Respiratory control in humans after 8 h of lowered arterial \( \text{Po}_2 \), hemodilution, or carboxyhemoglobinemia

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Ren, Xiaohui, Keith L. Dorrington, and Peter A. Robbins. Respiratory control in humans after 8 h of lowered arterial \( \text{Po}_2 \), hemodilution, or carboxyhemoglobinemia. *J Appl Physiol* 90: 1189–1195, 2001.—In humans exposed to 8 h of isocapnic hypoxia, there is a progressive increase in ventilation that is associated with an increase in the ventilatory sensitivity to acute hypoxia. To determine the relative roles of lowered arterial \( \text{Po}_2 \) and oxygen content in generating these changes, the acute hypoxic ventilatory response was determined in 11 subjects after four 8-h exposures: 1) protocol IH (isocapnic hypoxia), in which end-tidal \( \text{Po}_2 \) was held at 55 Torr and end-tidal \( \text{Pco}_2 \) was maintained at the preexposure value; 2) protocol PB (phlebotomy), in which 500 ml of venous blood were withdrawn; 3) protocol CO, in which carboxyhemoglobin was maintained at 10% by controlled carbon monoxide inhalation; and 4) protocol C as a control. Both hypoxic sensitivity and ventilation in the absence of hypoxia increased significantly after protocol IH (\( P < 0.001 \) and \( P < 0.005 \), respectively, ANOVA) but not after the other three protocols. This indicates that it is the reduction in arterial \( \text{Po}_2 \) that is primarily important in generating the increase in the acute hypoxic ventilatory response in prolonged hypoxia. The associated reduction in arterial oxygen content is unlikely to play an important role.

### Methods

**Subjects**

Twelve healthy subjects (9 men, 3 women) participated in the study. Their age ranged between 20 and 32 yr, with an average of 23 ± 4 (SD) yr. Their average height was 180 ± 19 cm, and their average weight was 74 ± 13 kg. All were nonsmokers except for subject 1,128, who smoked 10 cigarettes per day. None of the subjects had donated blood within the 6 mo before his or her participation in the study. All were requested to have a light breakfast and refrain from alcohol, caffeine-containing drink, and cigarettes on each experimental day. Female subjects only participated in the experiments during the first 14 days of their menstrual cycles. The basic experimental procedure was explained to all subjects, but they were naive as to the exact purpose of the experiments. Each subject visited the laboratory once or twice before undertaking any of the main experimental protocols to become familiar with the laboratory and its procedures. All subjects gave informed consent before participating in the study. The study was approved by the Central Oxford Research Ethics Committee.

**Protocols**

Each subject undertook four different protocols. *Protocol IH* consisted of an 8-h exposure to isocapnic hypoxia, in which end-tidal \( \text{Po}_2 \) (\( \text{PET}_{\text{Po}_2} \)) was held at 55 Torr and \( \text{PET}_{\text{Pco}_2} \)

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was maintained at the subject's air-breathing control value. During protocol PB, each subject underwent phlebotomy, with 500 ml of blood being withdrawn from an arm vein. During protocol CO, a ~10% level of carboxyhemoglobin (HbCO) was induced and maintained for 8 h by having the subjects intermittently breathe a dilute mixture of CO in air. Protocol C was a control protocol, in which the subjects breathed air with no other intervention. The order of the exposures was varied among subjects. At least 4 wk were allowed to elapse after protocol PB before another experimental protocol was undertaken. Each experiment started at 8–9 AM after the subject had rested for at least 0.5 h at the laboratory. A light lunch was served at 12:30–1 PM.

Air-breathing PETCO2 was measured before and after each 8-h protocol. AHVR was assessed before, 40 min after, and 8 h after the start of each 8-h protocol. During each measurement of AHVR, PETO2 was held at 100 Torr for the first 5 min. This was followed by six square waves of PETO2 with PETCO2 alternating between 1 min at 50 Torr and 1 min at 100 Torr. PETCO2 was held at 1–2 Torr above the subject's initial air-breathing value throughout. The end-tidal gas profiles used are illustrated in Fig. 1, which is from an actual determination of AHVR in one subject (subject 1,118).

