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Ventilatory acclimatization in response to very small changes in P_{O_2} in humans

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Donoghue, Simon, Marzieh Fatemian, George M. Balanos, Alexi Crosby, Chun Liu, David O'Connor, Nick P. Talbot, and Peter A. Robbins. Ventilatory acclimatization in response to very small changes in P_{O_2} in humans. *J Appl Physiol* 98: 1587–1591, 2005. First published December 10, 2004; doi:10.1152/japplphysiol.01019.2004.—Ventilatory acclimatization to hypoxia (VAH) consists of a progressive increase in ventilation and decrease in end-tidal P_{CO_2} ($P_{ET_{CO_2}}$). Underlying VAH, there are also increases in the acute ventilatory sensitivities to hypoxia and hypercapnia. To investigate whether these changes could be induced with very mild alterations in end-tidal P_{O_2} ($P_{ET_{O_2}}$), two 5-day exposures were compared: *1*) mild hypoxia, with $P_{ET_{O_2}}$ held at 10 Torr below the subject's normal value; and *2*) mild hyperoxia, with $P_{ET_{O_2}}$ held at 10 Torr above the subject's normal value. During both exposures, $P_{ET_{CO_2}}$ was uncontrolled. For each exposure, the entire protocol required measurements on 13 consecutive mornings: 3 mornings before the hypoxic or hyperoxic exposure, 5 mornings during the exposure, and 5 mornings postexposure. After the subjects breathed room air for at least 30 min, measurements were made of $P_{ET_{CO_2}}$, $P_{ET_{O_2}}$, and the acute ventilatory sensitivities to hypoxia and hypercapnia. Ten subjects completed both protocols. There was a significant increase in the acute ventilatory sensitivity to hypoxia (Gp) after exposure to mild hypoxia, and a significant decrease in Gp after exposure to mild hyperoxia ($P < 0.05$, repeated-measures ANOVA). No other variables were affected by mild hypoxia or hyperoxia. The results, when combined with those from other studies, suggest that Gp varies linearly with $P_{ET_{O_2}}$, with a sensitivity of 3.5%/Torr (SE 1.0). This sensitivity is sufficient to suggest that Gp is continuously varying in response to normal physiological fluctuations in $P_{ET_{O_2}}$. We conclude that at least some of the mechanisms underlying VAH may have a physiological role at sea level.

acclimatization to hypoxia; respiratory control; chemoreflexes; acute ventilatory response to hypoxia

VENTILATORY ACCLIMATIZATION to hypoxia involves a progressive rise in ventilation ($\dot{V}_E$) that in turn leads to a progressive rise in end-tidal P_{O_2} ($P_{ET_{O_2}}$) and fall in end-tidal P_{CO_2} ($P_{ET_{CO_2}}$). These changes begin within hours of the onset of hypoxia and take days or weeks to proceed to completion. Associated with ventilatory acclimatization to hypoxia, there are underlying rises in the acute ventilatory chemoreflex sensitivities to hypoxia (11, 20, 24) and hypercapnia (3, 14, 24). More recently, it has been shown that some of these changes can be detected with very modest levels of hypoxia, such as occur in an aircraft cabin (8), and furthermore that the converse of some of these changes can be detected after a period of moderate hyperoxia (17). These two findings raise the intriguing possibility that the mechanisms that underlie ventilatory acclimatization to altitude may have the sensitivity to be continuously "tuning" the respiratory control system in response to fluctuations in blood gas tension in normal life, rather than being responsive solely to gross changes in P_{O_2} such as occur with exposure to high altitude.

To explore this possibility further, we sought to determine whether any of the changes associated with ventilatory acclimatization to hypoxia could be detected in response to a very small reduction in $P_{ET_{O_2}}$ of 10 Torr and furthermore whether the converse changes could be detected in response to a very small increase in $P_{ET_{O_2}}$ of 10 Torr.

