Cardiovascular and cerebrovascular responses to acute isocapnic and poikilocapnic hypoxia in humans

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Steinback CD, Poulin MJ. Cardiovascular and cerebrovascular responses to acute isocapnic and poikilocapnic hypoxia in humans. J Appl Physiol 104: 482–489, 2008. First published November 29, 2007; doi:10.1152/japplphysiol.00553.2007.—We examined the cardiovascular and cerebrovascular responses to acute isocapnic (IH) and poikilocapnic hypoxia (PH) in 10 men (25.7 ± 4.2 yr, mean ± SD). Heart rate (HR), mean arterial pressure (MAP), and mean peak middle cerebral artery blood flow velocity (Vr) were measured continuously during two randomized protocols of 20 min of step IH and PH (45 Torr). HR was elevated during both IH (P < 0.01) and PH (P < 0.01), with no differences observed between conditions. MAP was modestly elevated across all time points during IH but only became elevated after with no differences observed between conditions. Mean arterial pressure (MAP) was elevated from baseline throughout the exposure with a consistent hypoxic sensitivity of ∼0.34 cm·s⁻¹·%desaturation⁻¹ (P < 0.05). The Vr response to PH was biphasic with an initial decrease from baseline occurring at 79 ± 23 s, followed by a subsequent elevation, becoming equivalent to the IH response by 10 min. The nadir of the PH response exhibited a hypoxic sensitivity of ∼0.24 cm·s⁻¹·%desaturation⁻¹. When expressed in relation to end-tidal PCO₂, a sensitivity of ∼1.08 cm·s⁻¹· Torr⁻¹ was calculated, similar to previously reported sensitivities to euoxic hypocapnia. Cerebrovascular resistance (CVR) was not changed during IH. During PH, an initial increase in CVR was observed. However, CVR returned to baseline by 20 min of PH. These data show the cerebrovascular response to PH consists of an early hypocapnia-mediated response, followed by a secondary increase, mediated predominantly by hypoxia.

The hypoxia of altitude, concomitant with a systemic alkalosis, places a unique stress on the cardiorespiratory system. At the onset of exposure, a rise in cardiac output is observed that is driven by increases in heart rate (HR). With longer exposure (days to weeks), cardiac output then falls in conjunction with stroke volume while HR remains elevated (6, 10, 29, 50). Under these conditions, inadequate adaptations may result in exercise fatigue or, worse, deteriorate into life-threatening conditions such as acute mountain sickness or pulmonary or cerebral edema. Further, in other pathological situations where respiratory and/or cardiovascular function is compromised (e.g., sleep apnea or pulmonary hypertension), secondary ailments may also evolve due to cardiorespiratory linkages. Thus an understanding of cardiorespiratory interactions is important from basic and applied physiology and clinical perspectives.

Previous investigations of the cardiovascular responses to acute hypoxia have typically focused on discreet “steady-state” time points many minutes into a hypoxic exposure. Additionally, experiments designed to investigate the cardiovascular response to specific carotid body stimulation have generally been carried out with isocapnia, thereby avoiding the concomitant hypocapnia that is typically associated with hypoxia at altitude. Since carbon dioxide is a known, potent regulator of blood flow (37), the influence of changes in Paco₂ need to be accounted for when studying the effects of hypoxia where concomitant hypocapnia may influence the local vasculature, the chemical regulation of cardiovascular responses, and integrated cardiorespiratory control.

The early work of Shapiro et al. (43) attempted to address the influence of euacapnic vs. isocapnic hypoxia on CBF in humans. This work elegantly illustrated a blunting of CBF due to alkalosis in the face of ongoing hypoxia. However, technical limitations precluded a comprehensive comparison between similar levels of hypoxia, nor was an investigation of other cardiovascular factors carried out. In a previous investigation from our laboratory, the cardiovascular and cerebrovascular responses to hypoxia were assessed using a multistep hypoxic design (4). In that study, hypocapnic hypoxia was shown to blunt cerebrovascular and cardiovascular sensitivities to hypoxia. However, the multistep approach did not allow the investigation of the time course of cerebrovascular and cardiovascular adaptation to hypoxia. Taken together, these data indicate a key role of arterial hypocapnia but highlight the need to further investigate the dynamic cardiovascular effects of hypoxia in the presence of hypocapnia.

