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Effects of Sodium Bicarbonate Ingestion on Hyperventilation and Recovery of Blood pH after a Short-Term Intense Exercise

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Summary

To determine the relationship between hyperventilation and recovery of blood pH during recovery from a heavy exercise, short-term intense exercise (STIE) tests were performed after human subjects ingested 0.3 g · kg^{-1} body mass of either $NaHCO_3$ (Alk) or $CaCO_3$ (Pla). Ventilation ($\dot{V}E$) - CO_2 output ($\dot{V}co_2$) slopes during recovery following STIE were significantly lower in Alk than in Pla, indicating that hyperventilation is attenuated under the alkalotic condition. However, this reduction of the slope was the result of unchanged $\dot{V}E$ and a small increase in $\dot{V}co_2$. A significant correlation between $\dot{V}E$ and blood pH was found during recovery in both conditions. While there was no difference between the $\dot{V}E$ - pH slopes in the two conditions, $\dot{V}E$ at the same pH was higher in Alk than in Pla. Furthermore, the values of pH during recovery in both conditions increased toward the preexercise levels of each condition. Thus, although $\dot{V}E$ - $\dot{V}co_2$ slope was decreased under the alkalotic condition, this could not be explained by the ventilatory depression attributed to increase in blood pH. We speculate that hyperventilation after the end of STIE is determined by the $\dot{V}E$ - pH relationship that was set before STIE or the intensity of the exercise performed.

Key words

Exercise • Recovery • Acid-base balance • Breathing • Ventilatory control

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Introduction

Changes in ventilation ($\dot{V}E$) during exercise (below the lactate threshold (LT)) are tightly coupled to changes in pulmonary CO_2 output ($\dot{V}co_2$). While the mechanisms remain unclear, this proportional matching between $\dot{V}E$ and $\dot{V}co_2$ is thought to yield the stability of arterial partial pressure of CO_2 ($Paco_2$). During heavy exercise (above LT), slope of the $\dot{V}E$ - $\dot{V}co_2$ relationship is elevated with a lowering of $Paco_2$. This phenomenon is referred to as hyperventilation related to respiratory compensation to constrain a fall in blood pH. An inability to maintain blood pH at about 7.4 is the most common explanation of the hyperventilation. However, since many factors other than blood pH are involved in ventilatory response during exercise, the cause-and-effect relationship between blood pH and hyperventilation has not been sufficiently investigated (Meyer *et al.* 2004, Péronnet *et al.* 2007).

In a short-term intense exercise (STIE), as shown by the fact that $Paco_2$ becomes lower than the resting level after the end of exercise (Kowalchuk *et al.* 1988a, Yunoki *et al.* 1999, Yunoki *et al.* 2000), hyperventilation occurs during the recovery. Of the stimuli proposed to act during exercise, arterial potassium (Paterson *et al.* 1989) and catecholamines (Warren *et al.* 1984) rapidly return to normal levels after the end of exercise. Neural factors such as central command and muscle mechanoreflex, which are thought to drive ventilation (Eldridge 1994, Ward 2007), are also excluded as possible causes of hyperventilation during the resting state following exercise. In contrast, it takes a longer time for blood pH to recover to the preexercise

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level (Kowalchuk *et al.* 1988b). Therefore, if the fall of blood pH is a cause of hyperventilation, a manipulation of blood pH will alter the $\dot{V}E$ - $\dot{V}co_2$ slope after the end of STIE. Administration of sodium bicarbonate ($NaHCO_3$) is expected to reduce a decrease in blood pH during and after exercise (Bishop *et al.* 2004, Stephens *et al.* 2002).

The aim of the present study was to 1) examine the effects of rise in blood pH induced by $NaHCO_3$ ingestion on the $\dot{V}E$ - $\dot{V}co_2$ relationship during recovery after the end of STIE and 2) examine the relationship between hyperventilation and blood pH.

Methods

Seven healthy, untrained male subjects gave informed written consent to participate in the study, which was conducted according to the Principles of the 1964 Declaration of Helsinki. The Ethics Committee of Hokkaido University Graduate School of Education approved the study. The mean age, mean height, and mean body mass of the subjects were 18.7±0.3 years, 172.7±2.2 cm, and 57.4±2.1 kg, respectively (mean ± S.E.M.). Each subject was instructed to refrain from intense physical exercise, drinking, and taking caffeine for 24 h prior to each test.

