O₂ uptake kinetics after acetazolamide administration during moderate- and heavy-intensity exercise

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Scheuermann, Barry W, John M. Kowalchuk, Donald H. Paterson, and David A. Cunningham. O₂ uptake kinetics after acetazolamide administration during moderate- and heavy-intensity exercise. J. Appl. Physiol. 85(4): 1384–1393, 1998.—Inhibition of carbonic anhydrase (CA) is associated with a lower plasma lactate concentration ([La-]) during fatiguing exercise. We hypothesized that a lower [La-] may be associated with faster O₂ uptake (V˙O₂) kinetics during constant-load exercise. Seven men performed cycle ergometer exercise during control (Con) and acute CA inhibition with acetazolamide (Acz, 10 mg/kg body wt iv). On 6 separate days, each subject performed 6-min step transitions in work rate from 0 to 100 W (below ventilatory threshold, <V˙ET) or to a V˙O₂ corresponding to ~50% of the difference between the work rate at V˙ET and peak V˙O₂ (>V˙ET). Gas exchange was measured breath by breath. Trials were interpolated at 1-s intervals and ensemble averaged to yield a single response. The mean response time (MRT, i.e., time to 63% of total exponential increase) for on- and off-transients was determined using a two- (<V˙ET) or three-component exponential model (>V˙ET). Arterialized venous blood was sampled from a dorsal hand vein and analyzed for [La-]. MRT was similar during Con (31.2 ± 2.6 and 32.7 ± 1.2 s for on and off, respectively) and Acz (30.9 ± 3.0 and 31.4 ± 1.5 s for on and off, respectively) for work rates <V˙ET. At work rates >V˙ET, MRT was similar between Con (69.1 ± 6.1 and 50.4 ± 3.5 s for on and off, respectively) and Acz (69.7 ± 5.9 and 53.8 ± 3.8 s for on and off, respectively). On- and off-MRTs were slower for >V˙ET than for <V˙ET. [La-] increased above 0-W cycling values during <V˙ET and >V˙ET exercise but was lower at the end of the transition during Acz (1.4 ± 0.2 and 7.1 ± 0.5 mmol/l for <V˙ET and >V˙ET, respectively) than during Con (2.0 ± 0.2 and 9.8 ± 0.9 mmol/l for <V˙ET and >V˙ET, respectively). CA inhibition does not affect O₂ utilization at the onset of <V˙ET or >V˙ET exercise, suggesting that the contribution of oxidative phosphorylation to the energy demand is not affected by acute CA inhibition with Acz.

blood lactate; carbonic anhydrase; on- and off-transients

DURING THE ADJUSTMENT to an abrupt increase in exercise intensity, pulmonary O₂ uptake (V˙O₂) increases with an initial rapid rise (phase 1) followed by an exponential increase (phase 2) to a new steady state (phase 3) if the exercise is of moderate intensity (i.e., below the ventilatory threshold (<V˙ET)). For exercise intensities that engender a sustained lactic acidosis (i.e., >V˙ET), an additional increase in V˙O₂ of delayed onset leads to a steady-state V˙O₂, which, if attained at all, is higher than predicted from the <V˙ET relationship between V˙O₂ and work rate (2, 6, 40, 41). During the transition, the time constant (τ) for phase 2 kinetics reflects the V˙O₂ at the muscle and, therefore, the contribution of oxidative phosphorylation to ATP resynthesis (1, 4, 5, 18). Because oxidative phosphorylation does not meet the total energy requirements (i.e., O₂ deficit), the breakdown of high-energy phosphate stores [phosphocreatine (PCr)] and increases in anaerobic glycolysis provide the balance of energy necessary for maintaining ATP turnover (2).

For moderate-intensity exercise, where a steady-state V˙O₂ is attained, Cerretelli and colleagues (11, 12) reported that the half time for V˙O₂ kinetics during the on-transition was slowed when accompanied by an accumulation of blood lactate (i.e., the early lactate concept). This suggested that increases in blood lactate concentration ([La-]) during the on-response associated with step increases in work rate reflected increases in ATP production via anaerobic glycolysis and caused a slowing of O₂ utilization by the muscle (11, 12). Casaburi and co-workers (8) also demonstrated a slowing of the V˙O₂ on-response during constant-load exercise not associated with sustained increases in blood [La-]. These researchers suggested that transient increases in [La-] production may slow the rate of O₂ utilization by muscle early in exercise and, thereby, affect V˙O₂ kinetics (8). These findings are consistent with earlier demonstrations of a slower V˙O₂ on-response and greater O₂ deficit during the adjustment to moderate exercise under hypoxic than under normoxic conditions (23). The slower V˙O₂ kinetics during hypoxia were associated with an increased reliance on anaerobic energy sources indicated by the lower muscle PCr and higher blood and muscle [La-] at the end of exercise (23). Thus the slowing of V˙O₂ kinetics during the on-response appears to be associated with increases in muscle and blood [La-].

For step increases in work rate resulting in sustained increases in blood [La-], V˙O₂ kinetics become more complex as an additional slow increase in V˙O₂ of delayed onset becomes evident. This V˙O₂ slow component has been shown to be highly correlated to the magnitude and rate of change of blood [La-] (32). However, a mechanism directly linking the V˙O₂ slow component to the lactic acidosis or a related metabolic event has not been established (for review see Refs. 16 and 39). There is evidence to suggest that overall V˙O₂ kinetics are slowed in association with increases in end-exercise blood [La-] (2). Interestingly, if the V˙O₂ response is modeled so that the kinetics of phase 2 (i.e., rapid exponential rise) and phase 3 (i.e., slow component) are determined independently, the relationship between V˙O₂ kinetics and blood [La-] is unclear. Compared with exercise intensities <V˙ET, the phase 2 V˙O₂
on-response has been shown to be slowed (29) or similar (2, 8), despite significant increases in blood \([La^2-]\).