METHODS

Subjects. Ten healthy subjects (8 men, 2 women) were studied. All were nonsmokers and had no history of cardiovascular or respiratory disease. The two female subjects were both using a combined oral contraceptive, and experiments were time tabled so that any influence of this was constant throughout. The study was explained to the subjects both verbally and in writing, although the technical and physiological content was limited to ensure that they remained naive as to its exact purpose. Subjects were familiarized with the equipment before the experiment, and their natural values for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ were determined as part of this process. The study had the approval of the Central Oxfordshire Research Ethics Committee.

Protocols. Each subject undertook two protocols. The two protocols were identical to each other except for the P_{O_2} to which the subjects were exposed over a 5-day period of residence inside a purpose-built chamber within the laboratory. For one protocol (*protocol A*), the subjects' $P_{ET_{O_2}}$ was reduced to 10 Torr below their natural air-breathing value during the 5 days of chamber residence. For the other protocol (*protocol B*), the subjects' $P_{ET_{O_2}}$ was elevated by 10 Torr above their natural air-breathing value during the 5 days of chamber residence. The two chamber exposures for each subject were always separated from one another by a minimum period of 1 wk. Five subjects undertook *protocol A* before *protocol B*, and five subjects undertook *protocol B* before *protocol A*. The allocation of subjects to one or other order was determined by lot.

Each of the two protocols lasted a total of 13 days, with measurements being made on each morning. For the first two mornings (*days −2* and *−1*), a control set of measurements was made, and the subject then returned home. On the third morning (*day 1*), a further set of control measurements was made before the subject entered the chamber. The subject then remained in the chamber for 5 days and nights, only leaving the chamber to visit the bathroom or to allow us to make our daily measurements. This time outside the chamber totaled ~1.5 h/day. The period of exposure to mild hypoxia or hyperoxia in the chamber ended on the morning of *day 6*. After the daily measurements had been made on the morning of *day 6*, the subject was allowed to go home. The subject then attended the laboratory in the morning for 5 days of follow-up measurements (*days 7–11*).

On the days when the subjects arrived in the laboratory from home (*days −2* to *1* and *7* to *11*), they rested in the laboratory for 60 min before any measurements being made. $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ were then measured for a period of 10 min by using a fine nasal catheter

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connected to a Datex Normocap O_2 and CO_2 analyzer. This was connected to a personal computer running a program to detect and store end-tidal gas tensions in real time. An arterialized capillary blood sample was then taken from the earlobe. The blood samples were analyzed for P_{CO_2}, P_{O_2}, pH, and HCO_3^- concentration (these variables are subsequently notated with the modifier "ac" to indicate when the values have been obtained from arterialized capillary blood). The acute hypoxic ventilatory response (AHVR) was then assessed, and this was followed, after a 10-min break, by an assessment of the acute hypercapnic ventilatory response (AHCVR).

On mornings when the subject had spent the previous night in the chamber (*days 2–6*), $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ were first measured for a period of 10 min within the chamber. With the subject still in the chamber, the arterialized capillary blood samples were taken. Once these measurements had been completed, the subject left the chamber and was allowed to breathe room air for 20 min. After this, a further measurement of $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ was made, this time while the subject was breathing air. After these measurements, the subject's AHVR and AHCVR were assessed. Once these measurements were complete, the subject returned to the chamber except on *day 6*, when he or she was then allowed home.

