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1 **The magnitude of the blood acid-base response but not time to peak is reliable**  
2 **following the ingestion of acute individualized sodium citrate**

3

4 **Abstract**

5 Enhanced buffering capacity following sodium citrate (SC) ingestion may be optimised when  
6 subsequent exercise commences at individual time-to-peak (TTP) alkalosis (blood pH or  
7 bicarbonate concentration ( $[\text{HCO}_3^-]$ ). While accounting for considerable inter-individual  
8 variation in TTP (188-300 min), a reliable blood alkalotic response is required for practical  
9 use. This study evaluated the reliability of blood pH,  $[\text{HCO}_3^-]$  and  $[\text{Na}^+]$  following acute SC  
10 ingestion. Fourteen recreationally active males ingested 0.4 or 0.5  $\text{g}\cdot\text{kg}^{-1}$  body mass (BM) of  
11 SC on two occasions each and 0.07  $\text{g}\cdot\text{kg}^{-1}$  BM of sodium chloride (CON), once. Blood pH and  
12  $[\text{HCO}_3^-]$  were measured for 4 h post-ingestion. Blood pH and  $[\text{HCO}_3^-]$  displayed good reliability  
13 following 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM SC ( $r = 0.819$ ,  $p = 0.002$ , sTE = 0.67 and  $r = 0.840$ ,  $p < 0.001$ , sTE =  
14 0.63, respectively). Following 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC, blood  $[\text{HCO}_3^-]$  retained good reliability ( $r =$   
15 0.771,  $p = 0.006$ , sTE = 0.78), versus moderate for blood pH ( $r = 0.520$ ,  $p = 0.099$ , sTE =  
16 1.36). TTP pH was moderately reliable following 0.5 ( $r = 0.676$ ,  $p = 0.026$ , sTE = 1.05) and  
17 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC ( $r = 0.679$ ,  $p = 0.025$ , sTE = 0.91) versus poor for  $[\text{HCO}_3^-]$  following 0.5 ( $r =$   
18 0.183,  $p = 0.361$ , sTE = 5.38) and 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC ( $r = 0.290$ ,  $p = 0.273$ , sTE = 2.50). While  
19 the magnitude of (and displacement in) blood alkalosis, particularly  $[\text{HCO}_3^-]$  appears reliable  
20 following potentially ergogenic doses of SC, strategies based on individual TTP cannot be  
21 recommended.

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23 **Keywords**

24 Acidity, buffering and individual response

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## Introduction

Exercise bouts including high-intensity and endurance-intensive efforts (>6 s to  $\geq 1$  min) are associated with high levels of glycolytic flux (van Loon et al., 2001; Romjin et al., 1993) and reductions in muscle and blood pH and bicarbonate concentration ( $[\text{HCO}_3^-]$ ) (Fitts, 1994). Peripheral fatigue may develop when any of the associated regulatory/support systems cannot promote the necessary muscular contractile force and/or sustain the bioenergetics and metabolic byproduct removal required to maintain exercise intensity (Keyser, 2010). For example, greater hydrogen ion ( $\text{H}^+$ ) production versus removal, represents the limits of endogenous  $\text{HCO}_3^-$  buffering capacity. Buffering agents such as sodium citrate (SC) are ingested to increase blood alkalosis (increasing both blood  $[\text{HCO}_3^-]$  and pH), with simultaneous increases in blood electrolytes, particularly sodium ( $\text{Na}^+$ ). The resultant alteration to the intracellular-extracellular pH gradient promotes upregulation of the lactate- $\text{H}^+$  co-transporter, supporting greater efflux of  $\text{H}^+$  from the muscle (Bishop et al., 2004). Current recommendations propose ingesting 0.4-0.5  $\text{g}\cdot\text{kg}^{-1}$  body mass (BM) SC to ensure sufficient alkalosis to improve performance, while greater doses may promote additional gastrointestinal symptoms (GIS) (Urwin et al., 2021b; Cerullo et al., 2020). Urwin et al. (2021b) found that SC was most frequently associated with performance improvements when 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM was ingested, relative to < 0.5 or > 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM. McNaughton et al. (1990) partly support this, observing greater total work and peak power output during a 60 s cycle sprint post-ingestion of 0.5 compared to 0.4, 0.3, 0.2 and 0.1  $\text{g}\cdot\text{kg}^{-1}$  BM SC and a placebo. In their review, Urwin et al. (2021b) noted that no studies implementing > 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM SC reported a performance benefit versus placebo, irrespective of exercise duration/intensity. Cerullo et al. (2020) recommend 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM based on a lone study by Hausswirth et al. (1995) who linked 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC with increased endurance time during prolonged isometric knee extension at 35% of the maximum voluntary contraction (MVC). Therefore, 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC potentially