All exercise tests were carried out on a bicycle ergometer with a built-in computer (POWERMAX-V_{II}, Combi, Tokyo, Japan). Power outputs during the exercise tests were calculated continuously by the built-in computer. Each subject performed one pretest and two short-term intense exercise (STIE) tests. In the pretest, the subject performed 30 s of maximal cycling with a load of 0.075 kp · kg^{-1} body mass in order to decide the load for the STIE test. A few days later, each subject performed two STIE tests with oral administration of either $NaHCO_3$ (alkalosis condition: Alk) or $CaCO_3$ (placebo condition: Pla) in a randomized order on separate days, separated by at least one day. Each subject came to the laboratory 3 h before the start of the STIE tests. First, the subjects ingested $NaHCO_3$ or $CaCO_3$ equivalent to a total dose of 0.3 g · kg^{-1} body mass (Jones *et al.* 1977). This total dose was equally divided into six parts and each of the six parts was ingested with 200 ml of water at intervals of 10 min. The order in experimental conditions remained unknown to the subjects (single-blind method). Since $NaHCO_3$ and $CaCO_3$ were wrapped in wafers, the subjects did not know which they were ingesting. Experimental instruments were fitted to each subject 60 min after this administration procedure had been completed. Then, after resting for 5 min on the bicycle seat, each subject started a STIE for 40 s with a load (3.8±0.2 kp, 90 rpm) corresponding to 80 % of the mean power output exerted during the last 5 s of the pretest (Yunoki *et al.* 2000).

Arterialized capillary blood samples (125 µl) were collected from fingertips. The subject's hand was prewarmed in 40-45 °C water prior to each test. Such blood samples have been shown to be representative of arterial blood (Sawka *et al.* 1982). The 25-µl samples were analyzed using a lactate analyzer (YSI-1500 sport, YSI, Tokyo, Japan) to measure blood lactate concentration ($[La^-]$). The lactate analyzer was calibrated by a standard lactate solution of 5 mM before each test. The 100-µl samples were analyzed at electrode temperature of 37 °C using a blood analyzer (i-STAT, i-STAT Corporation, Abbott Park, IL, USA) to measure pH, Pco_2, sodium concentration ($[Na^+]$), and potassium concentration ($[K^+]$). Bicarbonate concentration ($[HCO_3^-]$) was calculated using the Henderson-Hasselbach equation. Furthermore, standard HCO_3^- values ($[sHCO_3^-]$) were calculated using an equation shown by Stringer *et al.* (1992). The blood analyzer was calibrated by reference liquid (pH: 7.43, Pco_2: 30 torr, Po_2: 160 torr, $[Na^+]$: 140 mM, $[K^+]$: 4 mM) before each test. Blood was sampled 1 h after the administration and immediately after and at 5, 10 and 15 min after the end of STIE.

Ventilation, gas exchange variables, and heart rate (HR) were measured continuously breath-by-breath using a respiratory gas analyzer (AE-280S, Minato Medical Science, Osaka, Japan), starting from 5 min before the start of STIE to 15 min after the end of STIE. Inspired and expired flows were measured using a hot-wire flow meter that is linear with respect to a flow range of 0 - 600 l · min^{-1}. The inspired and expired fractions of O_2 and CO_2 were analyzed by a zirconium sensor and infrared absorption analyzer, respectively. The flow meter and gas analyzer were calibrated prior to each test with a standard 2-l syringe and precision reference gas (O_2: 15.17 %, CO_2: 4.92 %). Values for $\dot{V}E$, $\dot{V}co_2$, and HR were calculated from 20-s averages of the breath-by-breath data.

Results are presented as means ± S.E.M. Pearson's product-moment correlations were determined in order to examine the relationships of $\dot{V}E$ - $\dot{V}co_2$ and $\dot{V}E$ - pH under the two conditions. A paired t-test was used to compare the power output and the slope of the regression line for both conditions. Differences between

Table 1. Blood pH, Pco_2, and electrolyte concentrations at rest (Pre-Ex) before short-term intense exercise (STIE) and during each minute of the recovery (Post-Ex) after the end of STIE under the two experimental conditions (Alk: alkalotic condition, Pla: placebo condition).

