Is Individualization of Sodium Bicarbonate Ingestion Based on Time to Peak Necessary?

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ABSTRACT

FARIAS DE OLIVEIRA, L., B. SAUNDERS, G. YAMAGUCHI, P. SWINTON, and G. GIANNINI ARTIOLI. Is Individualization of Sodium Bicarbonate Ingestion Based on Time to Peak Necessary? Med. Sci. Sports Exerc., Vol. 52, No. 8, pp. 1801–1808, 2020. Purpose: To describe the reliability of blood bicarbonate pharmacokinetics in response to sodium bicarbonate (SB) supplementation across multiple occasions and assess, using putative thresholds, whether individual variation indicated a need for individualized ingestion timings. Methods: Thirteen men (age 27 ± 5 yr; body mass [BM], 77.4 ± 10.5 kg; height, 1.75 ± 0.06 m) ingested 0.3 g·kg−1 BM SB in gelatine capsules on three occasions. One hour after a standardized meal, venous blood was obtained before and every 10 min after ingestion for 3 h, then every 20 min for a further hour. Time to peak (Tmax), absolute peak (Cmax), absolute peak change (ΔCmax), and area under the curve were analyzed using mixed models, intraclass correlation coefficient, coefficient of variation, and typical error. Individual variation in pharmacokinetic responses was assessed using Bayesian simulation with multilevel models with random intercepts. Results: No significant differences between sessions were shown for blood bicarbonate regarding Cmax, ΔCmax or area under the curve (P > 0.05), although Tmax occurred earlier in SB2 (127 ± 36 min) than in SB1 (169 ± 54 min, P = 0.0088) and SB3 (159 ± 42 min, P = 0.05). Intraclass correlation coefficient, coefficient of variation, and typical error showed moderate to poor reliability. Bayesian modeling estimated that >80% of individuals from the population experience elevated blood bicarbonate levels above +5 mmol·L−1 between 75 and 240 min after ingestion, and between 90 and 225 min above +6 mmol·L−1. Conclusions: Assessing SB supplementation using discrete values showed only moderate reliability at the group level, and poor reliability at the individual level, whereas Tmax was not reproducible. However, when analyzed as modeled curves, a 0.3-g·kg−1 BM dose was shown to create a long-lasting window of ergogenic potential, challenging the notion that SB ingestion individualized to time-to-peak is a necessary strategy, at least when SB is ingested in capsules. Key Words: TIME-COURSE, ERGOGENIC SUPPLEMENT, BIOAVAILABILITY, BLOOD BICARBONATE, REPRODUCIBILITY

Sodium bicarbonate (SB) is an effective nutritional supplement to improve exercise performance and capacity during high intensity exercise (1–3). Acute ingestion of SB incurs an increase in blood pH and bicarbonate within approximately 30 to 60 min which lasts up to several hours (4,5). The metabolic alkalosis induced by SB ingestion leads to an increased efflux of lactate and hydrogen ions (H+) out of the working muscles during exercise (6), which can delay the negative impact of muscle acidosis on contractile processes (7) and improve exercise performance.

Despite the known ergogenic potential of SB supplementation, recent studies are moving away from typical mean group analyses toward individualized approaches (8). This is due to the identification of factors that may moderate the ergogenic effect of SB, including variability in blood responses after SB ingestion. The time course of blood bicarbonate responses to acute SB ingestion indicates large variability between individuals, with peak bicarbonate concentration occurring between 75 and 180 min when ingested in capsules (4) and between 10 and 140 min (5,9) in solution using the commonly used relative dose of 0.3 g·kg−1 body mass (BM) of SB. Coupled with recent evidence demonstrating consistent intraindividual response to the same dose taken on different days, it has been suggested that the optimal time to perform exercise would be at this time at which blood bicarbonate peaks (5). However, only one study to date has investigated the reproducibility of these blood responses across two sessions providing SB in solution (5). In addition, the time-course responses to SB ingestion when meal ingestion is...
controlled remain unknown, a procedure that is likely used by most athletes in real competitive situations. Thus, more information about the consistency of the time-course responses to SB ingestion is warranted, particularly after the ingestion of a standardized meal.