57 represents a minimum effective dose. Greater effects post-ingestion of extracellular buffers  
58 are purported when increases in blood  $[\text{HCO}_3^-]$  are medium (4-6  $\text{mmol}\cdot\text{L}^{-1}$ ) and large ( $> 6$   
59  $\text{mmol}\cdot\text{L}^{-1}$ ) compared to small ( $\leq 4 \text{ mmol}\cdot\text{L}^{-1}$ ) (de Oliveira et al., 2021). Accordingly, SC induces  
60 large increases in blood  $[\text{HCO}_3^-]$  of up to  $8.9 \text{ mmol}\cdot\text{L}^{-1}$ , although the time-to-peak (TTP) is  
61 subject to substantial inter-individual variability (Urwin et al., 2022; 2021a; 2019).

62

63 Post-ingestion of  $0.5 \text{ g}\cdot\text{kg}^{-1}$  BM SC, individual TTP  $[\text{HCO}_3^-]$  may range between 148-212 min  
64 when administered aqueously (Urwin et al., 2016; 2019), compared to 188-300 (Urwin et al.,  
65 2022; 2021a; 2019) and  $\sim 145 (\pm 28)$  min (Peacock et al., 2021) when encapsulated in gelatine  
66 and delayed-release forms, respectively. Given SC has typically been administered at  
67 generalised timepoints pre-exercise (i.e., 60 or 90 min), replicating responses following SB  
68 (de Salles Painelli & Junior, 2018), it is unlikely that research has appropriately timed exercise  
69 with increases in blood  $[\text{HCO}_3^-]$  at/around peak (Urwin et al., 2021b). Accordingly, an unclear  
70 effect of SC (0.0% ( $\pm 1.3\%$ )) on performance remains (Carr, Hopkins & Gore, 2011).

71

72 Commencing exercise alongside individual TTP alkalosis (blood pH and/or  $[\text{HCO}_3^-]$ ) provides  
73 a potential strategy to account for inter-individual variation post-ingestion of buffering agents,  
74 with a growing body of research in SB (Lassen et al., 2021; Boegman et al., 2020; Gough et  
75 al., 2017a; 2017b; Miller et al., 2016). Only Boegman et al. (2020) directly compared an  
76 individualised (40-160 min pre-exercise) to a generalised approach (60 min pre-exercise).  
77 They observed significantly improved 2000 m rowing time-trial performance for 18/23 world-  
78 class rowers (individualised =  $367.0 \pm 10.5$  s vs. generalised =  $369.0 \pm 10.3$  s). This followed  
79 only small differences in pre-exercise blood  $[\text{HCO}_3^-]$   
80 (individualised =  $+ 6 \text{ mmol}\cdot\text{L}^{-1}$  vs. generalised =  $+ 5.5 \text{ mmol}\cdot\text{L}^{-1}$ ) suggesting that a maximal  
81 increase rather than 'meaningful' increase within proposed thresholds (i.e.,  $4-6 \text{ mmol}\cdot\text{L}^{-1}$  +)  
82 could provide added benefit, although other mechanisms/perspectives are plausible (Newbury  
83 et al., 2021; de Oliveira et al., 2020).

84

85 For application of TTP, understanding the reliability of the blood alkalotic response ( $[\text{HCO}_3^-]$   
86 and pH) following acute SC is necessary. Many metabolic reactions either produce or  
87 consume acids and bases, with net endogenous acid production (NEAP) regulated primarily  
88 by diet. Given variations in NEAP may impact acid-base balance, the applicability of an  
89 individualised approach based on blood alkalosis is contingent on the reliability of these  
90 analytes day-to-day (Poupin et al., 2012; Remer, 2001).

91

92 Gough et al. (2017a) previously investigated the reliability of the blood alkalotic response post-  
93 ingestion of  $0.2\text{-}0.3\text{ g}\cdot\text{kg}^{-1}$  BM SB, provided aqueously. Data support the use of an  
94 individualised strategy, with blood  $[\text{HCO}_3^-]$  and pH demonstrating good reliability for TTP and  
95 absolute change. No such investigation has explored this following acute SC ingestion.  
96 Moreover, building evidence now favours encapsulation over solution to mitigate GIS post-  
97 ingestion of extracellular buffers (Peacock et al., 2021; Urwin et al. 2021b; 2019). Therefore,  
98 the aim of the current research was to evaluate the reliability of individual blood pH,  $\text{HCO}_3^-$   
99 and  $\text{Na}^+$  responses post-ingestion of  $0.4$  and  $0.5\text{ g}\cdot\text{kg}^{-1}$  BM of SC, provided in gelatine  
100 capsules.

