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Physiological and Genomic Consequences of Intermittent Hypoxia
Selected Contribution: Chemoreflex responses to CO_2 before and after an 8-h exposure to hypoxia in humans

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Fatemian, Marzieh, and Peter A. Robbins. Selected Contribution: Chemoreflex responses to CO_2 before and after an 8-h exposure to hypoxia in humans. *J Appl Physiol* 90: 1607–1614, 2001.—The ventilatory sensitivity to CO_2, in hyperoxia, is increased after an 8-h exposure to hypoxia. The purpose of the present study was to determine whether this increase arises through an increase in peripheral or central chemosensitivity. Ten healthy volunteers each underwent 8-h exposures to *1*) isocapnic hypoxia, with end-tidal P_{O_2} ($P_{ET_{O_2}}$) = 55 Torr and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) = eucapnia; *2*) poikilocapnic hypoxia, with $P_{ET_{O_2}}$ = 55 Torr and $P_{ET_{CO_2}}$ = uncontrolled; and *3*) air-breathing control. The ventilatory response to CO_2 was measured before and after each exposure with the use of a multifrequency binary sequence with two levels of $P_{ET_{CO_2}}$: 1.5 and 10 Torr above the normal resting value. $P_{ET_{O_2}}$ was held at 250 Torr. The peripheral (Gp) and the central (Gc) sensitivities were calculated by fitting the ventilatory data to a two-compartment model. There were increases in combined Gp + Gc (26%, $P < 0.05$), Gp (33%, $P < 0.01$), and Gc (23%, P = not significant) after exposure to hypoxia. There were no significant differences between isocapnic and poikilocapnic hypoxia. We conclude that sustained hypoxia induces a significant increase in chemosensitivity to CO_2 within the peripheral chemoreflex.

peripheral chemoreflex; central chemoreflex; multifrequency binary sequence; altitude; acclimatization; ventilation

AFTER VENTILATORY ACCLIMATIZATION to hypoxia (VAH), the relationship between minute ventilation ($\dot{V}_E$) and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) is altered. There is both an increase in the slope of the $\dot{V}_E$-$P_{ET_{CO_2}}$ response and a leftward shift of the intercept of this relationship with the $P_{ET_{CO_2}}$ axis, and these features persist when the relationship is determined under conditions of acute hyperoxia (5, 12, 18, 22, 24). More recently (10), we have reported that the increase in the slope of the hyperoxic $\dot{V}_E$-$P_{ET_{CO_2}}$ relationship may be detected early in VAH (within the first 8 h of hypoxia).

When measured under conditions of hyperoxia, the slope of the $\dot{V}_E$-$P_{ET_{CO_2}}$ relationship has generally been associated with the central component of the chemoreflex response to CO_2, as hyperoxia has been assumed either markedly to attenuate or to abolish the peripheral component of this response (6, 19). More recently, however, separation of the peripheral and central components of the chemoreflex response to CO_2 in humans on the basis of the differing dynamics of the two chemoreflexes has suggested that a peripheral component of the CO_2 response may persist under conditions of hyperoxia (7, 21). Such a result is in keeping with the results of more direct experimentation in the anesthetized cat (2, 11, 16). These findings led us to question whether the increase in the hyperoxic $\dot{V}_E$-$P_{ET_{CO_2}}$ response slope following VAH has its origins in a change in sensitivity of the central chemoreflex or whether this increase in slope arises through an increase in peripheral chemoreflex sensitivity to CO_2 that persists under hyperoxic conditions. Therefore, the purpose of the present study was to examine the hyperoxic $\dot{V}_E$-$P_{ET_{CO_2}}$ response relation before and after an 8-h exposure to hypoxia using a dynamic approach to separate the peripheral (fast) and central (slow) chemoreflex contributions to the overall ventilatory sensitivity to CO_2.

METHODS

Subjects. Ten healthy volunteers (7 men and 3 women) between 18 and 52 yr old took part in the study. The experiment was fully explained verbally and in written form to all participants. Informed consent was obtained from each sub-

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ject before each experiment. The study had approval from the Central Oxford Research Ethics Committee.

Protocols. All the subjects made short visits to the laboratory before the main experiments. During these visits, they were familiarized with the apparatus and initial measurements of their $P_{ET_{CO_2}}$ were taken. The main experiments were carried out in random order on 3 separate days at least 1 wk apart. Female subjects were always studied at the same phase of their menstrual cycle.

The subjects were told to have a good night's rest before each of the three main experiments, to have a light breakfast, and to come to the laboratory at a leisurely pace. After arrival, they were rested for at least 15 min before any experimental work was started. Preexposure measurements were then made, which lasted ~40 min. After this, the subjects entered a chamber in which the gas composition could be varied. The nature of the exposure in the chamber differed on the three different experimental days. The chamber exposure lasted for 8 h. The subjects were given a light lunch at ~1:00 PM. If the subjects needed to urinate, they were free to leave the chamber briefly for that purpose. Otherwise, they remained in the chamber for the full 8 h. After the 8-h exposure, the subjects left the chamber and breathed room air for 30 min. A second 40-min measurement period then followed.

