Ventilatory effects of specific carotid body hypocapnia and hypoxia in awake dogs

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Smith, Curtis A., Craig A. Harms, Kathleen S. Henderson, and Jerome A. Dempsey. Ventilatory effects of specific carotid body hypocapnia and hypoxia in awake dogs. J. Appl. Physiol. 82(3): 791–798, 1997.—Specific carotid body (CB) hypocapnia in the −10-Torr (less than eupneic) range reduced ventilation in the awake and sleeping dog to the same degree as did CB hyperoxia [CB PO2 (PBcO2); >500 Torr; C. A. Smith, K. W. Saupe, K. S. Henderson, and J. A. Dempsey. J. Appl. Physiol. 79: 689–699, 1995], suggesting a powerful inhibitory effect of hypocapnia at the carotid chemosensor over a range of Pco2 encountered commonly in physiological hyperpneas. The primary purpose of this study was to assess the ventilatory effect of CB hypocapnia on the ventilatory response to concomitant CB hypoxia. The secondary purpose was to assess the relative gains of the CB and central chemoreceptors to hypoxia. In eight awake female dogs the commonly isolated CB was perfused with hypoxic blood (mild, PBcO2 ≈ 50 Torr or severe, PBcO2 ≈ 36 Torr) in a background of normocapnia or hypocapnia (10 Torr less than eupneic arterial Pco2) in the perfusate. The systemic (and brain) circulation was normoxic throughout, and arterial Pco2 was not controlled. With CB hypocapnia, the peak ventilation (range 19–27 s) in response to hypoxic CB perfusion increased 48% (mild) and 77% (severe) due to increased tidal volume. When CB hypocapnia was present, these increases in ventilation were reduced to 21 and 27%, respectively. With systemic hypocapnia, with the isolated CB maintained normocapnic and hypoxic for >70 s, the steady-state polikilocapnic ventilatory response (i.e., to systemic hypocapnia alone) decreased 15% (mild CB hypoxia) and 27% (severe CB hypoxia) from the peak response, respectively. We conclude that carotid body hypoxia can be a major source of inhibitory feedback to respiratory motor output during the hyperventilatory response to hypoxic carotid body stimulation.

control of breathing; stimulus interaction; extracorporeal perfusion; chemoreceptors

ARTERIAL HYPOCAPNIA is a consequence of all types of hyperventilation and provides powerful negative feedback to the ventilatory control system presumably through both central and peripheral chemoreceptors (11, 22, 23). In a previous publication, it has been shown that specific carotid body hypocapnia in the unanesthetized awake or sleeping dog caused marked inhibition of ventilation (23) that was proportional to the degree of hypoxia. Furthermore, it has been shown that specific normoxic hypocapnia −10–14 Torr less than the eupneic level inhibited ventilation as much as did specific normocapnic carotid body hypoxia [carotid body PO2 (PBcO2) >500 Torr]. Hypoxia in this range has been shown to virtually silence afferent chemoreceptor traffic in the carotid sinus nerve (7, 12).

It seems clear that hypoxia at the level of the carotid body chemoreceptors is a strong inhibitor of afferent output from the carotid chemoreceptors and, therefore, of ventilation. Hypocapnia of up to ~10–15 Torr below the eupneic level commonly occurs as a result of powerful carotid chemoreceptor excitatory stimuli such as heavy exercise or chronic hypoxia. We hypothesized that specific carotid body hypocapnia would exert a significant inhibitory effect on ventilation in the face of simultaneous carotid chemoreceptor stimulation. Accordingly, this study was designed to assess the interactive effects of specific carotid body hypoxia and hypocapnia in the unanesthetized dog. We used a chronically instrumented, unanesthetized dog model that allowed perfusion of the carotid body with blood of defined Po2 and PcO2 in isolation from the systemic circulation.

METHODS

Eight unanesthetized, trained, female mixed-breed dogs (20–25 kg) were studied. Dogs were chosen because they can be readily trained to sit or lie quietly for long periods in the laboratory while wearing respiratory apparatus. Our perfusion techniques are based on techniques developed in the goat (2) and modified by us for use in the dog.