101

## 102 **Method**

### 103 **Participants**

104 Participants were invited based on their engagement in any sport/activity that may benefit from  
105 an enhanced buffering capacity (Urwin et al. 2021b). Fourteen recreationally active males  
106 (height  $1.81 \pm 0.55$  m, BM  $81.4 \pm 8.9$  kg, age  $27 \pm 4$  years, peak oxygen uptake  $[\text{VO}_{2\text{peak}}]$   $41.4$   
107  $\pm 13.0\text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) volunteered for this double-blind, randomised crossover study. Ethical  
108 approval was granted by institutional research ethics sub-committee (SPA-REC-2019-252R1).  
109 Each participant provided written informed consent and completed health screening before  
110 commencing data collection. Participants were also screened to confirm they had not ingested  
111 intra- or extracellular buffering agents within the last six months and were not restricting  $\text{Na}^+$   
112 intake.

113

**114 Pre-experimental Procedures**

115 Participants reported to the laboratory on six separate occasions, 4 h postprandial and at the  
116 same time of day (~09:00) to minimise circadian variability (Johnston, 2014). Participants were  
117 asked to avoid alcohol and any strenuous/unaccustomed exercise for 24 h prior to each visit  
118 (Lieber, 2000). Caffeine was also prohibited 12 h before each visit to limit disturbances to  
119 metabolic regulation (Westerterp-Platenga et al., 2006) and mitigate additional GIS risk  
120 (Boekama et al., 1999). Adherence to pre-experimental controls was confirmed verbally prior  
121 to each trial. Visits were conducted at least 48 h apart to facilitate washout of residual SC  
122 (Urwin et al., 2021a).

123

**124 Determination of  $VO_{2peak}$** 

125 Peak  $VO_2$  was determined utilising a ramp test. This test began with 5-min unloaded pedalling  
126 into a ramped increase of 0.5 Watts per second ( $W \cdot s^{-1}$ ), equating to  $30 W \cdot min^{-1}$ . A preferred  
127 cadence between 70-90 rpm was selected pre-test, with participants asked to maintain this  
128 cadence to within 10 rpm, until volitional exhaustion despite strong encouragement for 10 s.  
129 Tests were performed on an electromagnetically braked cycle ergometer (Lode Excalibur,  
130 Germany). Breath-by-breath gases were continuously analysed using a gas analyser (K5,  
131 Cosmed, Italy) to measure oxygen uptake ( $VO_2$ ), carbon dioxide production ( $CO_2$ ) and the  
132 respiratory exchange ratio (RER). The  $VO_{2peak}$  was determined by averaging  $VO_2$  over the final  
133 30 s of exercise.

134

**135 Supplementation Trials**

136 The five supplementation trials were randomised using a Latin square and involved one control  
137 trial requiring the ingestion of  $0.07 g \cdot kg^{-1}$  BM of sodium chloride (CON), two trials requiring the  
138 ingestion of  $0.4 g \cdot kg^{-1}$  BM (SC4a and SC4b) or  $0.5 g \cdot kg^{-1}$  BM (SC5a and SC5b) SC. Both  
139 sodium chloride and SC (Pro Athlete Supplementation, Rhymney, UK) were administered in  
140 opaque (white), size '00' gelatine capsules (Bulk Powders™, Colchester, UK), which were

141 prepared by a laboratory technician not involved with the research. Capsules were consumed  
142 with 500 ml of room temperature (18°C) water within 15 minutes (Urwin et al., 2021a). To aid  
143 blinding, capsule number was matched to that provided in the 0.5 g·kg<sup>-1</sup> BM trials (55 ± 6),  
144 using cornflour to fill the remaining capsules.

145 An initial arterialised fingertip capillary blood sample was obtained from participants whilst  
146 seated and rested pre-ingestion. After capsules were ingested (<10 min), blood samples were  
147 taken every 17 min for 4 h. A heated blanket (45°C) was used to warm the hand prior to each  
148 sample to assist with blood sampling (Gough et al., 2017a). At each interval, a GIS  
149 questionnaire was completed to assess the severity of a range of symptoms on a visual  
150 analogue scale (VAS) where 0 = no symptom and 10 = most severe (Gough et al., 2024).  
151 Participants were asked to remain seated with only toilet breaks allowed. No food was  
152 consumed during testing, although water was consumed *ad libitum* in the first trial and  
153 replicated thereafter. Blood samples were collected in 100 µl heparin-coated clinitubes  
154 (Radiometer Medical Ltd, Denmark) and analysed for blood pH, HCO<sub>3</sub><sup>-</sup> and Na<sup>+</sup> using a blood  
155 gas analyser (ABL800 BASIC, Radiometer Medical Ltd). This device has demonstrated low  
156 bias in the measurement of pH, partial pressure of CO<sub>2</sub> (PCO<sub>2</sub>) and Na<sup>+</sup> (Radiometer Medical,  
157 2015) and a correlation coefficient of  $r > 0.98$  for both HCO<sub>3</sub><sup>-</sup> and pH, against other blood gas  
158 analysers (Stadlbauer et al., 2011).

