Metabolic effects of induced alkalosis during progressive forearm exercise to fatigue

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Raymer, Graydon H., Greg D. Marsh, John M. Kowalchuk, and R. Terry Thompson. Metabolic effects of induced alkalosis during progressive forearm exercise to fatigue. J Appl Physiol 96: 2050–2056, 2004. First published February 6, 2004; 10.1152/japplphysiol.01261.2003.—Metabolic alkalosis induced by sodium bicarbonate (NaHCO3) ingestion has been shown to enhance performance during brief high-intensity exercise. The mechanisms associated with this increase in performance may include increased muscle phosphocreatine (PCr) breakdown, muscle glycogen utilization, and plasma lactate (Lac−p) accumulation. Together, these changes would imply a shift toward a greater contribution of anaerobic energy production, but this statement has been subject to debate. In the present study, subjects (n = 6) performed a progressive wrist flexion exercise to volitional fatigue (0.5 Hz, 14–21 min) in a control condition (Con) and after an oral dose of NaHCO3 (Alk: 0.3 g/kg; 1.5 h before testing) to evaluate muscle metabolism over a complete range of exercise intensities. Phosphorus-31 magnetic resonance spectroscopy was used to continuously monitor intracellular pH, [PCr], [P], and [ATP] (brackets denote concentration). Blood samples drawn from a deep arm vein were analyzed with a blood gas-electrolyte analyzer to measure plasma pH, PO2, and [Lac−p], and plasma [HCO3−] was calculated from pH and PO2. NaHCO3 ingestion resulted in an increased (P < 0.05) plasma pH and [HCO3−] throughout rest and exercise. Time to fatigue and peak power output were increased (P < 0.05) by ~12% in Alk. During exercise, a delayed (P < 0.05) onset of intracellular acidosis (1.17 ± 0.26 vs. 1.28 ± 0.22 W, Con vs. Alk) and a delayed (P < 0.05) onset of rapid increases in the [P]/[PCr] ratio (1.21 ± 0.30 vs. 1.30 ± 0.30 W) were observed in Alk. No differences in total [H+], [P], or [Lac−p] accumulation were detected. In conclusion, NaHCO3 ingestion was shown to increase plasma pH at rest, which resulted in a delayed onset of intracellular acidification during incremental exercise. Conversely, NaHCO3 was not associated with increased [Lac−p] accumulation or PCr breakdown.

sodium bicarbonate; intracellular pH; lactate; phosphorus-31 magnetic resonance spectroscopy; skeletal muscle; ergogenic aid

METABOLIC ALKALOSIS INDUCED by sodium bicarbonate (NaHCO3) ingestion has been shown to enhance intense exercise lasting ~1–7 min (1, 3, 22, 25, 32). Several explanations for this effect have been proposed, but the mechanism has not yet been clearly elucidated. A common explanation is that induced alkalosis leads to an enhanced muscle glycolytic ATP production and consequently a greater capacity for high-intensity exercise. Studies that have reported NaHCO3 ingestion increases the blood plasma lactate concentration ([Lac−p]) during exercise would be consistent with this explanation (2, 11, 25, 29). Furthermore, it has been reported by Hollidge-Horvat et al. (9) that induced alkalosis may increase muscle glycogen utilization, phosphocreatine breakdown, and inorganic phosphate (P) accumulation during 15 min of cycling at 75% maximal O2 uptake. In summary, these findings would tend to suggest that NaHCO3 ingestion results in a shift toward a greater contribution of anaerobic energy production during exercise.

During single- and repeated-bout sprint exercise, it is plausible that an increase in nonoxidative ATP production would be beneficial to performance. However, NaHCO3 ingestion has also been shown to improve endurance activity lasting 30–60 min (5, 23, 26). Fatigue in exercise lasting longer than 15 min has been associated with glycogen depletion and lactate accumulation, in which case a shift toward anaerobic energy production is expected to inhibit, rather than improve, muscle function. Recently, Stephens et al. (30) examined the effects of NaHCO3 ingestion on ~60 min of exhaustive endurance exercise and reported a decrease in muscle [H+] (brackets denote concentration) but no changes in phosphocreatine or glycogen utilization. These findings appear to contradict those of Hollidge-Horvat et al. (9) for 15 min of cycling at a similar intensity. Although differences in the amount of exercise time may account for the conflicting results, a possible explanation for these differences was the use of only a small number (<5) of muscle biopsies for in vivo monitoring of intracellular metabolism during continuous exercise. Consequently, the inherent limitations of infrequent sampling and poor time resolution associated with muscle biopsy analysis may have prevented a clear understanding of the data.