Chamber exposure. The hypoxic and hyperoxic exposures were conducted in a purpose-built chamber, which was large enough to allow subjects to sit or stand comfortably during the day and to sleep in a bed at night. It was equipped with a television, video, and laptop with an internet connection to entertain the subjects. Subjects were studied individually in the chamber so that the inspired gas composition could be tailored accurately to maintain their end-tidal gas composition at the predetermined level. Respired gas was sampled continuously via a fine nasal catheter at the opening of the subject's nostril and analyzed for P_{CO_2} and P_{O_2}. Arterial O_2 saturation was monitored by using a pulse oximeter. The desired value for $P_{ET_{O_2}}$ was entered into a computer running a program to regulate the composition of the gas within the chamber. The computer automatically adjusted the composition of the gas in the chamber every 5 min, or at manually overridden intervals, to minimize the error between desired and actual values for the end-tidal gases. This system has been described in detail elsewhere (10). Although the chamber is capable of regulating $P_{ET_{CO_2}}$ in addition to $P_{ET_{O_2}}$, this was left uncontrolled. During their time in the chamber, the subject was kept under continuous observation, and an environmental O_2 monitor was employed within the chamber as a further safety precaution.

Measurements of AHVR and AHCVR. During these measurements, the subject sat in a chair and was distracted by watching television. The subject breathed through a mouthpiece with his or her nose occluded by a clip. Respiratory volumes were measured by using a bidirectional turbine volume-measuring device (12), and respiratory phase transitions were detected by using a pneumotachograph. Respired gas was sampled via a fine catheter close to the mouth and analyzed continuously for P_{CO_2} and P_{O_2} by mass spectrometry. Inspired and expired volumes, end-inspiratory and end-expiratory gas tensions, and saturation were determined in real time by a computer.

A dynamic end-tidal forcing system was used to maintain the end-tidal gases at predetermined levels. A mathematical model was used to generate a file that contained the breath-by-breath predictions for the inspired P_{CO_2} and P_{O_2} necessary to produce the desired end-tidal sequences. During the experiment, a computer-controlled gas-mixing system was used to produce this sequence in a modified manner. The modifications resulted from feedback control based on the deviations of the measured $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ from the desired values. For the measurement of AHVR, $P_{ET_{CO_2}}$ was held constant throughout the protocol at 1–2 Torr above the subject's natural air-breathing value. For the first 5 min of the protocol, $P_{ET_{O_2}}$ was held constant at 100 Torr. After this, $P_{ET_{O_2}}$ was altered to produce a series of six square waves, each 120 s long, with $P_{ET_{O_2}}$ alternating between 100 Torr for 60 s and 50 Torr for 60 s. For the measurement of AHCVR, $P_{ET_{O_2}}$ was held at 100 Torr throughout. For the first 5 min, $P_{ET_{CO_2}}$ was held at 2 Torr above the subject's air-breathing $P_{ET_{CO_2}}$. After this, $P_{ET_{CO_2}}$ was varied dynamically according to a multifrequency binary sequence known as the Van den Bos Octave (9, 15). $P_{ET_{CO_2}}$ was switched repeatedly between a low value of +2 Torr above and a high value of +10 Torr above the subject's air-breathing $P_{ET_{CO_2}}$. Overall, the sequence lasted for a period of 1,408 s.

Modeling of the hypoxic and hypercapnic ventilatory responses. To quantify the ventilatory responses to acute variations in hypoxia and hypercapnia, dynamic models relating $\dot{V}_E$ to the end-tidal gas profiles were fitted to the data. For the measurements of AHVR, *model 3* of Clement and Robbins (4) was employed. This is a single-compartment model in which the parameter Gp_{O_2} reflects the ventilatory sensitivity to hypoxia, and the parameter $\dot{V}c$ reflects residual $\dot{V}_E$ in the absence of hypoxia. For the measurements of AHCVR, *model 2* of Pedersen et al. (15) was used. This is a two-compartment model in which the individual compartments describe separate peripheral and central chemoreflex contributions to $\dot{V}_E$. In this model, the parameter Gp_{CO_2} reflects the ventilatory sensitivity of the peripheral chemoreflex to CO_2, and parameter Gc reflects the sensitivity of the central chemoreflex to CO_2. The parameter B is the calculated $P_{ET_{CO_2}}$ for which $\dot{V}_E = 0$ l/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 (13).