Surgery

Two surgical procedures were required to instrument the dogs. In the first procedure, we cannulated a branch of the right femoral artery and, in four dogs, implanted diaphragm electromyograph (EMGdi) electrodes. The catheter and EMG wires were exteriorized on the dorsal aspect of the neck, and the catheter was filled with 10,000 U/ml heparin solution and sealed. At least 1 wk later, a second procedure was required to denervate the left carotid body, isolate the right carotid body, and prepare that carotid sinus region for extracorporeal perfusion. All surgery was performed with sterile techniques under general anesthesia (~1% halothane in O2). We premedicated with acepromazine (0.5 mg/kg sc) and induced with sodium thioglycollate (20 mg/kg iv). Paralyzing agents were never used. Analgesics (butorphanol, 0.3 mg/kg every 4–5 h for 1–2 days) and antibiotics (trimethoprim sulfa 15 mg/kg, 12 h for 5–7 days) were administered during each postoperative period. Our protocol was approved by the Animal Care and Use Committee of the University of Wisconsin, Madison.

The carotid sinus region on the left side was exposed and then denervated by stripping the adventitia from the entire area. Denervation was confirmed intraoperatively by lack of a ventilatory response to dose arterial injection of 400 µg of NaCN.

The right carotid sinus region was prepared for isolation and perfusion by ligation of the internal carotid, occipital, cranial laryngeal, and ascending pharyngeal arteries. At this
trodes were amplified and recorded both as raw signals and muzzlemask custom fitted to each dog. Ventilation was measured changing the relative concentrations of CO2, O2, and N2 by means of one head of a perfusion pump (Travenol). The extracorporeal perfusion circuit was primed with 120 ml canine blood (Animal Blood Bank, Dixon, CA), and 5,000 U heparin. PCO2, PO2, pH, and HCO3 concentration were matched to the subject dog’s arterial values. The perfusion cannulas were then connected to the primed extracorporeal perfusion circuit. Heparin (2,500 U) was added to the perfusion circuit. Heparin. PCO2, PO2, pH, and HCO3 were recorded with an automated blood gas analyzer (Radiometer ABL-2) validated daily with a tonometered blood. Airway PO2 and PCO2 were recorded continuously.

Blood pressure. Blood pressure was recorded continuously from the femoral artery.

Protocol

Each trial consisted of a 60-s control period (eupnea) during which perfusion of the carotid body was endogenous, i.e., systemic arterial blood. Then carotid body perfusion was abruptly switched to the perfusion circuit (<2 s), and the ventilatory responses were recorded for 90–300 s before the carotid body was returned to endogenous perfusion (Fig. 1). Arterial blood samples were obtained at ~70 s in four dogs, 138 s in one dog, and ~252 s in three dogs. Because there were no significant ventilatory changes beyond 70–90 s of perfusion in four dogs that were perfused for these longer durations (see RESULTS), the blood gas data have been pooled. All trials were performed during quiet wakefulness with the dog in sternal recumbency and unrestrained. Any trial in which postural movements occurred were excluded from analysis. The PCO2 of the perfusion circuit was set to either normocapnia (determined for each dog, each day) or to hypocapnia, ~10 Torr lower than the eupneic level for a given dog; the PO2 was set to one of two levels of hypoxia, 50 ± 1 Torr (“mild”) or 37 ± 2 Torr (“severe”). Thus four combinations of carotid body stimuli were used: mild hypoxia with normocapnia; mild hypoxia with hypocapnia; severe hypoxia with normocapnia; and severe hypoxia with hypocapnia. The dogs breathed room air throughout; arterial PO2 (PaO2) was not controlled, i.e., the dogs were poikilocapnic systematically.

Analysis and Statistics

All continuous variables were recorded on both a chart recorder (Gould ES 2001) and on the hard disk of a computer-based data-acquisition system utilizing custom-written software. Ventilatory variables were analyzed breath by breath for the last 60 s of control and the first 90–300 s of perfusion. We characterized the ventilatory responses to perfusion in two ways. 1) The three consecutive breaths that yielded the maximum inspiratory ventilation during the first 60 s of each perfusion trial were taken to represent the peak of the ventilatory response to each combination of carotid body stimuli. This approach was used because it should have avoided most non-carotid-chemoreceptor-mediated influences of changing PaCO2, and also minimized the effect of random fluctuations in breathing (Fig. 2; see also DISCUSSION). 2) The steady-state poikilocapnic ventilatory response to carotid body stimulation was taken to be the three consecutive breaths that bracketed the 70-s point of carotid body perfusion. In both cases, trials of a given type were averaged within a dog, and group averages were calculated from the averages of the individual dogs. Statistics were performed with the SYSTAT software package (SYSTAT). Significance of differences in mean data was determined with paired t-tests. Differences were considered significant if P ≤ 0.05.