The present study, therefore, is the first to use phosphorus-31 magnetic resonance spectroscopy (31P-MRS) to study the effects of NaHCO3 ingestion on muscle metabolism during continuous exercise. 31P-MRS is ideally suited for this type of experiment because it allows for continuous, noninvasive measurement of the kinetics of high-energy phosphate metabolites associated with muscle energy production and utilization. Unlike muscle biopsy analysis, in which intracellular metabolism is inferred from only a small number of discrete data points, 31P-MRS allows for rapid and continuous measurement of intracellular parameters. Previously, it has been shown with 31P-MRS that, during incremental exercise to fatigue, the kinetics of intracellular metabolism are not linear but that a power output or inflection point can be identified above which the rate of decline in the ratio of [PCr] to [P] and in intracel-

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ular pH (pH$_{L}$) is greater relative to that seen at lower power outputs (19). The slope, or rate of change in these variables, can thus be a useful parameter in describing the status of cellular metabolism. In the present study, therefore, an incremental exercise protocol was employed to examine the metabolic response to NaHCO$_3$ ingestion over the entire range of power output capable by the muscle [i.e., rest to peak power output (PO$_{peak}$)]. It is hoped that, with the improved time resolution of $^{31}$P-MRS, our study will help to clarify the changes occurring in intracellular metabolism with exercise during induced alkalosis.

In summary, the purpose of the present study was to use $^{31}$P-MRS and venous blood sampling to study the effects of NaHCO$_3$ ingestion on the metabolic and acid-base responses to incremental forearm wrist flexion exercise in humans. In contrast to previous muscle-biopsy studies that have reported either significant (9) or negligible (30) metabolic effects of induced alkalosis, we have utilized to our advantage the continuous in vivo measurement of intracellular metabolism to elucidate the metabolic effects that have been speculated to occur with NaHCO$_3$ ingestion. Specifically, it was hypothesized in our study that 1) an oral dose of 0.3 g/kg body wt NaHCO$_3$ delivered 1.5 h before exercise would significantly elevate plasma [HCO$_3$]$^{-}$ and lower plasma [H$^+$] at rest; 2) before exercise, this induced plasma alkalosis would not be associated with a decrease in intracellular [H$^+$]; 3) during progressive exercise, the onset of intracellular acidosis would be delayed after NaHCO$_3$ ingestion; and 4) an oral dose of NaHCO$_3$ would be associated with increased accumulation of [Lac$^{-}$]$_{pl}$ and increased breakdown of PCR.

**METHODS**

*Subjects.* Six male volunteers participated in the study [age 27 $\pm$ 3 (SD) yr; height 1.80 $\pm$ 0.07 m; weight 80.2 $\pm$ 8.1 kg]. All subjects were healthy and moderately active, but none was trained specifically in sports that involved extensive use of the forearm musculature, such as squash or tennis. Before the experiment, all procedures and any potential risks were explained to each subject, and an informed consent document was signed previous to participation. The study was approved by The University of Western Ontario Review Board for Health Sciences Research Involving Human Subjects.

*Experimental protocol.* Subjects were studied twice during each of two conditions, control (Con) and after NaHCO$_3$ ingestion (Alk). Two exercise tests were performed during each condition to evaluate 1) muscle metabolism and acid-base status using $^{31}$P-MRS and 2) [Lac$^{-}$]$_{pl}$ and acid-base status in venous blood draining the active forearm musculature via standard blood sampling techniques (Bld).

Subjects reported to the laboratory at least 2–3 h after a light meal and after abstaining from caffeine-containing foods and beverages; exercise tests were performed at the same time of day for each subject and were separated by at least 48 h. Before the Alk trial, each subject was given an oral dose of NaHCO$_3$ (0.3 g/kg body wt), which has been demonstrated consistently to elicit a state of metabolic alkalosis (16, 20). To achieve peak venous [HCO$_3$]$^{-}$, the oral dose of NaHCO$_3$ was administered 1.5 h before the start of the exercise (17). The oral dose of NaHCO$_3$ was contained within gel capsules and administered with $\approx$500 ml of water because it was found from earlier testing in our laboratory that this mode of administration was easier for the subjects to ingest than when mixed with a sports drink. In both Con and Alk, subjects rested comfortably during the period of time before exercise and were permitted to drink water ad libitum to minimize the potential gastrointestinal effects that are common with NaHCO$_3$ ingestion.