Three different 8-h exposures were employed for each subject while in the chamber: *1*) isocapnic hypoxia (IH), *2*) poikilocapnic hypoxia (PH), and *3*) control (C). During the exposure associated with protocol IH, end-tidal P_{O_2} ($P_{ET_{O_2}}$) was held at 55 Torr and $P_{ET_{CO_2}}$ was held at the subject's normal (prehypoxic) value. During the exposure associated with protocol PH, $P_{ET_{O_2}}$ was held at 55 Torr and $P_{ET_{CO_2}}$ was not controlled. During the exposure associated with protocol C, the subject was exposed to air while in the chamber.

Air-breathing $P_{ET_{CO_2}}$ was determined in the measurement periods before and 30 min after each 8-h exposure. These measurements were taken using a nasal catheter connected to a mass spectrometer while the subject was sitting upright and breathing normally. To obtain good control values for normal $P_{ET_{CO_2}}$, subjects were encouraged to watch television or read during these measurements. The first measurement of $P_{ET_{CO_2}}$ was used as the control value for the subsequent tests undertaken on that day.

After the measurements of air-breathing $P_{ET_{CO_2}}$ had been made, the ventilatory response to a dynamic variation in $P_{ET_{CO_2}}$ was determined in a protocol lasting ~29 min. In this protocol, $P_{ET_{O_2}}$ was held at 250 Torr throughout. $P_{ET_{CO_2}}$ was held constant at 1.5–2.0 Torr above its normal value for the first 5 min to ensure that ventilation reached an approximate steady state. Next, $P_{ET_{CO_2}}$ was varied according to a multifrequency binary sequence (MFBS), which lasted 1,408 s (23 min and 28 s). During this sequence, $P_{ET_{CO_2}}$ was switched between 1.5 and 10 Torr above the subject's normal value. The particular MFBS used was the Van den Bos octave (see Ref. 13) with a pulse duration of 11 s. The choice of MFBS together with the pulse duration was based on an optimization process for maximum separation between the fast (peripheral) and slow (central) components of the ventilatory response to CO_2 (21).

Technique. A purpose-built chamber was used during the 8-h exposures. The chamber had ample room, both for the subject to sit in and to move around comfortably. The composition of gas inside the chamber could be altered, which obviated the need for the subject to breathe via a face mask or mouthpiece. Fine nasal catheters were held at the opening of each of the subject's nostrils by a nasal oxygen-therapy mask. The respired gas was sampled (80 ml/min) via these catheters and analyzed for P_{O_2} and P_{CO_2} by a mass spectrometer. The subject also wore a pulse oximeter on a finger to monitor arterial O_2 saturation. The values for P_{O_2}, P_{CO_2}, and saturation were sampled by a computer every 20 ms. The computer program identified the ends of inspiration and expiration from the P_{CO_2} profile and recorded the inspired and end-tidal values for P_{O_2} and P_{CO_2} together with saturation at the end of each breath. Before the subject entered the chamber, the composition of the inspired gas necessary to produce the desired end-tidal partial pressures was estimated and set manually. During the exposure, the composition of the inspired gas was altered by a computer every 5 min to maintain the end-tidal partial pressures at the desired level. Manual alteration at other intervals was also possible. This system has been described in greater detail elsewhere (14).

During the measurement periods before and 30 min after the chamber exposures, the ventilatory response to the MFBS in $P_{ET_{CO_2}}$ was determined with the subject seated in an upright position and breathing through a mouthpiece, with his or her nose occluded by a clip. A turbine volume-measuring device fixed in series with the mouthpiece measured the respiratory volumes; a pneumotachograph was used to record flows and timing information. The total dead space associated with the apparatus was 100 ml. Gas was sampled (20 ml/min) from this dead space, close to the mouth, and analyzed by mass spectrometry for P_{O_2} and P_{CO_2}. A pulse oximeter was attached to the forefinger to monitor the O_2 saturation of the blood. All the data were sampled by a data-acquisition computer every 20 ms, and $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, and inspiratory and expiratory volumes and durations for each breath were recorded.

An end-tidal forcing system was used to generate the MFBS in $P_{ET_{CO_2}}$ and concurrently control the $P_{ET_{O_2}}$. Before the experiment, a "forcing function" containing the predicted inspired gas values required to achieve the desired $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ was entered into a second (controlling) computer. During the experiment, actual values of $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ were passed, breath-by-breath, to the controlling computer from the data-acquisition computer. The actual end-tidal values were compared with the desired values, and a new inspired gas mixture was calculated, by a computer program, using an integral-proportional feedback scheme. The controlling computer generated the new inspired gas mixture using a fast gas-mixing system, which was controlled from the program. This system has been described in more detail elsewhere (15, 23).

Data analysis. The fast (peripheral) and the slow (central) components of the ventilatory response to CO_2 were identified by fitting a two-compartment model (25) to the ventilatory data

$$\dot{V}_E = \dot{V}c + \dot{V}p + Ct$$

$$\tau c \frac{d\dot{V}c}{dt} + \dot{V}c = Gc[P_{ET_{CO_2}}(t - dc) - B]$$

$$\tau p \frac{d\dot{V}p}{dt} + \dot{V}p = Gp[P_{ET_{CO_2}}(t - dp) - B]$$

where $\dot{V}_E$ is the continuous output describing the breath-to-breath ventilation response, $\dot{V}c$ and $\dot{V}p$ are the slow (central) and fast (peripheral) components of this response, respectively, and C is a trend term. G represents the sensitivity for the chemoreflex loops, $P_{ET_{CO_2}}(t - d)$ is the stimulus to the chemoreflex loops at time (t) delayed by d, and τ represents the time constant. The indexes c and p denote the parameters associated with the slow (central) and fast (peripheral) che-

