Peripheral chemoreceptor function after carbonic anhydrase inhibition during moderate-intensity exercise

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Scheuermann, Barry W., John M. Kowalchuk, Donald H. Patterson, and David A. Cunningham. Peripheral chemoreceptor function after carbonic anhydrase inhibition during moderate-intensity exercise. J. Appl. Physiol. 86(5): 1544–1551, 1999.—The effect of carbonic anhydrase inhibition with acetazolamide (Acz, 10 mg/kg) on the ventilatory response to a step change in work rate from loadless to moderate-intensity exercise in humans has been previously investigated (18). The mechanism(s) mediating the ventilatory response after CA inhibition is less well described. Therefore, the first purpose of the present study was to use a modified Dejours O2 test to determine the peripheral chemoreflex contribution to the ventilatory drive after acute Acz-induced carbonic anhydrase inhibition.

METHODS

Subjects and protocol. Five male subjects participated in this study. All subjects were nonsmokers with no prior history of cardiovascular or respiratory disease. The study requirements, experimental protocol, and all possible risks associated with participation in the study were outlined, and

INHIBITION OF CARBONIC ANHYDRASE (CA), the enzyme responsible for the rapid hydration of CO2 and dehydrogenation of bicarbonate (HCO3−), results in increased minute ventilation (Ve) and a fall in alveolar PCO2 in dogs (1) and humans (17, 18, 20). Although the effect of CA inhibition on CO2 transport and reaction kinetics during exercise in humans has been previously investigated (18), the mechanism(s) mediating the ventilatory response after CA inhibition is less well described.

We recently reported (14) that acute CA inhibition with acetazolamide (Acz) slows the rate of adaptation of Ve and pulmonary CO2 output (VCO2) for a step increase in work rate from loadless to moderate-intensity exercise. Because the peripheral chemoreceptors (pRc) mediate the kinetics of ventilatory response to a step increase in work rate (5, 26), it remains possible that the slowed Ve kinetics after Acz may reflect reduced pRc chemosensitivity. The most widely used noninvasive method for determining the contribution of the pRc to the ventilatory drive is the Dejours O2 test (3). The Dejours test assumes that the drive to breathe from the pRc is effectively silenced by an abrupt switch in the pRc before the hyperoxic bout (for review see Refs. 23, 28).

Recently, Swenson and Hughes (17) examined the effect of acute Acz administration on the ventilatory response to hypoxia, and to hypercapnia in a background of hyperoxia and of hypoxia in humans under resting conditions. Compared with the uninhibited condition, acute Acz administration resulted in a similar hyperoxic hypercapnic ventilatory response and reduced hypoxic hypercapnic ventilatory response. Furthermore, the eucapnic hypoxic ventilatory response (HVR) was completely abolished by acute Acz administration (17). It was concluded from these observations that CA inhibition resulted in an attenuated pRc response. These findings are consistent with studies in animal models that have demonstrated, by direct measurement of carotid body output, reduced pRc activity after CA inhibition with Acz (19, 21).

Few studies have examined ventilatory control mechanisms in humans after Acz administration (17, 20), and none has examined the ventilatory response during moderate-intensity exercise after the acute administration of Acz. Moderate-intensity exercise was used in the present study to determine whether the slowed Ve kinetics observed previously at exercise onset after acute Acz administration (14) could be attributed in part to an Acz-induced attenuation of the pRc drive. Therefore, the first purpose of the present study was to use a modified Dejours O2 test to determine the peripheral chemoreflex contribution to the ventilatory drive after Acz-induced CA inhibition. Second, we wished to extend the previous findings of an Acz-induced suppression of the HVR under resting conditions (17) to conditions during moderate-intensity exercise, thereby further demonstrating a role for CA in the ventilatory response to hypoxia.