The ergogenic effects of SB have been suggested to be dependent on a minimum increase of circulating bicarbonate, with an increase of +5 mmol·L$^{-1}$ being considered a zone of potential ergogenic benefit, and increases above 6 mmol·L$^{-1}$ being almost certainly ergogenic (4,10,11). It is currently unclear whether the absolute increases at time to peak differ substantially from those generally seen at standardized timepoints. The mean +6.5 ± 1.3 mmol·L$^{-1}$ increase shown at time to peak by Gough et al. (12) is similar to the increases shown after 60 min (+6.1 Dias et al. (13); +5.1 Jones et al. (4); +5.7 Gough et al. [5]), 90 min (+6.5 Jones et al. (4) +6.1 Gough et al. (5), and 120 min (+6.5 Jones et al. (4); +5.6 Gough et al. [5]) with the same 0.3 g·kg$^{-1}$ BM dose. Furthermore, blood bicarbonate concentration was not shown to be different 60, 120, and 180 min after SB supplementation in gelatine capsules (14), which raises questions as to whether ingestion timing is an important factor for the ergogenic effects of SB in this form. It remains to be determined whether blood bicarbonate is consistently increased close to peak, or above +6 mmol·L$^{-1}$, for prolonged periods.

Although time to peak in blood bicarbonate has been touted as a strategy to optimize SB ingestion (12), there are several limitations that may preclude its applicability to actual training or competition settings. First, it requires athletes or coaches to have access to a reliable blood gas analyzer and to perform a subsequent time-course measurement of blood bicarbonate responses to SB ingestion over several hours. This procedure is laborious, costly, and not easily accessible for most athletes. Second, time to peak assumes that the increases in circulating SB are substantially greater when blood bicarbonate peaks than at standard timepoints, instead of assuming that blood bicarbonate will fluctuate around the peak value for a period. An in-depth analysis of the blood bicarbonate responses to SB ingestion could reveal whether the “window of ergogenicity” is limited to a fixed timepoint or extends across a broad period after SB ingestion. This could provide important practical information for athletes as to whether determination of time-to-peak is a necessary strategy.

To address these controversies, the aims of this investigation were to describe and determine the reliability of orally ingested SB pharmacokinetics over 4 h using multiple testing occasions (including a placebo trial). A secondary aim of this study was to assess whether individual variation in orally ingested SB pharmacokinetics indicated a need for individualized ingestion timings. Our hypothesis was that SB ingestion would result in a sustained increase in blood bicarbonate above the purported ergogenic thresholds. We also hypothesized that this pattern would result in inconsistent responses in time to peak ($T_{\text{max}}$), potentially challenging the need for individualized ingestion timings.

**METHODS**

**Participants.** Twenty-four young, physically active, healthy men were screened for eligibility; three of them did not meet inclusion criteria, and six other candidates did not wish to participate in the study. Fifteen participants enrolled in the study, but one withdrew after the first session due to personal reasons while a second participant withdrew after the third session due to gastrointestinal distress associated with SB ingestion. Therefore, complete data were obtained for 13 participants and used in all analyses herein reported (age, 27 ± 5 yr; BM, 77.4 ± 10.5 kg; height, 1.75 ± 0.06 m; BM index, 25.2 ± 2.9 kg·m$^{-2}$). Inclusion criteria were defined a priori as: healthy men age 18 to 35 yr. Exclusion criteria were defined a priori as: smoking, use of medications that may alter stomach pH and any diagnosed condition that could affect the gastrointestinal and blood pH balance. All volunteers were informed about the discomforts and risks associated with participation and, thereafter, provided written consent. The study was approved by the Institutional Ethics Committee (29181114.0.0000.5391).

**Study design.** This was a crossover, placebo-controlled study in which volunteers visited the laboratory on four separate occasions, 2 to 7 d apart, to receive SB (on three occasions) or placebo (PL, on one occasion). To control for order effects, treatments were randomly assigned to each visit in a balanced fashion using the Latin square. Participants were requested to refrain from strenuous physical activity and alcohol intake in the 24 h preceding each visit. They were also instructed to maintain a similar pattern of food intake on all days before the tests. Compliance with these requests was verbally confirmed with all participants. The participants arrived at the laboratory in the morning after an overnight fast, and a standardized breakfast (energy, 563 kcal; protein, 9.3 g; carbohydrate, 89.6 g; fats, 8.9 g) was served to avoid variations in blood responses due to differences in food intake before the tests. One hour after the breakfast, blood samples were taken before and during 4 h after the ingestion of SB or PL.