Table 1. *Air-breathing $P_{ET_{CO_2}}$ before and after chamber exposure and $P_{ET_{CO_2}}$ in chamber at beginning and end of exposure*

Subject No.	Isocapnic Hypoxia AM	Isocapnic Hypoxia PM	Poikilocapnic Hypoxia AM	Poikilocapnic Hypoxia PM	Control AM	Control PM
			Air-breathing $P_{ET_{CO_2}}$, Torr			
951	40.4	36.6	41.4	38.6	39.7	39.6
971	36.8	35.3	37.3	35.6	37.1	37.6
974	32.9	29.2	32.1	27.5	32.3	31.6
1,008	34.7	32.3	34.3	30.0	34.5	34.7
1,064	40.4	38.5	40.8	38.8	39.9	42.5
1,091	40.6	35.8	40.5	35.7	40.9	41.3
1,096	40.9	37.1	42.5	37.8	41.6	41.6
1,097	41.0	37.0	40.0	37.4	40.9	40.6
1,100	40.8	38.4	41.6	37.6	42.4	40.7
1,101	41.7	36.9	41.9	36.8	41.8	41.4
Means ± SD	39.0 ± 3.08	35.8 ± 2.93	39.2 ± 3.52	35.6 ± 3.79	39.1 ± 3.39	39.2 ± 3.51
			Chamber $P_{ET_{CO_2}}$, Torr			
951	39.8	39.7	41.1	38.7	38.9	39.2
971	37.1	37.1	37.7	32.3	36.9	37.4
974	32.7	32.9	31.6	28.1	30.3	30.7
1,008	34.7	34.9	33.1	31.2	35.5	34.7
1,064	40.8	40.8	40.3	36.7	41.4	42.0
1,091	40.6	40.4	38.1	32.5	40.6	41.2
1,096	41.1	40.6	41.3	34.3	42.6	41.2
1,097	40.4	40.9	36.1	33.7	40.7	37.6
1,100	40.7	40.8	43.3	42.0	39.3	40.1
1,101	42.0	41.7	40.3	36.2	41.9	40.7
Means ± SD	39.0 ± 3.10	39.0 ± 3.00	38.3 ± 3.76	34.6 ± 3.96	38.8 ± 3.72	38.5 ± 3.54

Air-breathing end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) refers to the average values obtained before the hypercapnic sensitivity test. Chamber $P_{ET_{CO_2}}$ refers to the average value for the second 5 min (AM) and the last 5 min (PM) in the chamber.

