Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide

Philip N. Ainslie and Marc J. Poulin.

Departments of Physiology and Biophysics and Clinical Neurosciences, Faculty of Medicine, and Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada T2N 4N1

Submitted 22 December 2003; accepted in final form 1 March 2004

Ainslie, Philip N., and Marc J. Poulin. Ventilatory, cerebrovascular, and cardiovascular interactions in acute hypoxia: regulation by carbon dioxide. J Appl Physiol 97: 149–159, 2004. First published March 5, 2004; 10.1152/japplphysiol.01385.2003.—This study examined the effect of high, normal, and uncontrolled end-tidal P CO 2 (P ET CO 2) on the ventilatory, peak cerebral blood flow velocity (V p), and mean arterial blood pressure (MAP) responses to acute hypoxia. Nine healthy subjects underwent, in random order, three hypoxic protocols (end-tidal P O 2 was held at eight steps between 300 and 45 Torr) in conditions of hypercapnia, isocapnia, or poikilocapnia (P ET CO 2 > +7.5 Torr, +1.0 Torr, or uncontrolled, respectively). Transcranial Doppler ultrasound was used to measure V p in the middle cerebral artery. The slopes of the linear regressions of ventilation, V p, and MAP with arterial O 2 saturation were significantly greater in hypercapnia than in both isocapnia and poikilocapnia (P < 0.05). Strong, significant correlations were observed between ventilation, V p, and MAP with each P ET CO 2 condition. These data suggest that 1) a high acute hypoxic ventilatory response (AHVR) decreases the acute hypoxic cerebral blood flow responses during poikilocapnia hypoxia, due to hypocapnic-induced cerebral vasoconstriction; and 2) in hypercapnic hypoxia, a high AHVR is associated with a high acute hypoxic cerebral blood flow response, demonstrating a linkage of individual sensitivities of ventilation and cerebral blood flow to the interaction of P ET CO 2 and hypoxia. In summary, the between-individual variability in AHVR is shown to be firmly linked to the variability in V p and MAP responses to hypoxia. Individuals with a high AHVR are found also to have high V p and MAP responses to hypoxia.

THE ACUTE HYPOXIC VENTILATORY response (AHVR) is enhanced by hypercapnia (8) and has substantial interindividual variability (13, 15). Such variability in hypoxic chemosensitivities may contribute to intersubject variation in pathophysiological responses under a variety of hypoxic conditions. For instance, a low AHVR is shown to be associated with poor performance at high altitude (35), more severe nocturnal desaturation in sleep apnea syndrome (19), hypercapnic respiratory failure in chronic obstructive pulmonary disease (21), and even near-death cases of bronchial asthma (17).

Acute hypoxia leads not only to changes in ventilation but also to changes in heart rate (HR), mean arterial blood pressure (MAP) (10, 11), and cerebral blood flow (CBF) (16, 30, 39). However, we have discovered no published evidence to suggest that the magnitude of the AHVR may also be reflected in similar changes in CBF and/or MAP during periods of acute hypoxia. Similarly, there seem to be no available data concerning the combined ventilatory, cerebrovascular, and cardiovascular responses to acute hypoxia in humans.

The aims of the present study, therefore, were 1) to examine the effect of high, normal, and uncontrolled end-tidal P CO 2 (P ET CO 2) levels on the ventilatory, peak cerebral blood flow velocity (V p) and MAP responses to acute hypoxia and 2) to examine the interrelationships between these responses to acute hypoxia during each different condition of P ET CO 2. We tested the hypothesis that changes in ventilatory sensitivities to hypoxia caused by changes in the background P ET CO 2 would also be reflected in, and potentially related to, subsequent changes in V p and cardiovascular sensitivities. Previously, it has been shown that the ventilatory responses to acute hypoxia were not different when the hypoxic stimulus was given in either a descending order or ascending order (20). Such data are not available regarding the effect of hypoxic stimulus on the cerebrovascular and cardiovascular responses. Therefore, a secondary objective of this study was to investigate whether the V p and cardiovascular responses to alterations in end-tidal P O 2 (P ET O 2) are different when P ET CO 2 is decremented from hyperoxia (P ET O 2 = 300 Torr) to hypoxia (P ET O 2 = 45 Torr) than when P ET O 2 is incremented from hypoxia (P ET O 2 = 45 Torr) to hyperoxia (P ET O 2 = 300 Torr).