Inhibition of carbonic anhydrase (CA) with an acute administration of acetazolamide (Acz) compared with control is associated with lower peak blood \([La^2-]\) after short-term high-intensity exercise (21). The metabolic consequence of this Acz-induced lowering of blood \([La^2-]\) during moderate- and heavy-intensity constant-load exercise has not been investigated. The lower blood \([La^2-]\) after CA inhibition may be due to a decreased rate of \(La^2-\) production, possibly by an increased flux of pyruvate through the pyruvate dehydrogenase complex and the subsequent oxidation of pyruvate. If the rate of pyruvate oxidation is increased, the kinetics of \(V\dot{O}_2\) may be expected to be faster after CA inhibition. Alternatively, CA inhibition may lead to acid-base changes on the extracellular surface of the sarcolemma that may impair the efflux of \(La^2-\) from the muscle to the blood (13). Under this condition, \(V\dot{O}_2\) kinetics would not be expected to be altered by CA inhibition. We hypothesized that CA inhibition after an acute administration of Acz would be associated with a lower blood \([La^2-]\) as a consequence of a faster rate of adjustment of \(V\dot{O}_2\) (i.e., phase 2) at the start of moderate- and heavy-intensity exercise, suggesting that CA inhibition was associated with a greater flux through pyruvate dehydrogenase and not with an impaired efflux of \(La^2-\). In addition, we hypothesized that the \(V\dot{O}_2\) slow component during heavy exercise would be reduced after Acz-induced CA inhibition in accordance with the lower blood \([La^2-]\).

**METHODS**

Subjects. Seven healthy men participated in the study. The experimental protocol and all possible risks associated with participation in the study were outlined, and informed consent was obtained from each subject. The study was approved by the University’s Review Board for Health Sciences Research Involving Human Subjects.

Material and methods. The subjects were studied on six separate occasions during control (Con) conditions and after acute Acz administration. The subjects reported to the laboratory after consuming only a light meal and abstaining from exercise and beverages containing caffeine for 12 h preceding the test. The exercise tests were performed at the same time of the day for each subject. To facilitate blood sampling and Acz administration, on one occasion during the Con studies and 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. The blood was arterIALIZED by wrapping the hand and forearm in a heating pad. After 15 min of rest, a blood sample was drawn, then Acz was infused (10 mg/kg over a 3-min period). The administration of Acz was randomly ordered during the six visits. A placebo was not administered, because in our experience the side effects of Acz administration, although producing minor discomfort, are still noticeable by the subject. After an additional 30 min of rest (15 min supine and 15 min seated upright), a blood sample was drawn, and the subject moved to the cycle ergometer. Breath-by-breath measurements of gas exchange and ventilation were made throughout the exercise protocol; blood samples were obtained on one occasion during each of the two conditions at specific times during exercise (0, 15, 30, and 45 s and 1, 1.5, 2, 3, 4, and 6 min) and recovery (30 s and 1, 2, 4, and 6 min).

Preliminary testing of each subject consisted of an incremental exercise test (work rate was increased as a ramp function at 25 W/min) to volitional fatigue on an electromagnetically braked cycle ergometer (model H-300-R, Lode) for the determination of \(V\dot{E}\) and peak \(V\dot{O}_2\) \((V\dot{O}_2\text{peak})\). The highest \(V\dot{O}_2\) averaged over a 20-s interval was taken as \(V\dot{O}_2\text{peak}\). The \(V\dot{E}\) was defined as the \(V\dot{O}_2\) at which there was a systematic increase in the ventilatory equivalent for \(V\dot{O}_2\) \((Ve/V\dot{O}_2\), where \(Ve\) is ventilation) and end-tidal P\(_O_2\), with no concomitant increase in the ventilatory equivalent for CO\(_2\) output \((Ve/V\dot{CO}_2)\) or decrease in end-tidal P\(_CO_2\).

For the determination of \(V\dot{O}_2\) kinetics, subjects performed two step transitions to an absolute work rate \(<V\dot{E}\) \((100 \text{ W})\) and one transition to a work rate \(>V\dot{E}\). At \(>V\dot{E}\), the work rate assigned was estimated to elicit a \(V\dot{O}_2\) responding to \(>50\%\) of the difference between the \(V\dot{O}_2\) at \(V\dot{E}\) and \(V\dot{O}_2\text{peak}\): \(V\dot{O}_2\text{peak} - V\dot{E} + [V\dot{O}_2\text{peak} - V\dot{E}] / 0.5\). Each step transition was 6 min in duration, with 6 min of loadless cycling between each bout. The exercise protocol was performed during three laboratory visits for each condition, resulting in six repetitions for the moderate-intensity exercise and three repetitions for the heavy-intensity exercise.

Inspired and expired airflow and volumes were measured during the exercise test by a low-resistance, low-dead-space (90 ml) bidirectional turbine and volume transducer (model VMM-110, Alpha Technologies); the volume signal was calibrated before each test with a syringe of known volume (990 ml). Respired gases were sampled continuously at the mouth (1 ml/s) by a mass spectrometer (model MGA-1100, Perkin-Elmer) for determination of the fractional concentrations of O\(_2\), CO\(_2\), and N\(_2\). The mass spectrometer was calibrated with precision-analyzed gas mixtures. Analog signals from the mass spectrometer and turbine transducer were sampled every 20 ms and stored on disk for later analysis. Breath-by-breath computations for \(V\dot{O}_2\), \(V\dot{CO}_2\), \(Ve\), and end-tidal P\(_O_2\) and P\(_CO_2\) were performed after accounting for delays in the analysis system and fluctuations in lung gas stores in the computer algorithms (7). Corrections for temperature and water vapor were made for conditions measured near the mouth. Heart rate was monitored using an electrocardiogram with the electrodes placed in a modified V5 configuration.