METHODS

Subjects and protocol. Five male subjects participated in this study. All subjects were nonsmokers with no prior history of cardiovascular or respiratory disease. The study requirements, experimental protocol, and all possible risks associated with participation in the study were outlined, and

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informed consent was obtained from each subject participant. The research protocol was approved by the University’s Review Board for Health Sciences Research involving Human Subjects.

Preliminary testing of each subject was performed for the determination of peak O\textsubscript{2} uptake (\textit{V\textsubscript{O}}\textsubscript{2}) and the ventilatory threshold (\textit{V\textsubscript{ET}}) by using a progressive exercise test to volitional fatigue on an electrically braked cycle ergometer (model H-300-R, Lode) in which the work rate was increased as a ramp function at a rate of 25 W/min. The \textit{V\textsubscript{ET}} was defined as the \textit{V\textsubscript{O}}\textsubscript{2} at which there was a systematic increase in the ventilatory equivalent for \textit{V\textsubscript{O}}\textsubscript{2} (\textit{V\textsubscript{E}/V\textsubscript{O}}\textsubscript{2}) with no concomitant increase in the ventilatory equivalent for \textit{V\textsubscript{CO}}\textsubscript{2} (\textit{V\textsubscript{E}/V\textsubscript{CO}}\textsubscript{2}) or decrease in end-tidal P\textsubscript{CO}\textsubscript{2} (P\textsubscript{ETO}\textsubscript{2}).

The subjects reported to the laboratory after consuming only a light meal and abstaining from exercise and beverages containing caffeine for at least 12 h preceding the test. The exercise tests were performed at the same time of the day for each subject. Before each of the Acz studies, the subjects rested supine while a percutaneous Teflon catheter (Angiocath, 21 gauge) was placed into a dorsal hand vein followed by Acz infusion (10 mg/kg iv over a 3-min period). The subjects rested for a further 30 min (15 min supine, 15 min upright) before being moved to the cycle ergometer.

The subjects performed a step increase in work rate from a baseline of loadless pedaling to a work rate estimated to elicit volitional fatigue on an electrically braked cycle ergometer (model H-300-R, Lode) in which the work rate was increased as a ramp function at a rate of 25 W/min. The \textit{V\textsubscript{ET}} was defined as the \textit{V\textsubscript{O}}\textsubscript{2} at which there was a systematic increase in the ventilatory equivalent for \textit{V\textsubscript{O}}\textsubscript{2} (\textit{V\textsubscript{E}/V\textsubscript{O}}\textsubscript{2}) with no concomitant increase in the ventilatory equivalent for \textit{V\textsubscript{CO}}\textsubscript{2} (\textit{V\textsubscript{E}/V\textsubscript{CO}}\textsubscript{2}) or decrease in end-tidal P\textsubscript{CO}\textsubscript{2} (P\textsubscript{ETO}\textsubscript{2}).

The subjects performed a step increase in work rate from a baseline of loadless pedaling to a work rate estimated to elicit a \textit{V\textsubscript{O}}\textsubscript{2} equal to 80% of \textit{V\textsubscript{ET}}. The exercise intensity was chosen to avoid the additional complications associated with a sustained lactic acidosis that accompanies heavy exercise and was similar to the exercise intensity used previously (14). A schematic of the hyperoxia-hypoxia experimental protocol is presented in Fig. 1. After 6 min of accommodation to exercise and euoxia (i.e., P\textsubscript{ETO}=\textsubscript{2} set to \textsubscript{100 Torr}), inspired \textit{PO}\textsubscript{2} was abruptly increased to achieve an P\textsubscript{ETO}=\textsubscript{2} of 450 Torr for a duration of 8 min. A 6-min euoxic recovery period followed the hyperoxic step, after which the subject was given a 2-min hypoxic step (P\textsubscript{ETO}=\textsubscript{2}=50 Torr). The protocol ended with 2 min of euoxic recovery. Throughout the test, P\textsubscript{ETCO}=\textsubscript{2} was not clamped (i.e., poikilocapnic).