Statistical analysis. Repeated-measures ANOVA was used as the principal method for assessing the statistical significance of the observations made in this study. The three baseline measurements before the chamber exposure, the measurements from the last 3 days of the chamber exposure and the measurements from the final 3 days of the follow-up period were included in the ANOVA to assess whether the changes over time were different for the hypoxic and hyperoxic protocols. 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 24.1 yr (SD 4.5). Their average height was 177 cm (SD 9.5), and average weight was 76.4 kg (SD 9.4). Their mean resting values for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ were 37.2 Torr (SD 1.7) and 105.4 Torr (SD 2.2), respectively.

Control over P_{O_2} of subjects within the chamber. Figure 1 shows the daily measurements of Pc_{O_2} made within the chamber together with the associated averages for $P_{ET_{O_2}}$. Also shown are the daily measurements of Pac_{O_2} and $P_{ET_{O_2}}$ made

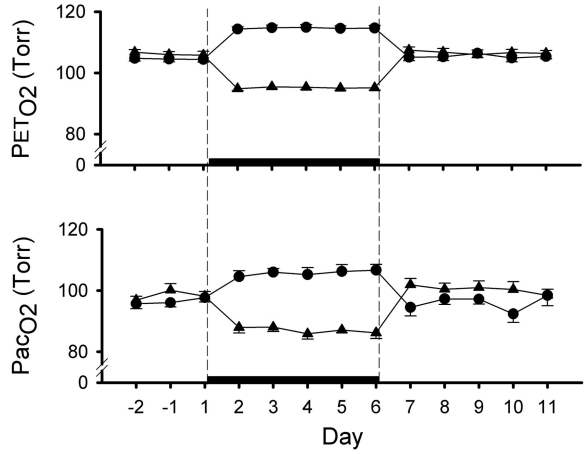

Fig. 1. Mean values for oxygen tensions for all subjects on each day of both protocols. *Top*: end-tidal P_{O_2} ($P_{ET_{O_2}}$). *Bottom*: corresponding arterialized capillary P_{O_2} (Pac_{O_2}). Solid bars and dashed lines indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). Error bars, 1 SE.

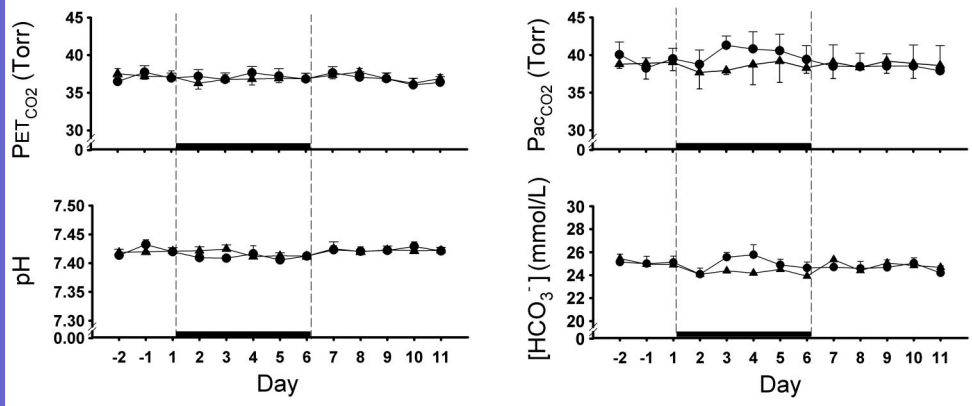

Fig. 2. Mean values for end-tidal P_{CO_2} ($P_{ET_{CO_2}}$), arterialized capillary P_{CO_2} (Pac_{CO_2}) and blood-gas data for all subjects on each day of both protocols. Solid bars and dashed lines indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). $[HCO_3^-]$, HCO_3^- concentration. Error bars, 1 SE.

before and after the chamber exposure. The figure shows that the experiment has been successful in generating the 10-Torr decrease (*protocol A*) or increase (*protocol B*) in $P_{ET_{O_2}}$ and that this has been reflected in the values for Pac_{O_2}. There was a relatively consistent small difference between the values for $P_{ET_{O_2}}$ and Pac_{O_2} of 7.4 Torr (SD 6.3), in keeping with previous experience (5).