Experimental Technique

At the beginning of each experimental day, a venous blood sample of 1–2 ml was taken to determine the total concentration of hemoglobin (Hb; g/dl), the percentage of methemoglobin (%MetHb), and the percentage of HbCO (%HbCO).

Protocol IIH. To undertake the 8-h exposures to hypoxia associated with this protocol, we employed a purpose-built chamber. The subject was seated comfortably inside the chamber and wore a fine catheter at the opening of each nostril through which respired gas was sampled and analyzed by mass spectrometry for Po2 and Pco2. A pulse oximeter was attached to the forefinger to monitor percent arterial oxygen saturation (SaO2). A computer was used to analyze and log the data on-line, to identify inspiratory and end-tidal values of Po2 and Pco2, and to control the gas composition within the chamber. At the start of each experiment, the composition of the inspired gas that would be required to produce the desired PetCO2 and PetO2 was estimated and set manually before the subject entered the chamber. After the subject entered the chamber, the inspiratory gas composition was adjusted automatically by the computer every 5 min or at manually overridden intervals, to minimize the difference between the actual and the target values for PetCO2 and PetO2. The system has been described in detail before (12).

Protocol PB. The phlebotomy associated with this protocol consisted of removing 500 ml of blood from a vein in the antecubital fossa. To determine the degree of hemodilution achieved, two further venous blood samples were taken at 40 min and at 8 h after phlebotomy.

Protocol CO. The CO inhalation associated with this protocol was undertaken by asking the subject to inspire a concentration of 0.4% CO in air through a loose fitting face mask. (For subject 1,136, who was the first subject to undergo this procedure, a concentration of 0.1% CO in air was used, which was found to increase the level of HbCO rather too slowly.) Before the start of CO inhalation, a catheter was inserted into a cephalic vein. During CO inhalation, blood samples of 1–2 ml were taken every 5 min through the catheter to measure %HbCO. The period of CO inhalation lasted 10–30 min, and the inhalation was stopped when %HbCO reached ~10%. After the period of inhalation, blood samples were taken every ~1.5 h to measure %HbCO. "Top-up" inhalations of CO were performed when %HbCO had declined to ~9%. Generally, this was necessary three to four times during the 8-h period.

Measurement of air-breathing PetCO2 and AHVR. These measurements were made with the subjects seated in an upright position. Values for air-breathing PetCO2 were determined by using a nasal catheter connected to a mass spectrometer. During measurements of AHVR, subjects breathed through a mouthpiece with their nose occluded with a clip. Ventilatory volumes were measured by a turbine volume-measuring device (15) fixed in series with the mouthpiece. Respiratory gas was sampled continuously and analyzed by mass spectrometry for Pco2 and Po2. A pulse oximeter was attached to the forefinger to monitor the SaO2. Data were recorded on-line by a computer, which also determined PetCO2 and PetO2 from the signals from the mass spectrometer. The desired end-tidal gas profiles were generated by using an end-tidal forcing system. Before the experiment started, a forcing function was calculated. This consisted of the predicted inspired gas compositions on a second-by-second basis that would be required to produce the desired levels of PetO2 and PetCO2 in the subject. The function was input into a controlling computer, which was used to regulate the gas mixtures breathed by the subject. During the course of the experiment, measured values for PetO2 and PetCO2 were fed to the controlling computer on a breath-by-breath basis from the data-acquisition computer. The deviations of these actual values from the desired values were used to adjust the new inspiratory gas mixtures by using an integral-proportional feedback control scheme. The controlling computer adjusted the inspired partial pressures of N2, O2, and CO2 through a
fast gas-mixing system (14). This control scheme has been described in more detail elsewhere (23).