**Supplementation protocol.** Sodium bicarbonate (0.3 g·kg$^{-1}$ BM; Farmácia Analítica, Rio de Janeiro, Brazil) was given on three different visits while an identical number of capsules was provided in PL (each capsule containing 56 mg of corn flour; Farmácia Analítica, Rio de Janeiro, Brazil). Supplements were given in gelatine capsules identical in size and appearance. Participants had 5 min to ingest all capsules. After ingestion of the last capsule, a stopwatch was started to control the exact times at which blood samples were to be taken.

**Blood sampling.** The cephalic vein was cannulated (catheter 20 G Safelet Nipro) and kept warm with the use of a fore-arm thermal blanket maintained at 48°C throughout the entire 4-h sampling period. A venous blood sample was taken for the determination of baseline blood parameters (i.e., before ingestion). The participants then ingested SB or PL in gelatine capsules along with 400 mL of water and then 100 mL·h$^{-1}$ throughout. After ingestion, blood samples were taken every 10 min for 3 h, and then every 20 min in the fourth hour. Blood
samples (1 mL) were collected in heparinized syringes and immediately analyzed for pH and pCO₂ using a blood gas analyzer (RAPIDLab 348, Siemens, Germany). Quality controls were performed each experimental day before data collection. Blood bicarbonate was calculated using the Henderson–Hasselbalch equation. The interassay coefficient of variation (CV) of blood bicarbonate was 6.4% (determined over the 4-h period during the PL trial). Blood bicarbonate was defined as the primary outcome.

**Side effects.** Side effects were recorded at the same timepoints as blood collection using an adapted questionnaire (15). Participants rated the intensity of the following 13 symptoms from 0 (no effect) to 10 (very intense effect): nausea, dizziness, headache, flatulence, urge to defecate, belching, heartburn, bloating, stomach cramps, intestinal cramps, urge to vomit, vomiting, and diarrhea.

**Statistical analysis.** Data are presented as mean ± standard deviation. Area under the curve (AUC) was calculated for bicarbonate and pH using the trapezoid method. Mixed models (proc mixed, SAS University Edition) were used to compare the following variables between visits: baseline, $T_{\text{max}}$ (defined as the first time in minutes that bicarbonate and pH variables took to reach its highest value), absolute peak ($C_{\text{max}}$, defined as the highest value in bicarbonate and pH variables), absolute peak change ($\Delta C_{\text{max}}$, defined as the absolute difference between baseline and $C_{\text{max}}$), and AUC. Individuals were considered random factors and session (three levels; SB1, SB2, SB3) and time (blood collection timepoints) were fixed factors. Mixed models were also used to compare blood bicarbonate concentration at $T_{\text{max}}$ and 60, 90, and 120 min after ingestion. To account for the time series nature of the data and subsequent underlying structure, four different covariance structures (compound symmetry, autoregressive, toeplitz, and unstructured) were tested to verify the model that best fit to each dataset, according to the Bayesian Information Criterion (lowest BIC value). Pairwise comparisons adjusted by Tukey–Kramer were used when a significant F-value was observed. Intraclass correlation coefficient (ICC), typical error using data from the three SB trials to determine within-subject reliability. Test–retest CV were calculated using the mean square root method (16). The frequency of side effects reported between visits, irrespective of intensity and duration, was analyzed using the $\chi^2$ test. Side effect scores for the 13 symptoms were summed within each visit and compared between visits using the Friedman test. Statistical significance was accepted at $P \leq 0.05$. Intrertrial reliability was assessed by calculating typical errors (sigma) and ICC from level 0 and level 1 residuals in the mixed models. Because all blood pH data and analysis were similar that of blood bicarbonate, herein we report blood bicarbonate data only although blood pH data are included as supplemental material (Supplemental Digital Content 1—Figure—Blood pH responses, http://links.lww.com/MSS/B945).