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## 160 **Statistical Analysis**

161 An a priori power calculation was completed using SPSS Sample Power 3 (IBM, Chicago, IL,  
162 USA) based upon an expected population correlation of  $r = 0.80$ , suggesting that a minimum  
163 of 11 participants were required to achieve 80% power ( $P < 0.05$ ). An additional 3 participants  
164 were recruited to account for any potential dropouts. Assessed variables were initially  
165 analysed for normality (Shapiro-Wilks and Q-Q plots) and homogeneity of variance/sphericity  
166 (Mauchly). Both one-way (treatment) and two-way (treatment/time) repeated measures  
167 analysis of variance (ANOVA) were used to deduce differences in blood parameters with  
168 Bonferroni pairwise comparisons. Where sphericity was violated, the Greenhouse Geiser

169 correction was applied. Effect sizes were calculated using generalised eta squared ( $\eta_G^2$ ),  
170 where 0.099-0.0587, 0.0588-0.1378 and  $\geq 0.1379$  represent small, medium and large effects,  
171 respectively (Cohen, 1988). For nonparametric data, where the distribution of data was similar  
172 between groups, such as GI symptom scores, the median test was used with H scores,  
173 degrees of freedom and significance reported. For GIS, total symptoms (sum of each  
174 individual reported score) and TTP severity (first instance at which the largest individual score  
175 occurred) were used to determine overall GIS responses. Statistical significance was set at  $p$   
176  $< 0.05$ . Heteroscedasticity was assessed using Bland-Altman plots. Test-retest reliability  
177 between conditions was evaluated using intraclass correlation coefficients (ICCs), coefficient  
178 of variation (CV) [(SD)/mean x 100] and standardised technical error (sTE) (Hopkins, 2000),  
179 based on dose-response, determined using area under the curve (AUC) analyses. For ICCs,  
180  $r < 0.5$  = poor, 0.5-0.75 = moderate, 0.75-0.9 = good and  $> 0.9$  = excellent reliability (Koo and  
181 Li, 2016). Ranges for CV (%) are interpreted as  $> 20\%$  (very poor),  $> 10\%$  (poor),  $< 10\%$   
182 (acceptable),  $< 5\%$  (good) and  $> 2\%$  (excellent) (Stables et al., 2021). Interpretation of sTE  
183 utilised a modified Cohen scale, describing  $< 0.2$  as trivial, 0.2-0.6 as small, 0.6-1.2 as  
184 moderate, 1.2-2.0 as large and  $> 2.0$  as very large (Sparks et al., 2016). Where data was non-  
185 normally distributed, log transformation was performed. Non-linear correlation (Spearman's)  
186 between absolute change and TTP was determined for both pH and  $[\text{HCO}_3^-]$ . Absolute change  
187 in pH and  $[\text{HCO}_3^-]$  and TTP pH and  $[\text{HCO}_3^-]$  were also assessed using Spearman's correlation.  
188 Calculations were completed using Microsoft® Excel 2019 (Microsoft Inc, Redmond, WA,  
189 USA) and statistical procedures were completed using SPSS version 29 (IBM, Chicago, IL,  
190 USA).

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## 192 **Results**

### 193 **Differences Between Ingestion Volumes**

194 A significant effect of condition was observed for blood  $[\text{HCO}_3^-]$  (F (1.8,24.0) = 5.836,  $p$  =  
195 0.002, ( $\eta_G^2$ ), = 0.0982), pH (F (3, 39) = 3.195,  $p$  = 0.034, ( $\eta_G^2$ ), = 0.0509) and  $[\text{Na}^+]$  (F (3,39) =



196 13.444,  $p < 0.001$ , ( $\eta_G^2$ ) = 0.2716) (Figure 1). Mean blood  $[\text{HCO}_3^-]$  was  $\sim 1 \text{ mmol}\cdot\text{L}^{-1}$  greater  
 197 following 0.5 versus 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC, which was significant in SC5b ( $29.26 \pm 0.30$ ) but not  
 198 SC5a ( $29.36 \pm 0.42$ ). Small elevations in blood pH from baseline were also apparent following  
 199 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM, although further analysis was unable to detect any specific differences between  
 200 each condition. Lastly, small significant increases ( $\leq 2 \text{ mmol}\cdot\text{L}^{-1}$ ) in blood  $[\text{Na}^+]$ , were noted  
 201 for SC5a ( $145 \pm 0.5 \text{ mmol}\cdot\text{L}^{-1}$ ) and SC5b ( $146 \pm 0.6 \text{ mmol}\cdot\text{L}^{-1}$ ) compared to SC4a ( $142 \pm 0.5$   
 202  $\text{mmol}\cdot\text{L}^{-1}$ , both  $p < 0.05$ ) but not SC4b ( $144 \pm 0.5 \text{ mmol}\cdot\text{L}^{-1}$ ).