Arterialized venous blood was drawn into syringes containing lithium heparin, mixed, placed in a slurry of ice and hypothermia. Breath-by-breath measurements of gases were made continuously via a low-resistance, low-dead-space 2-step transition to an absolute work rate \(<V\dot{E}\) \((100 \text{ W})\) and one transition to a work rate \(>V\dot{E}\). At \(>V\dot{E}\), the work rate assigned was estimated to elicit a \(V\dot{O}_2\) responding to \(>50\%\) of the difference between the \(V\dot{O}_2\) at \(V\dot{E}\) and \(V\dot{O}_2\text{peak}\): \(V\dot{O}_2\text{peak} - V\dot{E} + [V\dot{O}_2\text{peak} - V\dot{E}] / 0.5\). Each step transition was 6 min in duration, with 6 min of loadless cycling between each bout. The exercise protocol was performed during three laboratory visits for each condition, resulting in six repetitions for the moderate-intensity exercise and three repetitions for the heavy-intensity exercise.

**RESULTS**

Data analysis. Breath-by-breath data obtained during the step increases in work rate were linearly interpolated at 1-s intervals, time aligned, and ensemble averaged to provide a single response for each subject. The model utilized to describe the kinetic response (Fig. 1) provides an estimate of the baseline \((G_0)\), gains \((G_1, G_2, \text{and } G_3)\), time delays \((TD_1, TD_2, \text{and } TD_3)\), and time constants \((T_1, T_2, \text{and } T_3)\). For step changes in work rate \(<V\dot{E}\), the kinetic parameters for the on- and off-transitions in work rate were determined as a function of time \((t)\) using a two-component exponential model

\[
\dot{V}O_2\text{on} = G_0 + G_1 \cdot [1 - e^{-(t - TD_1t_1)}] \cdot u_1 + G_2 \cdot [1 - e^{-(t - TD_2t_2)}] \cdot u_2
\]

\[
\dot{V}O_2\text{off} = G_0 + G_1 \cdot [e^{-(t - TD_1t_1)}] \cdot u_1 + G_2 \cdot [e^{-(t - TD_2t_2)}] \cdot u_2
\]
where \( u_1 = 0 \) for \( t < TD_1 \), \( u_1 = 1 \) for \( t > TD_1 \), \( u_2 = 0 \) for \( t < TD_2 \), and \( u_2 = 1 \) for \( t > TD_2 \). For step changes in work rate \( \geq VET \), the kinetic parameters for the on- and off-transitions in work rate were determined using a three-component exponential model

\[
V_{O2on} = G_0 + G_1 [1 - e^{-(t-TD1)b}] u_1 + G_2
\]

\[
V_{O2off} = G_0 + G_1 [1 - e^{-(t-TD2)b}] u_1 + G_2
\]

\[
V_{O2diff} = G_0 + G_1 [e^{-(t-TD1)b} u_1 + G_2
\]

where \( u_1 = 0 \) for \( t < TD_1 \), \( u_1 = 1 \) for \( t > TD_1 \), \( u_2 = 0 \) for \( t < TD_2 \), and \( u_2 = 1 \) for \( t > TD_2 \). Model parameters were determined by least-squares nonlinear regression, in which the best fit was defined by minimization of the residual sum of squares. The overall time course of the response was determined from the mean response time (MRT), which is calculated from a weighted sum of TD and \( t \) for each component. The MRT is equivalent to the time required to achieve \(~63\% of the difference between \( G_0 \) and the new steadystate value.

The magnitude and slope of the \( V_{O2} \) slow component were determined as the difference between the \( V_{O2} \) at the end of exercise and the \( V_{O2} \) at 3 min of exercise \( \Delta V_{O2(6-3min)} \). \( V_{O2} \) at 3 min was taken as the mean \( V_{O2} \) from 10 s before and 10 s after 3 min, and the end-exercise \( V_{O2} \) was taken as the mean \( V_{O2} \) during the last 20 s of exercise. The kinetics of the slow component were described by the parameter estimates derived from the three-component exponential model fit. Similarly, the change in \( [La^-]_{pl} \) \( \Delta [La^-]_{pl(6-3min)} \) was determined as the difference between \( [La^-]_{pl} \) at the end of exercise and at 3 min of exercise.

Statistics. Kinetic parameter estimates were analyzed using a two-way repeated-measures ANOVA for Con vs. Acz and on- vs. off-transitions as the main effects. Blood data were analyzed for condition and time effects using a two-way repeated-measures ANOVA. A significant F ratio was further analyzed using Student-Newman-Keuls post hoc analysis.

\( \Delta V_{O2(6-3min)} \) and \( \Delta [La^-]_{pl(6-3min)} \) were analyzed using Student’s paired t-test. Statistical significance was accepted at \( P < 0.05 \). Values are means \( \pm SE \).

RESULTS

Subjects. The physical characteristics and peak values for the ramp exercise test are presented in Table 1. The individual work rates for the constant-load exercise tests are presented in Table 2. All subjects completed six repetitions at the \( <VET \) work rate and three repetitions at the \( >VET \) work rate for each condition. The work rates utilized during the constant-load tests were 100 W (73.5 \( \pm \) 2.9 \% \( VET \)) and 42.2 \( \pm \) 1.1 \% \( VET \peak \) and 237 \( \pm \) 8.6 W (138.4 \( \pm \) 2.1 \% \( VET \) and 79.7 \( \pm \) 1.2 \% \( VET \peak \) for the \( <VET \) and \( >VET \) exercise intensities, respectively.

\( [La^-]_{pl} \) and acid-base status. The mean group responses for the \( [La^-]_{pl} \) change during exercise intensities \( <VET \) and \( >VET \) are presented in Fig. 2. The experimental design required that \( <VET \) and \( >VET \) protocols be conducted within a single testing session, and therefore pre- and postinfusion values for \( [La^-]_{pl} \) were determined at rest before \( <VET \) exercise only. Preinfusion values for \( [La^-]_{pl} \) were similar between Con and Acz (0.8 \( \pm \) 0.1 and 0.9 \( \pm \) 0.2 mmol/l, respectively); infusion of Acz had no effect on resting \( [La^-]_{pl} \) (0.8 \( \pm \) 0.1 and 0.8 \( \pm \) 0.1 mmol/l in Con and Acz, respectively; Fig. 2A).