The present investigation was part of a larger, multifaceted study comparing the dynamic cardiorespiratory responses to...
isocapnic vs. poikilocapnic hypoxia in humans. In a previous study, we showed that controlling $P_{aCO_2}$ critically affected dynamic respiratory responses during systemic hypoxia (45). In this context, it appears that the concomitant alkalosis associated with poikilocapnic hypoxia blunts the overall ventilatory response and influences ventilatory components but does not play a role in the pattern of ventilatory adaptation to hypoxia. It remains unclear whether alkalosis affects the dynamic nature of the cardiovascular response to hypoxia similarly.

Thus the present study investigates dynamic cardiovascular and cerebrovascular responses to hypoxia, as influenced by changes in $P_{aCO_2}$ in the hypocapnic range. Furthermore, we examined the influence of respiration on cardiovascular control by combining the novel data and analyses on cardiorespiratory interaction presented in the present study with those previously published respiratory observations (45).

We utilized single-step hypoxic exposures with and without controlled $P_{CO_2}$ to separate the effects of predominant hypoxia from those of concomitant hypocapnia. Further, hypoxia was maintained during both conditions for a duration of 20 min such that the temporal aspects of the cardiovascular responses could be investigated. Although previous studies have investigated the effects of alkalosis on cardiovascular function during hypoxia, to our knowledge a rigorous comparison of the dynamic characteristics of the cardiovascular and cerebrovascular responses to poikilocapnic and isocapnic hypoxia has not been conducted in humans.

We hypothesized that the hypoxic stimulus would influence the shape of the dynamic pattern of cardiovascular and cerebrovascular responses, while hypocapnic alkalosis would act to suppress these patterns. Additionally, we predicted that the profiles of the cardiovascular and cerebrovascular responses undergo adaptation over time such that as hypoxia progresses a gradual fall in HR, mean arterial pressure (MAP), and CBF ensues. We speculate that this adaptation to hypoxia might be mediated by a cardioventilatory interaction, associated with the phenomenon of hypoxic ventilatory decline (HVD).

METHODS

Subjects. Ten healthy men (25.7 ± 4.2 yr, mean ± SD) participated in this study. All subjects provided informed written consent after receiving verbal and written instructions outlining the experimental procedures. Participants were not taking any medications, all were nonsmokers, and none had any history of cardiovascular or respiratory disease. This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (Grant ID no. 15671) and conforms to the standards set by the Declaration of Helsinki.

Protocol. Experiments were conducted at an elevation of 1,103 m and a barometric pressure of 665 ± 5 Torr. Subjects abstained from caffeine, alcohol, and strenuous exercise for 12 h before testing. During experimentation, subjects took part in two randomized protocols separated by a 40-min rest period.

Before each protocol, subjects’ resting end-tidal $P_{O_2}$ ($P_{ETO_2}$) and $P_{CO_2}$ ($P_{ETCO_2}$) were measured for ~10 min with the subject in a comfortable semisupine position. Respired gas was sampled continuously (20 ml/min) via a small-bore catheter (0.3-mm internal diameter) and analyzed for $P_{O_2}$ and $P_{CO_2}$ by mass spectrometer (AMIS 2000, Innovision, Odense, Denmark). Values for $P_{O_2}$ and $P_{CO_2}$ were sampled by computer every 10 ms, and $P_{ETO_2}$ and $P_{ETCO_2}$ were identified and recorded for each breath using a computer and dedicated software (Chamber v2.10, University Laboratory of Physiology, Oxford, UK).