Effects of altered P_{O_2} on blood-gas and end-tidal values. Figure 2 shows the arterialized capillary blood-gas data relating to CO_2 together with the associated averages for $P_{ET_{CO_2}}$. On *days 2–6*, the samples were taken from the subjects while they were inside the chamber. On the other days, samples were taken from the subjects while they were outside the chamber breathing air. The plots suggest that there may have been some increase in Pac_{CO_2} during the exposure to the mild hyperoxia of *protocol B*. However, this result was not statistically significant, nor was there a comparable change in the associated values for $P_{ET_{CO_2}}$.

Figure 3 shows the values for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ for the subjects that were obtained on each day after they had been removed from the chamber and allowed to breathe room air for 20 min. Also shown are the air-breathing data for the measurements made before and after the chamber exposure. In keeping with the measurements made inside the chamber, values for $P_{ET_{CO_2}}$ did not differ between protocols. Values for $P_{ET_{O_2}}$ appeared to be slightly higher on the chamber days (*days 2–6*) than on the days before and after chamber exposure. This result was statistically significant, but the effect did not differ between *protocol A* and *protocol B*.

Effect of altered P_{O_2} on AHVR. Figure 4 shows the average parameter values obtained from the measurement made of AHVR on each day of the protocol. For *protocol A*, Gp_{O_2} promptly rose on the first day of exposure to mild hypoxia in the chamber and promptly fell again on the first day of returning to air breathing at the end of the chamber exposure. For *protocol B*, the pattern was reversed, with Gp_{O_2} falling on the first day of exposure to mild hyperoxia in the chamber and Gp_{O_2} rising on the first day of returning to air breathing at the end of the hyperoxic exposure. During the chamber exposures, the average value for Gp_{O_2} for *protocol A* was always above that for *protocol B*. This was never the case before or after the chamber exposures. Overall, the effect of chamber exposure on Gp_{O_2} differed significantly between *protocol A* and

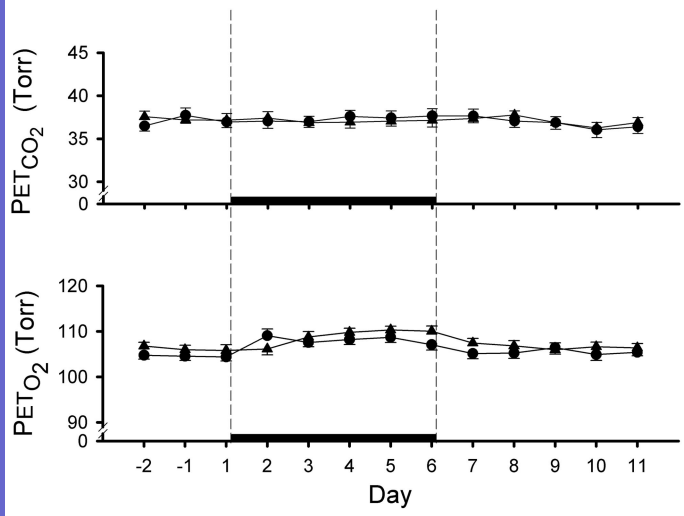

Fig. 3. Mean values for $P_{ET_{CO_2}}$ and $P_{ET_{O_2}}$ while breathing air for all subjects on each day of both protocols. Solid bars and dashed lines indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). Error bars, 1 SE.