Data Analysis

Calculation of \( \text{CaO}_2 \). In protocol IH, \( \text{CaO}_2 \) (ml/100 ml) was calculated as

\[
\text{CaO}_2 = 1.39 \cdot [\text{Hb}] \cdot \frac{100 - [%\text{HbCO} - %\text{MetHb}]}{100} \cdot \frac{\text{SaO}_2}{100}
\]

where the values for [Hb], %HbCO, and %MetHb were taken from the initial blood sample and for \( \text{SaO}_2 \) from the pulse oximeter reading. In protocol PB, the same equation was used, but the value for \( \text{SaO}_2 \) came from the initial reading from the pulse oximeter, values for %HbCO and %MetHb came from the initial blood sample, and the values for [Hb] were determined from the blood samples drawn during the exposure.

In protocol CO, accurate calculation of \( \text{CaO}_2 \) is a little more involved because of the cooperative nature of binding between the four subunits of the hemoglobin molecule. To calculate \( \text{CaO}_2 \), we used the basic assumption of Roughton and Darling (24) that the amount of deoxyhemoglobin present with a mixture of CO and O_2 is the same as if no CO were present and the \( P_O_2 \) values were replaced by \( P_O_2 + M \cdot P_Co \), where \( M \) is the relative affinity of hemoglobin between CO and O_2 given by

\[
\frac{P_O_2 \cdot [%\text{HbCO}]}{P_Co \cdot \text{SaO}_2} = M
\]

The value used for \( M \) was 218 (5). The initial air-breathing value for \( \text{PETO}_2 \) was used in this equation together with values for %HbCO, as obtained from venous blood samples. Values for \( P_Co \) and \( \text{SaO}_2 \) could then be obtained by numerically solving the above relationship simultaneously with the Adair equation for the hemoglobin dissociation curve, with the values for \( P_O_2 \) in the Adair equation replaced by \( (P_O_2 + M \cdot P_Co) \)

\[
\text{SaO}_2 = \frac{A_1 P + 2A_2 P^2 + 3A_3 P^3 + 4A_4 P^4}{4(1 + A_1 + A_2 P + A_3 P^2 + A_4 P^3)}
\]

where

\[
P = (P_O_2 + M \cdot P_Co)
\]

The coefficients \( (A_1, A_2, \ldots) \) used for the Adair equation were those obtained by Roughton and Severinghaus (25) to ensure accuracy in the upper range of the dissociation curve.

Model fitting. To quantify AHVR from the data, the responses to the six square waves of hypoxia were fitted by a single-compartment model (model 3) as described by Clement and Robbins (4). In this model, total \( V_e \) is divided into hypoxia-dependent (peripheral; \( V_p \)) and hypoxia-independent (central; \( V_c \)) components. In our assessment of AHVR, isocapnia was maintained, and so \( V_c \) can be assumed to be constant. As the hypoxic stimulus varied over time, \( V_p \) needs to be expressed in a time-varying form and is represented in the model as

\[
\tau \frac{dV_p}{dt} + V_p = G_p[100 - S(t - T_d)]
\]

where \( t \) is time, \( G_p \) is the hypoxic sensitivity, \( \tau \) is a time constant, \( T_d \) is a time delay, and \( S \) is \( \text{SaO}_2 \) (%) calculated from \( \text{PETO}_2 \) as described by Severinghaus (28).

To fit the model to the data, a difference equation was obtained from the model to describe the model output for the current breath in terms of the model output for the previous breath, the input function, and the parameters of the model. These calculations were described in detail for this model by Clement and Robbins (4).

The parameters of the model, \( G_p, V_p, \tau, \) and \( T_d \), were estimated by nonlinear regression. This was undertaken by using the Numerical Algorithms Group (Oxford, UK) FORTRAN library routine E04FDF to minimize the sum of squares of the residuals.