To describe individual variation in the pharmacokinetic responses to orally ingested SB and assess the need for individualized ingestion timings, a Bayesian perspective was adopted. A Bayesian perspective best facilitated probabilistic questions, such as the probability of an individual’s blood bicarbonate level exceeding a given absolute increase (i.e., +5 or +6 mmol·L⁻¹) or percentage increase within specific time windows. Using data collected across the participants’ three active testing sessions, Bayesian multilevel models with random intercepts and slopes were fitted using the brms package (17) in the programming language R. In contrast to treating observed data as independent points, it was assumed that changes in blood bicarbonate after SB ingestion followed a smooth response that could be adequately described by a polynomial function. Linear, quadratic, cubic, and quartic models were fitted, with Watanabe–Akaike Information Criterion used to identify a cubic model as the best fit for further evaluation. The Bayesian analysis required specification of prior beliefs regarding model parameters. To reflect a lack of prior information, default improper flat priors were selected for population-level regression parameters and the LKJ-prior selected for the multivariate normal distribution covariance matrix between group-level parameters. Posterior estimates of size $n = 10,000$ were generated for each parameter using Markov chain Monte Carlo sampling with four chains and 3500 iterations (warm-up, 1000 iterations). These posterior estimates described the typical (e.g., median) blood bicarbonate response representative of the group. To explore the likely range and distribution of responses across individuals from a similar population, posterior estimates were used to probabilistically sample regression parameters from a multivariate normal distribution. For each parameter set ($n = 10,000$), 100 individual blood bicarbonate traces (each a cubic polynomial) were produced and the total pool of 1 million traces used to estimate probabilities that an individual’s blood bicarbonate increased above +5 and +6 mmol·L⁻¹. A threshold of 80% probability was selected to assist with interpretation of results and identify time windows where for practical purposes it could be concluded that the vast majority of individuals met the criteria.

**RESULTS**

**Reliability.** Blood bicarbonate at baseline was not different between sessions (SB1, 25.7 ± 2.4; SB2, 25.0 ± 2.0; SB3, 26.0 ± 1.7; PL, 25.4 ± 2.1 mmol·L⁻¹; $P = 0.74$; $P = 0.5348$; Fig. 1). Reliability statistics were calculated for baseline (TE, 1.7 units; ICC, 0.26), $C_{\text{max}}$ (TE, 2.0 units; ICC, 0.20), $\Delta C_{\text{max}}$ (TE, 2.5 units; ICC, 0.1), and $T_{\text{max}}$ (TE, 38.7 units; ICC, 0.34). The ICC, typical error, and CV calculated for blood bicarbonate between sessions are presented in Table 1.

Area under the curve was not different between SB sessions (SB1 = 1447 ± 364 mmol·min·L⁻¹; SB2 = 1468 ± 421 mmol·min·L⁻¹; SB3 = 1210 ± 520 mmol·min·L⁻¹; $F = 0.87; P = 0.43$; Figure 1, panel B). No significant differences between sessions were shown for blood bicarbonate regarding $C_{\text{max}}$ (SB1, 36.8 ± 2.8 mmol·L⁻¹; SB2, 35.5 ± 1.4 mmol·L⁻¹; SB3 = 35.2 ± 2.0 mmol·L⁻¹; $F = 2.65; P = 0.10$; Figure 1, panel C) or $\Delta C_{\text{max}}$ (SB1, 11.1 ± 2.7 mmol·L⁻¹; SB2 = 10.5 ± 2.5 mmol·L⁻¹; SB3 = 9.3 ± 2.2 mmol·L⁻¹;
F = 1.30; P = 0.29, Figure 1, panel D), although T\text{max} occurred significantly earlier in SB2 (127 ± 36 min) than in SB1 (169 ± 54 min, P = 0.0088) and SB3 (159 ± 42 min, P = 0.05; Fig. 2) (main effect of session: F = 5.83; P = 0.0086) (Fig. 1, panel E). Individual analysis showed substantial intra-individual variation for T\text{max} in blood bicarbonate after SB ingestion, despite the lack of statistical differences between sessions for mean values (Fig. 2). Moreover, a prolonged period above the +5 mmol·L\text{−1} (light gray blocks) and +6 mmol·L\text{−1} (dark gray blocks) concentration.