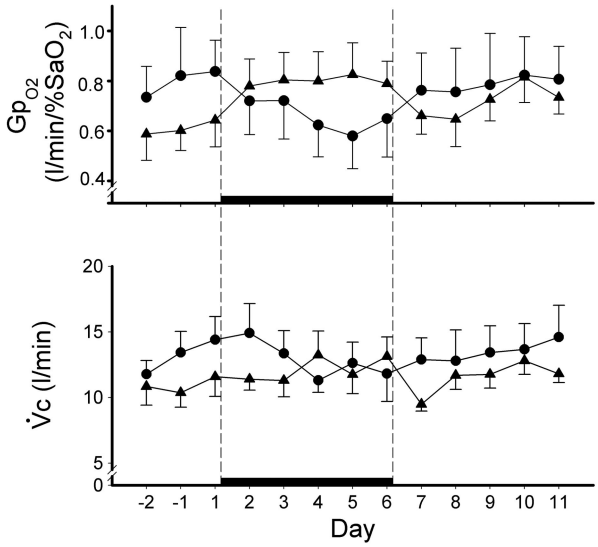

Fig. 4. Mean values for the parameters of the acute ventilatory response to hypoxia for all subjects on each day of both protocols. *Top*: acute ventilatory sensitivity to hypoxia (Gp_{O_2}). *Bottom*: estimated ventilation in the absence of hypoxia ($\dot{V}c$). Solid bars and dashed lines indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). Sa_{O_2}, arterial O_2 saturation. Error bars, 1 SE.

protocol B ($P < 0.05$, repeated-measures ANOVA). No comparable pattern was discernible in the values for parameter $\dot{V}c$.

Although not quite statistically significant, a noticeable feature of Fig. 4 is that the control values for Gp_{O_2} obtained before the chamber exposure did not match well between the two protocols. Analysis of the individual subject data revealed one subject for whom this was particularly noteworthy and for whom the difference between these values for the two protocols was significantly different compared with the other subjects ($P < 0.05$, after correction for multiple comparisons). Figure 5 shows the mean parameter values after the data obtained from this subject had been removed. First, it is clear that some difference between the control values before the chamber exposure still remains. However, this is now noticeably smaller than the difference that is present during the chamber period. Furthermore, the postexposure values for Gp (which form a second control period) match closely. When the analysis was restricted to these nine subjects, the level of statistical significance associated with the different effects of the chamber exposures between the two protocols rose to $P < 0.002$ (repeated-measures ANOVA).

Effect of altered P_{O_2} on AHCVR. Figure 6 shows the average parameter values obtained from the measurement made of AHCVR on each day of the protocol. There was no discernible effect of either *protocol A* or *protocol B* on any of these parameter values.

DISCUSSION

The small changes in $P_{ET_{O_2}}$ that were generated in this study did not generate or relieve a detectable degree of ventilatory acclimatization to hypoxia as judged by a significant change in $P_{ET_{CO_2}}$, nor did they generate any change in the acute ventilatory sensitivity to hypercapnia, which normally would occur as part of the acclimatization process. However, the small changes in $P_{ET_{O_2}}$ did generate quite marked changes in the acute ventilatory sensitivity to hypoxia, with the reduction in $P_{ET_{O_2}}$ generating an increase in Gp_{O_2} and the increase in $P_{ET_{O_2}}$ generating a decrease in Gp_{O_2}.

Comparison with other studies. Figure 7 illustrates the percent change in Gp_{O_2} obtained from a number of studies from our laboratory in Oxford (8, 11, 17, 22) plotted against the $P_{ET_{O_2}}$ of the exposure (with 100 Torr taken as the normal

