired P̄CO₂, the arterial P̄CO₂ was constant after the first 5 days. Jennings and Chen (20) and Jennings and Davidson (21) both report a triphasic ventilatory response in dogs exposed to 14 and 26 days of breathing 5% CO₂, respectively. The maximum V̇E occurred in response to acute CO₂ inhalation, the minimum V̇E occurred at either 2 days (20) or at 5–10 days (21) after the start of CO₂ inhalation, and after this there was a modest subsequent increase in V̇E. In rats exposed to 5 or 7% inspired CO₂ for up to 3 wk, Lai et al. (23) reported that V̇E was maximal on the day 1 and then slowly declined with the largest fall occurring on day 1. Nevertheless, V̇E remained substantially elevated throughout the 3-wk exposure. Kondo et al. (22) subsequently reported that V̇E remains elevated in rats in response to an 18-wk exposure to 10% inspired CO₂.

**Acid-Base Changes During Sustained Hypercapnia**

In the present study, some degree of metabolic alkalosis developed rapidly over the first 24–48 h compensating for the respiratory acidosis. There was little further change during the rest of the hypercapnic exposure. Radziszewski et al. (28) have previously reported similar findings after increases in inspired P̄CO₂. In the present study, this rapid compensation returned pHac ~25% of the way toward control air-breathing values. However, this degree of compensation would appear to be substantially less than that achieved in truly chronic respiratory acidosis such as occurs with lung disease. In such patients, the fall in arterial pH associated with a given rise in P̄CO₂ (6, 37) is about one-third of that for acute respiratory acidosis (1, 5). This suggests that there is a second, much slower phase of compensation for the respiratory acidosis.

The results from longer term exposures to hypercapnia are somewhat inconsistent in relation to the likely time course for this second, slower phase of compensation. Schaefer (33) report that the respiratory acidosis remains uncompensated for 23 days of a 42-day exposure to 1.5% inspired CO₂. Pingree (27) draws a similar conclusion that compensation occurs progressively over the second half of a 42-day exposure to 1% inspired CO₂. However, others have reported that compensation is complete at 4 days of a 30-day exposure to 3% inspired P̄CO₂ (9) and at 15 days for a 30-day exposure to 3% inspired P̄CO₂ (14).

**Ventilatory Sensitivity to CO₂**

The results of the present study suggest that the ventilatory sensitivity to CO₂ is unchanged but that the V̇E-P̄ETCO₂ response relation is shifted to the right (increase in parameter B). These results are consistent with those from previous studies. In particular, Schaefer (33) demonstrated that the acute ventilatory response to 5% CO₂ was less after acclimatization to a lower level (1.5%) of inspired CO₂ than before or after acclimatization. On its own, this observation does not distinguish between the possibilities of a decrease in slope or a rightward shift of the V̇E-P̄ETCO₂ relationship. However, Clark et al. (9) have reported a set of data in which there was no change in ventilatory sensitivity to CO₂, but a rightward shift in the response lines was present after chronic CO₂ inhalation.

The observation of an increase in air-breathing P̄ETCO₂ in the present study would seem consistent with the rightward shift of the V̇E-P̄ETCO₂ response relation. Chapin et al. (8) reported a similar increase in alveolar P̄CO₂ under conditions of acute air breathing.

**Ventilatory Sensitivity to O₂**

The standard deviation for the within-subject between-day variability in AHVR was ~22% of the mean value. This finding was consistent in magnitude with the findings of previous studies that have shown this variation to be significantly greater than the variation between successive measurements on the same day (30, 38). The origins of this variation remain obscure.

The present study found a relatively small, but significant, increase in the acute ventilatory sensitivity to hypoxia with chronic elevation of P̄ETCO₂. This occurred despite the fact that the arterial pH against which AHVR was measured would have increased because of the compensatory metabolic alkalosis that developed (AHVR was always measured at the same P̄ETCO₂).

In goats, Bisgard et al. (4) have reported that decreases in P̄O₂ confined to the carotid body will induce ventilatory acclimatization to hypoxia and, as part of this, an increase in AHVR. This has been thought to be a specific effect of hypoxia, because elevated P̄CO₂ at the carotid body did not induce ventilatory acclimatization (3). However, in these experiments with CO₂ confined to the carotid body, AHVR was never directly measured. Therefore, it remains possible that activity at the carotid body per se, rather than a specific effect of hypoxia, may underlie part of the increase in AHVR. Such a mechanism, nevertheless, would be unlikely to underlie the whole of the increase in AHVR observed with sustained hypoxia because the effects of sustained hypercapnia on AHVR are very much smaller than the effects of sustained hypoxia. In the present study of sustained hypercapnia, AHVR rose by ~25%, whereas 2 days of mild hypoxia (35) increased AHVR by ~160%.

In conclusion, the use of end-tidal forcing to hold P̄ETCO₂ constant over a 5-day period has not changed our notion of the degree of ventilatory acclimatization that occurs when CO₂ is administered over this period. Although some degree of compensatory metabolic alka-
lasis occurred, it was not nearly as complete as re-
ported for the truly chronic hypercapnia of chronic lung
disease. The question of what happens to a normal
individual who is rendered hypercapnic for a suffi-
cient period of time for full compensatory metabolic alkalosis
to occur remains unanswered. An unexpected result of
this study was the increase in ventilatory sensitivity to
hypoxia. This raises the possibility that sustained
period of time for full compensatory metabolic alkalosis
individual who is rendered hypercapnic for a suf-

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DISCLOSURES

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