RESULTS

Carotid Body Hypoxia in Normocapnia

All dogs showed increased ventilation in response to normocapnic carotid body hypoxia whether mild or as a moving time average (100 ms time constant; CWE). The moving time-averaged signal was quantified breath by breath as mean electrical activity (area of moving time-averaged waveform/duration of electrical activity; Ref. 13).

Blood gases. Arterial blood was analyzed on an automated blood gas analyzer (Radiometer ABL-2) validated daily with a tonometered blood. Airway PO2 and PCO2 were recorded continuously.

Blood pressure. Blood pressure was recorded continuously from the femoral artery.
severe (Fig. 3, Tables 1 and 2), although dog-to-dog hypoxic sensitivity varied. Peak ventilation increased 48% in mild hypoxia and 77% in severe hypoxia, respectively. Ventilation peaked at 26 s for mild hypoxia and 25 s for severe hypoxia, respectively. The ventilatory response was due entirely to increased tidal volume (VT) at both levels of hypoxia (Fig. 3). VT-to-inspiratory time (Ti) ratio (VT/Ti) increased 52 and 57%, respectively.

After the peak responses, ventilation at both levels of carotid body hypoxia then decreased slightly over time and by 70–90 s tended to reach plateaus that were still ~22 and 24%, respectively, above control (Fig. 4, Table 3). PaCO2 values during the plateau period were decreased below control by 4.3 and 8 Torr after 70 s of mild and severe carotid body normocapnic hypoxia, respectively. In four dogs, the response was followed to 250–300 s, but there were no further consistent changes in ventilation or PaCO2 beyond the 70-s period.

### Carotid Body Hypoxia in Hypocapnia

Specific carotid body hypocapnia caused a marked reduction in the peak ventilation in response to carotid body hypoxia in all dogs (Fig. 3, Tables 1 and 2), although dog-to-dog sensitivity to hypocapnic/hypoxia varied. Peak ventilation increased 22% in mild hypoxia and 26% in severe hypoxia, respectively. Ventilation peaked at 27 s for mild hypoxia and 19 s for severe hypoxia, respectively. Again, the ventilatory response was due entirely to increased VT at both levels of hypoxia (Fig. 4). VT/Ti increased 27 and 21%, respectively. Ventilation at both levels of carotid body hypoxia decreased over time and tended to reach plateaus by ~90 s that were still ~8 and 19%, respectively, above control. PaCO2 during the 70–90-s plateau period decreased by 3.5 and 5.9 Torr, respectively, relative to control. In four dogs, the response was followed out to 250–300 s, but there were no further consistent changes in ventilation or PaCO2 beyond the 70–90-s period.

### Interaction

Carotid body hypocapnia attenuated the ventilatory response to carotid body hypoxia in all of the 13...
comparisons of normocapnic vs. hypocapnic hypoxia. Figure 5 illustrates mean ventilatory responses to both levels of carotid body hypoxia during both carotid body normocapnia and carotid body hypocapnia. During carotid body normocapnia, the ventilatory response slope between 50 and 37 Torr carotid body PCO\(_2\) (PCBCO\(_2\)) was 0.17 l·min\(^{-1}\)·Torr\(^{-1}\). Carotid body hypocapnia reduced the slope of the ventilatory response between 50 and 37 Torr PCBCO\(_2\) to 0.07 l·min\(^{-1}\)·Torr\(^{-1}\), a reduction of 59%. Thus, although carotid body hypocapnia decreased the ventilatory response to carotid body hypoxia at both moderate and severe hypoxia, the effect of carotid body hypocapnia was more marked at the most severe levels of hypoxia.

Central vs. Peripheral Hypocapnia

We compared the ventilatory effects of carotid body hypocapnia alone to the ventilatory effects of systemic/brain hypocapnia alone in the presence of mild and severe carotid body hypoxia (Fig. 6). We determined the effects of carotid body hypocapnia alone by comparing the peak ventilatory responses to carotid body hypocapnia and hypoxia vs. carotid body normocapnia and hypoxia (ΔP_{CO2} = P_{CBCO2} − eupneic P_{ACO2}; Fig. 2). We determined the effects of systemic/brain hypocapnia alone by measuring the decrease in ventilation after P_{ACO2} had been allowed to decrease naturally for 70 s in the face of continued normocapnic and hypocapnic carotid body perfusion (ΔP_{CO2} = P_{ACO2} at 70 s − eupneic P_{ACO2}; Fig. 2; see DISCUSSION for assumptions involved). Both carotid body hypocapnia alone and systemic hypocapnia alone reduced the ventilatory response to carotid body hypoxia; the slope of the ventilatory response to carotid body hypocapnia was 18% (mild hypoxia) and 28% (severe hypoxia), respectively, less than to systemic hypocapnia.