METHODS

Subjects

Nine healthy male subjects [24.21 ± 3.54 (SD) yr] participated in this study. All subjects were given both verbal and written instructions outlining the experimental procedure, and written, informed consent was obtained. Participants were not taking any medication, all were nonsmokers, and none had any history of cardiovascular, cerebrovascular, or respiratory disease. The research study was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

Protocol

The experiments were conducted in our laboratory located 1,103 m above sea level, and the average barometric pressure for the study days was 663 ± 12 Torr. Each subject was studied on three occasions. Subjects were requested not to eat or drink caffeine-containing beverages within 4 h before their scheduled testing sessions in the laboratory. During the initial visit, resting end-tidal gases and estimates of hypoxic and hypercapnic ventilatory responses were measured, and the subjects became familiarized with the apparatus and experimental testing procedures. For the next two visits, subjects reported to the laboratory at the same time of day, with each visit separated by at least 3 days. During each of these visits, in a

Address for reprint requests and other correspondence: M. J. Poulin, Dept. of Physiology & Biophysics, Faculty of Medicine, Univ. of Calgary, Heritage Medical Research Bldg., Rm. 212, 3330 Hospital Drive NW, Calgary Alberta, Canada T2N 4N1 (E-mail: poulin@ucalgary.ca).

http://www.jap.org 8750-7587/04 $5.00 Copyright © 2004 the American Physiological Society

149
randomized design, subjects conducted three separate protocols. Each protocol was separated by a 45-min rest period. During each visit, the subject’s normal P$_{ETCO_2}$ and P$_{ETO_2}$ were measured before the experiment, while the subject was sitting quietly and comfortably for ~10 min. The inspired gas was sampled continuously (20 ml/min) via a fine catheter at the opening of one nostril by an adapted nasal O$_2$ therapy kit and analyzed for PO$_2$ and PCO$_2$ by mass spectrometer (AMIS 2000, Innovision, Odense, Denmark). Values for PO$_2$ and PCO$_2$ were sampled by a computer every 10 ms. P$_{ETO_2}$ and P$_{ETCO_2}$ were identified and recorded for each breath by using a computer and dedicated software (Chamber version 1.00, University Laboratory of Physiology, Oxford, UK).

**Incremental Step Hypoxic Protocol**

Each experimental protocol began with an 8-min period during which the subject breathed normally through a mouthpiece with the nose occluded by a nose clip. Respiratory volumes were measured with a turbine device and volume transducer (VMM-400, Interface Associates). Respiratory flow direction and timing information were obtained with a pneumotachograph and differential pressure transducer (RSS100-HR, Hans Rudolf, Kansas City, MO). Accurate control of the end-tidal gases was achieved by using the technique of dynamic end-tidal forcing and dedicated software (BreathM version 2.07, University Laboratory of Physiology, Oxford, UK). A controlling computer generated the inspired partial pressure of O$_2$ and CO$_2$ predicted to give the desired end-tidal partial pressures by using a fast gas-mixing system (33). The controlling computer received feedback of the measured end-tidal partial pressures on a breath-by-breath basis as the experiment progressed. These measured end-tidal values were then compared with the desired values, and the computer adjusted the initial predicted inspired gas mixture by using an integral proportional feedback algorithm based on the deviations of the measured end-tidal values from the desired end-tidal values (32). Using the same hypoxic ramp protocol, each subject conducted three protocols: 1) hypercapnic hypoxia (P$_{ETCO_2}$, held at 7.5 Torr above resting value), 2) isocapnic hypoxia (P$_{ETCO_2}$, held at 1.0 Torr above resting value), and 3) poikilocapnic hypoxia (P$_{ETCO_2}$ uncontrolled).

After an 8-min lead-in period of euoxia (P$_{ETO_2}$ = 88 Torr), the P$_{ETO_2}$ was increased to 300 Torr for 5 min. The hypoxic stimulus was then varied by holding the P$_{ETO_2}$ at eight different predetermined levels over the range of 300–45 Torr. These levels of hypoxia were calculated to provide equal steps in oxygen saturation of the arterial blood (S$_{aO_2}$), by using the relationship described by Severinghaus in 1979 (37). Each protocol was undertaken with the same steps of hypoxia, either in an ascending (P$_{ETO_2}$ = 45.0, 48.2, 52.0, 57.0, 64.0, 75.2, 88.0, and 300.0 Torr) or descending order (P$_{ETO_2}$ was increased to 300 Torr for 5 min. The hypoxic stimulus was then compared with the desired values, and the computer adjusted the initial predicted inspired gas mixture by using an integral proportional feedback algorithm based on the deviations of the measured end-tidal values from the desired end-tidal values (32). Using the same hypoxic ramp protocol, each subject conducted three protocols: 1) hypercapnic hypoxia (P$_{ETCO_2}$, held at 7.5 Torr above resting value), 2) isocapnic hypoxia (P$_{ETCO_2}$, held at 1.0 Torr above resting value), and 3) poikilocapnic hypoxia (P$_{ETCO_2}$ uncontrolled).

