Bicarbonate infusion and pH clamp moderately reduce hyperventilation during ramp exercise in humans

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Péronnet F, Meyer T, Aguilaniu B, Juneau CÉ, Faude O, Kindermann W. Bicarbonate infusion and pH clamp moderately reduce hyperventilation during ramp exercise in humans. J Appl Physiol 102: 426–428, 2007. First published September 7, 2006; doi:10.1152/japplphysiol.00559.2006.—To test the hypothesis that the decrease in plasma pH contributes to the hyperventilation observed in humans in response to exercise at high workloads, five healthy male subjects performed a ramp exercise [maximal workload: 352 W (SD 35)] in a control situation and when arterialized plasma pH was maintained at the resting level (pH clamp) by intravenous infusion of sodium bicarbonate [129 mmol (SD 23), beginning at 59% maximal workload (SD 5)]. Bicarbonate infusion did not modify O2 consumption (VO2) but significantly (P < 0.05) increased arterial PCO2, plasma bicarbonate concentration, and respiratory exchange ratio (P < 0.05). At the three highest workloads, pulmonary ventilation (VE) and VE/VO2 were ~5–10% lower (P < 0.05) when bicarbonate was infused than in the control situation, and hyperventilation was reduced by 15–30%. These data suggest that the decrease in plasma pH is one of the factors that contribute to the hyperventilation observed at high workloads.

ventilatory threshold; lactate; acid-base balance; chemoreceptors

ONE CHARACTERISTIC of the ventilatory response to exercise in humans is the development of hyperventilation at high workloads, i.e., the disproportionate increase in pulmonary ventilation (VE) vs. O2 consumption (VO2) and the increase in VE/VO2 (e.g., 5–7). On the basis of the relationship between changes in VE/VO2 and in arterial pH, it has been hypothesized that hyperventilation is a ventilatory compensation of the metabolic acidosis that develops at high workloads and could be triggered, at least in part, by the reduction in plasma pH (4, 17, 18). However, as shown, for example, by Busse et al. (1–3) and discussed in several reviews (5, 7, 11, 15, 16, 19), experimental support for a cause-and-effect relationship between the reduction in plasma pH and the development of exercise hyperventilation is far from being conclusive.

In the present experiment the ventilatory response to ramp exercise was described in a control situation and, in a following experiment, when bicarbonate was administered intravenously at a rate adjusted such that plasma pH at high-intensity exercise was not different from the resting value (pH clamp). Under the hypothesis that hyperventilation is at least in part under the control of the metabolic acidosis, we expected that, at high workloads, bicarbonate infusion will diminish the disproportionate increase in VE vs. VO2, i.e., the difference between the actual VE and the value of VE estimated from VO2 and from the lowest value of VE/VO2 observed, assuming a constant VE/VO2 up to the maximal workload (Wmax). Limited preliminary data from this work showing a delay in the respiratory compensation threshold when bicarbonate was infused have already been reported (12).

METHODS

Five healthy male subjects (1 trained long-distance runner and 4 recreational athletes) gave their informed written consent to participate in the study, which was conducted according to the Principles of the 1964 Declaration of Helsinki and was approved by the institutional review board. Their age, body mass, height, and maximal VO2 (VO2max) on cycle ergometer were 34.6 yr (SD 5.7), 72.6 kg (SD 2.8), 181 cm (SD 6), and 4.040 l/min (SD 0.435), respectively [mean (SD)].

The subjects completed two ramp exercises to exhaustion on a cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands), separated by at least 1 day. The exercise included a 3-min warmup at 50 W, after which the workload was increased by 25 or 35 W/min, depending on the fitness and body mass of the subject. The first exercise served as a control trial. In the experimental trial [which was interrupted after the same duration as the first exercise: 14.2 min (SD 0.8) and 352 W (SD 35)], sodium bicarbonate (1 M sterile solution; Braun, Melsungen, Germany) was infused through a catheter (Vasocan Braunu¨le, Braun) inserted in an antecubital vein to keep plasma pH near the values observed at rest. This second trial was conducted following the control trial since the amount of bicarbonate administered and the timing of infusion were determined by the reduction in pH and in standard plasma bicarbonate concentration in the control trial. For each subject, the infusion was initiated at the workload when, in the control situation, the pH decreased by 0.03 units below the resting value [59% Wmax (SD 5)] and was continued to the cessation of exercise. The amount of sodium bicarbonate administered [129 mmol (SD 23)] infused manually in a stepwise fashion according to the progressive decrease in pH observed in the control situation was adjusted to the bicarbonate lost due to the fall in plasma pH in the control situation, i.e., the product of the decrease in standard plasma bicarbonate concentration [9.3 mmol/l (SD 2.4)] by the extracellular volume (0.2 l/kg). Before the administration of the bicarbonate solution, the catheter was kept patent by a slow infusion of sterile isotonic saline.