Each protocol began with a 10-min baseline period during which the subject breathed normally through a facemask, which allowed for natural mouth and/or nasal breathing (model 16709, ResMed, Poway, CA). Accurate control of end-tidal gases was achieved using the technique of dynamic end-tidal forcing (4, 38, 39) and dedicated software (BreatheM v2.35, University Laboratory of Physiology).

After 10 min of euoxia ($P_{ETO_2}$ ~ 88 Torr), $P_{ETO_2}$ was decreased within 2–3 breaths to 45 Torr. During an isocapnic hypoxic protocol (IH), $P_{ETCO_2}$ was held constant at +1 Torr above resting (45). During a poikilocapnic hypoxic protocol (PH), $P_{ETCO_2}$ was allowed to vary naturally. Hypoxia was maintained for 20 min, after which period $P_{ETO_2}$ was returned to 88 Torr for 10 min.

Cardiovascular measurements. Backscatter Doppler signals from the right middle cerebral artery (MCA) were measured continuously using a 2-MHz pulsed Doppler ultrasound system (PCDOP 842, SciMed) using previously published methods and criteria (1, 32, 34).

Briefly, the MCA was sonomed through the right temporal window superior to the zygomatic arch. Focal depth and probe angle were varied to maximize the peak Doppler frequency shift. Instrumentation was carried out by the same investigator for all subjects. Our index of flow (VF) was calculated as the mean of the peak flow velocity envelope on a beat-by-beat basis. The total power spectrum signal was also collected as a representation of vessel cross-sectional area (5, 7).

MAP, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were calculated from the blood pressure waveform on a beat-by-beat basis using finger photoplethysmography (Portapres, TPD Biomedical Instrumentation, Delft, The Netherlands). MAP was calculated as the area under the blood pressure waveform with the peak and the nadir representing SBP and DBP, respectively. HR was calculated from a standard three-lead ECG (Micromon 7142B, Kontron Medical, Milton Keynes, UK).

Data analysis. One-minute averages were calculated for all variables immediately before the onset of hypoxia (time = −1 min), every 5 min during hypoxia (time = +5, +10, +15, and +20 min), and 5 min posthypoxia (time = +25 min). A 1-min average was also determined at the time point corresponding to the subject-specific nadir of the VP response during PH. This time point was also identified during the IH protocol for comparison between conditions. An index of cerebral vascular resistance was calculated from VF and MAP data.

To express cardiovascular gains as linear functions of the hypoxic stimulus, $P_{ETO_2}$ was converted to a calculation of $O_2$ saturation ($ScO_2$) (42). Use of $ScO_2$ avoided methodological limitations associated with pulse oximetry during conditions where changes finger blood flow may influence the accuracy of measurement (49). The gains of the acute cardiovascular response to hypoxia were calculated for VP (AHRVP), MAP (AHRMAP), and HR (AHRHR) using the following indexes:

$$AHR_{VP} = \Delta FV/\Delta ScO_2$$  
$$AHR_{MAP} = \Delta MAP/\Delta ScO_2$$  
$$AHR_{HR} = \Delta HR/\Delta ScO_2$$

All delta (Δ) values were calculated in relation to the time point immediately before the onset of hypoxia (time = −1 min).

A second, objective mathematical approach was also used to analyze VP data. The mathematical model described by Poulin et al. (34) was applied to the isocapnic data to corroborate our manually derived indexes. Because of a brief gap in data collection (~10 s), data for one subject could not be analyzed using this approach. As such, modeling data represent 9 of 10 subjects. This anomaly did not influence the mean values reported elsewhere.

Statistical analysis. All cardiovascular data were analyzed using a multivariate repeated-measures design, with two parallel conditions compared using preplanned contrasts. To account for multiple comparisons (c), $P$ values were corrected using the chosen comparison-
RESULTS

Mean traces of PETO2 and PETCO2, indicating gas control, during both protocols and the temporal profiles of ventilation (VE) and for all cardiovascular variables, expressed as percentages relative to baseline, are illustrated in Fig. 1; absolute values for cardiovascular variables at relevant time points are shown in Table 1.