After an 8-min lead-in period of euoxia (P$_{ETO_2}$ = 88 Torr), the P$_{ETO_2}$ was increased to 300 Torr for 5 min. The hypoxic stimulus was then varied by holding the P$_{ETO_2}$ at eight different predetermined levels over the range of 300–45 Torr. These levels of hypoxia were calculated to provide equal steps in oxygen saturation of the arterial blood (S$_{aO_2}$), by using the relationship described by Severinghaus in 1979 (37). Each protocol was undertaken with the same steps of hypoxia, either in an ascending (P$_{ETO_2}$ = 45.0, 48.2, 52.0, 57.0, 64.0, 75.2, 88.0, and 300.0 Torr) or descending order (P$_{ETO_2}$ = 300.0, 88.0, 75.2, 64.0, 57.0, 52.0, 48.2, and 45.0 Torr), with each step lasting 90 s, as illustrated in Fig. 1.

**Measurement of CBF, HR, and Blood Pressure**

Backscattered Doppler signals from the right middle cerebral artery (MCA) were measured continuously during the protocol by using a 2-MHz pulsed Doppler Ultrasound system (TC22, SciMed, Bristol, UK). The MCA was identified by an insonation pathway through the right temporal window just above the zygomatic arch by using search techniques described previously (28). The Doppler probe was secured with a headband device (Müller and Moll Fixation, Nicolet Instruments, Madison, WI) to maintain optimal insonation position and angle throughout the protocol. In this study, the peak blood velocity was acquired every 10 ms and averaged over each heartbeat (V$_{p}$), and this was used as the primary index of CBF (29). During each test, MAP and HR were measured continuously by using finger photoplethysmography (Portapress, TPD Biomedical Instrumentation) and a three-lead ECG arrangement (Micromon 7142B monitor, Kontron Medical), respectively.

**Data and Statistical Analyses**

The AHVR, the acute hypoxic CBF response (AHR$_{CBF}$), the acute hypoxic HR response (AHR$_{HR}$), and the acute hypoxic MAP response (AHR$_{MAP}$) were determined by linear regression between the mean ventilation (V$_{E}$), V$_{p}$, HR, and MAP with S$_{aO_2}$, (100 – S$_{aO_2}$) during the final 15 s of each incremental step of hypoxia. Sensitivity of these dependent variables was calculated from the slopes of the linear regressions between ventilation, CBF, and MAP with S$_{aO_2}$, (100 – S$_{aO_2}$) (see Table 2 and Figs. 4A, 5A, and 6A). To calculate the percent (%) change from baseline, data were averaged over the 5-min period of euoxia immediately preceding any changes in P$_{ETO_2}$. Because there were no discernible differences between the ascending and descending conditions, data from the two conditions were combined for further statistical analysis. Data were initially tested for normality, before being analyzed by repeated-measures analysis of variance, where appropriate. Post hoc tests (Tukey) were performed to isolate any significant differences. Resting end-tidal gases, V$_{E}$, V$_{p}$, HR, MAP, and the V$_{E}$, V$_{p}$, HR, and MAP sensitivities to hypoxia and hypercapnia between each day were compared statistically by using a Student’s paired t-test. Nonparametric equivalents included Wilcoxon matched pairs signed ranks and Kruskal-Wallis tests. The relationships between selected dependent variables was assessed by using a Pearson product-moment correlation (Figs. 4–6). Significance for all two-tailed tests was established at an α-level of P < 0.05, and data are expressed as means ± SD. The between-day intersubject variability in all of the dependent variables was assessed by determining the coefficients of variation (standard deviation of the difference/ grand mean × 100).

**RESULTS**

**Subjects**

All subjects completed each test in both the descending and ascending protocols. Four of the nine subjects reported subjec-

Fig. 1. Schematic of the experimental protocols illustrating the desired time-related alterations of end-tidal PO$_2$ (P$_{ETO_2}$), arterial oxygen saturation (S$_{aO_2}$), and end-tidal PCO$_2$ (P$_{ETCO_2}$). A: ascending protocol. B: descending protocol.
tive discomfort during the first step of the hypercapnic hypoxic protocol; these were more marked during the ascending protocol, compared with those reported during the descending protocol. These four subjects had the highest AHVR and acute hypercapnic ventilatory response sensitivities. Despite the reported discomfort, all data from the nine subjects were included in the final analysis.

**General Observations**

Resting $V_{p}$, ventilation, HR, MAP, and the ventilatory and CBF sensitivities to CO$_2$ were not different between the descending and ascending protocols and showed a low between-day variability (Table 1). Similarly, the ventilatory, CBF, HR, and MAP sensitivities to CO$_2$ (calculated from the slope of the isocapnic-to-hypocapnic PET$_{CO_2}$ relationship) were not different between trials (Table 1). The order of the hypoxic stimulus did not elicit any differences in the AHR$_{CBF}$, AHVR, AHR$_{HR}$, or AHR$_{MAP}$ (Table 2). Therefore, data from the ascending and descending conditions were combined.