Respiratory apparatus and gas analysis. During testing, subjects were seated on a cycle ergometer and breathed through a mouthpiece with the nose occluded. Inspired and expired ventilation flow rates were measured by using a low-resistance, low-dead-space (90 ml) bidirectional turbine (VMM 110, Alpha Technologies) and volumetransducer (VMM-2A, Sensor Medics), which were calibrated before each test by using a syringe of known volume (3.01 liters). Respiratory flow and timing were determined by using a pneumotachograph (model 3800, Hans Rudolph) and a differential pressure transducer (MPA45-871, Validyne). Inspired and expired air were sampled continuously (20 ml/min) at the mouth and analyzed by a mass spectrometer (MGA 2000, Airspec) for fractional concentrations of O\textsubscript{2}, CO\textsubscript{2}, and N\textsubscript{2}. The mass spectrometer was calibrated before each test by using precision-analyzed gas mixtures. Analog signals from the turbine, pressure transducer, and mass spectrometer were sampled and digitized every 20 ms by computer. Breath-by-breath computations for pulmonary gas exchange (\textit{V\textsubscript{O}}\textsubscript{2}, \textit{V\textsubscript{CO}}\textsubscript{2}) and \textit{V\textsubscript{E}} were performed after delays in the analysis system and fluctuations in lung gas stores in the computer algorithms were accounted for (15). Corrections for temperature and water vapor pressure were made for conditions measured near the mouth. Heart rate was continuously monitored by using an electrocardiogram with electrodes placed in a modified V5 configuration. Arterial oxyhemoglobin saturation (S\textsubscript{aO}=\textsubscript{2}) was measured noninvasively by using an ear probe (OXI3 Pulse Oximeter, Radiometer).

Two computers were used during testing. A data-acquisition computer collected the experimental variables every 20 ms and stored them on disk for later analysis. P\textsubscript{ETO}=\textsubscript{2} was accurately controlled by using a computer-controlled fast gas-mixing system, which was similar to that previously described in detail (13). The control computer compared the actual measured P\textsubscript{ETO}=\textsubscript{2} with the target P\textsubscript{ETO}=\textsubscript{2} which was entered into a forcing function program before the start of the experimental protocol. The difference between the measured and target P\textsubscript{ETO}=\textsubscript{2} served as the feedback signal, determined at the end of each breath, from which the control computer adjusted the gas mixture to force the P\textsubscript{ETO}=\textsubscript{2} toward the target value. The inspired O\textsubscript{2} required to achieve the desired P\textsubscript{ETO}=\textsubscript{2} was converted by an algorithm into appropriate values for

![Fig. 1. Schematic representation of poikilocapnic hyperoxic and hypoxic protocol. After 2 min of rest (not shown), 2 min of loadless cycling were initiated, and end-tidal P\textsubscript{O} (P\textsubscript{ETO}=\textsubscript{2}) was clamped to \textsubscript{100 Torr}. End-tidal P\textsubscript{CO} (P\textsubscript{ETCO}=\textsubscript{2}) was not controlled during the protocol (i.e., poikilocapnic). At 2 min, a step transition in work rate corresponding to O\textsubscript{2} uptake at 80% of ventilatory threshold (V\textsubscript{ET}) was initiated, which was performed for the remainder of the protocol. At minute 6 of moderate-intensity exercise, an abrupt hyperoxic step (P\textsubscript{ETO}=\textsubscript{2} = 450 Torr) occurred, lasting for 8 min. After the hyperoxic bout, P\textsubscript{ETO}=\textsubscript{2} returned to \textsubscript{100 Torr} for a 6-min period. After this recovery period, a 2-min step into hypoxia (P\textsubscript{ETO}=\textsubscript{2} = 50 Torr) was performed, which was followed by 2 min of recovery with P\textsubscript{ETO}=\textsubscript{2} returned to \textsubscript{100 Torr}.](http://jap.physiology.org/DownloadedFrom/10.220.22.246/to/about/journals/jap/1545 PERIPHERAL CHEMORECEPTOR AND CA INHIBITION)
flows of O2 and N2. PETCO2 was not controlled in the present study.