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206 A significant effect of time, with no combined interaction effects, was demonstrated for blood  
 207  $[\text{HCO}_3^-]$  (F (2.0, 25.8) = 212.3,  $p < 0.001$ , ( $\eta_G^2$ ) = 0.6544), pH (F (14, 182) = 71.638,  $p < 0.001$ ,  
 208 ( $\eta_G^2$ ) = 0.4342) and  $[\text{Na}^+]$  (F (14, 182) = 40.116,  $p < 0.001$ , ( $\eta_G^2$ ) = 0.2016). Comparing blood  
 209  $[\text{HCO}_3^-]$  at individual timepoints, a notable increase relative to the control was observed in all  
 210 conditions from 68 min post-ingestion (F (4, 52) = 23.862,  $p < 0.001$ , ( $\eta_G^2$ ) = 0.7525), and  
 211 remained 238 min post-ingestion (F (4,52) = 87.449,  $p < 0.001$ , ( $\eta_G^2$ ) = 0.7234). Differences  
 212 relative to control arose earlier for blood pH, starting from 51 min (F (2.6, 33.3) = 18.909,  $p <$   
 213  $0.001$ , ( $\eta_G^2$ ) = 0.3962) and again remaining 238 min post-ingestion (F (4, 52) = 46.890,  $p <$   
 214  $0.001$ , ( $\eta_G^2$ ) = 0.6543) in all conditions. While differences were highlighted at 102 and 153+  
 215 min, blood  $[\text{Na}^+]$  was similar between conditions throughout the sampling window. Further  
 216 analysis revealed no difference between conditions for absolute change in blood  $[\text{HCO}_3^-]$  or  
 217 pH (both  $p > 0.05$ ). For TTP pH, a difference of  $\sim 40$  min emerged between SC5b and SC4b  
 218 ( $182 \pm 51$  vs.  $143 \pm 47$  min,  $p = 0.048$ ), with no further differences between conditions, nor for  
 219 TTP $[\text{HCO}_3^-]$ .

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221 A moderate correlation between TTP and absolute change in  $[\text{HCO}_3^-]$  was observed post-  
 222 ingestion of 0.5  $\text{g}\cdot\text{kg}^{-1}$  BM SC ( $r_s(26) = 0.398$ ,  $p = 0.036$ ) but not 0.4  $\text{g}\cdot\text{kg}^{-1}$  BM SC ( $r_s(26) =$

223 0.245,  $p = 0.209$ ). Neither 0.5 or 0.4 g·kg<sup>-1</sup> BM demonstrated an acceptable correlation  
 224 between TTP and absolute change in blood pH ( $r_s(26) = -0.033$ ,  $p = 0.866$  and  $r_s(26) = 0.201$ ,  
 225  $p = 0.305$ , respectively). There was no correlation between TTP blood [HCO<sub>3</sub><sup>-</sup>] and TTP blood  
 226 pH following 0.5 ( $r_s(26) = 0.286$ ,  $p = 0.141$ ) or 0.4 g·kg<sup>-1</sup> BM ( $r_s(26) = 0.235$ ,  $p = 0.228$ ). For  
 227 absolute change in both measures, a moderate correlation was apparent following 0.5 g·kg<sup>-1</sup>  
 228 BM SC ( $r_s(26) = 0.416$ ,  $p = 0.028$ ), but not 0.4 g·kg<sup>-1</sup> ( $r_s(26) = 0.329$ ,  $p = 0.087$ ).