During moderate-intensity exercise (acetylcarnitine) \( <VET \), \( [La^-]_{pl} \) increased above loadless cycling values during Con \( (P < 0.05, t \geq 7.5 \text{ min}) \) and Acz \( (P < 0.05, t \geq 9 \text{ min}; \text{ Fig. } 2A) \). At 2 min after the onset of exercise, \( [La^-]_{pl} \) was higher during Con than during Acz \( (P < 0.05) \), a difference that persisted until 2 min after the end of the exercise bout. Even at this moderate-intensity exercise, end-exercise \( [La^-]_{pl} \) was higher during Con than during Acz \( (2.0 \pm 0.2 \text{ and } 1.4 \pm 0.2 \text{ mmol/l}) \), respectively). The \( [La^-]_{pl} \) returned to resting values during the recovery period for Con \( (P > 0.05, t = 18 \text{ min}) \) and Acz conditions \( (P > 0.05, t = 13 \text{ min}) \).

With the onset of \( >VET \) exercise, \( [La^-]_{pl} \) increased above loadless cycling values during Con \( (P < 0.05, t \geq 7.5 \text{ min}) \) and Acz \( (P < 0.05, t \approx 8 \text{ min}) \) and remained elevated for the remainder of the protocol (Fig. 2B). \( [La^-]_{pl} \) was higher \( (P < 0.05) \) during Con than during Acz by 2 min of exercise and remained higher for the duration of exercise. End-exercise \( [La^-]_{pl} \) was higher

### Table 1. Subject physical characteristics and \( V_{O2peak} \) for maximal ramp exercisetest

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Body Mass, kg</th>
<th>( V_{O2} ) at ( VET ), ml/min</th>
<th>( V_{O2peak} ), ml/kg ( \cdot \text{min}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>184</td>
<td>80.5</td>
<td>2708</td>
<td>58.8</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>177</td>
<td>74.0</td>
<td>2748</td>
<td>59.6</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>180</td>
<td>95.1</td>
<td>2366</td>
<td>44.0</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>176</td>
<td>83.4</td>
<td>2670</td>
<td>53.9</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>176</td>
<td>70.4</td>
<td>2297</td>
<td>59.5</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>178</td>
<td>82.5</td>
<td>2431</td>
<td>50.8</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>178</td>
<td>75.8</td>
<td>2079</td>
<td>49.7</td>
</tr>
</tbody>
</table>

\( VET \), ventilatory threshold; \( V_{O2peak} \), peak \( O2 \) uptake.
Table 2. Individual WR and \(\dot{V}_O_2\) responses for constant-load exercise above and below \(\dot{V}_E T\)

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>WR, W</th>
<th>(\dot{V}_O_2) &lt;(\dot{V}_E T), ml/min</th>
<th>(\dot{V}_O_2) &lt;(\dot{V}_E T),% (\dot{V}_E T)</th>
<th>WR, W</th>
<th>(\dot{V}_O_2) &gt;(\dot{V}_E T), ml/min</th>
<th>(\dot{V}_O_2) &gt;(\dot{V}_E T),% (\dot{V}_O_2)peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>1,985</td>
<td>73.3</td>
<td>228</td>
<td>3,607</td>
<td>76.2</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>1,828</td>
<td>66.5</td>
<td>237</td>
<td>3,718</td>
<td>84.3</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>1,841</td>
<td>77.8</td>
<td>210</td>
<td>3,236</td>
<td>77.3</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>1,636</td>
<td>61.3</td>
<td>263</td>
<td>3,744</td>
<td>83.3</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>1,842</td>
<td>80.2</td>
<td>240</td>
<td>3,323</td>
<td>79.3</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>1,760</td>
<td>72.4</td>
<td>240</td>
<td>3,212</td>
<td>76.6</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>1,726</td>
<td>83.0</td>
<td>225</td>
<td>3,045</td>
<td>80.9</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>100 ± 0</td>
<td>1,802 ± 42</td>
<td>73.5 ± 2.9</td>
<td>238 ± 9</td>
<td>3,412 ± 104</td>
<td>79.7 ± 1.2</td>
</tr>
</tbody>
</table>

WR, work rate. *Steady-state O\(_2\) uptake (\(V_O_2\)) expressed as a percentage of \(V_O_2\) at \(V_E T\). † \(V_O_2\) determined as a 20-s mean 3 min after on-transition to exercise to avoid a significant \(V_O_2\) slow component. ‡ \(V_O_2\) determined at 3 min (20-s interval) of exercise expressed as a percentage of \(V_O_2\)peak.

(P < 0.05) during Con than during Acz (9.8 ± 0.9 vs. 7.1 ± 0.5 mmol/l). During recovery, \([La]_pl\) remained elevated above loadless cycling values in both conditions, with Con \([La]_pl\) remaining higher (P < 0.05) than Acz.

To determine the effect of CA inhibition on \(V_O_2\) kinetics, the confounding influence of the metabolic acidosis that occurs with chronic Acz administration was avoided by acute administration of Acz. Plasma pH, determined 30 min after infusion at rest, was not different between Con and Acz (500 ± 6 vs. 499 ± 3 ml/min, respectively). During 0-W pedaling, plasma pH was slightly, but significantly, higher (P < 0.05) during Acz than during Con (7.429 ± 0.007 vs. 7.412 ± 0.008). At the end of moderate-intensity exercise, plasma pH decreased (P < 0.05) below loadless cycling values in Con and Acz; end-exercise plasma pH was higher (P < 0.05) in Con than in Acz (7.413 ± 0.005 vs. 7.390 ± 0.007). Similarly, during heavy-intensity exercise, plasma pH decreased (P < 0.05) to end-exercise plasma pH values that were higher (P < 0.05) during Con than during Acz (7.353 ± 0.011 vs. 7.335 ± 0.012). When the plasma acid-base status was expressed as the difference in end-exercise plasma H\(^+\) concentration between Con and Acz, the difference, although significant (P < 0.05), was small (2.1 and 1.9 mmol/l for <\(\dot{V}_E T\) and >\(\dot{V}_E T\), respectively).