Data analysis. The experimental protocol was repeated twice during each visit to the laboratory on two separate occasions for each of the control (Con) and Acz conditions. For each subject, the breath-by-breath data for each condition were time aligned, interpolated over 1-s intervals, and ensemble averaged to yield a single response for each subject per condition to increase the signal-to-noise ratio. The prehyperoxic and prehypoxic VE were taken as the mean (determined from the ensemble-averaged response for each subject) during the last 30 s before the hyperoxic and hypoxic step, respectively. Previous work from our laboratory (16) has shown that the nadir in Ve typically occurs within 20–30 s of the switch into hyperoxia and that no difference is observed in the nadir with the use of either 1- or 5-s averaged data for determination of the decline in Ve. Thus the data during hyperoxia were averaged over 5-s intervals from time 0 to 1 min, over 15-s intervals from 1 to 3 min, and over 30-s intervals from 3 to 8 min. The nadir of the individual ventilatory response to hyperoxia, determined from the 5-s mean data, was analyzed by using Student’s paired t-test. The HVR was determined from the changes in Ve, PETO2 (ΔVe/ΔPETO2), and SaO2 (ΔVe/ΔSaO2) averaged over the last 60 s of hypoxia. Differences in the HVR between Con and Acz were analyzed by using Student’s paired t-test. Statistical significance was accepted at P < 0.05. All values are reported as means ± SE.

RESULTS

The physical characteristics of the subjects and the results of the maximal ramp exercise test are presented in Table 1. The work rate for the moderate-intensity, constant-load exercise tests corresponded to the VO2 at 80% of the VeT (76.9 ± 2% VeT) and ranged from 132 to 197 W for the five subjects. The group mean response to PETO2 was set at 450 Torr. The effects of acute Acz administration on Ve, breathing pattern, and gas exchange are presented in Table 2. Compared with Con, acute Acz administration resulted in a higher Ve (14.6%) during loadless cycling. The higher Ve was attributed to the 13.3% higher tidal volume during Acz, because there were no differences in either inspiratory or expiratory duration or breathing frequency between conditions. At the onset of loadless cycling and during moderate-intensity exercise, PETO2 was set at ~100-105 Torr, resulting in similar values for Con and Acz conditions throughout the test. During loadless cycling, Acz resulted in a lower PETCO2 than did Con. Although VO2 and VCO2 were unchanged from Con conditions with Acz, the ventilatory equivalents for VO2 (VE/VO2) and VCO2 (VE/VCO2) were higher during Acz than Con because of the higher Ve after Acz administration.

Ventilatory response during steady-state exercise and hypoxia. All subjects achieved a steady-state response (i.e., Ve, VO2, and VO2) to the step increase in exercise intensity within ~4 min of the onset of the transition. The effects of acute Acz administration on Ve, breathing pattern, and gas exchange during steady-state exercise (i.e., prehyperoxic values) are presented in Table 3. During the 30-s interval before hyperoxia, Ve was 15.4% higher during Acz than Con, which is attributed to the 16.5% higher tidal volume during Acz compared with Con; breath timing (inspiratory and expiratory time) and breathing frequency were similar between conditions. With exercise, PETCO2 increased above loadless cycling values during both Acz and Con conditions; PETCO2 was lower during Acz compared with Con.

During the hypoxic step (PETO2 ~450 Torr), Ve remained unchanged from prehyperoxic values during Acz (Table 4, Fig. 3). In contrast, Ve decreased transiently during Con (9.9 ± 1.5 l/min; 20.4 ± 4.4%) before returning to prehyperoxic values (Table 4, Fig. 3). In all subjects, the nadir of the individual Ve response was observed within 20–25 s after the step into hyperoxia.