The general pattern of ventilatory, $V_{p}$, MAP, and PET$_{CO_2}$ responses during each condition are illustrated in Fig. 2. A trend was present in the isocapnic condition (Fig. 2). Representative sample results from one subject (identification no. 0037) during the descending and ascending experimental protocols are illustrated in Fig. 3, which highlights the main dependent outcome variables measured during each experiment from one typical subject.

**Hypoxic Sensitivities and Comparison to Hyperoxic Controls**

**Ventilatory data.** On average, compared with the isocapnic conditions, the AHVR was increased by 1.07 l.min$^{-1}$·%$^{-1}$ (47%; $P < 0.05$) in the hypocapnic conditions and increased by 1.75 l.min$^{-1}$·%$^{-1}$ (77%; $P < 0.05$) in the poikilocapnic conditions. As mentioned, the order of the hypoxic stimulus did not elicit any differences in the AHVR responses, although a trend was present in the isocapnic condition ($P = 0.09$) (see Table 2). Compared with the hyperoxic control baseline, VE at the lowest level of hypoxia (PET$_{O_2}$ = 45 Torr) was increased by 9.1, 41.1, and 57.4 l/min in the poikilocapnic, isocapnic, and hypocapnic conditions, respectively (Table 3). Compared with the isocapnic hyperoxic baseline at the lowest level of hypoxia, VE was increased by 6.2 and 95.3 l/min in the poikilocapnic and hypocapnic conditions, respectively (Table 3). Furthermore, when expressed as the change from the relative hyperoxic control, increases in ventilation of 9.1 l/min (86%; $P < 0.001$) in the poikilocapnic condition and 19.4 l/min (180%; $P < 0.001$) in the hypocapnic condition were observed.

### Table 1. Reproducibility of measurements between each of the ascending and descending hypoxic protocols

<table>
<thead>
<tr>
<th></th>
<th>Ascending</th>
<th>Descending</th>
<th>$P$ Value</th>
<th>$R$</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resting measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting $V_{p}$, cm/s</td>
<td>56.6±6.9</td>
<td>57.4±6.8</td>
<td>0.91</td>
<td>0.93</td>
<td>4.9</td>
</tr>
<tr>
<td>Resting VE, l.min$^{-1}$</td>
<td>9.7±3.5</td>
<td>9.3±3.3</td>
<td>0.19</td>
<td>0.82</td>
<td>6.7</td>
</tr>
<tr>
<td>Resting PET$_{CO_2}$, Torr</td>
<td>37.4±1.5</td>
<td>37.6±1.7</td>
<td>0.91</td>
<td>0.90</td>
<td>3.5</td>
</tr>
<tr>
<td>Resting PET$_{O_2}$, Torr</td>
<td>89.8±3.3</td>
<td>88.9±2.4</td>
<td>0.94</td>
<td>0.92</td>
<td>3.4</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>56.5±11.9</td>
<td>56.5±6.9</td>
<td>0.95</td>
<td>0.94</td>
<td>2.3</td>
</tr>
<tr>
<td>Resting MAP, mmHg</td>
<td>82.6±12.4</td>
<td>79.8±10.7</td>
<td>0.46</td>
<td>0.87</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>CO$_2$ sensitivities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHVR, 1·min$^{-1}$·%$^{-1}$</td>
<td>4.8±2.4</td>
<td>4.7±1.9</td>
<td>0.36</td>
<td>0.90</td>
<td>12.4</td>
</tr>
<tr>
<td>Vp-CO$_2$ sensitivity, cm·s$^{-1}$·Torr$^{-1}$</td>
<td>2.8±1.1</td>
<td>2.5±1.3</td>
<td>0.83</td>
<td>0.89</td>
<td>10.4</td>
</tr>
<tr>
<td>HR-CO$_2$ sensitivity, beats·min$^{-1}$·Torr$^{-1}$</td>
<td>1.3±1.0</td>
<td>1.4±0.6</td>
<td>0.21</td>
<td>0.91</td>
<td>9.7</td>
</tr>
<tr>
<td>MAP-CO$_2$ sensitivity, mmHg/Torr</td>
<td>1.0±1.1</td>
<td>1.1±1.1</td>
<td>0.87</td>
<td>0.91</td>
<td>14.2</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 9$. AHVR, acute hypoxic ventilatory response; pHVR, poikilocapnic hypoxic ventilatory response; $\Delta$, change; SaO$_2$, arterial O$_2$ saturation; AHR$_{CBF}$, acute hypocapnic cerebral blood flow response; AHR$_{HR}$, acute hypocapnic HR response; AHR$_{MAP}$, acute hypoxic MAP response. Significant difference from poikilocapnic conditions: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. Significant difference from isocapnic conditions: †‡$P < 0.05$. There were no significant between-condition (ascending vs. descending) differences.