	Trial	Pre-Ex	Post-Ex			
			0 min	5 min	10 min	15 min
pH	*Alk*	7.51±0.01*	7.37±0.01*, **	7.39±0.01*, **, ***	7.43±0.01*, **, ***	7.46±0.01*, **, ***
	Pla	7.44±0.01	7.31±0.01**	7.32±0.01**, ***	7.36±0.01**, ***	7.38±0.01**, ***
Pco_2 (torr)	*Alk*	42.9±0.9	55.6±1.3**	41.5±0.8***	41.4±0.8**	41.2±1.2**
	Pla	41.9±0.8	52.2±1.5**	39.6±1.1***	38.4±0.8**	39.3±0.8**
[$sHCO_3^-$] (mM)	*Alk*	33.25±0.76*	28.28±0.76*, **	24.66±0.74*, **, ***	26.67±0.76*, **, ***	28.49±0.81*, **, ***
	Pla	27.73±0.44	23.43±0.58**	20.28±0.52**, ***	22.05±0.52**, ***	23.21±0.57**, ***
[La^-] (mM)	*Alk*	0.89±0.33	7.77±0.38**	9.05±0.48**, ***	7.40±0.38**, ***	5.65±0.30**, ***
	Pla	0.95±0.08	7.77±0.33**	8.81±0.38**, ***	7.29±0.36**, ***	5.69±0.34**, ***
[Na^+] (mM)	*Alk*	144±0.5*	147±0.4*, **	144±0.3*, ***	144±0.4*	144±0.4*
	Pla	140±0.5	143±0.5**	140±0.6***	139±0.6	140±0.8
[K^+] (mM)	*Alk*	3.84±0.06	5.00±0.12**	3.81±0.10***	3.89±0.10	3.93±0.12
	Pla	4.19±0.04	5.14±0.11**	3.89±0.07***	4.16±0.17	4.07±0.06

*Significantly different from Pla ($P < 0.05$).
**Significantly different from Pre-Ex ($P < 0.05$).
***Significantly different from the previous value ($P < 0.05$).

conditions at each time during the STIE test were examined using a two-way ANOVA with a repeated measures design. When appropriate, the means were compared using a Tukey-Kramer *post hoc* test. If a significant interactive effect was indicated, one-way ANOVA for repeated measures was used to examine the time effect, and a paired t-test was used to examine the condition effect. Kinetics of $\dot{V}E$, $\dot{V}co_2$, and HR in each condition was analyzed using a one-way ANOVA for repeated measures in order to examine the difference between the resting value and the value at specific time points. Dunnett's test was used as a post hoc test. $P<0.05$ value was regarded as statistically significant.

Results

There were no significant differences in mean power output (Alk, 319±12 W; Pla, 315±15 W) and total work (Alk, 12.8±0.5 kJ; Pla, 12.6±0.6 kJ) during STIE between the two conditions.

The results of the blood gas analysis and electrolytes concentrations are summarized in Table 1. The preexercise [$sHCO_3^-$] and pH after ingestion of $NaHCO_3$ were significantly higher than those in the placebo condition. During recovery after STIE, the values of [$sHCO_3^-$] and pH were significantly higher in the Alk condition than in the Pla condition. In both conditions, pH increased toward the preexercise level of each condition after showing a minimum at the end of STIE. The time courses of [La^-] and [$sHCO_3^-$] showed a mirror image pattern with a maximum and a minimum at the fifth minute of recovery, but the difference in [La^-] between the two tests was not significant. The magnitude of decrease in [$sHCO_3^-$] (difference between preexercise level and level at the fifth minute of recovery) was higher in the Alk condition than in the Pla condition. [Na^+] and [K^+] showed transient increases at the end of STIE and returned to preexercise levels within 5 min after the end of STIE. Throughout the STIE test, [Na^+] in the Alk condition was significantly higher than that in the Pla condition, while no significant difference in [K^+] was found between the two tests. No statistically significant effect of ingestion of $NaHCO_3$ was found on Pco_2 before and after STIE. In both tests, Pco_2 decreased below the preexercise level of each condition after reaching peak values at the end of exercise.