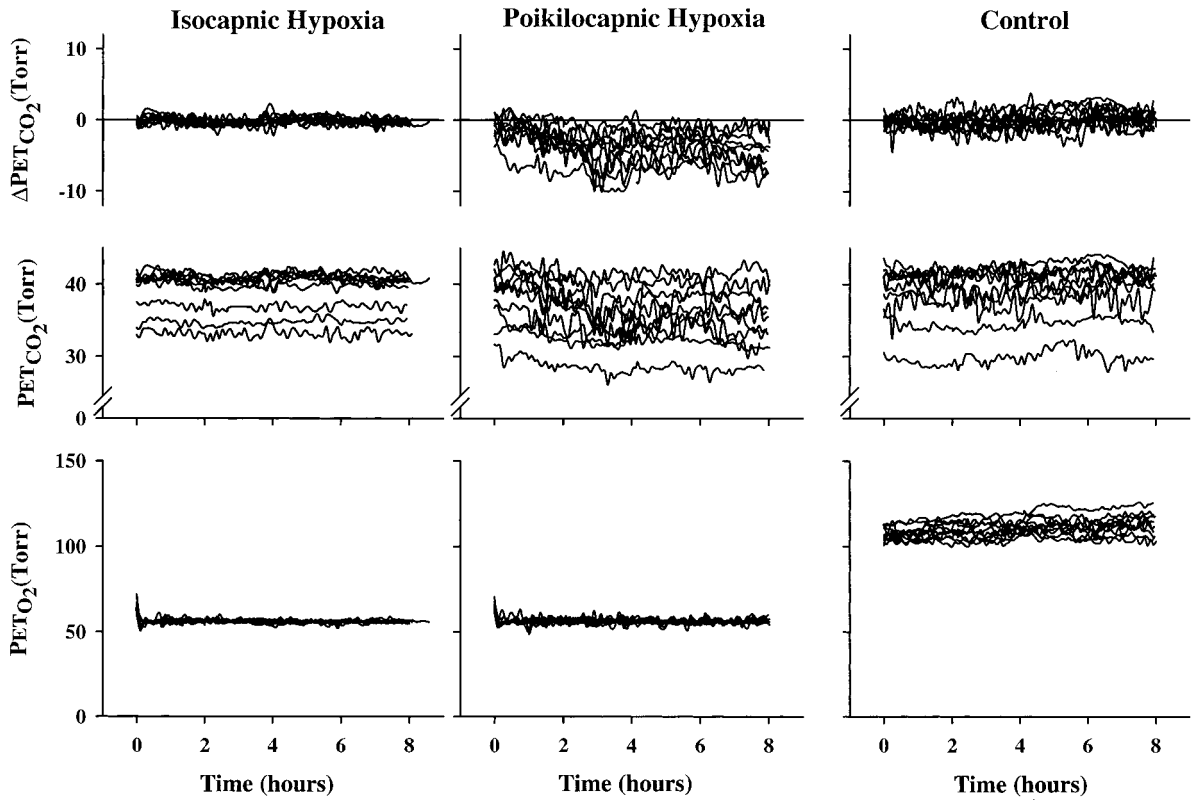

Fig. 1. Control of end-tidal gases in chamber. Deviation of end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) from the prechamber control value ($\Delta P_{ET_{CO_2}}$; *top*) and $P_{ET_{CO_2}}$ (*middle*) and end-tidal P_{O_2} ($P_{ET_{O_2}}$; *bottom*) values averaged every 5 min from data collected breath-by-breath over 8 h for all 10 subjects during isocapnic hypoxia (IH; *left*), poikilocapnic hypoxia (PH; *middle*), and control (C; *right*) protocols.

moreflex loops, respectively. B is the value for $P_{ET_{CO_2}}$ at $\dot{V}_E$ = 0, extrapolated from the steady-state relationship between $\dot{V}_E$ and $P_{ET_{CO_2}}$.

If $P_{ET_{CO_2}}$ is assumed to remain constant over a single breath, a solution to these differential equations can be obtained as a set of difference equations. These relate the peripheral and central chemoreflex outputs for the current breath to the $P_{ET_{CO_2}}$, the breath duration, and the peripheral and central chemoreflex outputs for the previous breath.

To model the stochastic component of the data, a state-space model was used that has previously been shown to describe the correlation that exists between successive breaths (17)

$$x(n + 1) = fx(n) + v(n)$$

$$y(n) = x(n) + w(n)$$

where $x(n)$ is the system state for breath n, $y(n)$ is the observation at breath n, and f is the system gain; $v(n)$ and $w(n)$ are mutually independent, white noise sequences, representing the process and the measurement noise, respectively, with means of zero and a constant variance ratio of Rv/Rw. If f, Rv, and Rw are known, the system state (and variance) for breath $n + 1$ can be predicted from the measurement $y(n)$ through a Kalman filter (1) and updated once $y(n + 1)$ becomes known. The Kalman filter equations for the particular model that was employed are given by Liang et al. (17).

The parameters of the model were obtained by using a standard subroutine to minimize the sum of squares of the residuals (subroutine E04FDF, Numerical Algorithms Group, Oxford, UK). To detect any statistically significant changes after the 8-h exposures, the estimated values of all the parameters of the model were compared using ANOVA. Fixed factors in the analysis were protocol and time (i.e., before vs. after the exposure), and subjects were treated as a random factor. Because the variations in the dynamic parameters (τc, dc, τp, and dp) and Kalman filter parameters (f and Rv/Rw) were negligible between the different fixed factors in the ANOVA, the model was refit to the data with a constraint that there should be a common estimate for these parameters for each pair of data sets that were obtained before and after