Statistical analysis. ANOVA was used to test for possible differences in the parameters among the four protocols, where protocol and time of measurements were treated as fixed factors and the subject as a random factor. Statistical significance was accepted at \( P < 0.05 \).

RESULTS

Subjects

From the 12 subjects originally recruited for the study, 11 finished all of the experiments. Subject 1,132 felt faint during phlebotomy and subsequently decided to leave the study. Subject 1,138 felt faint at the end of phlebotomy, and his heart rate decreased to 45 beats/min. Atropine (0.6 mg) was administrated intravenously, the subject recovered within minutes, and he then completed the experiment. All other subjects completed all protocols eventfully.

\( \text{PETO}_2, \text{SaO}_2, [\text{Hb}], %\text{HbCO}, \) and \( \text{CaO}_2 \) During the Protocols

Table 1 lists the values for \( \text{PETO}_2 \) and \( \text{SaO}_2 \) (obtained via pulse oximetry) for all 11 subjects before and during the 8 h of isocapnic hypoxia associated with protocol IH. During the first 80 min of each hypoxia protocol, the subject was hyperventilated to achieve a mean end-expiratory \( P_CO_2 \) of 30 mmHg, and the remaining time was spent at a mean end-expiratory \( P_CO_2 \) of 40 mmHg. After hyperventilation, subjects were paced to complete the protocol. Subjects were instructed to maintain a breathing pattern of 10 breaths/min.

Table 2 lists the values for [Hb] for all of the subjects before, 40 min after, and 8 h after the phlebotomy associated with protocol PB. Although the blood loss was ~10% of total blood volume, the overall change in [Hb] after 8 h was only 0.5 g/100 ml. Values for \( \text{CaO}_2 \) were calculated from \( \text{SaO}_2 \) and the oxygen-carrying capacity of the blood, as determined from the venous blood sample drawn at the start of the experiment. These values are shown in Table 1. During the hypoxic exposure, a 7.5% reduction in \( \text{CaO}_2 \) was generated.

Table 3 lists the values for %HbCO for all 11 subjects before, 40 min after, and 8 h after the phlebotomy associated with protocol CO. Although the relative change in %HbCO (with CO exposure) was 7.4%, which represented an increase of 7.3% over the control level of 2.4%. Values for \( \text{CaO}_2 \) were calculated in the manner described in Methods and are listed in Table 3. The mean reduction in \( \text{CaO}_2 \) with CO exposure was 7.4%.

Air-Breathing \( \text{PETCO}_2 \) and AHVR

Values for air-breathing \( \text{PETCO}_2 \) before and after each protocol are shown in Table 4. ANOVA revealed that
Table 1. $P_{ETO_2}$, $SaO_2$, and $CaO_2$ before ($t = 0$) and during ($t = 1–8$ h) protocol IH

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>$P_{ETO_2}$, Torr</th>
<th>$SaO_2$ %</th>
<th>$CaO_2$, ml/100 ml</th>
<th>$P_{ETO_2}$, Torr</th>
<th>$SaO_2$ %</th>
<th>$CaO_2$, ml/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,091</td>
<td>109.9</td>
<td>97.1</td>
<td>18.4</td>
<td>56.2 ± 1.6</td>
<td>90.8 ± 0.8</td>
<td>17.2 ± 0.2</td>
</tr>
<tr>
<td>1,116</td>
<td>102.5</td>
<td>96.8</td>
<td>19.2</td>
<td>56.3 ± 1.1</td>
<td>90.8 ± 0.8</td>
<td>18.0 ± 0.2</td>
</tr>
<tr>
<td>1,118</td>
<td>100.0</td>
<td>97.8</td>
<td>15.6</td>
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</tr>
<tr>
<td>Mean ± SE</td>
<td>104.6 ± 1.2</td>
<td>97.3 ± 0.1</td>
<td>18.7 ± 0.5</td>
<td>56.4 ± 0.1</td>
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</table>

Values are means ± SE for $t = 1–8$ h. $P_{ETO_2}$, end-tidal PO$_2$; $SaO_2$, arterial O$_2$ saturation; $CaO_2$, arterial O$_2$ content; t, time; protocol IH, isocapnic hypoxia protocol.