The exercise protocol was identical for each of the four tests and consisted of progressive wrist-flexion exercise to volitional fatigue performed on a custom-built wrist ergometer. Previous to the start of exercise, subjects lay supine on a table positioned next to the ergometer. The dominant arm of each subject was then placed inside the ergometer by placing the arm in full extension and then abducting to 90°. The forearm was placed in the pronated position so that subjects were able to grasp the lever of the ergometer, which was aligned such that the pivot of the lever centered on the axis of the wrist joint. With the arm in this position, the contracting forearm musculature was positioned at heart level, thus ensuring adequate perfusion during the relaxation phase of each contraction-relaxation cycle. The subjects remained supine throughout the protocol.

The exercise consisted of repeatedly depressing the lever at a frequency of 0.5 Hz (1-s contraction/1-s relaxation) through a range of motion of $\approx$70°. This action raised and lowered a water reservoir through the use of a cable-and-pulley system. The resistance was increased in a ramplike fashion by pumping water by means of a roller pump (Cole-Parmer Instruments, Chicago, IL) into the reservoir at a constant rate (0.22 l/min). A metronome set at 0.5 Hz was used to keep subjects on pace, and the experimenters monitored the movement of the water reservoir to ensure that subjects exercised within the full range of motion through to the completion of exercise. A 5-min period during which resting measurements were taken, subjects accommodated to the exercise protocol with 3 min of wrist flexion against low resistance (1.0 kg). After this initial accommodation period, subjects continued to exercise while water was continuously added to the reservoir at a rate of 0.22 kg/min. Subjects exercised to volitional fatigue, which was defined as the point at which subjects failed on repeated attempts to raise the reservoir through the full range of motion. The work done by the subject was calculated by using the known repetition rate (0.5 Hz), the arc distance of the lever (0.10 m), and the weight of the reservoir and water (1.08 kg + (flow rate-exercise time)) using standard physical relationships. This produced a ramp slope of $\approx$0.11 W/min from an initial load of 0.53 W (accommodation period). The actual flow rate of water into the reservoir was calculated as the total volume of water added during the exercise test divided by the time to fatigue.

$^{31}$P-MRS. Forearm muscle metabolism was studied by using $^{31}$P-MRS with the wrist flexion ergometer positioned within the bore of the magnet. Data were obtained using a 30-cm-bore 1.89-Tesla superconducting magnet interfaced with a SMIS/IMRIS console (Surrey Medical Imaging Systems, Guildford, UK; Innovative Magnetic Resonance Imaging Systems, Winnipeg, MB, Canada). When the subject's arm was placed in the ergometer within the bore of the magnet, the belly of the forearm was situated over a 4-cm dual-tuned $^{1}$H,$^{31}$P surface coil, $\approx$7–9 cm distal to the medial epicondyle of the humerus. In this position, the nuclear magnetic resonance signal was obtained primarily from the flexor digitorum superficialis muscle. All spectra were acquired with a 3-ms 90° adiabatic radio-frequency pulse, a 3.3 kHz receiver bandwidth, 8-$\mu$s delay time, and 2,048 complex data points with a 300-$\mu$s dwell time. Each spectrum was produced from an average of six free induction decay signals with a repetition time of 6 s (total acquisition time of 36 s).

Quantification of the $^{31}$P-MRS metabolite data was performed in the time (acquisition) domain by fitting each $^{31}$P free induction decay to a sum of damped sinusoids, which could be varied in terms of amplitude, phase, delay time, damping constant, and frequency. This method utilized a priori knowledge and a nonlinear least squares algorithm to iteratively reduced the difference between the data and the experimental model. The concentrations of the phosphate metabolites PCr and P$_i$ were determined from the amplitude of the exponential model function at time equal zero. [ATP] was calculated from the area under the concentration of the three phosphate resonances: $\alpha$-ATP, $\beta$-ATP, and $\gamma$-ATP. For each parameter, metabolite concentration was expressed relative to total phosphate signal, and, because only ratios of metabolites were used, correction factors were not applied. Intra-
cellular [H\(^+\)] and pH were determined from the chemical shift of P, with respect to PCr.

**Blood sampling.** During Bld trials, blood was drawn from a deep arm vein at the following times: 3 min and 1 min before the beginning of exercise; at the end of the 3-min accommodation period; and at 1-min intervals during the ramp protocol (including the point of fatigue). Blood was drawn into syringes containing lithium heparin, mixed, placed in ice water, and analyzed after a short delay. Whole blood samples (200 μl) were analyzed at 37°C for plasma pH, PCO\(_2\), [Na\(^+\)], [Cl\(^-\)], [K\(^+\)], and [Lac\(^-\)] by using selective electrodes (StatProfile 9 Plus blood gas-electrolyte analyzer, Nova Biomedical Canada, Mississauga, ON, Canada). The electrodes were calibrated before each test and at regular intervals during analysis. Plasma [H\(^+\)] was calculated from the measured pH, and plasma [HCO\(_3^-\)] was calculated from pH and PCO\(_2\).