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### 231 **Reliability of blood HCO<sub>3</sub><sup>-</sup>, pH and Na<sup>+</sup>**

232 Blood [HCO<sub>3</sub><sup>-</sup>] displayed good reliability post-ingestion of both 0.5 ( $r = 0.840$ ,  $p < 0.001$ ) and  
 233 0.4 g·kg<sup>-1</sup> BM SC ( $r = 0.771$ ,  $p = 0.006$ ), with moderate sTE (0.63 and 0.78, respectively)  
 234 (Figure 2a). Blood pH also displayed good reliability following 0.5 g·kg<sup>-1</sup> BM SC ( $r = 0.819$ ,  $p =$   
 235  $0.002$ , sTE = 0.67), but only moderate reliability following 0.4 g·kg<sup>-1</sup> BM SC, although this was  
 236 non-significant ( $r = 0.520$ ,  $p = 0.099$ , sTE = 1.36) (Figure 2b). Blood [Na<sup>+</sup>] displayed moderate  
 237 reliability for both 0.5 ( $r = 0.728$ ,  $p = 0.013$ , sTE = 0.86) and 0.4 g·kg<sup>-1</sup> BM SC ( $r = 0.667$ ,  $p =$   
 238  $0.029$ , sTE = 1.00) (Figure 2c).

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243 Reliability of TTP was greater for pH, with moderate reliability following both 0.5 ( $r = 0.676$ ,  $p$   
 244  $= 0.026$ , sTE = 1.05) and 0.4 g·kg<sup>-1</sup> BM SC ( $r = 0.679$ ,  $p = 0.025$ , sTE = 0.91). Comparatively,  
 245 blood [HCO<sub>3</sub><sup>-</sup>] displayed poor reliability for both 0.5 ( $r = 0.183$ ,  $p = 0.361$ , sTE = 5.38) and 0.4  
 246 g·kg<sup>-1</sup> BM SC ( $r = 0.290$ ,  $p = 0.273$ , sTE = 2.50). Absolute change in blood [HCO<sub>3</sub><sup>-</sup>] and pH  
 247 both demonstrated good reliability following 0.5 g·kg<sup>-1</sup> BM SC ( $r = 0.844$ ,  $p = < 0.001$ , sTE =  
 248 0.81 and  $r = 0.811$ ,  $p = 0.003$ , sTE = 0.01, respectively). Post-ingestion of 0.4 g·kg<sup>-1</sup> BM SC,  
 249 absolute change was moderately reliable for both [HCO<sub>3</sub><sup>-</sup>] ( $r = 0.505$ ,  $p = 0.109$ , sTE = 1.29)  
 250 and pH ( $r = 0.536$ ,  $p = 0.090$ , sTE = 0.02). Both TTP and absolute change in [HCO<sub>3</sub><sup>-</sup>] and pH  
 251 displayed large inter-individual variation (Table 1).

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Table 1 About Here

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### Gastrointestinal Symptoms

Total symptoms displayed excellent reliability following 0.5 g·kg<sup>-1</sup> BM SC ( $r = 0.932$ ,  $p < 0.001$ ,  $sTE = 0.38$ ) and good reliability post-ingestion of 0.4 g·kg<sup>-1</sup> BM ( $r = 0.863$ ,  $p < 0.001$ ,  $sTE = 0.56$ ). Across all conditions, all participants reported a pooled total GIS of 566 AU. In total, 8 of 14 participants reported no GIS across SC5 and SC4 (see Table 2 for individual symptoms). One participant (14) reported a total GIS of 357 AU across all conditions, equating to 63% of all AU. Total symptom scores (ranks) were similar between conditions ( $H(3) = 0.929$ ,  $p = 0.818$ ) with the highest score in SC5a (30.43), compared to SC4a (29.39), SC5b (27.93) and SC4b (26.25), respectively.

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Table 2 About Here

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Overall, TTP GIS was not significantly different between conditions ( $H(3) = 0.929$ ,  $p = 0.818$ ). Reliability of TTP GIS following 0.5 g·kg<sup>-1</sup> BM SC was excellent ( $r = 0.918$ ,  $p < 0.001$ ,  $sTE = 0.42$ ) demonstrating a range of 85 (102-17) and 34 (51-17) min for SC5b and SC5a, respectively. The largest range in TTP GIS occurred in SC4a (204 min (221-17)) compared to SC4b (34 min (64-34)), corresponding to good reliability for 0.4 g·kg<sup>-1</sup> BM ( $r = 0.791$ ,  $p = 0.004$ ,  $sTE = 0.73$ ).