Ventilatory response during steady-state exercise and hypoxia. After the hyperoxic bout, the PETO2 was returned to ~100-105 Torr for 6 min to establish a steady state before the hypoxic step. The effects of acute Acz administration on Ve, breathing pattern, and gas exchange during steady-state exercise before the hypoxic step were similar to conditions before the hypoxic period (Table 3).

The HVR results are presented in Fig. 4. The HVR was lower after Acz than Con as indicated by both the ΔVe/ΔPETO2 and ΔVe/ΔSaO2. There were no differences between Acz and Con conditions during hypoxia for either PETO2 (Acz, 49.3 ± 0.3 Torr; Con, 49.2 ± 1.1 Torr) or SaO2 (Acz, 78.3 ± 0.9%; Con, 78.5 ± 0.9%). Thus the reduced HVR during Acz was attributed to a lower ΔVe, despite the higher absolute Ve induced by the administration of Acz.

The PETCO2 response agreed with the ventilatory response such that the fall in PETCO2 was less (P < 0.05) during Acz (ΔPETCO2, 5.7 ± 1.2 Torr) compared with Con

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>VO2peak, ml·kg−1·min−1</th>
<th>VO2-VeT, ml/min</th>
<th>VO2-VeT, 80%, ml/min</th>
<th>Work Rate, W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>188</td>
<td>88.3</td>
<td>58.3</td>
<td>2,730</td>
<td>2,118</td>
<td>149</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>178</td>
<td>82.5</td>
<td>67.6</td>
<td>3,343</td>
<td>2,519</td>
<td>197</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>178</td>
<td>95.1</td>
<td>47.4</td>
<td>2,589</td>
<td>2,140</td>
<td>137</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>176</td>
<td>83.1</td>
<td>50.9</td>
<td>2,515</td>
<td>1,771</td>
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<tr>
<td>5</td>
<td>24</td>
<td>177</td>
<td>84.0</td>
<td>57.4</td>
<td>3,089</td>
<td>2,421</td>
<td>177</td>
</tr>
</tbody>
</table>

VO2, O2 uptake; VO2peak, peak VO2; VeT, ventilatory threshold. Work rate is for the constant-load, moderate-intensity exercise test (determined as 80% of the VO2 at the individual’s VeT).
resulting in similar PETCO2 values (Acz, 31.2 ± 1.1 Torr; Con, 32.3 ± 0.35 Torr) at the time of comparison.

**DISCUSSION**

This study examined the effect of CA inhibition after an acute administration of Acz on the hyperoxic ventilatory response and HVR in the steady state of moderate-intensity exercise in humans. The results of this study suggest that, in humans, acute Acz administration (at a dose of 10 mg/kg) effectively abolishes the ventilatory response to hyperoxia and reduces the ventilatory response to hypoxia, probably by a reduced drive from the peripheral chemoreflex (pRc).

**Limitations due to CA inhibition.** The experiment was begun 30 min after an acute infusion of Acz to examine the ventilatory response to acute CA inhibition without the confounding effects of a metabolic

![Fig. 2. Mean ventilatory, PETCO2, and PETO2 responses to hyperoxic and hypoxic protocol during control (A) and after acute acetazolamide administration (B). Mean response represents individual subject responses, which were interpolated to 1-s intervals and ensemble averaged, with each subject contributing 4 repetitions for each of control and acetazolamide conditions. Dotted lines represent onset and end of hyperoxic and hypoxic challenges, respectively.](http://jap.physiology.org/)
Acidosis that develops with longer periods of Acz administration (7, 18). Although arterial PCO2 (PaCO2) and pH were not measured during this protocol, we have previously demonstrated that an acute infusion of Acz does not produce a metabolic acidosis under resting conditions, as determined by measurements made on equilibrated blood samples (6, 14). The determination of PaCO2 and pH in vivo is complicated by the fact that the effective inhibition of erythrocyte CA activity results in CO2-HCO3 disequilibrium. The incomplete equilibration of CO2 species between erythrocytes and plasma during the transit through the pulmonary capillaries causes a widening of the arterial-alveolar PCO2 difference, particularly at higher exercise intensities (18). This apparent arterial-alveolar PCO2 difference reflects the measurements made at equilibrium but does not reflect the in vitro conditions at the time of sampling.