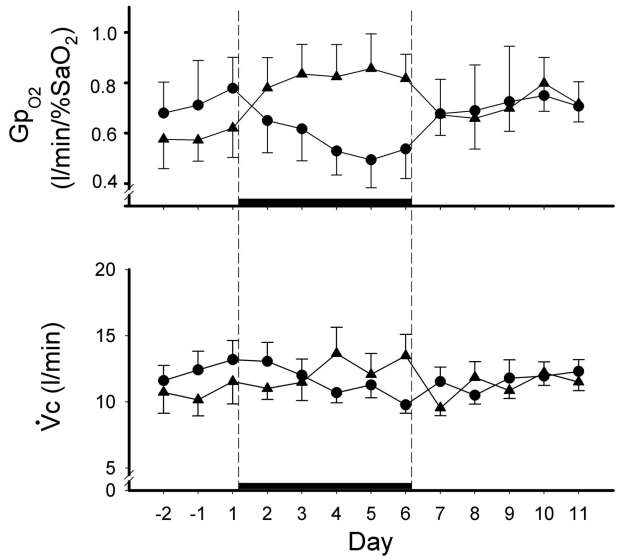

Fig. 5. Mean values for the parameters of the acute ventilatory response to hypoxia for 9 of 10 subjects on each day of both protocols. The excluded subject had a set of prechamber control values for Gp_{O_2} that differed significantly between protocols when compared with the other subjects. *Top*: Gp_{O_2}. *Bottom*: $\dot{V}c$. Solid bars and dashed lines, indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). Error bars, 1 SE.

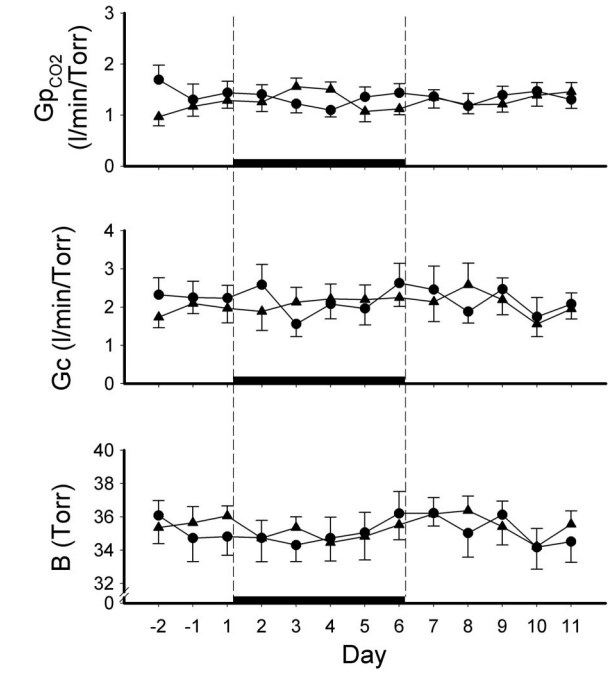

Fig. 6. Mean values for the parameters of the acute ventilatory response to hypercapnia for all subjects on each day of both protocols. *Top*: rapid (peripheral) chemoreflex sensitivity to CO_2 (Gp_{CO_2}). *Middle*: slow (central) chemoreflex sensitivity to CO_2 (Gp). *Bottom*: extrapolated value for $P_{ET_{CO_2}}$ for which ventilation is zero (B). Solid bars and dashed lines indicate period of exposure in chamber to either mild hypoxia (*protocol A*, ▲) or mild hyperoxia (*protocol B*, ●). Error bars, 1 SE.