The main finding of the present study was that, whereas 8 h of reduced Pa$_O_2$ and Ca$_O_2$ induced significant elevations in both $G_p$ and $V_c$ and a significant decrease in air-breathing $P_{ETCO_2}$, 8 h of reduced Ca$_O_2$ with Pa$_O_2$ maintained at normal levels did not affect $G_p$, $V_c$, or air-breathing $P_{ETCO_2}$. This finding indicates that it is the prolonged reduction of Pa$_O_2$, that is primarily important in inducing the increase in AHVR in the early stages of VAH. The associated modest decrease in Ca$_O_2$ does not appear to play an important role. We consider that the results from this study provide further support for the notion that the early phases of ventilatory acclimatization to modest hypoxia arise through the effects of hypoxia at the carotid body rather than within the central nervous system.

**Experimental Limitations of the Study**

The intention of the study design was to generate the same reduction in Ca$_O_2$ in each of the three protocols. In protocol IH, the reduction in Ca$_O_2$ was 7.5%; in protocol PB, the reduction was 4.2%; and in protocol CO, the reduction was 7.4%. Thus protocols IH and CO were well matched in terms of the reduction in Ca$_O_2$, but this was not the case for protocol PB. In retrospect, a better study design for protocol PB would have been to replace the 500 ml of blood with 500 ml of a plasma expander. The relatively small fall in Ca$_O_2$ in protocol PB limits the usefulness of these observations. However, our laboratory has recently observed (8) that a very modest reduction in inspired PO$_2$ over an 8-h period, which resulted in a fall in Ca$_O_2$ of only ~2.7%, can induce acclimatization in terms of a significant increase in $G_p$ and $V_c$ and fall in air-breathing $P_{ETCO_2}$.

Table 2. [Hb] and Ca$_O_2$ before ($t = 0$), 40 min after, and 8 h after phlebotomy in protocol PB

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>[Hb], g/dl</th>
<th>Ca$_O_2$, ml/100 ml</th>
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</tbody>
</table>

[Hb], Hb concentration; protocol PB, plebotomy protocol.
This finding suggests that the 4.2% reduction in CaO2 in protocol PB should have been sufficient to induce acclimatization, if the acclimatization process had indeed been triggered by a reduction in CaO2 in the absence of a change in PETO2.

Other Limitations and Assumptions of the Study

In relation to drawing any conclusions about the site of action of hypoxia in early VAH, it is necessary to make some assumptions on the likely effect of the three intervention protocols on the tissue PO2 of the sites in question. The first assumption is that protocol IH would have had a significant effect on the PO2 at the carotid body but that neither protocol PB nor protocol CO would have done so. In relation to protocol IH, it was clearly the case that the reduction in PETO2 had a substantial acute effect on Ve. However, Ayres et al. (1) have reported that, during modest increases in %HbCO of ~9% in patients, there may also be some reduction in PaO2. They attributed this to a widening of the alveolar-arterial PO2 gradient, brought about by an increase in the effect of shunt within the lungs because of the reduction of PO2 in venous blood. However, these effects were only really significant for patients who had abnormally high alveolar-arterial PO2 gradients; in patients with normal alveolar-arterial PO2 gradients, the effect was small. Furthermore, other studies in humans have found that neither 9% HbCO (11) nor 18–20% HbCO (30) had any significant effect on Ve. In animal studies of CO inhalation, Ve did not increase until %HbCO had reached 45–50% (2, 7, 9). In an animal study of acute anemia, Ve did not increase until hematocrit had fallen to 50–60% of the original value (19). In studies of carotid body function in animals, neither increases in %HbCO that were considerably greater than in the present study nor decreases in hematocrit that were considerably greater than in the present study had any significant effect on the nerve discharge frequency from the carotid body (10, 17).