As a consequence of the CO2-HCO3 disequilibrium in the postpulmonary capillary blood, it is not possible to accurately determine the PaCO2 or pH that either the pRc or central chemoreceptor (cRc) may be sensing. Swenson and Maren (18) calculated the half-time for the dehydration reaction of HCO3 to CO2 to be 1.5 and 0.4 s for rest and maximal exercise, respectively. Because the lung-to-carotid-body transit time is ~7 s in moderate-intensity exercise (24, 29), the predicted level of PaCO2 that either the pRc or cRc is sensing would be higher than that estimated from PETCO2. Whether the magnitude of the rise in PaCO2 would be great enough to cause an equivalent level of stimulation at the carotid bodies during Acz and Con cannot be determined with certainty from the results of this study. However, if the assumption is made that the pRc and cRc are sensing PaCO2 values close to the equilibrated value, then the results of our previous study (14) suggest that the PaCO2 is actually higher at the chemoreceptor sites during Acz than Con.

We did not measure CA activity; however, we estimate, assuming an even distribution of Acz in the vascular and extracellular compartment, that the extracellular fluid concentration of Acz would be 225 µmol/l (or 45 µmol/kg). The dose of Acz used in the present study (10 mg/kg Acz) would result in a plasma concentration of Acz severalfold higher than required to inhibit 99.95% of the total erythrocyte CA activity (30). In addition, the dose used in the present study was similar to that used in a study by Maren and Swenson (18) in which they reported the erythrocyte isozymes CA I and CA II to be 93.3 and 99.3% inhibited, respectively, with a dose of 7–10 mg/kg Acz.

### Table 4. Magnitude of the ventilatory decline in response to hyperoxia

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Control</th>
<th>Acetazolamide</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>V̇E pre, l/min</td>
<td>V̇E nadir, l/min</td>
</tr>
<tr>
<td>1</td>
<td>52.7</td>
<td>44.1</td>
</tr>
<tr>
<td>2</td>
<td>68.9</td>
<td>61.9</td>
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<tr>
<td>3</td>
<td>42.4</td>
<td>26.9</td>
</tr>
<tr>
<td>4</td>
<td>38.9</td>
<td>30.7</td>
</tr>
<tr>
<td>5</td>
<td>59.2</td>
<td>48.6</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>52.4 ± 5.5</td>
<td>42.4 ± 6.3</td>
</tr>
</tbody>
</table>

Ventilatory nadir during Control was taken as the lowest V̇E after the onset of hyperoxia and was compared with the V̇E at the same time during Acetazolamide. V̇E pre, before V̇E. *Significantly different from Control (P < 0.05).

Fig. 3. Group mean (±SE) ventilatory response before (Pre) and during hyperoxic step during control (●) and after carbonic anhydrase inhibition with acetazolamide (○). Dotted line represents onset of hyperoxic challenge.

Fig. 4. Group mean (±SE) hypoxic ventilatory response expressed as a function of change (Δ) in PETCO2 (left) and arterial oxyhemoglobin saturation (SaO2; right) during control (solid bars) and after acetazolamide administration (open bars). V̇E, minute ventilation. a Significantly different compared with control (P < 0.05).
The purpose of this study required human subjects to perform whole body exercise, and thus a further limitation is our inability to state with certainty which CA isozymes (other than erythrocyte isozymes) may have been affected by the infusion of Acz. Specifically, CA has been localized in the glomus cells of the carotid bodies (9, 12) and in glial cells neighboring the Rr, (4), both of which may be susceptible to Acz administration.