\(V_O_2\) uptake kinetics. A summary of the model parameters derived for the \(V_O_2\) on- and off-response to a step increase of moderate-intensity exercise is presented in Table 3. An example of the \(V_O_2\) response for a single subject during <\(\dot{V}_E T\) exercise is presented in Fig. 3. The baseline value for \(V_O_2\) during 0-W pedaling (G\(_0\)) was similar between Con and Acz conditions. The total gain (G\(_T = G_1 + G_2\)) in \(V_O_2\) from baseline to steady-state exercise was similar in Con and Acz (963 ± 18 and 970 ± 14 ml/min, respectively), resulting in a similar end-exercise \(V_O_2\) (1,797 ± 41 and 1,777 ± 44 ml/min during Con and Acz, respectively). For Con and Acz conditions, \(V_O_2\) returned to baseline values within 6 min of recovery.

At the onset of moderate-intensity exercise, \(V_O_2\) increased similarly between Con and Acz, as indicated by the similar MRT (31.2 ± 2.6 and 30.9 ± 3.0 s during Con and Acz, respectively). In addition, no differences were observed in the model parameters for phase 1 (TD\(_1\) and \(\tau_1\)) or phase 2 (TD\(_2\) and \(\tau_2\)) for the \(V_O_2\) response between Con and Acz. The time course for the \(V_O_2\) off-response, as indicated by MRT, was similar to that of the \(V_O_2\) on-response during each condition. The model parameters (TD and \(\tau\)) for the \(V_O_2\) off-response were similar to those for the \(V_O_2\) on-response for Con and Acz. The O2 deficit (MRT·GT, on-transient) was not different between Con and Acz (500 ± 40 and 503 ± 56 ml, respectively). The O2 debt (MRT·GT, off-transient) was similar between conditions (510 ± 17 and 499 ± 25 ml for Con and Acz, respectively) and was not different from the O2 deficit in either condition.

The model parameters determined for the \(V_O_2\) on- and off-response to a step increase to heavy-intensity exercise are summarized in Table 4. An example of the \(V_O_2\) response for a single subject during >\(\dot{V}_E T\) exercise is presented in Fig. 4. During 0-W pedaling, baseline \(V_O_2\) (G\(_0\)) was similar between Con and Acz. At the onset...
120 ml/min in Con and Acz, respectively). $\dot{V}O_2$ returned to baseline values during the 6-min recovery period in Con and Acz. $\dot{V}O_2$ increased with similar kinetics at the onset of the step increase to heavy-intensity exercise, with no difference between conditions as shown by the similar MRT (69.1 ± 6.1 and 69.7 ± 5.9 s in Con and Acz, respectively). No differences were observed between Con and Acz for any of the model parameters (TD and $\tau$) during the $\dot{V}O_2$ on-response. During the $\dot{V}O_2$ off-transient, MRT was similar in Con and Acz (50.4 ± 3.5 and 53.8 ± 3.8 s, respectively); no differences were observed in the model parameters (TD and $\tau$) for the off-response between conditions. The $\dot{V}O_2$ on-response was slower (P < 0.05) than the $\dot{V}O_2$ off-response during Con and Acz as indicated by the slower MRT and $\tau$. The delayed onset of phase 3 during the on-transient as shown by TD2 (146.5 ± 16.7 and 121.2 ± 13.4 s in Con and Acz, respectively) was not apparent in the off-transient, inasmuch as the values for TD2 (24.8 ± 4.0 and 22.2 ± 3.2 s in Con and Acz, respectively) were similar to those observed for TD3 (17.0 ± 0.8 and 15.0 ± 1.0 s for Con and Acz, respectively).

Moderate-intensity exercise resulted in a faster $\dot{V}O_2$ on-response (P < 0.05) than did heavy-intensity exercise during Con and Acz, as indicated by the faster MRT and $\tau$. During the off-response, $\dot{V}O_2$ recovered faster during moderate- than during heavy-intensity exercise during Con and Acz, as demonstrated by the slower MRT (Tables 3 and 4).

$\dot{V}O_2$ slow component and $[La^−]_{pl}$. A summary of the $\dot{V}O_2$ slow component and corresponding changes in $[La^−]_{pl}$ during heavy-intensity exercise is presented in Table 5. No differences were observed in the magnitude ($G_3$ in Table 4 and $\Delta \dot{V}O_2$ (6-3min) in Table 5) or the time course (TD3 and $\tau$ in Table 4) over which the $\dot{V}O_2$ slow component developed during Con and Acz. The $\Delta [La^−]_{pl}$ and end-exercise $[La^−]_{pl}$ were higher during Con than during Acz; however, the change in $\dot{V}O_2$ when expressed relative to the change in $[La^−]_{pl}$ ($\Delta \dot{V}O_2$ (6-3min)/$\Delta [La^−]_{pl}$ (6-3min)) did not reach statistical significance (P = 0.055).

**DISCUSSION**

In the present study, constant-load exercise was performed after acute Acz administration to examine the effect of CA inhibition on the kinetics of the $\dot{V}O_2$ adjustment to and from moderate- and heavy-intensity cycling exercise. In agreement with previous studies (21), we showed that the acute administration of Acz to inhibit CA was associated with a lowering of $[La^−]_{pl}$ during moderate- and heavy-intensity constant-load exercise and recovery. However, in contrast to our hypotheses, the results of the present study demonstrate that 1) acute CA inhibition with Acz, despite lower $[La^−]_{pl}$, did not affect the overall time course for $\dot{V}O_2$ or phase 2 $\dot{V}O_2$ kinetics during moderate- or heavy-intensity exercise and 2) the magnitude and time course of the $\dot{V}O_2$ slow component were independent of the absolute increase in $[La^−]_{pl}$.

Exercise was initiated 30 min after an infusion of Acz to examine the effects of CA inhibition alone without the confounding effects of a metabolic acidosis that usually develops with prolonged Acz administration (22, 37). In the present study the small but significant acidosis that developed was probably not of any physiological significance. Although CA activity was not measured in the present study, it has previously been shown that CA inhibition is essentially complete in most body tissues at Acz doses of 5–20 mg/kg (24). The Acz dose of 10 mg/kg used in the present study was similar to that in the work of Swenson and Maren (37), in which they reported that the erythrocyte isozymes CA I and CA II were ~93.3 and 99.3% inhibited, respectively, with an Acz dose of 7–10 mg/kg. In addition, we observed slower $\dot{V}O_2$ kinetics after Acz administration, indicating that the dose and protocol used in this study effectively inhibited CA activity (unpublished observations).