**Analyses.** Because exercise time to fatigue (TTF) and PO\(_{\text{peak}}\) varied among individuals, group mean comparisons were facilitated by plotting the data as a percentage of PO\(_{\text{peak}}\). To perform this normalization, the metabolite concentration recorded over the 5-min rest period and were case of resting metabolite data, values were taken as the average onset of [Lac\(^-\)].

The above normalization allowed for comparison between individuals with varying TTF or PO\(_{\text{peak}}\); however, to compare between trials (i.e., Con vs. Alk), the data also required an additional control. It was expected that, because of a training effect or an ergogenic benefit of NaHCO\(_3\) ingestion on pH during the forearm exercise protocol was presented in Fig. 1. In both Con and Alk, pH and [H\(^+\)] decreased/increased, respectively (P < 0.05), with increasing power output, reaching similar values at the end of exercise (Con: 6.35 ± 0.05 pH, 447 ± 50 mmol/l [H\(^+\)]; Alk: 6.41 ± 0.08 pH, 382 ± 75 mmol/l [H\(^+\)]). In both conditions, the rate of intracellular [H\(^+\)] accumulation was biphasic (P < 0.05), slope and intercept parameters of two regression functions and determined an inflection at which the slope of the two lines diverged. An F test (P < 0.05) was used to evaluate whether a single or multiple regression provided the optimal fit of the data.

**Statistical analysis.** Statistical analyses were performed using SPSS v10.0.7 statistical program for the personal computer (SPSS, Chicago, IL). Muscle and plasma metabolic data were analyzed for main Con, Alk, time, and interaction effects by two-way repeated-measures ANOVA. A significant F ratio was further analyzed via Student-Newman-Keuls post hoc analysis. In addition, metabolite inflections, TTF, and PO\(_{\text{peak}}\) values were analyzed via a dependent-samples paired Student’s t-test. In all cases, statistical significance was considered at P < 0.05. Data presented in the text and tables are given as means ± SD, and figures are represented by means ± SE.

### RESULTS

**Exercise performance.** Two series of exercise tests were performed to allow separate collection of muscle and blood metabolite data. The protocol for each series was identical in every respect except for the use of 31P-MRS to collect muscle metabolic and acid-base data and venous catheterization for blood sampling and collection of blood metabolite and acid-base data. Resistance increased in a ramplike fashion, with no difference in the rate of ramp increase (~0.11 W/min; ~0.225 l/min H\(_2\)O) between 31P-MRS and Bld or Con and Alk. However, TTF and PO\(_{\text{peak}}\) were ~12% greater (P < 0.05) during the ramp tests performed after NaHCO\(_3\) ingestion (Table 1). There was no difference between 31P-MRS and Bld in either instance.

**Intramuscular metabolic and acid-base status.** The effect of NaHCO\(_3\) ingestion on pH during the forearm exercise protocol is presented in Fig. 1. In both Con and Alk, pH and [H\(^+\)] decreased/increased, respectively (P < 0.05), with increasing power output, reaching similar values at the end of exercise (Con: 6.35 ± 0.05 pH, 447 ± 50 mmol/l [H\(^+\)]; Alk: 6.41 ± 0.08 pH, 382 ± 75 mmol/l [H\(^+\)].) In both conditions, the rate of intracellular [H\(^+\)] accumulation was biphasic (P < 0.05),
displaying an initial slow and later fast component separated by a distinct point of inflection (pHT). The slope of the pH-power output relationship was less ($P < 0.05$) below the pHT than above, but in neither instance was there any difference between conditions (Table 2). However, the onset of intracellular acidosis was delayed ($P < 0.05$) in Alk (Table 3). Compared with Con, the pHT in Alk was right-shifted and occurred at a higher power output during exercise (Con: 11.7 ± 0.26 W; Alk: 1.28 ± 0.22 W). These changes corresponded to a higher ($P < 0.05$) pH$_i$ in Alk than in Con at any relative power output beyond the pHT (Fig. 1).

The effects of NaHCO$_3$ ingestion on the high-energy phosphates PCr, P$_i$, and ATP are presented in Fig. 2. With increasing power output, [PCr] decreased ($P < 0.05$), [P$_i$] increased ($P < 0.05$), and [ATP] remained similar to resting levels. No differences were observed between Con and Alk in either case. From these data, log[P$_i$]/[PCr] was also calculated, and the rate of change of log[P$_i$]/[PCr] was found to be biphasic ($P < 0.05$), displaying an initial slow and later fast component separated by a distinct point of inflection (Fig. 2). The slope of the log[P$_i$]/[PCr]-power output relationship was less ($P < 0.05$) below the PT than above, but in neither instance was there any difference between conditions. However, the onset of rapid changes in log[P$_i$]/[PCr] (Table 3) was delayed ($P < 0.05$) in Alk (Con: 1.21 ± 0.30 W; Alk: 1.30 ± 0.30 W).