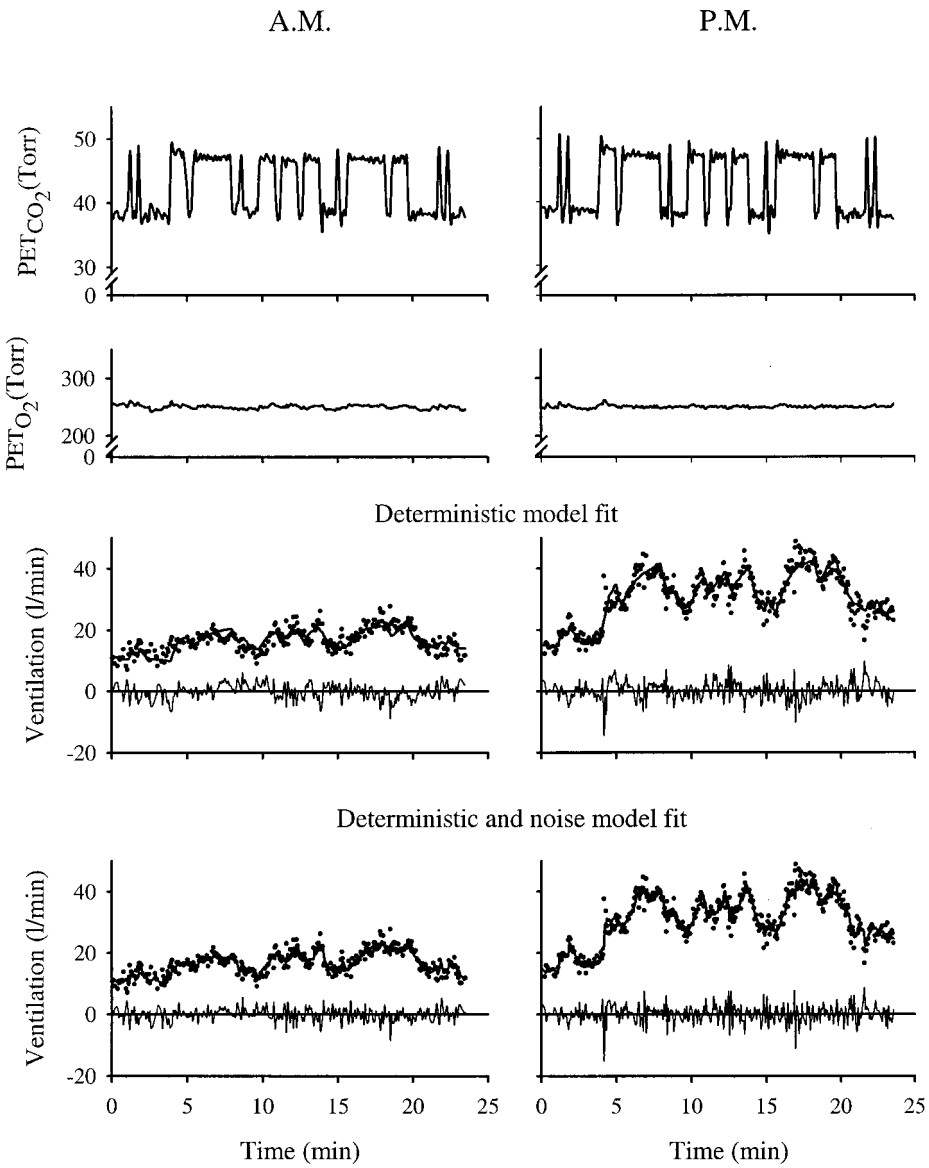

Fig. 2. Example of data and model fit before (AM, *left*) and after (PM, *right*) an 8-h exposure for 1 subject. From *top* to *bottom*: multifrequency binary sequence (MFBS) in $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, model fit without noise model, and model fit with noise model. In the *bottom* 2 panels, dots represent ventilation data, and lines represent the model output; residuals are shown below each fit.

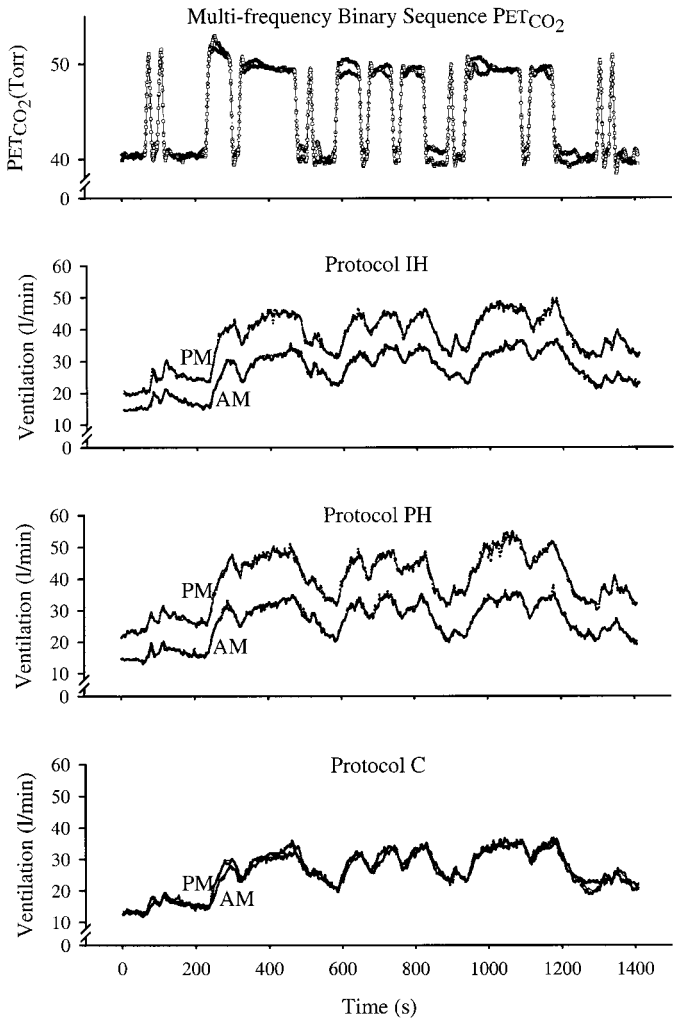

Fig. 3. Average data and model fits for all 10 subjects. *Top*: MFBS in $P_{ET}CO_2$ before (◇) and after (□) the 8-h exposure. The other 3 panels show ventilation data and model fits for protocol IH (2nd panel), protocol PH (3rd panel), and protocol C (*bottom*) before (AM) and after (PM) the 8-h exposure. Dots represent the ventilation data, and lines represent the model output.

the 8-h exposure. This method of fitting the model to the data reduced the variances associated with the remaining parameters. ANOVA was then performed on Gc, Gp, B, and C. The statistical package SPSS was used for these analyses.

RESULTS

Subjects. All subjects completed the series of experiments and provided data that were suitable for analysis. During the 8-h exposures, subjects were generally comfortable and spent their time reading, watching television, or playing computer games. Some subjects reported mild headaches toward the end of some of the exposures, and one subject had a more severe headache for all exposures. Control values for $P_{ET}CO_2$ for each subject for each protocol are given in Table 1.