### Table 2. Ventilatory, cerebrovascular, and cardiovascular sensitivities during poikilocapnic, isocapnic, and hypocapnic hypoxic conditions in both ascending and descending protocols

<table>
<thead>
<tr>
<th>Sensitivities</th>
<th>Poikilocapnia</th>
<th>Isocapnia</th>
<th>Hypocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ascending</td>
<td>Descending</td>
<td>Ascending</td>
</tr>
<tr>
<td>AHVR, 1·min$^{-1}$·%$^{-1}$</td>
<td>0.43±0.34</td>
<td>0.61±0.51</td>
<td>2.60±1.15*</td>
</tr>
<tr>
<td>pHVR, Torr%/($\Delta$PET$_{CO_2}$/ΔSaO$_2$)</td>
<td>0.23±0.29</td>
<td>0.27±0.3</td>
<td>0.73±0.30*</td>
</tr>
<tr>
<td>AHR$_{CBF}$, cm·s$^{-1}$·%$^{-1}$</td>
<td>0.14±0.24</td>
<td>0.11±0.40</td>
<td>1.05±0.47</td>
</tr>
<tr>
<td>AHR$_{HR}$, beats·min$^{-1}$·%$^{-1}$</td>
<td>0.84±0.36</td>
<td>0.92±0.31</td>
<td>0.70±0.31*</td>
</tr>
<tr>
<td>AHR$_{MAP}$, mmHg%/</td>
<td>0.24±0.27</td>
<td>0.31±0.33</td>
<td>0.73±0.30*</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 9$. AHVR, acute hypoxic ventilatory response; pHVR, poikilocapnic hypoxic ventilatory response; $\Delta$, change; SaO$_2$, arterial O$_2$ saturation; AHR$_{CBF}$, acute hypocapnic cerebral blood flow response; AHR$_{HR}$, acute hypocapnic HR response; AHR$_{MAP}$, acute hypoxic MAP response. Significant difference from poikilocapnic conditions: *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. Significant difference from isocapnic conditions: †‡$P < 0.05$. There were no significant between-condition (ascending vs. descending) differences.
Values are means ± SD; n = 9. ▲, Hypercapnic protocol; ○, isocapnic protocol; ●, poikilocapnic protocol.

Fig. 2. Ventilatory, peak cerebral blood flow velocity (Vp), and mean arterial blood pressure (MAP) responses to acute hypercapnic, isocapnic, and poikilocapnic hypoxia. Data are combined from ascending and ascending conditions.
the isocapnic \((r = 0.46; P = 0.56)\) condition (Fig. 5A). When all of the individual data points are included in the regression analysis, significant relationships were evident between \(V_T\) and \(V_E\) in the hypercapnic \((r = 0.70; P < 0.01)\), isocapnic \((r = 0.69; P < 0.01)\), and poikilocapnic \((r = -0.39; P < 0.05)\) conditions (Fig. 5B).

MAP and AHVR. There were significant correlations between the AHRMAP and AHVR sensitivities in the hypercapnic \((r = 0.76; P < 0.01)\) but not in the isocapnic \((r = 0.32; \text{NS})\) or the poikilocapnic \((r = -0.27; \text{NS})\) conditions (Fig. 6A). When all of the individual data points are included into regression analysis, significant relationships were evident between MAP and \(V_E\) in both the hypercapnic \((r = 0.72; P < 0.01)\) and isocapnic \((r = 0.71; P < 0.01)\) conditions, but not in the poikilocapnic \((r = 0.03; \text{NS})\) condition (Fig. 6B).

DISCUSSION

Main Findings

This study reports three main findings. First, the integrative ventilatory, cerebrovascular, and cardiovascular responses to hypoxia are strongly influenced by \(\text{PETCO}_2\), regardless of
whether or not the hypoxic stimulus was in a descending or ascending order. These findings imply that the order of the hypoxic stimulus to the level of 45 Torr (SaO2 ~80%) does not influence the pattern of the cerebrovascular or cardiovascular responses. Second, with poikilocapnia, a high AHVR blocks much of the hypoxic Vp response. Conversely, during periods of hypercapnic hypoxia, a high AHVR is associated with a high AHRCBF, demonstrating a linkage of individual sensitivities of ventilation and CBF to the interaction of PCO2 and hypoxia. Finally, the between-individual variability in AHVR is shown to be firmly linked to the variability in Vp and MAP responses to hypoxia. Individuals with a high AHVR are found also to have high Vp and MAP responses to hypoxia. The following discussion details the evidence and assumptions that underlie these conclusions.