**TABLE 1.** Reliability analyses. Intraclass correlation coefficients (ranges from 0 to 1), typical error and CV calculated for each timepoint across the three SB supplementation sessions and for the T\text{max}, C\text{max}, and ΔC\text{max} concentration.

| Timepoints (min) | Intraclass Correlation | Typical Error (mmol·L\text{−1}) | CV (%) |
|------------------|------------------------|----------------------------------|--------|
|                  | Confidence Interval     | Confidence Interval              |        |
| Baseline         | 0.389 0.208            | 0.665 1.77 1.40 1.94             | 5.88   |
| 10               | 0.330 0.080            | 0.681 1.44 1.10 1.96             | 3.31   |
| 20               | 0.268 0.002            | 0.664 1.92 1.44 2.62             | 9.40   |
| 30               | 0.218 0.002            | 0.611 2.09 1.60 2.79             | 7.63   |
| 40               | 0.453 0.037            | 0.764 1.93 1.47 2.71             | 6.20   |
| 50               | 0.535 0.010            | 0.698 2.11 1.63 2.85             | 6.29   |
| 60               | 0.318 0.007            | 0.709 2.16 1.66 2.92             | 7.34   |
| 70               | 0.367 0.016            | 0.726 1.70 1.29 2.33             | 4.90   |
| 80               | 0.361 0.013            | 0.717 1.80 1.37 2.50             | 4.03   |
| 90               | 0.388 0.042            | 0.746 2.26 1.73 3.10             | 5.91   |
| 100              | 0.338 0.007            | 0.688 2.43 1.88 3.33             | 6.64   |
| 110              | 0.263 0.003            | 0.645 2.81 2.16 3.79             | 7.46   |
| 120              | 0.305 0.008            | 0.679 2.49 1.92 3.35             | 7.24   |
| 130              | 0.266 0.003            | 0.646 2.68 2.08 3.62             | 8.23   |
| 140              | 0.083 <0.001           | 0.451 2.92 2.31 3.78             | 8.67   |
| 150              | 0.106 <0.001           | 0.511 2.13 1.69 2.79             | 6.68   |
| 160              | 0.123 <0.001           | 0.523 2.65 2.07 3.44             | 10.48  |
| 170              | 0.036 <0.001           | 0.307 2.40 1.91 3.14             | 9.67   |
| 180              | 0.049 <0.001           | 0.363 2.58 2.07 3.45             | 9.87   |
| 200              | 0.214 0.002            | 0.686 2.37 1.84 3.11             | 8.13   |
| 220              | 0.199 0.002            | 0.577 1.88 1.44 2.49             | 5.25   |
| 240              | 0.218 0.002            | 0.633 2.10 1.63 2.76             | 7.59   |
| C\text{max}     | 0.459 0.100            | 0.790 1.580 1.040 2.078          | 5.41   |
| ΔC\text{max}    | 0.294 0.002            | 0.694 2.104 1.429 2.633          | 19.55  |
| T\text{max}     | 0.568 0.263            | 0.833 3.10 2.95 4.107            | 32.58  |
| AUC              | 0.263 0.001            | 0.638 347.7 244.7 423.9          | 26.66  |
blocks) thresholds was shown in nearly all participants in all three sessions (Fig. 2).

**T**<sub>max</sub> versus standard timepoints. Comparison between T<sub>max</sub> and standard timepoints showed statistically significant differences in absolute bicarbonate values between all prespecified timepoints (T<sub>max</sub>, 35.9 ± 2.2 mmol·L<sup>-1</sup>; 60 min: 30.8 ± 2.4 mmol·L<sup>-1</sup>; 90 min: 32.1 ± 2.6 mmol·L<sup>-1</sup>; 120 min 33.0 ± 3.0 mmol·L<sup>-1</sup>; F = 45.87; P < 0.0001), except for 90 versus 120 min (P = 0.1852). Delta change for blood bicarbonate was different between T<sub>max</sub> versus all prespecified timepoints (all P < 0.001), but no significant differences were shown between 90 and 120 min (P = 0.1852; Fig. 3).

**Modeling approaches.** Bayesian modeling and subsequent simulations estimate that over 80% of individuals from the population experience elevated blood bicarbonate levels greater than 5 mmol·L<sup>-1</sup> between 75 and 240 min after ingestion. For absolute increases greater than 6 mmol·L<sup>-1</sup>, the expected window decreased to between 90 and 225 min (Table 2). Results of the Bayesian modeling and subsequent simulations with a multilevel cubic model are illustrated in Figure 4.