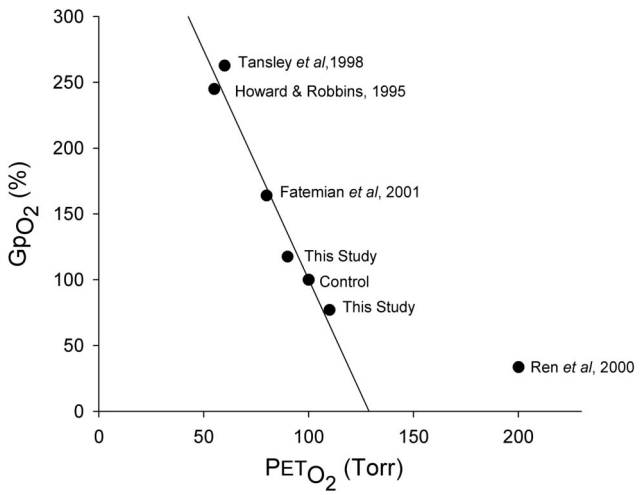

Fig. 7. Percent change in Gp_{O_2} from control (100%) at several different levels of conditioning $P_{ET_{O_2}}$ calculated from a number of studies (8, 11, 17, 22) undertaken with the chamber in Oxford, including the present one. Data have been extrapolated for studies (8, 11, 17) to provide a common duration exposure to hypoxia of 48 h. Regression line has been fitted to all data except for (17). Slope of the regression line is 3.5%/Torr (SE 1.0).

air-breathing value). For some studies, the actual change in Gp_{O_2} has had to be extrapolated so that all points relate to an exposure of 48-h duration. With the exception of the exposure to moderate hyperoxia, the percent changes in Gp_{O_2} relate reasonably linearly to the actual variations in $P_{ET_{O_2}}$. This is in contrast to the acute effects of hypoxia on ventilation where the relationship between $\dot{V}_E$ and $P_{ET_{O_2}}$ is curvilinear. (Although the effects of acute hypoxia are mediated through changes in arterial P_{O_2} and not saturation, the size of the effect nevertheless tends to be linearly related to the degree of desaturation of arterial blood rather than to the fall in P_{O_2}.)

Relationship to ventilatory acclimatization to altitude. Over the past two decades, considerable evidence has accumulated to suggest that ventilatory acclimatization to hypoxia, at least during the early stages, is driven to a large degree by a specific effect of sustained hypoxia at the carotid body (for reviews, see Refs. 1, 2). However, in addition to this, there is also evidence that ventilatory acclimatization to hypoxia may arise in part through alterations within the central nervous system that affect the peripheral chemoreflex sensitivity to hypoxia (6), and there may also be effects arising through "hyperventilation-induced hyperpnea" (7, 18, 21). In the present study, the alterations in P_{O_2} clearly affected the sensitivity of the peripheral chemoreflex but failed to affect either $\dot{V}_E$ or air-breathing $P_{ET_{O_2}}$ or $P_{ET_{CO_2}}$, despite the fact that changes in these variables form the cardinal feature of ventilatory acclimatization to hypoxia. One possible explanation for our observations is that, for the progressive increase in Gp_{O_2} to feed through into changes in $\dot{V}_E$ and consequently $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$, a significant degree of peripheral chemoreceptor stimulation is required, and this simply would not have occurred in relation to the very modest changes in P_{O_2} of the present study. A similar explanation can be evoked for the failure to observe any change in the acute ventilatory sensitivity to CO_2.

Significance for control of breathing near sea level. Figure 7 illustrates a regression line for the relationship between Gp_{O_2} and $P_{ET_{O_2}}$. The slope of this relationship is 3.5%/Torr (SE 1.0), which suggests that small variations over time in arterial P_{O_2} would have marked effects on the ventilatory sensitivity to acute hypoxia. For example, there is a natural fall in arterial P_{O_2} of 3–18 Torr with sleep (16), which if sustained would result in a rise in Gp_{O_2} of 10–60%. Interestingly, it has previously been reported that sleep deprivation results in a substantial reduction in the acute ventilatory sensitivity to hypoxia (23).

It is a relatively well-known phenomenon that the ventilatory sensitivity to hypoxia varies markedly within an individual from day to day for reasons that are not understood (19, 25). This study indicates that natural variations in P_{O_2} over the course of the day may underlie at least part of this observation. Overall, it would seem likely that this phenomenon is part of an overall process of continuous calibration of the respiratory chemoreflexes to ensure that the respiratory control system remains stable and effective over time. However, the exact nature of how such regulatory mechanisms may function remains poorly understood.

GRANTS

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