**Ventilatory and Vp Responses to Hypoxia**

CBF rises in proportion to the severity of isocapnic hypoxia in all mammals. However, during poikilocapnic hypoxia, considerable variability exists between individuals and species because of the wide variability in AHVR, which determines how far the PCO2 falls (36). A strong AHVR and a large fall in PCO2 in experimental subjects led to early reports that hypoxia-induced cerebral vasodilation was a threshold phenomenon, scarcely beginning until arterial PO2 (Pao2) had fallen to ~30 Torr (39). Our results from the poikilocapnic protocol are not inconsistent with this “threshold phenomenon,” i.e., the vasodilatory effects of the hypoxia appear to be balanced by the vasoconstrictive effects of hypocapnia throughout the range of hypoxia, resulting in little change in the CBF.

Using isocapnia in nine healthy male volunteers, Cohen et al. (45) reported that step reduction of Pao2 to 40 Torr increased CBF by 156% in isocapnia but only by 68% during poikilocapnic conditions (arterial Pco2 decreased from 36 to 28 Torr). These aforementioned studies would suggest that the effect of isocapnia is a doubling of the hypoxic increase in CBF compared with poikilocapnia. The present study, using transcranial Doppler ultrasound, would suggest that, at the lowest level of hypoxia (PETCO2 = 45 Torr), values in parentheses represent percent change, at the lowest level of hypoxia, from hyperoxic control within each condition. Significant difference from poikilocapnic conditions: *P < 0.05, *P < 0.01, *P < 0.001. Significant difference from isocapnic conditions: dP < 0.05, cP < 0.01, bP < 0.001.

### Table 3. Change in PETCO2, V̇E, Vp, and MAP from isocapnic hyperoxic protocol and from within each hyperoxic control baseline at the lowest level of hypoxia (PETO2 = 45 Torr) during poikilocapnic, isocapnic, and hypercapnic conditions

<table>
<thead>
<tr>
<th>PETCO2, Torr</th>
<th>Poikilocapnia</th>
<th>Isocapnia</th>
<th>Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>PETCO2 (at PETO2 = 45 Torr)</td>
<td>32.0 ± 3.2</td>
<td>38.9 ± 1.9e</td>
<td>46.3 ± 1.8f</td>
</tr>
<tr>
<td>ΔPETCO2 (at PETO2 = 45 Torr)</td>
<td>−4.9 ± 2.0</td>
<td>−0.01 ± 0.01e</td>
<td>0.03 ± 0.01c</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hyperoxic control</th>
<th>Poikilocapnia</th>
<th>Isocapnia</th>
<th>Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇E, l/min</td>
<td>10.5 ± 3.2</td>
<td>13.4 ± 3.1</td>
<td>51.3 ± 17.0e</td>
</tr>
<tr>
<td>V̇E, cm/s</td>
<td>51.8 ± 8.9</td>
<td>55.5 ± 7.3</td>
<td>737 ± 12.3f</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>86.6 ± 13.0</td>
<td>79.1 ± 10.8</td>
<td>85.6 ± 10.9</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 9. ΔPETCO2, change in PETCO2 at lowest level of hypoxia (PETO2 = 45 Torr) from hyperoxic baseline (see Fig. 1): hyperoxic control, data averaged over the hyperoxic control period (PETO2 = 300 Torr) in each condition; Δ from isocapnic hyperoxic control (PETO2 = 45 Torr), poikilocapnic, isocapnic, and hypercapnic data as the change from the isocapnic hyperoxic control values. Values in parentheses represent percent change, at the lowest level of hypoxia, from isocapnic hyperoxic control (PETO2 = 300 Torr). Δ from hyperoxic control, change from hyperoxic control within each condition at the lowest level of hypoxia (PETO2 = 45 Torr). Values in parentheses represent percent change, at the lowest level of hypoxia, from hyperoxic control within each condition. Significant difference from poikilocapnic conditions: *P < 0.05, *P < 0.01, *P < 0.001. Significant difference from isocapnic conditions: dP < 0.05, cP < 0.01, bP < 0.001.
creases in MAP. We speculate on two possible, potentially related explanations for this relationship. The first explanation is related to the effect of an enhanced cardiovascular response on peripheral chemosensitivity. Both acute hypoxia (44) and acclimatization to altitude (3, 12) have been shown to elicit large increases in sympathetic overactivity. The effect of such an enhanced sympathetic activation on respiration might be mediated through sympathetic efferents innervating the carotid bodies (24). An alternative explanation for the relationship is a modulatory effect of afferent nerve traffic from pulmonary stretch receptors on sympathetic neurons in the brain stem mediated through central connections between respiratory and sympathetic neurons (4). The second explanation for the significant correlations between ventilatory chemosensitivity and the MAP explores the opposite possibility: the effect of enhanced chemosensitivity on maintenance of MAP during hypoxic stimulation. It is accepted that systemic arterial blood pressure is maintained primarily by the carotid chemoreceptor reflex during hypoxic stimulation, that is, pressor responses, which are caused by vasoconstriction in the peripheral vascular beds and by enhanced cardiac output (6). Because there was a significant increase in carotid chemoreceptor reflex sensitivities during the isocapnic- and hypercapnic-hypoxic conditions, it is conceivable that this is an important mediator of the enhanced MAP sensitivity.