Blood pressure. There was a modest increase in MAP during both protocols. However, while the increase in MAP occurred immediately following the initiation of IH, the response during PH was delayed. During IH, MAP rose from 68.7 ± 11.7 to 74.9 ± 11.9 mmHg at the nadir time point but was not elevated until time = +5 min during PH (67.7 ± 7.6 to 72.5 ± 9.2 mmHg). Subsequently, the increase in MAP was maintained throughout hypoxia during both conditions. At the offset of hypoxia, MAP returned toward baseline during IH. However, during PH, MAP remained elevated with respect to baseline at time = +25 min (76.7 ± 13.1 mmHg, P < 0.05). Calculation of AHRMAP indicated a consistent gain across all time points during IH (∼0.37 mmHg%/desaturation). During PH, AHRMAP was significantly lower than during IH at the nadir time point (0.05 ± 0.29 vs. 0.39 ± 0.48 mmHg%/desaturation, P < 0.05), rising to a similar level as IH by time = +5 min. No further differences were observed between conditions.

CBF. Our index of MCA cross sectional area (power) was unchanged from baseline during both conditions. Therefore, VR was used as our index of CBF. During IH, VR was significantly elevated throughout the hypoxic exposure and remained modestly elevated at time = +25 min (102.5 ± 2.8%; +1.9 ± 1.4 cm/s, P < 0.01). Alternatively, the response during PH was biphasic, with an initial decrease in VR (94.0 ± 5.3%, −3.1 ± 2.7 cm/s, P < 0.01), reaching its nadir at 79 ± 26 s. This was followed by a subsequent rise in VR, becoming significantly elevated above baseline by time = +5 min (103.2 ± 5.0%, +2.0 ± 2.4 cm/s, P < 0.01). As in IH, VR following PH remained modestly increased above baseline (102.4 ± 6.2%, +1.8 ± 2.8 cm/s, P < 0.05).

The nadir of the VR response during PH was found to correspond closely with the timing of the peak ventilatory response during PH (80 ± 42 s). When correlation analyses of the change in VR vs. changes in VE or PETCO2 were performed, no significant relationships were found [r = −0.08, not significant (NS), and r = −0.09, NS]. However, on removing one subject who exhibited no change in VR at the onset of PH, the relationship between VR and VE became significant (r = −0.68, P < 0.05), although the relationship with PETCO2 remained nonsignificant (r = −0.2, NS). Further analysis of

\[
P^1 = \alpha (P^0 / \alpha')
\]

(4)

\[
\alpha' = \alpha / c
\]

(5)

\[
\alpha_s = 1 - (1 - \alpha')
\]

(6)