Steady-state $\dot{V}O_2$. Inhibition of CA with an acute infusion of Acz did not affect steady-state $\dot{V}O_2$ during loadless cycling or moderate- or heavy-intensity constant-load exercise (Tables 3 and 4). These results are in agreement with previous studies that examined the effects of CA inhibition during submaximal exercise (28, 34, 36). Studies using short-term high-intensity exercise (21, 22) or progressive exercise (34) report lower $\dot{V}O_2$peak with Acz. The reason for the lower $\dot{V}O_2$peak reported by Kowalchuk et al. (21) is not apparent, inasmuch as the maximum peak power, average power, and total work performed during the 30-s exercise bout in that study were not affected by Acz. However, the lower $\dot{V}O_2$peak reported for progressive maximal exercise may be a function of the reduced maximal work rate achieved with this type of protocol (34). Interestingly, Stager and colleagues (36) reported a similar $\dot{V}O_2$peak during progressive maximal exercise, despite a significant reduction in peak work rate after Acz administration. Although there is evidence from isolated rat muscle preparations that $\dot{V}O_2$ may be increased by as

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On-Transient</th>
<th>Off-Transient</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_0$, ml/min</td>
<td>834 ± 37</td>
<td>806 ± 39</td>
</tr>
<tr>
<td>$G_1$, ml/min</td>
<td>383 ± 66</td>
<td>436 ± 28</td>
</tr>
<tr>
<td>$G_2$, ml/min</td>
<td>581 ± 68</td>
<td>534 ± 21</td>
</tr>
<tr>
<td>TD1, s</td>
<td>-0.9 ± 2.0</td>
<td>1.0 ± 1.5</td>
</tr>
<tr>
<td>TD2, s</td>
<td>18.9 ± 2.2</td>
<td>20.1 ± 0.8</td>
</tr>
<tr>
<td>$\tau_1$, s</td>
<td>16.6 ± 3.7</td>
<td>16.2 ± 3.2</td>
</tr>
<tr>
<td>$\tau_2$, s</td>
<td>19.5 ± 4.2</td>
<td>21.5 ± 4.6*</td>
</tr>
<tr>
<td>MRT, s</td>
<td>31.2 ± 2.6*</td>
<td>30.9 ± 3.0*</td>
</tr>
</tbody>
</table>

Values are means ± SE. G, gain; TD, time delay; $\tau$, time constant; MRT, mean response time; Con, control; Acz, acetazolamide. *Significantly different from corresponding parameter for >VeT exercise (see Table 4).
much as 27% after CA inhibition, this increase appears to be a function of the fiber type (i.e., oxidative fibers demonstrate increased \( \dot{V}O_2 \) after CA inhibition) and the amount and activity of the intracellular CA isozyme (i.e., CA III) (17). Alternatively, the degree of intracellular CA inhibition may be minor compared with the inhibition of erythrocyte and extracellular CA isozymes, and thus the effect on \( \dot{V}O_2 \) by this mechanism may be small. Furthermore, several muscle groups of mixed-fiber composition are involved in cycle ergometer exercise in humans, and therefore any difference in \( \dot{V}O_2 \) as a result of CA inhibition may not be detectable on examination of pulmonary \( \dot{V}O_2 \).

\( \dot{V}O_2 \) on-transient kinetics. The results of the present study demonstrate that the kinetics of the \( \dot{V}O_2 \) on-response for \(<\dot{V}ET\) and \(>\dot{V}ET\) exercise were not affected by CA inhibition, despite reductions in [Lac\(^{-}\)]\(_{pl}\) early in exercise. These findings are in contrast to previous studies demonstrating a close association between \( \dot{V}O_2 \) on-kinetics and early blood Lac\(^{-}\) accumulation (11, 12, 14). An increase in blood [Lac\(^{-}\)] during the transition may be a consequence of inadequate O\(_2\) delivery or an inability to utilize O\(_2\) and PCr stores at a rate sufficient to support ATP production without any contribution from anaerobic glycolysis. Cerretelli and di Prampero (10) proposed a control model that suggested \( \dot{V}O_2 \) on-kinetics were slowed as a consequence of ATP production by anaerobic glycolysis. According to their control model, the metabolic drive for oxidative phosphorylation was related to a net increase in free creatine (Cr) and a decrease in PCr. They hypothesized that regeneration of ATP by anaerobic glycolysis would not only result in Lac\(^{-}\) production but would attenuate the increase in Cr and decrease in PCr, thereby slowing the \( \dot{V}O_2 \) on-kinetics by reducing the drive for oxidative phosphorylation. Although this mechanism is consis-
tent with the observation of slowed V\textsubscript{\text{O}}\textsubscript{2} on-kinetics in association with early La\textsuperscript{-} accumulation (11, 12, 14), the lower [La\textsubscript{pl}] during Acz in the present study was not associated with a faster V\textsubscript{\text{O}}\textsubscript{2} on-response. If in our study the lower [La\textsubscript{pl}] during Acz reflects a lower intramuscular La\textsuperscript{-} production, then this suggests that V\textsubscript{\text{O}}\textsubscript{2} during the on-transition is independent of La\textsuperscript{-} accumulation and that the energy derived from anaerobic glycolysis does not spare or slow O\textsubscript{2} utilization. However, if La\textsuperscript{-} production was similar in Con and Acz conditions but La\textsuperscript{-} efflux from muscle was impaired during Acz, then the similar V\textsubscript{\text{O}}\textsubscript{2} kinetics observed for the on-transitions would be appropriate. Using an isolated muscle preparation, De Hemtijne et al. (13) demonstrated that during recovery from an induced propionic acid load the muscle surface pH transiently acidified (independent of the acid-base status of the bulk solution) and that the sarcolemmal acidification was magnified in the presence of Acz. A similar mechanism acting in vivo during Acz may explain the lower [La\textsubscript{pl}] in this study. Inhibition of the outward-facing sarcolemmal CA IV isozyme may lead to increased acidification on the extracellular surface as acid equivalents generated during heavy-intensity exercise are transported from the muscle interior. An increased acidification on the muscle surface may act to inhibit La\textsuperscript{-} efflux, inasmuch as the monocarboxylate transporter and diffusion of undisassociated lactic acid are slowed by an extracellular acidosis (20). However, this mechanism remains speculative, inasmuch as muscle La\textsuperscript{-} production during acute Acz administration has not been examined previously.