\( V_p \) and \( AHVR \). During the poikilocapnic condition, a strong negative relationship was found between the AHVR and the AHRBF sensitivities. This relationship is perhaps not surprising because a higher AHVR will block much of the CBF response due to hypocapnic-induced cerebral vasoconstriction secondary to the increased ventilation (36). In the present study, there were significant correlations between the ventilatory and \( V_p \) responses and their sensitivities during the hypoxic-hypercapnic condition. The effect of hypoxia and hypercapnia is known to attenuate normal cerebral autoregulatory mechanisms, and, therefore, increases in MAP are likely to cause increases in cerebral perfusion pressure and \( V_p \) (2, 26). Activation of the sympathetic nervous system explains the

![Graph](http://jap.physiology.org.org)
correlation between ventilatory and \( V_p \) responses to hypoxia during hypercapnia only under the assumption that \( V_p \) passively follows MAP. Our data clearly show a strong, positive relationship between the increases in MAP and \( V_p \). Such a relationship raises the possibility that, when normal cerebral autoregulatory mechanisms are attenuated, \( V_p \) passively follows blood pressure; however, this has yet to be confirmed in humans, and a number of other explanations should be considered. For example, increased tidal volume will make pleural pressures more negative and, in turn, will reduce venous and cerebral spinal fluid pressures, thus increasing the perfusion pressure (26). Therefore, the strong correlations between \( V_p \) and AHVR may be explained, at least in part, by the mechanical effects of hyperventilation.

**Role of Increased Respiratory Effort**

Both the isocapnic- and hypercapnic-hypoxic conditions stimulated large increases in ventilation and thus respiratory effort. Previously, it has been suggested that increases in respiratory effort per se can produce sympathoexcitation via a number of pathways (43). In addition, feedback pathways involving mechanoreflexes or metaboreflexes, arising from the respiratory muscles, might be activated during the hypercapnic-hypoxic-induced hyperventilation (41). An important question that arises is, to what extent are our results caused by the hypercapnic-hypoxic-induced peripheral and central chemoreflex stimulation per se to that of the secondary influence of the hyperpnea? From the data in the present study, we cannot address this question. However, an elegantly designed study by Halliwill et al. (10), using isocapnic hypoxia (\( \text{SaO}_2 \sim 85\% \)) and matched isocapnic hyperpnea, provides data to suggest that the increases in HR and sympathetic outflow observed at altitude or during exposure to hypoxia are indeed the result of peripheral activation per se and not secondary to the concomitant hyperpnea and hypocapnia. In contrast, very little has been reported on the role of isocapnic hyperpnea in the regulation of

![Graphs](http://jap.physiology.org/)
CBF. In the highly controlled, anesthetized cat model, Neubauer et al. (22) provided data to show that an increase in respiratory output, produced by either hindlimb stimulation or carotid sinus nerve (without any change in blood-gas composition), is associated with an increase in blood flow (19–22%). The authors conclude that such increase in ventilatory medulla blood flow reflects an increase in the metabolism of the ventilatory medulla due to activation of respiratory neurons. As mentioned, the mechanical effects of hyperventilation may also play a role in producing increases in cerebral perfusion pressure and, therefore, CBF. To the best of our knowledge, we have not found any human studies that have investigated the effect of isocapnic hyperpnea or hyperventilation on inducing changes in CBF. However, we acknowledge the distinct possibility that isocapnic hyperpnea per se may play a significant role in increasing ventilatory medulla blood flow and, therefore, is important in the interpretation of our results. Although we measured the blood velocity in the MCA, and not in the basilar artery, which provides the blood supply to the brain stem, the important finding from the present study is the linkage of responses within each subject.