### Discussion

This study determined the reliability of blood [HCO<sub>3</sub><sup>-</sup>], pH and [Na<sup>+</sup>] following acute, individualised doses of encapsulated SC, to inform the efficacy of an approach to SC ingestion based on individual TTP alkalosis (blood [HCO<sub>3</sub><sup>-</sup>] and/or pH). Firstly, blood [HCO<sub>3</sub><sup>-</sup>] and pH responses displayed good reliability post-ingestion of 0.5 g·kg<sup>-1</sup> BM SC. Post-ingestion of 0.4 g·kg<sup>-1</sup> BM SC, blood [HCO<sub>3</sub><sup>-</sup>] maintained good reliability, versus moderate reliability for pH. The

281 blood  $[\text{Na}^+]$  response was moderately reliable post-ingestion of both 0.5 and  
282  $0.4 \text{ g}\cdot\text{kg}^{-1}$  BM SC. Secondly, TTP alkalosis demonstrated limited reliability for both blood pH  
283 and  $[\text{HCO}_3^-]$ . Blood pH displayed moderate reliability between repeated ingestion of 0.5 and  
284  $0.4 \text{ g}\cdot\text{kg}^{-1}$  BM SC against poor reliability for  $[\text{HCO}_3^-]$ . Collectively, data suggest that while the  
285 magnitude of blood alkalosis, particularly  $[\text{HCO}_3^-]$ , appears reliable between repeated  
286 ingestion of potentially ergogenic doses of SC (Urwin et al., 2021b; Cerullo et al., 2020), a  
287 strategy based on individual TTP alkalosis cannot be recommended. Indeed, blood  $[\text{HCO}_3^-]$   
288 peaked earlier (102-221 min) post-ingestion of  $0.5 \text{ g}\cdot\text{kg}^{-1}$  BM SC than previously reported (188-  
289 300 min) (Urwin et al., 2021a; 2021b; Cerullo et al., 2020), which was similar within-and-  
290 between doses. This may be partly explained by the provision of a carbohydrate meal ( $1.75$   
291  $\text{g}\cdot\text{kg}^{-1}$  BM) in some studies (Urwin et al., 2021a), opting to resemble real-world practice rather  
292 than isolate supplementation effects through a 4 h fast. Whilst 10% of food may remain in the  
293 stomach after this period (Jones et al. 2016), meaning residual effects may remain even when  
294 fasted, it is possible that meal volume, composition and texture may have contributed to the  
295 differing timeframes (Gough et al. 2017a). Herein, it is also possible that capsule volume and  
296 size may have contributed to variability in TTP. Indeed, Middlebrook et al. (2021)  
297 demonstrated that TTP  $[\text{HCO}_3^-]$  was significantly faster in smaller (size '0' =  $94 \pm 24$  min)  
298 compared to medium (size '00' =  $141 \pm 27$  min) and larger capsules (size '000' =  $121 \pm 29$   
299 min) demonstrating a non-linear relationship between capsule size and TTP.

300

301 Previous discussion has criticised individualised TTP as a strategy to optimise extracellular  
302 buffer ingestion (de Oliveira et al., 2020). This approach requires access to a blood gas  
303 analyser, for lengthy time-course measurement of blood  $[\text{HCO}_3^-]$  responses. de Oliveira et al.,  
304 (2020) also suggest that TTP assumes that increases in circulating  $[\text{HCO}_3^-]$  are substantially  
305 greater at peak, versus standardised timepoints. When provided aqueously, mean increases  
306 in  $[\text{HCO}_3^-]$  shown at TTP by Gough et al. (2017b) ( $6.5 \pm 1.3 \text{ mmol}\cdot\text{L}^{-1}$ ) were similar to increases  
307 shown following 60 min; 6.1, 5.1 and 5.7  $\text{mmol}\cdot\text{L}^{-1}$  (Gough et al., 2017a; Jones et al., 2016;  
308 Dias et al., 2015), 90 min; 6.5 and 6.1  $\text{mmol}\cdot\text{L}^{-1}$  (Gough et al., 2017a; Jones et al., 2016) and

309 120 min; 6.5 and 5.6 mmol·L<sup>-1</sup> (Gough et al., 2017a; Jones et al., 2016) post-ingestion of 0.3  
310 g·kg<sup>-1</sup> BM SB. Blood [HCO<sub>3</sub><sup>-</sup>] was also similar 60, 120 and 180 min post-ingestion of gelatine-  
311 encapsulated SB (Siegler et al., 2012), leading de Oliveira et al. (2020) to question the utility  
312 of ingestion timing overall. Authors proposed a “window of ergogenicity”, estimating that >80%  
313 of individuals from the population may experience increased blood [HCO<sub>3</sub><sup>-</sup>] of +5 mmol·L<sup>-1</sup>  
314 between 75-240 min post-ingestion and +6 mmol·L<sup>-1</sup> between 90-225 min. Subsequently, de  
315 Oliveira et al. (2021) linked greater exercise performance effects to medium (4-6 mmol·L<sup>-1</sup>)  
316 and large (> 6 mmol·L<sup>-1</sup>) increases in blood [HCO<sub>3</sub><sup>-</sup>], relative to small (≤ 4 mmol·L<sup>-1</sup>). While  
317 blood acid-base kinetics may vary, a similar window of ergogenicity may exist for SC.