Plasma lactate and acid-base status. The effect of NaHCO$_3$ ingestion on the equilibrated forearm venous [Lac$^{-}\text{b}$] during progressive forearm exercise is presented in Fig. 3. Venous [Lac$^{-}\text{b}$] increased ($P < 0.05$) with increasing power output, reaching similar end-exercise values in Con and Alk (Con: 7.1 ± 2.5 mmol/l; Alk: 7.5 ± 2.4 mmol/l). In both conditions, the rate of [Lac$^{-}\text{b}$] accumulation was biphasic ($P < 0.05$), displaying an initial slow and later fast component separated by a distinct point of inflection (LT). The slope of the [Lac$^{-}\text{b}$]-power output relationship was less ($P < 0.05$) below the LT than above, but in neither instance was there any difference between conditions (Table 2). The onset of [Lac$^{-}\text{b}$] accumulation (Table 3) was similar ($P = 0.241$) between conditions (Con: 1.17 ± 0.19 W; Alk: 1.30 ± 0.21 W).

The effect of NaHCO$_3$ on the equilibrated forearm venous plasma pH during the forearm exercise protocol is presented in Fig. 4. Plasma pH was higher ($P < 0.05$) at rest (Con: 7.43 ± 0.01 pH, 37 ± 1 nmol/l [H$^+$]; Alk: 7.48 ± 0.01 pH, 33 ± 1 nmol/l [H$^+$]). Plasma pH decreased ($P < 0.05$) with increasing power output and was higher ($P < 0.05$) during the entire exercise protocol in Alk compared with Con. At the end of exercise in Con (100% ConPO$_{\text{peak}}$) and Alk (112% ConPO$_{\text{peak}}$), plasma pH and [H$^+$] reached a similar values (Con: 7.26 ± 0.09 pH, 56 ± 11 nmol/l [H$^+$]; Alk: 7.29 ± 0.10 pH, 52 ± 11 nmol/l [H$^+$]).

The equilibrated forearm venous plasma [HCO$_3^-$], [Na$^+$], [K$^+$], and [Cl$^-$] are given in Table 4. Compared with Con, Alk resulted in an increased ($P < 0.05$) [HCO$_3^-$] at rest (Con: 31.9 ± 2.6 mmol/l; Alk: 39.0 ± 2.5 mmol/l). An elevated ($P < 0.05$) [HCO$_3^-$] during Alk was also observed throughout the entire exercise protocol. Plasma [Na$^+$] was not different at rest.

### Table 2: Biphasic parameters of intracellular pH, log [P$_i$]/[PCr], and blood plasma lactate occurring during progressive exercise in Con and Alk

<table>
<thead>
<tr>
<th></th>
<th>Initial Phase (Below Threshold)</th>
<th>Rapid Phase (Above Threshold)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Slope ($m_1$)</td>
<td>Intercept ($b_1$)</td>
<td>Slope ($m_2$)</td>
</tr>
<tr>
<td>pHT</td>
<td>Con: -0.14 ± 0.10</td>
<td>7.09 ± 0.04</td>
<td>-0.69 ± 0.23</td>
</tr>
<tr>
<td>PT</td>
<td>Con: 0.65 ± 0.24</td>
<td>-0.80 ± 0.16</td>
<td>1.43 ± 0.34</td>
</tr>
<tr>
<td>LT</td>
<td>Con: 0.67 ± 0.41</td>
<td>1.62 ± 0.44*</td>
<td>5.01 ± 2.03</td>
</tr>
</tbody>
</table>

Values are means ± SD. Slope and intercept parameters are given for the piecewise linear regression function: $y = m_1x + b_1$ ($x <$ threshold); $y = m_2x + b_2$ ($x \geq$ threshold). pHT, intracellular pH threshold; PT, log[P$_i$]/[PCr] threshold; LT, plasma lactate threshold. *Significant difference ($P < 0.05$) between Con and Alk.