**Side effects.** All participants reported one or more side effects in each of the three SB trials, with a total of 39 symptoms being reported in SB1, 46 symptoms in SB2 and 37 symptoms in SB3. No significant differences between sessions were shown for the frequency of side effects symptoms (χ<sup>2</sup> = 1.45, P < 0.485). The Friedman test showed that intensity of symptoms throughout the time course was not different between visits (P = 0.7627; Supplemental Digital Content 2—Figure—Side effects, http://links.lww.com/MSS/B946).

**DISCUSSION**

This study is the first to investigate a 4-h time-course response of blood bicarbonate, pH and side effects after the ingestion of 0.3 g·kg<sup>-1</sup> BM SB in gelatine capsules on three
distinct sessions. We hypothesized that, due to the dynamic nature of blood acid–base regulation and natural fluctuation in blood bicarbonate concentration, a single timepoint for peak blood bicarbonate would not properly represent the sustained increase in blood bicarbonate after acute SB ingestion Jones et al. (4). We also sought to gather further information on the within-subject consistency of blood bicarbonate responses to acute SB ingestion in gelatine capsules. Repeated administration of SB in gelatine capsules did not elicit consistent responses for bicarbonate $T_{\text{max}}$, which is in agreement with our initial hypothesis, and potentially challenges the necessity of individualized ingestion timings. Overall, our results indicate that blood bicarbonate continuously rises for ~120–160 min after SB ingestion before reaching a plateau, with elevated values being shown until the end of the 4-h period.

The Bayesian analysis revealed an interesting pattern of elevated probabilities of increased blood bicarbonate levels (above the theoretical ergogenic threshold) from ~60 min after ingestion to the end of the measurement period. Although performance assessment was beyond the objectives of this study, our data might challenge the notion that a single timepoint at which blood bicarbonate peaks is necessary to optimize the ergogenic effects of SB. Instead, the Bayesian model and reliability analyses, collectively, suggest that it is not possible to accurately determine when peak blood bicarbonate has been reached because slight variations in blood bicarbonate, including the peak values, are most likely due to random error (owing to measurement error and biological variation) around the already elevated blood bicarbonate concentrations. Therefore, it appears that the ergogenic potential of SB is likely to be in place for at least 3 h, starting ~60 min after ingestion. This finding is consistent with a previous study that measured blood bicarbonate for 3 h in response to SB ingestion and found a similar plateau-shaped curve of increased blood bicarbonate (4). However, our data contrast with another similar study that showed a trend toward a rapid decline in blood bicarbonate after reaching its peak (5). Perhaps, the best explanation for the difference between these studies may be related to the form of SB administration. While our study and Jones et al. (4) provided SB in gelatine capsules and found a more sustained increase in blood bicarbonate, Gough et al. (5) provided SB in solution and found a more rapid profile of blood bicarbonate appearance and disappearance. These differences in the shape of the blood bicarbonate curves (i.e., more sustained vs rapid decline) seem to also explain why the reliability of $T_{\text{max}}$ was poor in our study (random error around a long-lasting elevation in blood bicarbonate) in contrast with a good reliability in the study by Gough et al. (sharp peak and rapid decline allow a clear identification of $T_{\text{max}}$). There is a slight difference in pharmacokinetics when SB is ingested in capsules compared with SB ingested in solution (18), meaning any conclusions in this article are restricted to supplementation in gelatine capsules.

Another important difference between studies is the provision of a meal before SB ingestion. Although we started blood collection 1 h after a standardized breakfast, Gough et al. (5) requested their participants to refrain from food 4 h before SB ingestion. It is possible that the time at which an individual consumes their precompetition or training meal influences the subsequent response to SB ingestion. Although unexplored, the influence of meal ingestion on the pharmacokinetic responses to SB is of great practical implication. In our study, we opted to provide a standardized breakfast to better simulate a practical training or competition situation, assuming that athletes typically train or compete in a well-fed postprandial state. It must be noted, however, that although our preingestion meal strategy represents the responses to SB ingestion under a general postprandial state, we did not explore the impact of meal composition on these responses, which remain a largely overlooked topic of investigation. Another interesting point is that our $\Delta C_{\text{max}}$ values (~ +10 mmol·L$^{-1}$) were considerably higher than the +7 mmol·L$^{-1}$ shown by Gough et al. (5) when supplemented with the same 0.3 g·kg$^{-1}$ BM dose of SB. We speculate that this too could be explained, at least in part, by the timing of food intake before supplementation. Because