For heavy-intensity exercise at > VeT, characterizing the V\textsubscript{\text{O}}\textsubscript{2} on-response is further complicated because of an additional increase in V\textsubscript{\text{O}}\textsubscript{2} of delayed onset that results in a higher asymptotic value for V\textsubscript{\text{O}}\textsubscript{2} than that predicted from the V\textsubscript{\text{O}}\textsubscript{2}-power output relationship for < VeT exercise (2, 6, 40, 41). Phase 2 kinetics have been reported to be longer than (19, 29) or similar to (2, 6, 8) the response during < VeT exercise and to be closely associated with increases in end-exercise [La\textsubscript{pl}] (2, 8, 9). In the present study the longer MRT for the > VeT on-transient demonstrates that the overall rate of adaptation was slowed compared with < VeT exercise. In addition, values for T\textsubscript{2} indicate that the primary increase in V\textsubscript{\text{O}}\textsubscript{2} was also slowed during the step increase in > VeT exercise compared with < VeT exercise, despite the gain (i.e., G\textsubscript{2}) projecting to similar ΔV\textsubscript{\text{O}}\textsubscript{2}/Δ work rate values (9.7 ± 0.4 and 10.4 ± 1.1 ml·min\textsuperscript{-1}·W\textsuperscript{-1} for < VeT and > VeT, respectively). This finding is in agreement with the results of Paterson and Whipp (29). In contrast to these studies, Barstow and colleagues (2, 6) argued that the kinetics of the primary rise in V\textsubscript{\text{O}}\textsubscript{2} (i.e., phase 2) were invariant across power outputs and end-exercise [La\textsubscript{pl}]. Possible explanations for the differences observed between studies are unclear. However, a slowing of V\textsubscript{\text{O}}\textsubscript{2} kinetics in this exercise intensity domain is consistent with a slower rate of PCr breakdown (27) and, therefore, may reflect a slowed drive for oxidative phosphorylation. As discussed above, V\textsubscript{\text{O}}\textsubscript{2} kinetics were similar between Con and Acz conditions, despite a lower [La\textsubscript{pl}] after Acz. This suggests that V\textsubscript{\text{O}}\textsubscript{2} adapts at a rate independent of an absolute change in [La\textsubscript{pl}] and that this slowing of V\textsubscript{\text{O}}\textsubscript{2} kinetics with heavy-intensity exercise may not be associated with the accumulation of plasma La\textsuperscript{-}, especially if [La\textsubscript{pl}] does not reflect intracellular La\textsuperscript{-} production (see above).

\textit{V\textsubscript{\text{O}}\textsubscript{2}} off-transient kinetics. During the off-transient, V\textsubscript{\text{O}}\textsubscript{2} decreased to loadless, cycling values by the end of the 6-min recovery for < VeT and > VeT exercise, with no difference in kinetics between Con and Acz. For < VeT exercise, symmetry between on- and off-transients was observed as demonstrated by the similar MRT, T\textsubscript{\text{2}}, and other model parameters. However, although > VeT exercise resulted in a slower off-transient.

Table 4. Summary of parameter estimates for model fit of V\textsubscript{\text{O}}\textsubscript{2} response at onset and recovery from heavy-intensity exercise above VeT during Con and Acz

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On-Transient</th>
<th>Off-Transient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Con</td>
<td>Acz</td>
</tr>
<tr>
<td>G\textsubscript{0} ml/min</td>
<td>861±34</td>
<td>817±39</td>
</tr>
<tr>
<td>G\textsubscript{1} ml/min</td>
<td>1,014±164</td>
<td>799±78</td>
</tr>
<tr>
<td>G\textsubscript{2} ml/min</td>
<td>1,453±95</td>
<td>1,637±59</td>
</tr>
<tr>
<td>G\textsubscript{3} ml/min</td>
<td>381±26</td>
<td>483±114</td>
</tr>
<tr>
<td>T\textsubscript{D1} s</td>
<td>-0.6±0.6</td>
<td>1.0±0.9</td>
</tr>
<tr>
<td>T\textsubscript{D2} s</td>
<td>14.6±0.9</td>
<td>13.1±0.6</td>
</tr>
<tr>
<td>T\textsubscript{D3} s</td>
<td>146.5±16.7†</td>
<td>121.2±13.4†</td>
</tr>
<tr>
<td>T\textsubscript{1} s</td>
<td>16.5±3.2</td>
<td>13.9±1.5</td>
</tr>
<tr>
<td>T\textsubscript{2} s</td>
<td>33.8±5.6††</td>
<td>33.5±5.2††</td>
</tr>
<tr>
<td>T\textsubscript{3} s</td>
<td>134.0±13.5</td>
<td>134.7±11.5</td>
</tr>
<tr>
<td>MRT, s</td>
<td>69.1±6.1††</td>
<td>69.7±5.9††</td>
</tr>
</tbody>
</table>

Values are means ± SE. * Significantly different from corresponding parameter for < VeT exercise (see Table 3). † Significantly different from off-transient.
MRT than <V˙ET exercise, the fast recovery phase (i.e., phase 2) was similar between exercise intensities, as indicated by the similar $t_2$. In addition, recovery from >V˙ET exercise was faster than the onset of exercise as indicated by the faster MRT and $t_2$. These results are consistent with previous studies demonstrating a slowed recovery from >V˙ET exercise compared with recovery from moderate-intensity exercise (29) but are inconsistent with findings of symmetrical on- and off-transients during heavy-intensity exercise (3). The similar off-transient kinetics of phase 2 across exercise intensities found in this study may reflect the restoration of PCr and venous O2 stores to preexercise levels. However, evidence indicates that PCr recovery may be slowed after high-intensity exercise (27), suggesting that the rate of oxidative phosphorylation may not reflect the rate of PCr resynthesis after heavy-intensity exercise.