Chamber control. Figure 1 shows the end-tidal gases recorded while the subjects were in the chamber, averaged every 5 min, for all three protocols for all 10 subjects. Initial and final values of $P_{ET}CO_2$ in the chamber are given in Table 1. Generally, the control over the end-tidal gases was good. $P_{ET}O_2$ for protocols IH and PH and $P_{ET}CO_2$ for protocol IH were maintained at the desired levels throughout the 8-h exposure. In protocol PH, in which $P_{ET}CO_2$ was unregulated, there was a progressive fall in $P_{ET}CO_2$ over the 8-h period of hypoxia ($P < 0001$, paired t-test). Average values for saturation obtained from the pulse oximeter at the beginning and end of the chamber exposure were 90.5 ± 3.0% (mean ± SD) and 89.8 ± 1.0% for protocol IH, 89.2 ± 1.6% and 89.2 ± 1.4% for protocol PH, and 97.6 ± 1.1% and 97.8 ± 0.6% for protocol C, respectively.

Air-breathing $P_{ET}CO_2$. Values for air-breathing $P_{ET}CO_2$ 30 min after the end of the chamber exposures are given along with the control values in Table 1. $P_{ET}CO_2$ fell after the completion of protocol IH by 3.3 Torr, fell after protocol PH by 3.6 Torr, but was unaltered after protocol C (rise of 0.1 Torr). ANOVA revealed that the fall in $P_{ET}CO_2$ associated with the hypoxic protocols was significantly different from protocol C ($P < 0.001$) but that any difference between protocol IH and protocol PH was not significant.

Table 2. *Model parameters for isocapnic hypoxia protocol*

Subject No.	Gc, l·min^{-1}·Torr^{-1}		Gp, l·min^{-1}·Torr^{-1}						B, Torr		C, l·min^{-1}·min^{-1}			Rv/Rw
	AM	PM	AM	PM	τc, s	τp, s	dc, s	dp, s	AM	PM	AM	PM	f	
951	2.19	4.08	0.49	0.23	172.4	26.8	8.8	16.6	34.6	36.9	0.384	0.504	0.86	0.55
971	1.61	1.58	0.80	0.98	246.0	29.2	19.4	4.4	33.7	30.1	0.198	0.000	0.69	0.67
974	1.36	1.64	0.69	0.76	48.1	3.4	13.9	7.1	28.6	24.0	0.444	0.306	0.78	0.44
1,008	1.59	1.45	0.11	0.45	28.6	3.1	5.8	3.5	30.4	27.4	0.462	0.384	0.96	0.07
1,064	1.89	1.89	0.78	0.92	67.9	7.6	11.1	3.4	38.0	33.7	0.246	0.180	0.93	0.25
1,091	2.18	2.21	1.51	1.50	298.0	15.3	15.8	5.7	37.5	34.4	0.084	0.006	0.76	0.73
1,096	1.09	1.25	0.41	0.46	78.8	7.0	13.7	2.8	31.5	29.1	0.186	0.474	0.87	0.10
1,097	1.23	1.38	0.05	0.13	71.3	0.2	14.2	7.8	29.3	33.2	0.336	0.282	0.92	0.30
1,100	0.95	0.91	0.10	0.15	81.1	0.9	11.2	9.1	30.6	34.5	0.204	0.486	0.83	1.06
1,101	1.04	1.32	2.32	3.05	104.1	17.7	19.6	4.9	37.5	34.0	0.000	0.732	0.92	0.51
Average	1.51	1.77	0.73	0.86	119.6	11.1	13.4	6.5	33.2	31.7	0.254	0.335	0.85	0.47
±SD	±0.46	±0.89	±0.71	±0.88	±89.7	±10.6	±4.3	±4.1	±3.6	±4.0	±0.152	±0.231	±0.09	±0.31

Gc, central chemoreflex sensitivity; Gp, peripheral chemoreflex sensitivity; τc, central chemoreflex time constant; τp, peripheral chemoreflex time constant; dc, central chemoreflex delay; dp, peripheral chemoreflex delay; B extrapolated value for $P_{ET}CO_2$ at which minute ventilation = 0; C, trend term; f, system gain for noise component; Rv/Rw, variance ratio for process and measurement noise.

Table 3. *Model parameters for poikilocapnic hypoxia protocol*

Subject No.	Gc, l·min^{-1}·Torr^{-1}		Gp, l·min^{-1}·Torr^{-1}						B, Torr		C, l·min^{-1}·min^{-1}			Rv/Rw
	AM	PM	AM	PM	τc, s	τp, s	dc, s	dp, s	AM	PM	AM	PM	f	
951	1.02	2.66	0.68	0.46	108.6	29.0	6.5	14.1	33.5	35.4	0.270	0.414	0.90	0.94
971	0.83	2.93	0.74	1.23	257.8	26.0	14.2	2.6	32.8	35.3	0.090	0.0018	0.72	0.63
974	1.92	2.45	0.26	0.82	33.8	5.0	10.5	5.8	23.3	24.1	0.096	0.408	0.89	0.60
1,008	1.47	0.81	0.62	1.68	59.7	8.1	14.5	4.4	31.4	25.9	0.402	0.372	0.82	0.20
1,064	1.94	2.12	0.66	0.76	50.3	4.7	8.9	3.7	36.8	36.4	0.090	0.540	0.84	1.71
1,091	2.05	1.97	1.09	1.50	297.1	13.1	15.1	4.9	35.5	32.2	0.012	0.192	0.56	1.97
1,096	1.20	1.32	0.49	0.59	58.2	4.1	17.3	7.1	35.3	31.6	0.240	0.348	0.79	0.28
1,097	0.82	1.26	0.20	0.20	70.6	29.0	7.0	19.9	31.5	29.3	0.510	0.294	0.98	0.26
1,100	1.07	1.18	0.18	0.46	182.7	7.0	17.6	11.2	37.9	42.2	0.132	0.396	0.76	0.83
1,101	3.96	4.32	0.97	1.31	79.7	3.5	3.9	6.7	39.3	35.6	0.138	0.000	0.85	0.90
Average	1.63	2.10	0.59	0.90	119.9	13.0	11.6	8.0	33.7	32.8	0.198	0.298	0.81	0.83
±SD	±0.94	±1.05	±0.31	±0.50	±93.2	±10.8	±4.8	±5.4	±4.5	±5.4	±0.157	±0.176	±0.12	±0.60