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**TABLE 2.** Probability estimates (%) of elevating blood bicarbonate above 5 mmol·L$^{-1}$ and 6 mmol·L$^{-1}$ (from baseline) at different timepoints after SB ingestion.

| Time after Ingestion (min) | Probability of Increases above 5 mmol·L$^{-1}$ | Probability of Increases above 6 mmol·L$^{-1}$ |
|----------------------------|-----------------------------------------------|-----------------------------------------------|
| 0                          | 0%                                            | 0%                                            |
| 15                         | 0%                                            | 0%                                            |
| 30                         | 0%                                            | 0%                                            |
| 45                         | 8.6%                                          | 0%                                            |
| 60                         | 69%                                           | 14%                                           |
| 75                         | 93%                                           | 60%                                           |
| 90                         | 97%                                           | 86%                                           |
| 105                        | 99%                                           | 93%                                           |
| 120                        | 99%                                           | 95%                                           |
| 135                        | 99%                                           | 96%                                           |
| 150                        | 99%                                           | 96%                                           |
| 165                        | 99%                                           | 96%                                           |
| 180                        | 98%                                           | 94%                                           |
| 195                        | 97%                                           | 92%                                           |
| 210                        | 95%                                           | 88%                                           |
| 225                        | 91%                                           | 80%                                           |
| 240                        | 85%                                           | 70%                                           |

Probability values were estimated using Bayesian simulation ($n =$ 1 million).
our volunteers had eaten only 1 h before supplementation, they could have been presenting a slight metabolic alkalosis due to the “alkaline tide” effect that accompanies food ingestion (19). Alternatively, the presence of food in their stomach could have resulted in higher luminal pH (20), which could result in less bicarbonate reacting with stomach acids, allowing more bicarbonate to enter the intestine to be absorbed. Differences in blood gas analyzers and in blood collection methods (e.g., vein vs capillary blood taken with or without arterialization) may have also played some role in the different results between studies; however, it is important to note that different methods may yield different absolute values but they unlikely will result in an entirely different pharmacokinetic curve.

Analysis of classical timings of bicarbonate supplementation (60, 90, and 120 min postingestion) identified a progressive step pattern with significant increases over each 30 min period. On average, blood bicarbonate at time to peak was 2.4 mmol·L\(^{-1}\) higher than that obtained 120 min postingestion. However, given typical error at baseline was estimated as 1.8 mmol·L\(^{-1}\), differences can be explained by random errors, especially given the large number of data points measured and the probable extended plateau period. Nevertheless, mean values were very near or above the purported ergogenic thresholds in all timepoints. Importantly, there is currently no evidence for a linear association between the magnitude of the blood bicarbonate increase with the magnitude of the ergogenic effect of SB. Thus, one cannot assume that the higher the blood bicarbonate value, the greater the effects on performance. In fact, evidence so far points toward a minimum increase in blood bicarbonate necessary for SB to exert its ergogenic effects (4,10,11). In that sense, the Bayesian modeling presents a significant advance in data interpretation, as it allows for direct probabilistic questions to be addressed. For example, models can be used to estimate the probability that an individual from the population will experience an increase of at least +5 mmol·L\(^{-1}\) (or any other value) over a specified time interval. The Bayesian modeling clearly indicated a high probability for ergogenic effects (assuming the validity of the +5 and +6 mmol·L\(^{-1}\) thresholds) over a prolonged period although there was large interindividual variability (Fig. 2). Future research should corroborate the use of these ergogenic thresholds for exercise performance.