The VO2 slow component is delayed relative to the onset of exercise (TD$_3 = 121.2$–146.5 s); however, during recovery the time delay for the slow recovery phase (TD$_3 = 22.2$–24.8 s) converged toward TD$_2$

| Table 5. ΔVO2(6-3min), plasma Δ[La$^-$(6-3min)] and end-exercise [La$^-$]pl during heavy-intensity exercise above V˙ET for Con and Acz |
|--------------------------------------------------|-----------------|-----------------|
| Con                                             | Acz             |
| ΔVO2(6-3min), ml/min                            | 198 ± 28        | 218 ± 33        |
| Δ[La$^-$]pl, mmol/l                             | 3.4 ± 0.5       | 2.3 ± 0.4*      |
| EE [La$^-$]pl, mmol/l                           | 9.8 ± 0.9       | 7.1 ± 0.5*      |
| ΔVO2(6-3min)/Δ[La$^-$]pl, (6-3min)              | 60 ± 8          | 97 ± 9          |

Values are means ± SE. ΔVO2(6-3min) and Δ[La$^-$]pl change in VO2 and lactate concentration from 3 min to end of exercise; EE [La$^-$]pl, end-exercise plasma lactate concentration. *Significantly lower than Con.
(15.0–17.0 s). These findings suggest that the kinetic characteristics of the underlying mechanism of the slow component are different between exercise and recovery or, perhaps, different mechanisms may underlie the slow component of VO2 during recovery and exercise. Our results clearly demonstrate that recovery from moderate- or heavy-intensity exercise is not affected by [La−]pl accumulation, despite the difference in end-exercise and recovery [La−]pl after CA inhibition. The decline in VO2 was temporally (i.e., similar recovery kinetics for Con and Acz) and quantitatively (i.e., similar O2 debt for Con and Acz) similar for each of the respective exercise intensities, which has also been shown in studies that manipulate blood [La−] by prior glycogen depletion (35) or leg blood flow occlusion (33) during exercise. These results cast considerable doubt on the traditional hypothesis that the “lactacid” O2 debt (26) is equivalent to the oxidative removal of La− formed during exercise and the subsequent conversion of La− to glycogen. Further investigations utilizing on- and off-transients during heavy-intensity exercise to determine the relationship between oxidative phosphorylation (i.e., VO2 kinetics), PCR degradation-resynthesis, and anaerobic glycolysis-glucoseogenesis are warranted.

VO2 slow component. Contrary to our hypothesis, the magnitude and time course of the VO2 slow component to the overall VO2 response were not affected by CA inhibition. Although the time course of the slow component has been well described (2, 8) and was shown to arise predominantly from the exercising muscle (31), the underlying mechanism(s) of the slow component is not clearly evident (see Refs. 16 and 39 for review). The dynamics of the slow component appear to be related to the magnitude and time course of the increase in blood [La−] (32). However, increases in blood [La−] by infusion of L-(+)-lactate (30) did not increase VO2, suggesting that La− in itself does not have a cause-effect relationship with the slow component. Our results support this hypothesis, inasmuch as VO2 was similar, despite the lower [La−]pl after CA inhibition by 2 min of heavy-intensity exercise. Indeed, the ΔV O2(26–3min)−Δ[La−]pl(6–3min) relationship, although not statistically different (Table 5; P = 0.055), strongly suggests that VO2 was actually higher relative to the change in [La−]pl during Acz.

The results of the present study provide evidence against the proposal made by Wasserman and colleagues (38) that there is a direct link between the increase in blood [La−] and the slow component. They suggest that the lactate acidosis and consequent decrease in arterial pH associated with heavy-intensity exercise result in a rightward shift in the oxyhemoglobin dissociation curve in the capillaries of exercising muscles, thereby allowing a greater unloading of O2 (i.e., Bohr effect) and aerobic ATP resynthesis (38). In blood the Bohr effect involves the diffusion of CO2 and O2 through the erythrocyte membrane and cytoplasm as well as the generation of H+ from the intracellular CO2 hydration-dehydration reaction. The kinetics of this process are sufficiently fast so that, under normal conditions, equilibrium is reached within the capillary transit time of 0.75–1 s (25). However, when CA is completely inhibited, the generation of H+ from the hydration of CO2 is slowed, and therefore the rate of O2 off-loading may also be slowed (15). Maren and Swenson (25) noted that, in humans, there is an ~360-fold excess of erythrocyte CA activity, such that the Bohr effect may proceed normally and CO2 hydration is not rate limiting. We observed that VCO2 kinetics were slowed during the on-transient, suggesting that CO2 hydration may be slowed (unpublished observations). Inasmuch as the VO2 slow component was not affected by CA inhibition (either in kinetics or magnitude), this suggests that the Bohr effect is not altered by CA inhibition at the level of the muscle or, alternatively, the Bohr effect does not contribute to the development of the VO2 slow component.

Summary. In conclusion, Acz-induced CA inhibition resulted in lower [La−]pl during moderate- and heavy-intensity exercise but did not affect VO2 on- or off-transitions at either exercise intensity. Compared with moderate-intensity exercise, phase 2 and MRT were slowed for VO2 kinetics during the on-transition to heavy-intensity exercise. Recovery from heavy-intensity exercise was associated with slower VO2 off-kinetics with no difference between Con and Acz; the slower off-kinetics were due to the appearance of a slow recovery phase (i.e., phase 3), since the kinetics of the fast recovery phase (i.e., phase 2) were similar to those observed after moderate-intensity exercise. The longer kinetics of the slow phase of recovery were not associated with an elevated [La−]pl. The dissociation between the VO2 slow component and [La−]pl suggests that mechanisms other than plasma La− appearance or the associated change in acid-base status determine the time course and magnitude of the slow component.

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REFERENCES