Ventilatory response to hyperoxia. A unique finding of this study was that a transient decrease in VE at the onset of hyperoxic breathing was completely abolished after CA inhibition. The Pr contribution to the ventilatory drive, which we found to be 20%, is in close agreement with earlier estimates for moderate-intensity exercise (5, 10, 16, 25). The results of this study provide indirect evidence for a suppression of Pr activity to breathe after acute Acz administration during moderate-intensity exercise in humans. Our results are in agreement with a previous study (17) that demonstrated a suppressed Pr activity determined by the ventilatory response to hyperoxic hypercapnic breathing after acute Acz administration in resting humans.

Direct assessment of peripheral and central chemoreflex outputs and, therefore, their role in the modulation of Ve is not possible in humans. Teppema and colleagues (19) observed a reduction in Pr activity in anesthetized cats given a much larger dose of Acz (50 mg/kg) than used in the present study. However, at doses as low as 4 mg/kg (i.e., the lowest dosage possible without causing an alveolar-arterial PaCO2 gradient), a decrease in Pr sensitivity to CO2 was still apparent in this cat preparation (22).

We are not aware of any reports that specifically identify the mechanism of action of Acz-induced CA inhibition on the carotid bodies. Although CA is found within the glomus cells of the carotid bodies (9), its function in chemoreception is not well understood. It has been suggested that, during CA inhibition, the uncatalyzed hydration reaction is slowed, resulting in a slowed generation of H+, which is required to stimulate pH-sensitive receptors and thereby allow chemotransduction to proceed normally (8). This mechanism may also affect the ventilatory response to hypoxia (discussed in Ventilatory response to hypoxia) because the pR, response to hypoxia is dependent on the response to CO2 (8).

Ventilatory response to hypoxia. In the present study, the HVR was attenuated for the same ΔSaO2 and ΔPETCO2 after Acz compared with the uninhibited condition (Fig. 4). Suppression of hypoxic ventilatory sensitivity with Acz is consistent with CA inhibition affecting the Pr input to the central respiratory center. The complete suppression of ventilatory sensitivity and carotid body output to hypoxia has been demonstrated in anesthetized cats during Acz-induced CA inhibition (19, 21), adding support to the contention that Acz may indeed reduce Pr activity in humans.

The blunted HVR found in the present study is in partial agreement with previous reports that have examined the possible mechanisms responsible for the mediation of the ventilatory response to CA inhibition in humans at rest (17, 20). In contrast to the attenuated HVR with Acz in our study, Swenson and Hughes (17) reported a complete suppression of hypoxic ventilatory responsiveness under isocapnic conditions after an acute infusion of Acz in resting humans. It is difficult to reconcile the difference in the HVR between these studies. It is interesting that, in the present study, PETCO2 was not controlled during either Con or Acz conditions; however, in the study by Swenson and Hughes, PETCO2 was maintained at levels similar to the uninhibited condition by adding CO2 to the inspirate, a condition that may be expected to further augment the HVR. Moreover, of significant importance in the study by Swenson and Hughes, the HVR was determined in only mild hypoxia (SaO2 = 88%). In the present study, SaO2 was 78%, which represents a greater hypoxic ventilatory stimulus (i.e., steeper portion of the Ve-alveolar PaO2 curve). In addition, Wal and colleagues (27) have shown that the HVR is potentiated when hypoxia is introduced during moderate-intensity exercise. Although these researchers suggested that the increased HVR was associated with augmented Pr sensitivity, they could not conclude that central chemoreception did not play a role.