Ventilatory response to MFBS in $P_{ET}CO_2$. An example of the MFBS in $P_{ET}CO_2$ is shown in Fig. 2, *top*. In general, the sequence was produced well by dynamic end-tidal forcing. Average sequences for all 10 subjects for one protocol (both before and after the chamber exposure) are shown in Fig. 3, *top*. Only slight differences between the sequences before and after the chamber exposure were observed. $P_{ET}O_2$ was well controlled at 250 Torr (Fig. 2).

An example of the ventilatory response to the MFBS in $P_{ET}CO_2$ together with an example of the fit of the model to the data is shown in Fig. 2. The fit of the model to data is illustrated both including and excluding the stochastic component of the model that was obtained as part of the overall fitting process. Residuals calculated using just the deterministic component of the model were clearly nonwhite, but they appeared to become white when the stochastic component of the model was included. Ensemble averages, obtained by first interpolating data and model output every second, are shown in Fig. 3. During the MFBS, $\dot{V}E$ was higher for the data obtained following the hypoxic exposures than for those obtained before the hypoxic exposures; furthermore, this difference in $\dot{V}E$ appeared greater in those sections of the MFBS that were associated with higher levels of ventilation. This suggests that the change was not just an upward displacement of $\dot{V}E$ but that the sensitivity of $\dot{V}E$ to CO_2 had also increased. No differences in the response to the MFBS were apparent in the data obtained before and after exposure in the control protocol.

Individual and mean parameter values for the model fits are given in Tables 2–4 for the three protocols. There was a significant increase (ANOVA, $P < 0.01$) in the total ventilatory sensitivity to CO_2 (Gp + Gc) following the hypoxic exposures (protocol IH, from 2.24 to 2.63 l·min^{-1}·Torr^{-1}; protocol PH, from 2.22 to 3.00 l·min^{-1}·Torr^{-1}) compared with the control exposure (protocol C, from 2.59 to 2.46 l·min^{-1}·Torr^{-1}). The chemoreflex sensitivity of the slow (central) component of the ventilatory response to CO_2, Gc, increased by ~17% after protocol IH (from 1.51 to 1.77 l·min^{-1}·Torr^{-1}) and by ~29% after protocol PH (from 1.63 to 2.10 l·min^{-1}·Torr^{-1}) but was hardly changed (0.5% increase) after protocol C (from 1.57 to 1.65 l·min^{-1}·Torr^{-1}). However, this increase in Gc following the two types of hypoxic exposure did not reach statistical significance. The chemoreflex sensitivity of the fast (peripheral) component of the ventilatory response to CO_2, Gp, increased by ~18% after protocol IH (from 0.73 to 0.86 l·min^{-1}·Torr^{-1}) and by ~52% after protocol PH (from 0.59 to 0.90 l·min^{-1}·Torr^{-1}) but decreased by ~20% after protocol C (from 1.02 to 0.81 l·min^{-1}·Torr^{-1}). This difference between the hypoxic protocols and control was significant (ANOVA, $P < 0.005$). No statistically significant effects were detected for parameters B or C of the model.

Table 4. *Model parameters for control protocol*

Subject No.	Gc, l·min^{-1}·Torr^{-1}		Gp, l·min^{-1}·Torr^{-1}						B, Torr		C, l·min^{-1}·min^{-1}			Rv/Rw
	AM	PM	AM	PM	τc, s	τp, s	dc, s	dp, s	AM	PM	AM	PM	f	
951	1.87	2.87	1.02	0.56	254.6	21.6	19.6	12.5	34.0	35.5	0.072	0.012	0.95	0.15
971	1.30	0.99	0.49	0.26	71.4	16.6	15.5	1.4	33.6	26.9	0.198	0.288	0.57	1.27
974	3.03	2.22	1.11	1.05	158.3	12.8	13.5	6.7	28.8	27.5	0.000	0.024	0.87	0.73
1,008	1.49	1.90	1.02	0.82	194.9	16.7	18.0	4.5	32.2	31.5	0.030	0.000	0.67	0.63
1,064	1.14	1.53	1.05	0.85	68.2	11.4	14.2	4.0	37.1	39.1	0.192	0.438	0.87	0.37
1,091	1.07	1.42	1.28	1.51	289.7	27.0	10.8	5.8	36.7	35.2	0.432	0.126	0.90	0.13
1,096	1.25	0.55	1.11	0.80	191.2	24.4	3.4	3.9	37.0	35.3	0.012	0.336	0.81	0.23
1,097	2.11	0.80	0.28	0.30	152.1	28.8	16.0	6.5	37.4	35.0	0.000	0.336	0.95	0.37
1,100	0.36	0.70	0.21	0.46	59.4	4.2	19.9	10.8	30.9	38.9	0.324	0.336	0.72	0.41
1,101	2.07	3.54	2.62	1.48	179.3	18.6	16.2	3.5	39.0	41.3	0.222	0.522	0.81	0.71
Average	1.57	1.65	1.02	0.81	161.9	18.2	14.7	6.0	34.7	34.6	0.148	0.242	0.81	0.50
±SD	±0.73	±0.99	±0.68	±0.44	±78.0	±7.6	±4.8	±3.4	±3.3	±4.8	±0.150	±0.188	±0.12	±0.35