where \(P^0\) and \(P^1\) represent the original and corrected \(P\) values, respectively, and \(\alpha'\) represents the adjustment factor based on the chosen level of significance. The number of multiple comparisons differed with the variable analyzed.
Table 1. Absolute values for end-tidal gases, ventilation, and cardiovascular variables during isocapnic and poikilocapnic hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isocapnia</th>
<th>Poikilocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PETCO}_2$, Torr</td>
<td>88.9 ± 1.7</td>
<td>88.1 ± 0.8</td>
</tr>
<tr>
<td>Isocapnia</td>
<td>44.7 ± 0.5</td>
<td>44.6 ± 0.5</td>
</tr>
<tr>
<td>Poikilocapnia</td>
<td>45.2 ± 0.9</td>
<td>45.4 ± 2.3</td>
</tr>
<tr>
<td>$\text{PETCO}_2$, Torr</td>
<td>37.2 ± 1.8</td>
<td>36.4 ± 2.5</td>
</tr>
<tr>
<td>Isocapnia</td>
<td>37.3 ± 1.9</td>
<td>31.8 ± 2.4</td>
</tr>
<tr>
<td>Poikilocapnia</td>
<td>37.3 ± 1.9</td>
<td>32.1 ± 2.7</td>
</tr>
<tr>
<td>$\text{VE}$, l/min</td>
<td>12.6 ± 2.4</td>
<td>10.0 ± 2.7</td>
</tr>
<tr>
<td>Isocapnia</td>
<td>40.6 ± 11.6</td>
<td>19.6 ± 6.2</td>
</tr>
<tr>
<td>Poikilocapnia</td>
<td>24.0 ± 7.2</td>
<td>12.7 ± 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. The AHRVP during IH was 0.29 ± 0.25 cmH$_2$O·%desaturation$^{-1}$ at the nadir time point and remained unchanged throughout the hypoxic exposure. The AHRVP exhibited an increase across time with an initial nadir sensitivity of 0.25 ± 0.19 cmH$_2$O·%desaturation$^{-1}$ increasing to 0.08 ± 0.16 cmH$_2$O·%desaturation$^{-1}$ at time = +5 min (P < 0.001 with respect to nadir) and further rose to 0.28 ± 0.22 cmH$_2$O·%desaturation$^{-1}$ at time = +20 min (P < 0.001 with respect to nadir). The relationships of AHRVP between conditions and across time are shown in Table 2.

Table 2. Cardiovascular sensitivities during isocapnic and poikilocapnic hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nadir</th>
<th>+5 min</th>
<th>+10 min</th>
<th>+15 min</th>
<th>+20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHR$_{HR}$, beats·min$^{-1}$·%desaturation$^{-1}$</td>
<td>1.32 ± 0.47</td>
<td>1.09 ± 0.26</td>
<td>0.94 ± 0.39</td>
<td>0.73 ± 0.28</td>
<td>0.75 ± 0.24</td>
</tr>
<tr>
<td>Isocapnia</td>
<td>1.07 ± 0.41</td>
<td>1.00 ± 0.26</td>
<td>0.72 ± 0.23</td>
<td>0.64 ± 0.26</td>
<td>0.64 ± 0.23</td>
</tr>
<tr>
<td>Poikilocapnia</td>
<td>0.40 ± 0.48</td>
<td>0.45 ± 0.37</td>
<td>0.39 ± 0.30</td>
<td>0.31 ± 0.28</td>
<td>0.32 ± 0.30</td>
</tr>
<tr>
<td>AHR$_{SBP}$, mmHg/°C</td>
<td>0.05 ± 0.29</td>
<td>0.29 ± 0.22</td>
<td>0.26 ± 0.24</td>
<td>0.28 ± 0.27</td>
<td>0.37 ± 0.34</td>
</tr>
<tr>
<td>Isocapnia</td>
<td>0.28 ± 0.25</td>
<td>0.35 ± 0.14</td>
<td>0.32 ± 0.14</td>
<td>0.38 ± 0.14</td>
<td>0.36 ± 0.15</td>
</tr>
<tr>
<td>Poikilocapnia</td>
<td>0.08 ± 0.16</td>
<td>0.21 ± 0.16</td>
<td>0.27 ± 0.14</td>
<td>0.28 ± 0.22</td>
<td>0.28 ± 0.22</td>
</tr>
</tbody>
</table>