Respiratory exchanges were computed continuously (MetaMax I, Cortex, Leipzig, Germany), and arterialized blood samples were withdrawn from an earlobe rubbed with Finalgon (Boehringer Ingelheim) at rest and during the exercise period for the measurement of whole blood lactate concentration at 1-min intervals (automated assay using lactate dehydrogenase to convert lactate into pyruvate with formation of NADH H+; Greiner, Flach, Germany), and of plasma pH and arterial partial pressure of CO2 (PaCO2) at 2-min intervals (Blood Gas Analyzer 288, CIBA-Comin, Fernwald, Germany). Re-
cent data from Zavorsky et al. (20) indicate that pH, PaCO₂, and lactate concentration measured in arterialized blood samples predict with accuracy the corresponding values measured by arterial puncture: no systematic bias, and 95% confidence intervals = 0.00 pH units, 0.6–1.4 Torr, and 0.4–1.2 mmol/l. Actual plasma bicarbonate concentration was computed from pH and PaCO₂ by using the Henderson-Hasselbalch equation.

The effect of pH clamp on hyperventilation at high workloads was estimated by comparing the disproportionate increase in Vₑ vs. Vₒ₂ in the control and experimental situations. For this purpose, in each situation, the Vₑ expected in the absence of hyperventilation was computed by assuming a constant Vₑ/Vₒ₂ up to Wmax, as the product of the actual Vₒ₂ and of the minimal value of Vₑ/Vₒ₂ observed. Hyperventilation was estimated as the difference between the actual Vₑ and the Vₑ expected.

The data (reported as mean and SD) were compared by using two-way ANOVA for repeated measures (control vs. bicarbonate; workload expressed in % Wmax). When appropriate, Newman-Keuls post hoc tests were performed. The comparisons were made at the 0.05 level of significance.

RESULTS AND DISCUSSION

In the control situation, plasma pH significantly decreased below resting values and reached 7.270 (SD 0.045) at the end of exercise vs. 7.414 (SD 0.014) at rest (Fig. 1). When bicarbonate was infused, plasma pH significantly decreased below the resting value [7.408 (SD 0.009)] at 51 and 66% Wmax. However, pH increased thereafter and at high workloads was not significantly different from at rest and significantly higher than in the control situation [7.418 (SD 0.017) at the end of exercise] (Fig. 1).

Bicarbonate infusion and the associated changes in pH did not modify Vₒ₂ but significantly increased plasma bicarbonate concentration, PaCO₂, CO₂ production (data not shown), and respiratory exchange ratio at high workloads (Fig. 1). Also, as frequently reported (8–10, 14), plasma lactate concentration at high workloads was slightly but significantly higher when bicarbonate was administered, presumably because the lower H⁺ concentration in the intracellular fluid favored H⁺ and lactate efflux from the muscle (14).

Hyperventilation developed both in the control situation and when bicarbonate was infused, as shown by the curvilinear increase in Vₑ and by the progressive increase in Vₑ/Vₒ₂ (significant at 77% Wmax; Fig. 1). However, when the plasma pH at the three highest workloads was clamped at or near the values observed at rest by infusing bicarbonate, Vₑ and Vₑ/Vₒ₂ were significantly 5–10% lower than in the control situation (Fig. 1 and Table 1).

Table 1. Ventilatory response at the three highest workloads

<table>
<thead>
<tr>
<th></th>
<th>85% Wmax</th>
<th>92% Wmax</th>
<th>100% Wmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vₒ₂, l/min</td>
<td>3.52 (0.60)</td>
<td>3.74 (0.43)</td>
<td>4.00 (0.45)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>3.53 (0.67)</td>
<td>3.75 (0.58)</td>
<td>4.01 (0.54)</td>
</tr>
<tr>
<td>Vₑ expected, l/min</td>
<td>74.7 (8.5)</td>
<td>79.7 (7.4)</td>
<td>85.1 (7.5)</td>
</tr>
<tr>
<td>Control</td>
<td>74.4 (13.3)</td>
<td>79.2 (11.7)</td>
<td>84.9 (11.3)</td>
</tr>
<tr>
<td>Vₑ actual, l/min</td>
<td>98.9 (11.0)</td>
<td>114.5 (17.8)</td>
<td>142.9 (21.0)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>91.4* (11.1)</td>
<td>108.8* (15.6)</td>
<td>128.8* (21.5)</td>
</tr>
<tr>
<td>Hyperventilation, l/min</td>
<td>24.2 (2.9)</td>
<td>34.8 (11.5)</td>
<td>57.8 (15.7)</td>
</tr>
<tr>
<td>Control</td>
<td>17.0 (7.7)</td>
<td>29.5 (4.8)</td>
<td>43.9 (13.7)</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>17.0 (7.7)</td>
<td>29.5 (4.8)</td>
<td>43.9 (13.7)</td>
</tr>
</tbody>
</table>