DISCUSSION

General findings. The results from this study confirm those of our previous report (10) that there is a significant rise in ventilatory sensitivity to CO_2, in hyperoxia, following an 8-h exposure to hypoxia. The results suggest that there may have been a rise in both slow (central) and fast (peripheral) chemoreflex sensitivity. However, in this study, only the results for the fast component (Gp) reached significance. The statistically insignificant change in B suggests that the intercept of the $\dot{V}E$-$P_{ET_{CO_2}}$ relationship is not affected early in the acclimatization process, a result that is in keeping with our previous report.

Relationship between fast and slow components of CO_2 response and peripheral and central chemoreflex sensitivities. A fundamental assumption of this study is that the fast component of the CO_2 response reflects that part of the chemoreflex response arising from the peripheral chemoreceptors and that the slow component of the CO_2 response reflects that part of the response arising from the central chemoreceptors. This issue has been discussed in detail elsewhere (21). In brief, in experimental animals, the fast and slow components of the CO_2 response have been shown to correlate well with sensitivities obtained subsequently with an artificial brain stem perfusion technique (8). Step changes in the arterial P_{CO_2} of blood perfusing just the brain stem produce a single, slow component within the ventilatory response (4). In humans who have undergone bilateral carotid body resection, the fast component of the ventilatory response to CO_2 is very small (3).

Comparison with previous studies. The total combined ventilatory sensitivity to CO_2 in this study was 2.35 $l \cdot min^{-1} \cdot Torr^{-1}$ (combined preexposure values from all three protocols). This is similar to values obtained from previous studies under hyperoxic conditions from our laboratory of 2.75 (21) and 2.35 $l \cdot min^{-1} \cdot Torr^{-1}$ (10) (combined preexposure values). In the present study, the fast component of the CO_2 response accounted for 33% of the total CO_2 response (combined preexposure values from all three protocols). This is broadly similar to the 27% determined in a previous study using MFBS (21) but substantially greater than the 13% that was obtained with $P_{ET_{O_2}}$ >500 Torr (7).

The increment in total CO_2 sensitivity after the 8-h exposure to hypoxia in the present study was 0.59 $l \cdot min^{-1} \cdot Torr^{-1}$ or 26% of total CO_2 sensitivity (combined data from protocols IH and PH). This compares with an increment of 1.0 $l \cdot min^{-1} \cdot Torr^{-1}$ or 43% of total CO_2 sensitivity in a previous study of the effects of 8 h of hypoxia (10) and an increment of ~44% of total CO_2 sensitivity in a previous study of the effects of 48 h of hypoxia (26). Longer studies involving acclimatization to the hypoxia of altitude have recorded increments of ~47% (4 days at 3,100 m; Ref. 12), ~128% (6 days at 3,810 m; Ref. 24), and ~115% (45 days at 3,100 m; Ref. 12).

Mechanisms underlying the changes in the acute ventilatory sensitivity to CO_2. The finding of a significant rise in the peripheral chemoreflex sensitivity to CO_2 following sustained hypoxia does not on its own help to localize the effect of hypoxia, as this may be anywhere in the peripheral chemoreflex loop. However, in experimental studies conducted on goats, it was possible to localize the site of action of hypoxia to the carotid bodies. Dwinell et al. (9) found that sustained exposure of a single carotid body to hypoxia altered the $\dot{V}E$-$P_{ET_{CO_2}}$ relationship. In contrast, Weizhen et al. (27), who rendered the central nervous system hypoxic while maintaining a normal P_{O_2} at the peripheral chemoreceptors, found that hypoxia had no effect on the $\dot{V}E$-$P_{ET_{CO_2}}$ relationship.

The absence of a significant effect of sustained hypoxia on central chemoreflex sensitivity in the present study should be treated with some caution because the absolute magnitude of the increase in Gc (0.37 $l \cdot min^{-1} \cdot Torr^{-1}$, protocols IH and PH combined) was greater than for Gp (0.22 $l \cdot min^{-1} \cdot Torr^{-1}$, protocols IH and PH combined). This raises the possibility that a type II statistical error has occurred. In general, the increase in overall ventilatory sensitivity to CO_2 was not as great as that observed in other studies (see above), and it may be that a repeat of this study on more completely acclimatized individuals would clarify this point. If there is an increase in central chemoreflex sensitivity, then an interesting question that arises is whether this is due to central nervous system hypoxia or whether it is due to increased peripheral stimulation slowly increasing central chemoreflex sensitivity. In relation to the latter, it is noteworthy that Pan et al. (20) have reported that removal of peripheral chemoreceptor input has a slow effect in reducing the sensitivity of the central chemoreflex response to CO_2.

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