All values are means ± SD and are expressed as a change per percent desaturation. The AHR$_{HR}$ corresponds to the time associated with the initial decrease in peak middle cerebral artery blood flow velocity (Vp) during poikilocapnic hypoxia (PH). For ventilation (Vt), AHRVP corresponds to the maximal ventilatory response at the onset of hypoxia. The AHR$_{SBP}$ during IH was 0.29 ± 0.25 cmH$_2$O·%desaturation$^{-1}$ at the nadir time point and remained unchanged throughout the hypoxic exposure. The AHR$_{SBP}$ exhibited an increase across time with an initial nadir sensitivity of 0.25 ± 0.19 cmH$_2$O·%desaturation$^{-1}$ increasing to 0.08 ± 0.16 cmH$_2$O·%desaturation$^{-1}$ at time = +5 min (P < 0.001 with respect to nadir) and further rose to 0.28 ± 0.22 cmH$_2$O·%desaturation$^{-1}$ at time = +20 min (P < 0.001 with respect to nadir).
This study confirms the relationship between $V_{\dot{E}}$ and HR. In cause HR to increase via parasympathetic withdrawal (30). The tachycardia exhibited by the systemic response to hypoxia is there hypoxia in humans when breathing is controlled. The tachycardia of isolated carotid body stimulation in animals document a derived calculations. The steady-state $V_{\dot{E}}$ response during IH and PH, with a subsequent progressive decline with time. This response pattern has been shown previously during isocapnic protocols (46, 47), with steady-state gains (at $20 \text{ min}$) very similar to our own (30). Studies of isolated carotid body stimulation in animals document a reflex bradycardia when ventilation is constrained (31), and no change (47) or a decrease (11) in HR is observed during hypoxia in humans when breathing is controlled. The tachycardia exhibited by the systemic response to hypoxia is therefore related to the stimulation of lung mechanoreceptors, which cause HR to increase via parasympathetic withdrawal (30). This study confirms the relationship between $V_{\dot{E}}$ and HR. In this way, the progressive decline in HR with time, despite a maintained level of hypoxia, may be linked to the development of hypoxic ventilatory decline, wherein a decline in ventilation results in a gradual decrease in HR as we have documented. Indeed, in a study of longer duration, the secondary rise in ventilation associated with the onset of hypoxic acclimatization was mirrored by similar changes in HR (46). Further, during sustained hypcapnia, ventilation is elevated with no evidence of ventilatory decline as seen during prolonged hypoxic exposures (33). The increase in HR is similar, remaining consistently elevated throughout sustained hypcapnic exposures (27).

These direct linkages between ventilation and HR are not surprising in light of respiratory sinus arrhythmia, where ventilation “gates” HR (13). However, in the present study, no significant difference in HR was observed between IH and PH, whereas ventilation was significantly higher during IH. While this disparity may tend to contradict a major role of lung stretch receptors, two factors may explain these results. First, a recent paper by Rutherford et al. (40) proposes an additional tachycardic effect due to hypocapnic coronary vasoconstriction. Second, blunting of the chemosensory response to hypoxia during hypocapnia could be expected to result in a decreased reflex bradycardia; therefore a smaller $V_{\dot{E}}$ may act to withdraw parasympathetic tone and cause HR to rise to the same extent as during isocapnia. This may help explain the equivalency in HR responses during IH and PH, despite differing ventilatory responses (45). Interestingly, the above relationship is strongest with respect to changes in total ventilation, not changes tidal volume. This would tend to indicate that rate of lung stretch, not just volume, also plays a role in the tachycardic response to hypoxia.

**Blood pressure response.** In the present study our subjects exhibited MAP of $\sim 70 \text{ mmHg}$ and SBP and DBP of $\sim 110 \text{ mmHg}$ and $\sim 55 \text{ mmHg}$, respectively, at rest. These values are lower than the stereotypical norms of $93 \text{ mmHg}$, $120 \text{ mmHg}$, and $80 \text{ mmHg}$ for mean, systolic, and diastolic pressures, respectively. There are a number of factors that may contribute to this apparent difference. First, the subjects taking part in the present investigation were all young healthy men who were regularly active in various cardiovascular exercises and may be expected to have slightly lower resting blood pressures. Second, the extensive research of Imholz et al. has assessed the accuracy of photoplethysmography during many interventions (for reviews see Refs. 21, 22). Their research indicates that various devices utilizing this technique, including the Portapres system used in the present study, may tend to underestimate both mean and diastolic pressures in a range of $-1.6 \pm 8 \text{ mmHg}$ (22). However, this same research shows that these devices accurately track broad changes in arterial blood pressure compared with intra-arterial measures. In the context of the present study, our values for mean and diastolic blood pressure may be slightly below expected values, but we are confident that the temporal pattern of changes in blood pressure are an accurate representation of true blood pressure.