Values are means (SD). The pulmonary ventilation (Vₑ) expected in the absence of hyperventilation was computed at each workload, assuming a linear increase in Vₑ vs. O₂ consumption (Vₒ₂), from Vₒ₂ and from the minimal value of Vₑ/Vₒ₂ [21.4 (SD 0.9) and 21.1 (SD 1.4) in the control and experimental situations, respectively]; hyperventilation is the difference between the actual and expected Vₑ. Wmax, maximal workload. *Significantly different from control, P < 0.05.
This was due to a slight reduction in breathing frequency ($f_R$) that was significant at 100% $W_{\text{max}}$ only (Fig. 1), with no significant change in tidal volume ($V_T$) [3.31 (SD 0.52) and 3.26 liters (SD 0.33) in the control and experimental situations, respectively]. These findings are in line with results from two previous studies of bicarbonate infusion during exercise (13, 14). In the study by Mitchell et al. (13), although this did not reach statistical significance, a 9.3% reduction in $V_E$ was observed during exercise to exhaustion at 80% $W_{\text{max}}$ (30 min) when plasma pH was maintained at the resting level (7.42 vs. 7.40 at rest) by infusion of bicarbonate (−7.5% in $V_E/V_O_2$, computed by us). In the study by Nielsen et al. (14), both $V_E$ (−8.6%, statistically significant) and $V_E/V_O_2$ (−12%, computed by us) were decreased in subjects performing a −6.5-min all-out rowing exercise at −100% $V_O_2$ when bicarbonate was infused, although the large reduction in plasma pH observed from rest to exercise in the control situation (from 7.42 to 7.07) was not fully compensated (from 7.42 to 7.34). The significant reduction in $V_E$ reported by Nielsen et al. (14) was due to a nonsignificant 6% decrease in $f_R$ associated with a small and not significant increase in $V_T$ (2.39 vs. 2.31 liters). These consistent observations from Mitchell et al. (13) and Nielsen et al. (14) and from the present experiment suggest that the fall in plasma pH could be responsible for up to −10% of the ventilatory response at high workloads, mainly by increasing $f_R$, possibly because $V_T$ levels off at high workloads.

The reduction in $V_E$ and $V_E/V_O_2$ when bicarbonate was infused understimates the contribution of the fall in pH to the control of hyperventilation since $V_E$ at high workloads includes a proportionate linear increase of $V_E$ vs. $V_O_2$ that is present across all workloads, as well as an additional disproportionate curvilinear increase vs. $V_O_2$ that is only present at high workloads and is thought to be at least in part triggered by the fall in pH. As shown in Table 1, the $V_E$ expected in the absence of hyperventilation was estimated at the three highest workloads, assuming a linear increase with $V_O_2$ from the corresponding $V_E$ and from the minimal values of $V_E$/$V_O_2$ [21.4 (SD 0.9) and 21.1 (SD 1.4) observed at 31.3% $W_{\text{max}}$ (SD 14.1) and 32.9% $W_{\text{max}}$ (SD 14.8) in the control and experimental situations, respectively]. The disproportionate increase in $V_E$ vs. $V_O_2$, estimated as the difference between the actual and expected $V_E$, was decreased by 7−14 l/min or 15−30% when the pH was clamped at or near resting values (Table 1). This suggests that the contribution of the metabolic acidosis to the control of hyperventilation at high workloads could reach −30%. It could actually be somewhat higher since bicarbonate administration not only modified changes in pH in response to exercise but also increased $P_acO_2$ at high workloads (Fig. 1). This cannot be avoided not only because bicarbonate was infused but also because bicarbonate infusion slightly depressed $V_E$. The higher $P_acO_2$ could play a role in the maintenance of hyperventilation despite pH values higher than in the control situation.

As summarized in a recent review (4), hyperventilation at high-intensity exercise could be driven by several stimuli, such as the increases in the arterial concentration of $H^+$, $K^+$, and ANG II, in temperature, and/or in central command and sensory input from locomotor muscles, because of the development of fatigue. However, the respective roles of these stimuli remain to be established: none of them seem to be obligatory (4), and they are generally believed to be redundant (6). Results from the present experiment confirm that the increase in plasma $H^+$ concentration contributes to the control of hyperventilation at high workloads. This stimulus could be responsible for at least −30% of the disproportionate increase in $V_E$ observed in this situation and when suppressed by bicarbonate infusion was not fully compensated by the remaining putative control mechanisms of hyperventilation.

**REFERENCES**