### Table 3: Piecewise linear regression analysis for the determination of an onset (or threshold) of a rapid decrease in intracellular pH and the rapid increases in log [P$_i$]/[PCr] and blood plasma lactate during Con and Alk

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PO, W</th>
<th>%PO$_{\text{peak}}$</th>
<th>log[P$_i$]/[PCr]</th>
<th>PO, W</th>
<th>%PO$_{\text{peak}}$</th>
<th>[Lac$^{-}\text{b}$]</th>
<th>PO, W</th>
<th>%PO$_{\text{peak}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Con</td>
<td>6.93 ± 0.13</td>
<td>1.17 ± 0.26*</td>
<td>60.4 ± 5.0</td>
<td>-0.049 ± 0.21</td>
<td>1.21 ± 0.30*</td>
<td>62.7 ± 7.1</td>
<td>2.4 ± 0.4</td>
<td>1.17 ± 0.19</td>
<td>53.1 ± 5.4</td>
</tr>
<tr>
<td>Alk</td>
<td>6.94 ± 0.07</td>
<td>1.28 ± 0.22*</td>
<td>61.3 ± 2.1</td>
<td>-0.026 ± 0.13</td>
<td>1.30 ± 0.30*</td>
<td>61.6 ± 4.1</td>
<td>1.9 ± 0.5</td>
<td>1.30 ± 0.21</td>
<td>52.3 ± 6.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. PO, power output. *Significant difference ($P < 0.05$) between Con and Alk.
between Con and Alk; however, the increase (P < 0.05) in [Na⁺] with increasing power output was greater (P < 0.05) in Alk compared with Con from warm-up to ~70% Con PO peak. Plasma [K⁺] was lower at rest (Con: 4.1 ± 0.1 mmol/l; Alk: 3.7 ± 0.1 mmol/l). [K⁺] increased (P < 0.05) with increasing power output in both conditions; however, [K⁺] was lower in Alk compared with Con throughout exercise. Finally, plasma [Cl⁻] was greater (P < 0.05) at rest in Con compared with Alk (Con: 104.1 ± 3.3 mmol/l; Alk: 99.4 ± 1.6 mmol/l). [Cl⁻] decreased (P < 0.05) with increasing power output in both Con and Alk; however, [Cl⁻] was lower in Alk compared with Con through exercise.

**Muscle-to-plasma [H⁺] gradient.** The effects of NaHCO₃ on the muscle-to-venous plasma [H⁺] gradient are presented in Fig. 5. At rest, the [H⁺] gradient was similar in both conditions (Con: 45 ± 7 mmol/l; Alk: 51 ± 2 mmol/l). The [H⁺] gradient remained at resting levels until the power output reached ~60% Con PO peak, at which point it abruptly rose (P < 0.05) in both Con and Alk. The [H⁺] gradient was higher (P < 0.05) in Con compared with Alk at power outputs >60% Con PO peak. At the end of exercise, the [H⁺] gradient remained higher in Con compared with Alk (Con: 391 ± 52 mmol/l; Alk: 330 ± 79 mmol/l).

**DISCUSSION**

In the present study, we examined the effects of induced alkalosis on the metabolic and acid-base responses to progressive forearm wrist flexion exercise to fatigue using a combination of ³¹P-MRS and blood sampling techniques. The major findings of this study were: 1) Alk resulted in an increased TTF and PO peak; 2) the pHₐ power output relationship was shifted rightward in Alk, such that, although the rate of intracellular acidification was similar in both conditions, the onset of this acidification was delayed in Alk; 3) the [P_i]/[PCr]-power output relationship was also shifted rightward in Alk such that the onset of rapid increases in this ratio was delayed in Alk; and 4) no differences in venous [Lac⁻]pl were found between conditions.

The NaHCO₃ protocol (1.5 h before exercise) and dose (0.3 g/kg body wt) used in the present study significantly elevated plasma [HCO₃⁻] and lowered plasma [H⁺] by amounts similar to those reported in previous studies (3, 6, 9, 17, 23, 24, 30). Our observation that, before exercise, muscle intracellular [H⁺] (or pHₐ) was unaffected by NaHCO₃ ingestion has also been reported previously (3, 9, 11) and is consistent with the hypothesis that the muscle membrane is relatively impermeable to HCO₃⁻.

In the present study, the effects of induced alkalosis on pHₐ were not evident until ~60% Con PO peak, which corresponded approximately to the onset of intracellular acidosis. Examination of the time-dependent pH relationship reveals that, whereas the onset of intracellular acidification was delayed in Alk, the rate (or slope) of this acidification did not differ between conditions. This would suggest that although the initial accumulation of H⁺ is delayed in Alk, the metabolic processes involved in the production and removal of H⁺ remain in a similar state of balance in both conditions. These processes may include an increased glycolytic flux and/or increased lactate efflux.