DISCUSSION

Summary and Conclusions

Our findings show that carotid body hypocapnia attenuates to a significant degree the stimulation of
ventilation caused by carotid body hypoxemia. The ventilatory response to mild hypoxia was virtually eliminated when combined with 210 Torr carotid body hypocapnia, and the ventilatory response to severe hypoxia was substantially reduced. We estimated that the gain of the ventilatory inhibition in response to carotid body hypocapnia was slightly less than that to systemic hypocapnia. We conclude that carotid body hypocapnia can be a major source of inhibitory feedback to respiratory motor output during the hyperventilatory response to hypoxic carotid body stimulation.

**Assumptions/ Limitations**

Our study provides unique data in the unanesthetized animal. The lack of anesthesia and intact chemoreceptor afferents ensure that the gains of both central and peripheral chemoreceptors are preserved so that ventilation caused by carotid body hypoxemia. The ventilatory response to mild hypoxia was virtually eliminated when combined with −10 Torr carotid body hypocapnia, and the ventilatory response to severe hypoxia was substantially reduced. We estimated that the gain of the ventilatory inhibition in response to carotid body hypocapnia was slightly less than that to systemic hypocapnia. We conclude that carotid body hypocapnia can be a major source of inhibitory feedback to respiratory motor output during the hyperventilatory response to hypoxic carotid body stimulation.

**Table 2. Peak (see Methods) ventilatory responses to CB hypoxia with normocapnia or hypocapnia**

<table>
<thead>
<tr>
<th>CB Stimulus</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>P_{\text{BCO}_2}, Torr</th>
<th>Time to Peak V′I, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, normocapnic hypoxia (n = 8)</td>
<td>49.9 (1.6)</td>
<td>37.0 (1.0)</td>
<td>7.354 (0.007)</td>
<td>11 (1.2)</td>
<td>0.59 (0.04)</td>
<td>20.3 (1.9)</td>
<td>0.41 (0.04)</td>
</tr>
<tr>
<td>Mild, hypocapnic hypoxia (n = 8)</td>
<td>50.8 (1.1)</td>
<td>26.4 (1.3)</td>
<td>7.453 (0.013)</td>
<td>8.9* (1)</td>
<td>0.47* (0.04)</td>
<td>21.1 (2.9)</td>
<td>0.33 (0.03)</td>
</tr>
<tr>
<td>Severe, normocapnic hypoxia (n = 5)</td>
<td>36.6 (1.8)</td>
<td>37.0 (3.4)</td>
<td>7.362 (0.023)</td>
<td>13.2 (2.1)</td>
<td>0.67 (0.08)</td>
<td>21.9 (2.1)</td>
<td>0.47 (0.08)</td>
</tr>
<tr>
<td>Severe, hypocapnic hypoxia (n = 5)</td>
<td>37.3 (1.4)</td>
<td>25.8 (3.3)</td>
<td>7.482 (0.04)</td>
<td>9.8* (1.8)</td>
<td>0.55* (0.06)</td>
<td>19.5 (3.5)</td>
<td>0.35 (0.06)</td>
</tr>
</tbody>
</table>

Nos. in parentheses, 1 SE; n, no. of dogs. P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}, P_{\text{BCO}_2}. Mean CB perfusate P_{\text{CO}_2}, P_{\text{O}_2}, and P_{\text{H}_2} are shown for each stimulus condition. *Significantly different from CB normocapnia at same level of hypoxia, P < 0.05. †Borderline, P = 0.07.

Our study provides unique data in the unanesthetized animal. The lack of anesthesia and intact chemoreceptor afferents ensure that the gains of both central and peripheral chemoreceptors are preserved so that ventilation caused by carotid body hypoxemia. The ventilatory response to mild hypoxia was virtually eliminated when combined with −10 Torr carotid body hypocapnia, and the ventilatory response to severe hypoxia was substantially reduced. We estimated that the gain of the ventilatory inhibition in response to carotid body hypocapnia was slightly less than that to systemic hypocapnia. We conclude that carotid body hypocapnia can be a major source of inhibitory feedback to respiratory motor output during the hyperventilatory response to hypoxic carotid body stimulation.

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their relative responses may be assessed. However, there are several potential limitations that should be considered.