**Limitations of Experimental Approach**

*Estimation of CBF.* We used Doppler ultrasound to measure flow velocity, rather than blood flow, in the MCA. Nevertheless, we believe that velocity is a reasonable estimate of flow in our experiments because 1) the diameter of the MCA has been shown to vary by <4% during changes in arterial pressure and CO₂ tension (9), and 2) velocity and flow through the MCA are highly correlated (9). Our estimates of cerebrovascular CO₂ reactivity [2.68 cm²·s⁻¹·mmHg⁻¹ (4–5%/Torr) for hypercapnia] are consistent with previous reports based on measurements of tissue nitrous oxide uptake (16), functional magnetic resonance imaging (34), positron emission tomography (31), ¹³⁵Xe washout (42), and other transcranial Doppler ultrasound studies (14, 28). In further support, previously studies by Poulin and Robbins (29, 30) have investigated the relative changes in MCA diameter by using the transcranial Doppler power signal. The authors demonstrated that MCA diameter remained relatively constant during conditions comparable to these in the present study (29, 30). In our study, over the course of each protocol and condition, Doppler power remained relatively constant.
unchanged, suggesting that there was little, if any, change in cross-sectional area of the MCA.

An important consideration is whether steady-state \( V_p \) was reached during the hypoxic steps of 90 s. Earlier studies in humans (7, 38) and in the anesthetized monkey (46) suggested that 6–7 min were required for the CBF response to hypoxia to reach its maximal response. More recent work incorporating transcranial Doppler ultrasound and dynamic end-tidal forcing, a system that can provide rapid changes in \( \text{PE}_{\text{CO}_2} \) within one or two breaths, has shown that the \( V_p \) responses to hypoxia are much faster than previously considered (28). Furthermore, the \( V_p \) responses to isocapnic hypoxia reported in this study are comparable with those of previous studies using shorter (i.e., 60 s) and longer (i.e., 20 min) (27, 28) hypoxic stimuli, compared with those used in this study, suggesting that the 90-s incremental steps at each level of hypoxia were sufficiently long for the \( V_p \) responses to unfold.

**Blood pressure measurements.** We used photoplethysmography to measure finger arterial pressure at rest and during the acute hypoxic tests. Although photoplethysmographic measurements correlate well with intra-arterial measurements during experimental manipulations of arterial pressure (25), the absolute values can sometimes be inaccurate. Nonetheless, in our laboratory under carefully controlled conditions, the resting photoplethysmographic measurements compared closely with manual measurements from sphygmomanometer recordings (<4.6% difference between photoplethysmographic and manual measurements, \( n = 37 \) measurements; unpublished observations). Furthermore, the relative change in MAP is the relevant variable for the calculated sensitivity measurements used in the present study.

**Statistical power and correlational analyses.** Due to the relatively small number of subjects studied, an important consideration is whether or not this study had adequate statistical power to support the conclusions reached. The repeated-measures design of the study, combined with a very strong within-subjects intraclass correlation and low coefficients of variation (Table 1) for the dependent variables of interest, largely offsets the potential lack of power risked by using a small number of subjects. This is evidenced by highly significant effects for many of the dependent variables. In addition, post hoc power calculations revealed an average power of >0.81 for the calculations involving the majority of the dependent variables. Another important consideration is the use of correlations and the subsequent proposals of physiological mechanisms for a link between such data. To avoid any spurious correlations, and hence false conclusions, we avoided investigating relationships between variables that have “common divisors.” The use of such common divisors would result in probable spurious correlations (18) and hence wrongful interpretation of our results. Although we recognize the limitations of correlational analysis, we feel justified in the proposal of physiological mechanisms for a link between our data and are confident that the data are not spuriously related or as a result of a statistical artifact.

In summary, the results of the present study provide insight into the complex integration of the ventilatory, cardiovascular, and cerebrovascular control systems during periods of acute hypoxia in awake humans. The between-individual variability in AHVR is shown to be firmly linked to the variability in \( V_p \) and MAP responses to hypoxia. Individuals with a high AHVR are found also to have high \( V_p \) and MAP responses to hypoxia.

**ACKNOWLEDGMENTS**

We extend our gratitude to Professor P. A. Robbins for assistance in setting up the dynamic end-tidal forcing technique in Calgary. We extend our thanks to Professor J. E. Remmers for informative discussions and feedback on the manuscript.

**GRANTS**

This project was supported by the Alberta Heritage Foundation for Medical Research (AHFMR), Heart and Stroke Foundation of Alberta, NWT, and Nunavut, and the Canadian Institutes of Health Research (CIHR). P. N. Ainslie is supported by a Focus-on-Stroke postdoctoral fellowship (Heart and Stroke Foundation of Canada, the Canadian Stroke Network, CIHR, and AstraZeneca Canada). M. J. Poulin is a CIHR New Investigator and AHFMR Medical Scholar.

**REFERENCES**

19. Kunimoto F, Kimura H, Tatsumi K, Okita S, Tójima H, Kuriyama T, and Honda Y. Abnormal breathing during sleep and chemical control of...