Fig. 1 shows the time courses of $\dot{V}E$, $\dot{V}co_2$, and HR during the two STIE tests. No statistically significant effect of alkalization on these variables was found. However, $\dot{V}co_2$ and HR tended to be higher in the Alk condition than in the Pla condition (significant when a paired t-test was used). Figure 2 shows the $\dot{V}E$ - $\dot{V}co_2$

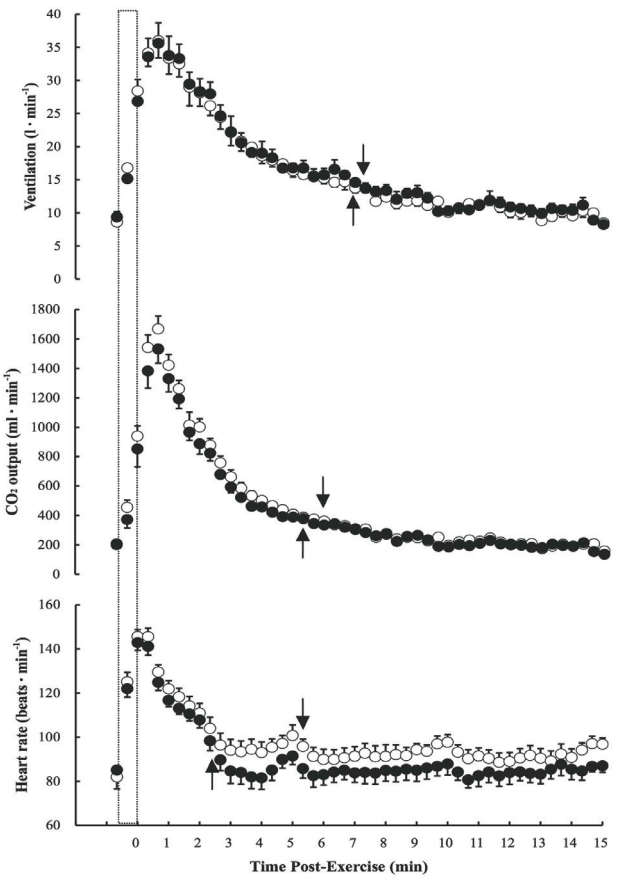

Fig. 1. Ventilation, CO_2 output, and heart rate during two short-term intense exercise (STIE) tests with oral administration of either $NaHCO_3$ (Alk: open circles) or placebo (Pla: filled circles). Resting value is the average during 5 min of rest. Dotted rectangle indicates STIE. Downward arrow (Alk) and upward arrow (Pla) indicate when the variables returned to the resting value (when p became > 0.05). Data presented are means ± S.E.M.

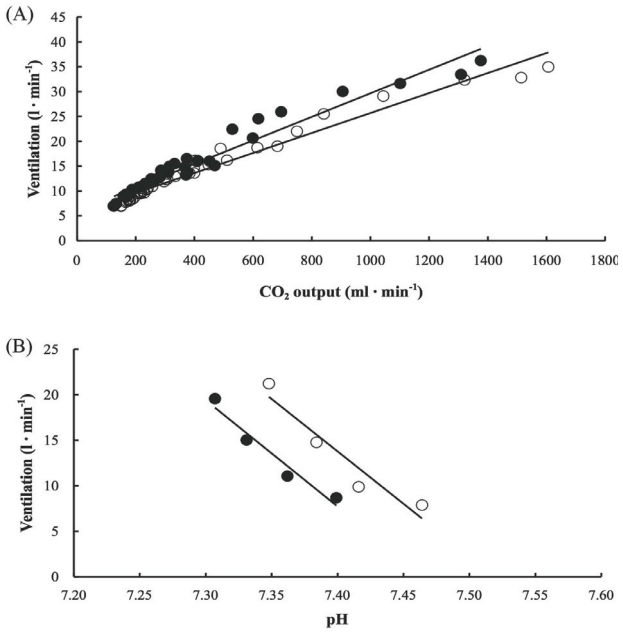

Fig. 2. (A) Ventilation - CO_2 output relationship during recovery from STIE under the alkalotic condition (open circles, y = 0.020x + 5.63; r = 0.982, p<0.01) and the placebo condition (filled circles, y = 0.024x + 5.93; r = 0.977, p<0.01). (B) Ventilation - pH relationship during recovery from STIE under the alkalotic condition (open circles, y = -115.2x + 866; r = 0.956) and placebo condition (filled circles, y = -116.6x + 871; r = 0.975). Ventilation - pH plots were obtained from the values of blood pH measured immediately after and at 5, 10 and 15 min after the end of STIE and the values of ventilation averaged at 60-s intervals. Data presented are for an individual subject.