Lactate efflux across the sarcolemma occurs via a monocarboxylate cotransporter (MCT1) (21, 27, 28). The MCT1 transporter displays concentration dependence, saturation, stereosepecificity, and temperature sensitivity and is stimulated by H⁺ and Lac⁻ gradients (13). However, in the present study increased Lac⁻ efflux seems unlikely because the [H⁺] gradient was observed to be lower in Alk during exercise above 70% Con PO peak. In fact, a decrease in the muscle-to-blood [H⁺] gradient would be expected to decrease [Lac⁻] efflux. Indeed, Stephens et al. (30) reported ~10 and 20% lower [H⁺] and [Lac⁻] gradients, respectively, from contracting muscle to the blood during Alk and suggested that the increased [Lac⁻] efflux often seen after NaHCO₃ ingestion is a consequence of decreased Lac⁻ uptake by inactive tissue. This suggestion is supported by the study of Granier et al. (7), who observed a lower arteriovenous Lac⁻ difference across the inactive forearm during repeated sprint cycling after NaHCO₃ infusion.

**Fig. 3.** Effect of NaHCO₃ ingestion (Alk) on forearm venous plasma lactate concentration ([Lac⁻]pl) during incremental wrist flexion exercise to fatigue. In both Con and Alk, venous [Lac⁻]pl during exercise is expressed relative to % Con PO peak. Dotted lines indicate power outputs corresponding to the onset of [Lac⁻]pl accumulation (lactate threshold) in Con (LT CON) and Alk (LT ALK). Values are means ± SE. No significant differences between Con and Alk for [Lac⁻]pl or LT (P = 0.255, 0.241).

**Fig. 4.** Effect of NaHCO₃ ingestion (Alk) on forearm venous plasma pH during incremental wrist flexion exercise to fatigue. In both Con and Alk, muscle pH during exercise is expressed relative to % Con PO peak. Values are means ± SE. *Alk significantly different from Con (P < 0.05).
contrast to these findings, Hollidge-Horvat et al. (9) reported an increase in [Lac] efflux was associated with an increase in the muscle-to-blood [H+] gradient in Alk. However, one might naively expect these results when intramuscular [H+] for determining the [H+] gradient is estimated from muscle biopsy measures of intracellular [Lac]. Nevertheless, an increased muscle Lac efflux with NaHCO3 cannot be completely ruled out, because Lac kinetics were not assessed in the present study.

It is important to note that changes in [Lac] detected in blood samples reflect the balance between Lac production and efflux from active tissues and Lac removal by inactive tissues. Although numerous studies have reported increases in [Lac] during exercise after NaHCO3 ingestion (2, 4, 7–9, 11, 25, 26, 30, 32), our results did not show any difference between conditions, suggesting a possible decrease in [Lac] production and/or efflux. Thus the present study is in contrast with previous studies that have reported increases in muscle Lac efflux (2) and/or increased by similar or lower [Lac] during exercise after NaHCO3 ingestion (3, 10, 12, 15, 23, 31). Although the present study cannot reconcile these apparent contradictory findings, it is possible that differences in the types of exercise protocols and muscle groups used in these studies may be an important and often overlooked factor.

The results of the present study do not agree with those of Hollidge-Horvat et al. (9), who observed that increased Lac production and efflux caused by 15 min of cycling exercise at 75% maximal O2 uptake with NaHCO3 lead to increased glycogen utilization, increased PCr utilization, and increased ADP, AMP, and Pi accumulation. Furthermore, these perturbations were associated with a greater pyruvate dehydrogenase activation, which presumably allowed for increased glycogenolytic flux in the face of rising [H+]. Although glycogen and pyruvate dehydrogenase activity were not assessed in the present study, we believe that none of these effects would be present in our study because there did not appear to be an enhanced rate of high-energy phosphate metabolism as seen in the Hollidge-Horvat et al. study. Rather, our results indicate that, for the contracting forearm, no significant differences in ATP breakdown, PCr utilization, or Pi accumulation were detected between Con and Alk (Table 1). Furthermore, when the ratio [PCr]/[Pi] (or log[Pi]/[PCr]) was plotted against power output for each subject, the transition from slow-to-rapid increases in this ratio was delayed (P < 0.05) with Alk. Presumably, these intracellular concentrations of PCr and Pi reflect the metabolic activity of the muscle and as such have often been used in an in vivo estimate of the phosphorylation potential or [ATP]-[ADP] ratio. Stable values of this ratio indicate an adequate energy status, whereas rapid increases in this ratio reflect an inability of the cell to meet ATP demands. Therefore, it is our conclusion that the delay before the rapid increases in [Pi]/[PCr] with Alk was associated with the delayed accumulation of intracellular [H+]. In other words, the enhanced exercise performance with induced alkalosis is related to the ability of NaHCO3 to maintain a more optimum pH in the face of increasing metabolic demand.