While the blood pressure response to isocapnic hypoxia is the result of a complex interaction between neural and local effects on vascular tone as well as the influence of cardiac output, a modest increase in MAP has been documented in response to systemic hypoxia in humans (16, 31). Similarly, in the present study, MAP was elevated during both IH and PH, but with the response developing earlier during the isocapnic condition. The disparity in the response dynamics during PH may be attributable to the concomitant hypcapnia. Both Richardon et al. (37) and Kontos et al. (28) have documented a biphasic blood pressure response during hyperventilation-induced hypcapnia, with a transient decrease within the first 1–5 min due to histamine-mediated decreases in vascular resistance (28) and subsequent rise to baseline levels over the next 5 min due to the local vasoconstrictor actions of alkalosis (12). Although hypoxia is also a vasodilating agent, it also causes a large increase in sympathetic vasoconstrictor nerve activity (52). In this way, the combined effects of hypcapnia and hypoxia may result in a blood pressure response that is suppressed early in hypoxia but becomes significantly elevated with longer exposure. The steady-state gains (time $= +20 \text{ min}$) of the response were similar to that reported previously during IH (3) and PH (4) from our laboratory.

**CBF response.** To accurately study CBF dynamics, $P_{O2}$ and $P_{CO2}$ must be finely controlled. The technique of end-tidal gas forcing has been shown to significantly reduce variability in
middle cerebral artery flow (17), in part by controlling variations in PO2 and PCO2, which can have profound effects on the cerebral circulation (20). In the present study, the response to IH was characterized by an increase in CBF with a steady-state gain of ~0.3 cm/s per percent desaturation and a time constant of ~81 s, whereas the response to PH was biphasic. A recent study by Ainslie et al. (2) has also documented a initial decrease in Vp at the onset of PH. However, while Vp returned toward baseline with maintained exposure, they did not document a subsequent rise in Vp as we have reported in the present investigation.

In our study, no changes in middle cerebral artery resistance (or conductance) were observed during IH. These data would suggest that the flow profile during IH is mediated via changes in perfusion, and not hypoxic vasodilation in the brain. This is counter to previous reports indicating a decrease in cerebral vascular resistance (8, 25, 43) during IH and data indicating that the level of hypoxia utilized in the present study exceeds the threshold for hypoxic cerebral vasodilation (15, 25). However, our hypoxic stimulus may have been potent enough to cause a significant rise in cardiac output greater than the vasodilation occurring in the brain, masking any changes in vascular resistance. However, without a measure of cardiac output in the present study, this remains unclear. During PH, the onset of hypoxia was characterized by an increase in cerebral vascular resistance, causing a decrease in blood flow. By 10 min, the change in resistance was normalized, and blood flow rose significantly. As blood pressure was not decreased at the onset of hypoxia during the PH condition, the initial increase in resistance may be mediated by a hypocapnia-induced constriction in the brain. However, we were unable to document any significant relationships between changes in Vp and changes in PETCO2. That being said, our indirect measure of arterial CO2 may not accurately represent changes in brain tissue pH. The subsequent normalization of middle cerebral artery resistance, and an increase in blood flow equivalent to the IH condition by time = +10 min, would appear to indicate an elimination of any hypocapnic constriction and a dominance of perfusion-related mechanisms similar to that seen during IH.

Support for the role of decreased brain PCO2/pH at the onset of PH comes from the similarity of the Vp profile compared with that reported during hyperventilation-induced hypcapnia (14, 35). The CBF response to eugonic hypcapnia is characterized by an initial decrease in Vp, followed by a secondary slow rise over time similar to what we report during PH. If we express the percentage reduction in Vp at the onset of PH as a function of PETCO2, a nadir sensitivity of ~2.13%/Torr is calculated. This is very similar to previous investigations of the cerebrovascular responses to hypcapnia (14, 35). However, although Vp exhibits a progressive rise during euoxic hypcapnia, it does not return to baseline levels (14, 35), whereas we document significantly elevated Vp by time = +20 min. The near equivalency of Vp during IH and PH at time = +20 min indicates that the hypoxic stimulus dominates late in the PH exposure. The resultant Vp-time curve represents an interaction between these two competing variables.