relationship and $\dot{V}E$ - pH relationship obtained during recovery after the end of STIE under the two conditions in an individual subject. Correlation coefficients for each subject were 0.97±0.002 ($\dot{V}E$ - $\dot{V}co_2$ relationship) and 0.91±0.03 ($\dot{V}E$ - pH relationship). The correlation between $\dot{V}E$ and $\dot{V}co_2$ were significant ($p<0.01$) in all subjects, and the slope of the $\dot{V}E$ - $\dot{V}co_2$ regression line was significantly ($P<0.01$) lower in the Alk condition (0.0194±0.0007) than in the Pla condition (0.0210± 0.0009). On the other hand, there was no significant difference in the $\dot{V}E$ - pH slopes between the two tests (Alk, –184±21; Pla, –194±27).

Discussion

The main finding of the present study was that preexercise metabolic alkalization of blood, induced by ingestion of $NaHCO_3$, did cause a significant decrease in the slope of the $\dot{V}E$ - $\dot{V}co_2$ relationship during recovery after the end of STIE. This result suggests that hyperventilation is attenuated under the alkalotic condition. However, this reduction of the slope is the result of a small increase in $\dot{V}co_2$ and unchanged $\dot{V}E$, and it is not clear whether the consequent unchanged $\dot{V}E$ is due to ventilatory depression by alkalization or due to a pH-independent mechanism. Therefore, we discuss these points below.

In the present study, although pH was significantly higher in the Alk condition than in the Pla condition, there was no difference in $[La^-]$ between the two conditions. This is supported by results of a previous study (Kowalchuk *et al.* 1988b) showing that several factors in addition to increase in $[La^-]$ contribute to the change in hydrogen ion concentration ($[H^+]$). As pointed out by Stewart (1981), $[H^+]$ is dependent not only on $[La^-]$ but also on strong ion difference ([SID] = the net difference between total concentration of strong cations and strong anions). La^- is only one of the anions.

The magnitude of decrease in $[sHCO_3^-]$

(difference between the preexercise level and the level at the fifth minute of recovery) was greater in the Alk condition than in the Pla condition. This result indicates that in the Alk condition more HCO_3^- was consumed for H^+ buffering and more CO_2 was produced. Thus, in the alkalotic condition, CO_2 flow to the central circulation would be increased by increase in buffering-derived CO_2. Furthermore, despite the fact that the exercise intensities were the same in the two conditions, HR in the Alk condition tended to be greater than that in the Pla condition. This increase in HR might be due to a mechanism compensating for a decrease in O_2 diffusion in the muscles by a leftward shift of the O_2 dissociation curve induced by alkalosis (Hayashi *et al.* 1999). Although we cannot clarify the mechanism, the increase in HR could also contribute to the increase in CO_2 flow.

The close relationship between $\dot{V}E$ and $\dot{V}co_2$ has been explained by the hypothesis that an increase in CO_2 flow to the central circulation brings about an increase in $\dot{V}E$ (Schneider and Berwick 1998, Wasserman and Whipp 1983). However, in the present study, the ingestion of $NaHCO_3$ altered $\dot{V}co_2$ without effect on $\dot{V}E$. If alkalization of blood attenuates stimuli to ventilatory chemoreceptors, increase in $\dot{V}E$ due to CO_2 flow could be inhibited by the increase in pH. However, these explanations seem unlikely because the present results (Fig. 2) show that $\dot{V}E$ at the same pH is higher in the Alk condition than in the Pla condition and that the $\dot{V}E$ - pH slope related to chemoreflex sensitivity to pH is not altered by ingestion of $NaHCO_3$. Although there is a possibility that the higher Pco_2 contributes to the upward shift of $\dot{V}E$ - pH relation, there was no difference between the values of Pco_2 in the two conditions. Therefore, the increase in $\dot{V}E$ could not have been inhibited by the change of stimuli to the chemoreceptors with the alkalization of blood.