Unilateral carotid body denervation. Our technique requires unilateral carotid body denervation. We have not addressed this experimentally in the dog, but this question has been examined in the goat by Busch et al. (3). They demonstrated that there was little quantitative difference in the ventilatory response to NaCN, dopamine, and doxapram in goats that were studied intact and then after unilateral carotid body denervation. Kiwulla et al. (9) came to similar conclusions in the anesthetized rabbit.

Blood-gas oscillations. The mechanics of the extracorporeal gas-exchange circuit abolishes normal blood-gas oscillations to the carotid body during perfusion. However, it has been shown previously (23) that transitions from endogenous perfusion of the carotid body to extracorporeal perfusion with matched mean blood gases and pH (but no oscillations) suggest that there is no effect of loss of oscillations, at least during eupnea. In this regard, it is important to recall that, before each experiment, 30 min of perfusion were used to thoroughly mix the dog and extracorporeal circuit blood to minimize potential effects of using bank blood.

Carotid sinus pressure. Another potential complication of our perfusion technique is that perfusion pressure must be slightly higher than systemic arterial pressure to produce retrograde flow through the carotid sinus region. It has been shown previously (23) that our perfusion method raised the pressure, at most, 5–10 Torr above systemic. However, the absence of a ventilatory response to control (normocapnic, normoxic, normohydric) perfusions mentioned above provides no evidence that this slightly increased blood pressure had any ventilatory effects. In addition, it has been shown in the dog that pressure changes of this magnitude have no measurable effect on ventilation (21). Consequently, we do not think the imposed pressure gradient is a significant limitation to this study.

Use of poikilocapnic responses. Our major purpose was to determine the effects of carotid body hypocapnia on the ventilatory response to carotid body hypoxia. We used the peak ventilatory responses during isolated carotid body hypoxia to quantify the magnitude of this response. We chose not to control the systemic PaCO2 (by

Table 3. Comparison of peak (19–27 s) ventilatory responses to CB hypoxia with ventilatory and blood-gas changes obtained at 70 s of CB hypoxia

<table>
<thead>
<tr>
<th>CB Stimulus</th>
<th>At 19–27 s of CB Hypoxia</th>
<th>At 70 s of CB Hypoxia</th>
<th>V̇I, l/min</th>
<th>∆PaCO2, Torr</th>
<th>∆pHa</th>
<th>V̇I19–27–V̇I70/ΔPaCO2, l·min⁻¹·Torr⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild, normocapnic hypoxia (n = 8)</td>
<td>9.3 (1.1)</td>
<td>9.7 (1.1)</td>
<td>6.7 (2.0)</td>
<td>-4.3 (2.0)</td>
<td>0.045 (0.011)</td>
<td>-0.28</td>
</tr>
<tr>
<td>Severe, normocapnic hypoxia (n = 5)</td>
<td>13.2 (2.1)</td>
<td>9.7 (1.1)</td>
<td>7.5 (3.1)</td>
<td>-8 (2.0)</td>
<td>0.068 (0.026)</td>
<td>-0.44</td>
</tr>
</tbody>
</table>

Nos. in parentheses, 1 SE; n, no. of dogs. V̇I19–27, 19- to 27-s ventilation; V̇I70, 70-s ventilation; ∆, change. ∆PaCO2, ∆pHa, differences from eupneic control.
increased inspired CO₂ fraction) during the ventilatory response to carotid body hypoxia because we were concerned that even very small variations (± 1 Torr) in steady-state systemic Pa₃CO₂ would have profound effects on, and therefore mask, our ability to quantify the ventilatory response to carotid body stimulation alone. We attempted to control Pa₃CO₂ in a number of trials early in the study, but the complex nature of the preparation, the variability in eupneic Pa₃CO₂ in the awake animal, and the rapidly changing ventilation in response to hypoxia did not allow us to control systemic CO₂ to our satisfaction. Accordingly, our key assumption was that the peak (i.e., 19- to 27-s) poikilocapnic ventilatory response was mediated entirely by the carotid body (but see below) and was equally representative of the response to isolated carotid body hypoxic stimulation when the carotid body was normocapnic compared with when it was hypocapnic. The major factor affecting the ventilatory responses to carotid chemoreceptor stimulation over time would be the reduction of systemic Pa₃CO₂ resulting from the increased ventilation. In the present study, the average peak ventilatory responses to isolated carotid body hypoxia occurred between 19 and 27 s after the initiation of hypoxia. Given the estimated temporal dissociations between peripheral and central responses (4), we think it is reasonable to assume that the peak ventilatory responses to specific carotid body hypoxia in all conditions were mediated by the carotid bodies; i.e., central chemoreceptor-mediated reductions in respiratory motor output secondary to brain hypcapnia did not have time to be expressed. Also included in the peak ventilatory response was that portion of the response due to short-term potentiation, a centrally mediated process (5), because our experiments did not allow us to distinguish the relative contribution of the direct peripheral vs. the central short-term potentiation. We do not consider this to be a major limitation because short-term potentiation is an integral part of the ventilatory response to any peripheral stimulus and, in our study, should have remained essentially constant once a steady state had been achieved (i.e., a few seconds; Ref. 5).