Another aim of our study was to confirm whether blood bicarbonate responses and, more importantly, the time to peak in blood bicarbonate, are consistent across 3 identical trials conducted on different days. Although \(C_{\text{max}}\) and \(\Delta C_{\text{max}}\) were similar between trials, we showed a significant difference in \(T_{\text{max}}\) between trials, indicating poor repeatability of this measure. Intraclass correlation coefficient and CV also showed moderate-to-poor reliability for these variables, especially \(\Delta C_{\text{max}}\) and \(T_{\text{max}}\). In support of this, individual analysis also showed a considerable intrindividual variability in blood bicarbonate responses to acute SB ingestion (Fig. 2). Thus, we suggest that determination of \(T_{\text{max}}\) for subsequent implementation before exercise may not be the most suitable method when ingesting SB in gelatine capsules. This moderate-to-poor reliability for blood bicarbonate measures shown in our study is somewhat in contrast with recent studies that showed consistent blood bicarbonate responses between trials (5,13), but in agreement with a study that showed larger intra-individual variation in blood responses to SB ingestion (21). The large variation shown here may be a reflection of the long plateau-shaped curve we showed for blood bicarbonate, where values fluctuate around \(C_{\text{max}}\) for a prolonged period, allowing the peak value to occur anytime within this period. This reinforces the notion that the peak value is, in our case, only slightly different than the other similarly elevated values, and that identification of a solitary peak value might represent random variation rather than a true peak value which would coincide with the best opportunity for SB to be ergogenic. Therefore, it appears likely that there is a broad window of opportunity, and not a single timepoint, where SB supplementation is more likely to be effective. This is supported by the Bayesian modeling used in the current study, and by previous studies showing no differences in the performance effects of SB between different timepoints after ingestion (14). Again, the differences between our results and those by Gough et al. (5) might be due to different experimental settings (including preingestion meal and SB being taken in capsules vs dissolved in water), which might have resulted in different types of blood bicarbonate curve (i.e., long-plateau vs sharp increase followed by sharp decrease). Nonetheless, further work should confirm our assertions by investigating the effect of SB supplementation on exercise performance performed at various timepoints after supplementation.

Importantly, SB ingestion resulted in significant and frequent side effects in all sessions, with no differences being shown between sessions. The consistent and widespread occurrence of important side effects remains a major obstacle for SB use in practical settings, and this is yet to be solved. Future studies should look for ways to promote the ergogenic effects of SB while minimizing its side effects.

This study has some limitations. First, although we designed the experiment to have the highest possible external validity, we acknowledge that the participants remained rested for the entire experimental protocol. This means that the commencement of exercise, either a warm-up or a competition, could alter the time-responses shown herein. The exact window of ergogenic potential shown here can only be assumed to be valid if the athlete remains rested between SB ingestion and the beginning of the exercise. Future studies should examine how exercise of different intensities affects the pharmacokinetics and the time course of ergogenic properties of SB. Another limitation is the use of a single 0.3 g·kg\(^{-1}\) SB dose, which does not allow any extrapolation of the current findings to smaller doses (e.g., 0.2 g·kg\(^{-1}\)) or other supplementation strategies (e.g., split-dose strategy). In fact, because previous studies showed a shorter period of blood bicarbonate elevations (above the purported ergogenic thresholds) with smaller doses (4), it is possible that time to peak remains as a relevant strategy when smaller doses are used, although this is yet to be confirmed. Indeed, the study by Gough et al. (12) showed that
individualized strategies based on time-to-peak may allow for the use of smaller doses without any measurable loss in SB ergogenicity. However, this study did not directly compare the effect of SB at time to peak with standard timepoints that are typically used in SB literature (e.g., 60, 90, or 120 min after SB ingestion). Third, we were unable to perform PO2 analysis in our samples, meaning we could not ensure venous blood arterIALIZATION, despite the use of a thermal blanket specifically designed for the arterIALIZATION of venous blood in the forearm. Lastly, the interpretation of our data is based on the current assumption that increases in +5 and +6 mmol L−1 in blood bicarbonate are true thresholds for SB to be ergogenic. Because we were unable to associate the pharmacokinetic data with true performance effects in our participants, some caution should be exercised when extrapolating our findings to performance.

To conclude, supplementation with SB in gelatine capsules after a standardized breakfast across three sessions showed only moderate reliability at the group level, but at the individual level, reliability appears to be poor. In particular, $T_{max}$ was not reproducible across the three sessions, suggesting it may not be the most effective way by which to optimize SB supplementation. This is probably related to the long, sustained increases in blood bicarbonate after SB ingestion, so that solitary peak values are more a reflection of random error rather than true maximal increases in blood bicarbonate. Nonetheless, our data show that a 0.3-g·kg−1 BM dose results in a long-lasting (~3 h, starting from ~60 min after SB ingestion) window of ergogenic potential considering an ergogenic threshold of +5–6 mmol L−1 in blood bicarbonate from baseline. This challenges the notion that SB ingestion individualized to time to peak is a necessary strategy, at least when a dose of 0.3 g·kg−1 is taken in gelatine capsules.

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