An alternative explanation for the lowered $\dot{V}E$ - $\dot{V}co_2$ slope is that CO_2 flow is not the cause of the close relationship between $\dot{V}E$ and $\dot{V}co_2$. Péronnet and Aguilaniu (2006) argued that $\dot{V}co_2$ follows $\dot{V}E$ rather than *vice versa* on the basis of results of a study by Clark *et al.* (1996) showing that when $\dot{V}E$ was voluntarily multiplied by ~1.75 (versus the value observed in the control experiment), $\dot{V}co_2$ was ~25 % higher than that in the control experiment. The decrease in the $\dot{V}E$ - $\dot{V}co_2$ slope in the Alk condition suggests that increase in CO_2 flow does not always stimulate $\dot{V}E$.

If that is in fact the case, it is necessary to examine why $\dot{V}E$ levels were similar in the two conditions even though there was a marked difference between blood pH values in the two conditions. Two possible mechanisms can be proposed from the present results. One is a change in the set point of blood pH. In the Alk condition, the $\dot{V}E$ - pH relationship was shifted to the right without any change of slope, and $\dot{V}E$ was higher than the resting level even after pH had returned to the normal value (nearly 7.4). The values of pH in both conditions seem to return to preexercise levels of each condition. This phenomenon suggests that the hyperventilation occurred to maintain the pH that was set newly before STIE. Since the administration was performed slowly and gradually, the set point of pH could have been altered. According to the alphastat hypothesis of Reeves (1972), constancy of pH is not the goal of acid-base homeostasis; rather, pH must be regulated in relation to the pK of protein histidine imidazole groups to maintain the degree of ionization of the imidazole groups. Ventilation is also regulated to maintain a constant fractional dissociation of the imidazole groups (Reeves 1972, Burton 2002). Although changes in temperature, strong ions, and osmolality are included as factors affecting the pK of protein histidine imidazole groups (Reeves 1972, Somero 1986, Jennings 1993, Burton 2002), there would have been no difference in the pK of protein histidine imidazole groups between the two experimental conditions in the present study. Consequently, $\dot{V}E$ could have been similar in the two conditions even though there was a difference between blood pH values in the two conditions. Another possible mechanism is a pH-independent mechanism. It is known that afterdischarge or short-term potentiation of neurons in the medulla (Eldridge *et al.* 1985, Eldridge 1994) or motor cortex (Fink *et al.* 1995) makes an important contribution to the driving of respiration adjustment during recovery from exercise, and it has been shown that the short-term potentiation of ventilation is unrelated to metabolic acidosis (Clement *et al.* 1996). Since the exercise intensities in the two conditions were similar, there might be no difference in the short-term potentiation and ventilatory decay between the two conditions. Ventilatory response after the end of STIE can be determined by exercise intensity.

A reflex evoked by a decrease in skeletal muscle pH has been suggested to contribute to hyperventilation (Oelberg *et al.* 1998, Scott *et al.* 2003). However, we did not measure the muscle pH. The literature data on the effect of ingestion of $NaHCO_3$ on the muscle pH are not consistent (Costill *et al.* 1984, Stephens *et al.* 2002,

Nielsen *et al.* 2002, Bishop *et al.* 2004). If muscle pH were affected by ingestion of $NaHCO_3$, the present results would suggest that muscle pH is not a major determinant for hyperventilation after intense exercise. However, it needs further investigations to clarify the involvement of muscle afferents in the present results.

In conclusion, increase in blood pH with ingestion of $NaHCO_3$ decreased the slope of the $\dot{V}E$ - $\dot{V}co_2$ relationship during recovery after STIE, suggesting that hyperventilation was attenuated under the alkalotic condition. However, this decrease in the slope was not due to the ventilatory depression attributed to the increase in blood pH. We speculate that ventilatory response after the end of STIE is determined by the $\dot{V}E$ - pH relationship at the start of exercise or the intensity of the exercise performed.

Conflict of Interest

There is no conflict of interest.

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