The use of a secondary, objective mathematical model applied to the IH data served to verify our derivations of cerebrovascular sensitivities. The complexity of the response occurring during PH precludes the use of this model on these data. However, on the basis of the strong correlation between modeled gain (gh) and AHRVP during IH, we are confident that our calculation of AHRVP during PH is also accurate.

Methodological considerations. The present study was conducted at an altitude of ~1,100 m. This must be taken into consideration when interpreting our results, particularly considering 7 of 10 subjects were native to altitudes lower than 500 m and/or returned to near sea level altitude multiple times yearly. As such, we could expect that our subjects may be representative of sojourners, but not natives, of mild altitude. Previous studies have shown that acclimatization to both mild (1,560 m) (2) and moderate (3,810 m) (23) altitude is characterized by augmented cardiovascular gains. As such, we may expect our cardiovascular gains to be slightly higher than those reported at near sea level.

The use of transcranial Doppler (TCD) ultrasound has been used extensively in clinical and research settings as a noninvasive method of measuring CBF. However, this is based on some basic assumptions that must be taken into consideration when interpreting results (26). First, here we have used VP as our index of flow while assuming that cross-sectional area of the MCA remains constant. We have based this assumption on previously published data indicating no appreciable change in MCA caliber during similar interventions as used in the present study (41). Further, the total power spectrum of the Doppler signal has been previously shown to be an accurate representation of vessel cross-sectional area (5, 7) and in keeping with the results of the present investigation does not change during the chosen level of hypoxia (36). Second, we have assumed that Vp is the most accurate representation of flow velocity in the MCA. This is in keeping with previously published data (24) and the observation that the intensity-weighted mean velocity exhibited the same responses as Vp (not shown). As such, we believe that Vp represents an accurate index of MCA blood flow in the present study.

The present study sought to investigate the dynamic cardiovascular responses to both isocapnic and poikilocapnic hypoxia. This required a prolonged and finely controlled stimulus. The use of dynamic end-tidal forcing allowed for precise control of end-tidal (=arterial) PO2 and PCO2 on a breath-by-breath basis. Recent work by Vantanajal from our laboratory (48) using similar methods has shown this particular technique to be precise to within ±0.6 Torr for PETCO2 and ±2.0 Torr for PETO2. In this way, we were certain that the delivered stimulus was consistent and accurate, avoiding oscillations that could interfere with analysis and interpretation. However, one limitation of our experimental approach is its use of one specific hypoxic stimulus. As such, data from this particular protocol may not be representative of the response at more extreme or less severe hypoxic levels.

Summary

The alterations in cardiovascular gains over time observed here may not be specific to hypoxia per se. From these data we provide evidence of the effect of ventilation and arterial or tissue PCO2/pH in the cardiovascular and cerebrovascular adaptation to sustained hypoxia. Furthermore, the local and neural mechanisms of hypoxia may also independently adapt. The cerebrovascular response to poikilocapnic (hypocapnic) hypoxia contains an early response, which appears to be mediated predominantly by the decrease in PCO2, followed by

\[ \text{V}_{p}\]
a secondary response, mediated predominantly by hypoxia. However, these effects appear to be due to an increase in cerebral perfusion, not a change in cerebral resistance. As such, the overall response likely involves multiple, possibly interacting, mechanisms. The protocols in the present study, specifically the inclusion of a poikilocapnic design, are more representative of in vivo environments and illustrate the dynamic nature by which hypocapnic alkalosis critically alters the cardiovascular and cerebrovascular responses to hypoxia.

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