Although the reason(s) for the varied HVR during acute Acz administration is not readily apparent, a number of factors may have contributed to the divergent ventilatory responses. Under normal conditions, hypoxia-induced increases in Ve cause a progressive decrease in PaCO2 and arterial H+ concentration. Consequently, this reduction in PaCO2 and arterial H+ concentration acting at the Pr reduce Ve may result in an underestimation of the true HVR if it is not corrected for by the addition of CO2 to the inspirate to maintain isocapnia. During Acz, PETCO2 was lower before the hypoxic bout and, therefore, could not be discounted as possibly attenuating the HVR during CA inhibition. We do not believe this to be the case, however, because the relative decrease in PETCO2 during the hypoxic challenge was actually greater during Con than Acz so that at the end of the hypoxic period PETCO2 was similar in both conditions. The wide acceptance that the interaction of hypoxia and CO2 occurs at the carotid bodies (2) supports the notion that CA inhibition directly affects the HVR through actions at the Pr. In addition, the fact that the isocapnic HVR was completely abolished with acute Acz in resting humans (17) provides further evidence that the Pr is directly affected by CA inhibition.

Ventilatory response in hyperoxia vs. hypoxia during CA inhibition. The brief hypoxic exposure was given only 6 min after the hyperoxic bout, and, therefore, the degree of Pr inhibition should not have changed in this brief time period. Thus it is somewhat difficult to reconcile the observations that Acz completely suppressed Pr function during the step into hyperoxia but only attenuated the response during the hypoxic step. Possible mechanisms contributing to the ventilatory response to hyperoxia and hypoxia during Acz are discussed below.
Recently, Rapanos and Duffin (11) confirmed that, under resting conditions, VE does not increase in response to hypoxia if the PETCO₂ (and presumably PAO₂) is lower than the peripheral chemoreflex threshold for CO₂ of ~39 Torr. Determination of the peripheral chemoreflex threshold as reported by Rapanos and Duffin requires that CO₂ be rapidly equilibrated in the postpulmonary capillaries. The disequilibrium of CO₂ species in the postpulmonary capillaries consequent to CA inhibition will result in a widening of the end-tidal arterial difference as blood flows toward the pHₐ, and thus the PETCO₂ will underestimate the PAO₂ that the pHₐ is sensing. Although PETCO₂ was lower during Acz than Con before the hyperoxic step, PETCO₂ was similar in Acz studies before the hyperoxic (36.5 ± 0.8 Torr) and hypoxic (36.9 ± 0.5 Torr) bouts. The immediate increase in VE during hypoxia suggests that PAO₂ was not below the CO₂ threshold for pHₐ stimulation, and thus the lack of a ventilatory decline in hypoxia does not appear to be a function of low CO₂ stimulus (i.e., below the CO₂ threshold).

Previous studies in resting humans (17, 20) have demonstrated a hypoxia-mediated increase in VE after chronic Acz. This finding has lead to the hypothesis that CA inhibition at the pHₐ is not complete, allowing for some residual activity to respond to the low PO₂. Possibly, if the pHₐ response is not completely inhibited by Acz, an increase in VE may occur during severe hypoxia (PETO₂ < 60 Torr), where the sensitivity of the pHₐ is functioning on the steep part of the VE-alveolar PO₂ curve. Similarly, reduced pHₐ sensitivity because of CA inhibition in combination with the relatively low gain of the pHₐ normally present at high O₂ levels may explain the lack of a ventilatory response to the hyperoxic step.

Summary. In summary, this study examined the effects of acute CA inhibition with Acz on the ventilatory response to poikilocapnic hypoxia and hypoxia during moderate-intensity exercise in humans. There does not appear to be any pHₐ contribution to the ventilatory drive in the steady state of moderate-intensity exercise after Acz-induced CA inhibition, as indicated by the failure of an abrupt hyperoxic stimulus to induce a decline in VE. However, acute Acz administration did not completely attenuate the pHₐ response to hypoxia. These findings suggest that CA inhibition affects ventilatory control mechanisms in humans in a very complex manner that must consider changes in acid-base status and the inhibition of pHₐ.

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