In this respect, we may consider that the fatiguing effects of a declining pH during exercise include allosteric inhibition of the rate-limiting enzymes phosphofructokinase and glycolcose phosphorylase, decreased release of Ca2+ from the sarcoplasmic reticulum, and a reduction in the number and force of muscle cross-bridge activations. Hence, it may be possible that the maintenance of a more favorable pH during exercise may enhance performance; however, the mechanisms responsible

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**Table 4. Venous plasma concentrations of HCO₃⁻, Na⁺, K⁺, and Cl⁻ during progressive exercise in Con and Alk**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Start</th>
<th>Progressive Exercise (% ConPOpeak)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>[HCO₃⁻]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>31.9±2.6*</td>
<td>32.7±2.0*</td>
<td>32.4±1.8*</td>
</tr>
<tr>
<td>Alk</td>
<td>39.0±2.5*</td>
<td>38.7±2.1*</td>
<td>38.5±2.0*</td>
</tr>
<tr>
<td>[Na⁺]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>132.2±1.1</td>
<td>135.8±5.3*</td>
<td>137.5±1.3*</td>
</tr>
<tr>
<td>Alk</td>
<td>133.3±3.0</td>
<td>139.9±5.4*</td>
<td>141.0±2.4*</td>
</tr>
<tr>
<td>[K⁺]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>4.1±0.1*</td>
<td>4.7±0.2*</td>
<td>4.6±0.2*</td>
</tr>
<tr>
<td>Alk</td>
<td>3.7±0.1*</td>
<td>4.1±0.2*</td>
<td>4.2±0.2*</td>
</tr>
<tr>
<td>[Cl⁻]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>104.1±3.3*</td>
<td>101.2±5.4*</td>
<td>100.8±4.4*</td>
</tr>
<tr>
<td>Alk</td>
<td>99.4±1.6*</td>
<td>94.9±2.6*</td>
<td>94.0±1.9*</td>
</tr>
</tbody>
</table>

Values are means ± SD. Concentration expressed in mmol/L. % ConPOpeak percent peak power output in Con. *Significant difference (P < 0.05) between Con and Alk; †Significant difference from rest (P < 0.05).

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**Fig. 5. Effect of NaHCO₃ ingestion (Alk) on forearm muscle-to-venous H⁺ gradient during incremental wrist flexion exercise to fatigue.** In both Con and Alk, the H⁺ gradient during exercise is expressed relative to % ConPOpeak. Values are means ± SE. *Alk significantly different from Con (P < 0.05).
for the reduced muscle $[H^+]$ in Alk are unclear. In the present study, we believe that a more prolonged maintenance of normal pH was achieved by either increased Na$^+$/$H^+$ transport and/or an increased intracellular strong ion difference (SID). Because blood plasma $[Na^+]$ was significantly elevated in Alk throughout the entire exercise protocol (Table 4), a similar increase in muscle $[Na^+]$ may also have occurred. As a result, an increased $H^+$ efflux via the skeletal muscle $Na^+$/H$^+$ transporter (14) and/or an increased intracellular SID may have occurred. Although the measurement of muscle $[Na^+]$ was not possible with the techniques used in the present study, it has been shown previously that metabolic alkalosis increased muscle $[Na^+]$ during exercise in a perfused rat hindlimb model (18).

An intracellular alkalosis may also have resulted from disruptions in the balance of strong cations and anions within the muscle. The increase in plasma $[Na^+]$ and decrease in plasma $[Cl^-]$ (Table 4) in the present study would have the combined effect of increasing the plasma SID, which has been shown to be the major contributor to plasma alkalosis with NaHCO$_3$ ingestion (17). If a similar increase in the SID in the intracellular compartment was present before exercise, then it is expected that the elevated SID would partially counteract the acidifying effect (through a fall in SID) of the rise in muscle $[Lac^-]$, attenuating the acidification of both the intracellular and extracellular compartments.

In summary, the metabolic effects of induced alkalosis were shown to include an increased plasma pH at rest that led to a delayed onset of intracellular acidification during incremental exercise. In our study, NaHCO$_3$ was not associated with increased $[Lac^-]_{pl}$ accumulation or increased PCr breakdown. We have concluded therefore that the oral ingestion of NaHCO$_3$ appears to effect intracellular metabolism primarily by inducing a small but measurable decrease in $[H^+]$ that is not evident until $~60\%$ $PO_{peak}$. It is believed that this effect may have been consequence of increased skeletal muscle $Na^+$/H$^+$ exchange and/or an increased intracellular SID. Furthermore, we suggest that previous reports in the literature of increased blood $[Lac^-]$ during Alk are not due to increases in muscle Lac$^-$ production but instead may be due to decreased Lac$^-$ uptake by inactive tissues.

REFERENCES