A second assumption that we make is that protocols PB and CO would have induced a reduction in brain...
tissue PO₂ that would have been quantitatively similar to that observed with protocol IH. Figure 3 illustrates the calculated fall in venous PO₂ (PvO₂) as a function of the amount of oxygen extracted from the blood for protocol IH, and for idealized versions of protocols PB and CO, where the initial reduction in CaO₂ is precisely matched to that of protocol IH. The horizontal line indicates the PO₂ calculated from the Adair equation (25) for a venous O₂ saturation of 60.4%, which is a typical value for jugular venous blood under control conditions (6). The vertical lines indicate lower and upper limits for the likely range for jugular venous O₂ content (C O₂). The vertical line at the lower CO₂ was calculated by assuming that there was no increase in cerebral blood flow, and the vertical line at the higher CO₂ was calculated by assuming that cerebral blood flow increased by 8.7%, as measured for isocapnic hypoxia with PETO₂ of 50 Torr (20). The calculated fall in PvO₂ was less for protocol PB than for the other two protocols and is only ~1 Torr below normal. The calculated falls in PvO₂ for protocols IH and CO were similar and are ~3.5 Torr below normal. The calculated fall for protocol CO was ~0.5 Torr more marked than for protocol IH. These calculations suggest that, even if protocol PB had engendered a reduction in CaO₂ equal to that of the other two protocols, it would not have been as effective in lowering brain PO₂. On the other hand, protocols IH and CO are likely to have been well matched with respect to their effect on brain PO₂.

Another issue that is related to protocol CO is that CO could have some physiological effects other than those associated with the reduction in CaO₂ (16, 21, 22). It has been shown that exogenous CO at very high partial pressure (500–550 Torr) stimulated carotid body sensory discharge under normoxic conditions. A relatively low level of PCO₂ ≤ 140 Torr did not stimulate the chemosensory response during normoxia but inhibited the chemosensory response to hypoxia (16). Obviously, these levels of PCO₂ are orders of magnitude greater than those used in protocol CO.

**Comparison of Results with Other Long Term Studies of CO Inhalation and Hemodilution in Animals**

There are very few data from animal studies to compare with our results in humans. In ponies, Lowry et al. (18) increased %HbCO to ~25% over a period of ~1 h and then maintained it at this level for a further 5 h. During this period, there was a progressive decrease in arterial PO₂, which was similar to that observed with a 5-h exposure to low PaO₂. In goats, progressive hemodilution produced a consistent increase in AHVR after 3 days when [Hb] was reduced from ~10–12 to 6–7 g/100 ml. However, a reduction in [Hb] to 7–8 g/100 ml had little effect (26). In both of these studies, the stimulus employed to obtain a progressive effect of increased %HbCO or hemodilution on VE and/or AHVR was substantially greater than in the

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**Fig. 2.** Group means ± SE of hypoxic sensitivity (Gp) and hypoxia-insensitive VE (Vc) across all subjects before (time = 0), at 40 min, and at 8 h during each exposure. IH, PB, CO, and C: isocapnic hypoxia, phlebotomy, carboxyhemoglobin, and control protocols, respectively. Significantly different from previous time points of same protocol: **P < 0.001, *P < 0.005.

**Fig. 3.** Calculated fall in blood PO₂ with decreasing blood O₂ content (C O₂) for protocol IH (solid curve), protocol PB (long dashed curve), and protocol CO (short dashed curve). Vertical lines, likely upper and lower estimates for C O₂ of jugular venous blood. Horizontal line, equivalent PO₂ from Adair equation associated with jugular venous O₂ saturation of 60.4%.
present study. The present study suggests that these effects of %HbCO and hemodilution do not occur in humans unless a fairly substantial degree of tissue hypoxia is induced, and, therefore, they are unlikely to underlie ventilatory acclimatization to mild or moderate hypoxia.

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