A secondary purpose of our study was to determine the ventilatory gain to central hypoxia during carotid body hypoxic and normocapnic stimulation and to contrast this gain with that of carotid body hypoxia (see Fig. 6). We estimated the gain in response to systemic hypoxia by using the difference between the ventilation at 70 s of continued carotid body normocapnic and hypoxic perfusion with that at the earlier peak (19–27 s) of the ventilatory response to carotid body normocapnic and hypoxic perfusion (Fig. 2). Our assumption here was that, when the carotid body was held hypoxic but normocapnic via perfusion, the change in ventilation from the peak (19–27 s) to the steady state (> 70 s) of carotid body perfusion would represent only the central effect of hypoxia resulting from the ventilatory response to hypoxic carotid body stimulation. With the use of this approach, our estimates of the relative gains of the ventilatory response to systemic vs. carotid chemoreceptor hypoxia were very similar to those estimated for hypercapnia by Heeringa et al. (8), who used isolated pontomedullary perfusion in the anesthetized cat (see also below). We do not think the difference in ventilation between the peak and 70 s is related to the ventilatory roll-off phenomenon because there was no brain hypoxia in the present study and the response was too rapid (14).

Relevance to Feedback Inhibition During Hypoxic Hyperventilation

Our data show that carotid body hypoxia can exert powerful inhibitory effects on the ventilatory response to carotid body hypoxia. Reductions in PCO₂ of 10 Torr at the carotid body reduced the ventilatory response to carotid body hypoxia by 27–50%. Furthermore, this inhibitory effect of carotid body hypoxia was greater the more severe the carotid body hypoxia; i.e., carotid body hypoxia substantially reduced the gain of the ventilatory response to carotid body hypoxia. In naturally occurring hypoxic exposures, Pa₃CO₂ also falls progressively during acclimatization to chronic hypoxia. Accordingly, this local inhibitory effect could potentially counteract, at least partially,
the enhanced ventilatory response resulting from increased sensitivity of the carotid chemoreceptor produced by exposure to long-term hypoxia (16). The direct inhibitory effect of carotid body hypocapnia then, together with the rising arterial Po2, might be expected to substantially reduce the relative contribution of increased carotid body sensitivity to hypoxia to total ventilatory acclimatization in normal, physiological conditions.

In heavy-exercise metabolic acidosis, increased catecholamine levels and increased K+ concentration can all be encountered, sometimes in conjunction with hypoxia. All of these stimuli have been shown to excite the carotid chemosensors and thereby stimulate ventilation (6, 18, 24, 25) or increase the afferent traffic in the carotid sinus nerve (1, 19). Hyperventilation also accompanies heavy exercise, and the resultant hypocapnia would be expected to oppose the excitatory effects of these stimuli at the carotid body. It has been shown previously that moderate and physiologically achievable decreases in PCaCO2 of ~10–15 Torr in normoxia inhibit ventilation to the same degree as does arterial Po2 >500 Torr (23). One might predict, therefore, that with arterial hypocapnia in this range, the carotid body afferent output would be reduced to zero or nearly so. Despite this effect, the present study demonstrates that, although moderate hypocapnia reduces the ventilatory response to carotid body hypoxia, it does not abolish it. Others have made similar observations by using hyperoxia to inhibit the carotid bodies. Hypoxia reduced, but did not abolish, the carotid body’s increase in neural output in response to hypercapnia (7, 10) or metabolic acidosis (15, 20). Accordingly, we predict that carotid chemoreceptor hypocapnia would also significantly attenuate the carotid body’s response to other humoral stimuli such as metabolic acidosis and hyperkalemia. If so, then the hyperventilatory response to heavy exercise may involve a strong inhibitory effect of hypocapnia acting on the carotid chemoreceptor and might explain some of the enhanced ventilatory response observed by Pan et al. (17) in the carotid body-denervated pony at the onset and during the steady state of heavy exercise.

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