318

319 Blood [HCO<sub>3</sub><sup>-</sup>] was elevated above control in all conditions from 68 min, remaining elevated at  
320 238 min post-ingestion. Absolute change ranged between 1.8-8.3 mmol·L<sup>-1</sup> post-ingestion of  
321 0.5 g·kg<sup>-1</sup> BM SC and 4.6-8.6 mmol·L<sup>-1</sup> following 0.4 g·kg<sup>-1</sup> BM SC. Except four instances (all  
322 SC5) where absolute change did not exceed 4 mmol·L<sup>-1</sup> (1.5, 1.8, 2.9 and 3.8 mmol·L<sup>-1</sup>), SC  
323 increased by 4, 5 and 6+ mmol·L<sup>-1</sup> in 93%, 76% and 48% of all instances, respectively.  
324 Excluding outliers, absolute change in blood [HCO<sub>3</sub><sup>-</sup>] remained lower than the  
325 6.8-8.9 mmol·L<sup>-1</sup> previously reported (Urwin et al., 2022; 2021a; 2019), demonstrating variable  
326 HCO<sub>3</sub><sup>-</sup> kinetics, albeit within a potentially ergogenic range. Moreover, absolute change in blood  
327 [HCO<sub>3</sub><sup>-</sup>] displayed good reliability ( $r = 0.844$ ) post-ingestion of 0.5 g·kg<sup>-1</sup> BM SC, versus  
328 moderate reliability following 0.4 g·kg<sup>-1</sup> BM SC ( $r = 0.505$ ). An ingestion strategy based on  
329 absolute, rather than TTP responses post-ingestion of 0.5 g·kg<sup>-1</sup> BM SC, may present the most  
330 effective strategy to achieve an ergogenic effect.

331

332 Alongside inducing sufficient blood alkalosis, reducing the incidence/severity of GIS remains  
333 a key component of effective SC ingestion strategies. Previously, SC has been associated  
334 with reduced incidence of GIS versus SB (Requena et al., 2005) although recently, GIS has  
335 been found to be minor for both substances, emerging 80-90 min post-ingestion for  
336 encapsulated SC, compared to 35-50 min for SB (Urwin et al., 2022). In total, 8 of 14 (57%)

337 participants reported zero GIS. However, one participant experienced marked symptoms,  
338 representing 63% of the total pooled AU (357/566), suggesting that while GIS may be minor  
339 for most, some participants may still respond negatively to SC. Despite associations between  
340 greater ingested dose and GIS incidence/severity (Urwin et al., 2019; McNaughton, 1990),  
341 GIS was similar between conditions. Furthermore, both TTP peak and total symptoms  
342 provided excellent-to-good reliability for 0.5 and 0.4 g·kg<sup>-1</sup> BM SC, respectively. This may be  
343 explained by 7/9 instances (78%) of peak symptoms following 0.5 g·kg<sup>-1</sup> BM SC emerging at  
344 the first timepoint post-ingestion (17 min). Participants linked this finding to the large volume  
345 of capsules ingested, contributing to a less palatable experience. Palatability may be  
346 characterized as the overall sensory experiences and level of preference for a food/fluid. Urwin  
347 et al. (2019) observed an improved palatability for encapsulated over aqueous SC, with similar  
348 GIS. This preference may relate to the excessively salty taste in the latter, an effect potentially  
349 lost here due to the larger volumes of capsules (55 ± 6 vs. 36 ± 6) ingested – without a  
350 carbohydrate-rich meal. Individuals may seek to utilize split-dosing (Heibel et al., 2018) or  
351 more novel carbohydrate hydrogel delivery systems (Gough & Sparks, 2024) to limit the total  
352 capsules consumed, without impacting GIS.

353

354

### 355 **Conclusion**

356 The magnitude of (and displacement in) blood alkalosis following acute, individualized doses  
357 of SC, particularly [HCO<sub>3</sub><sup>-</sup>], displays good reliability. Conversely, TTP blood alkalosis was not  
358 reliable. This may be explained by the impact of capsule volume/size on blood acid-base  
359 kinetics, which may also explain reported GIS.. Alternatively to TTP approaches, strategies  
360 supported by the sustained/absolute increases in [HCO<sub>3</sub><sup>-</sup>] observed between 68-238 min post-  
361 ingestion, may commence exercise within a generalised timeframe post-ingestion of 0.5 g·kg<sup>-1</sup>  
362 <sup>1</sup> BM SC (>68 min) for a more precise, reliable response than previously reported. The  
363 reliability of subsequent exercise performance thereafter should be addressed, alongside  
364 alternate, practical approaches to SC ingestion than large quantities of capsules.

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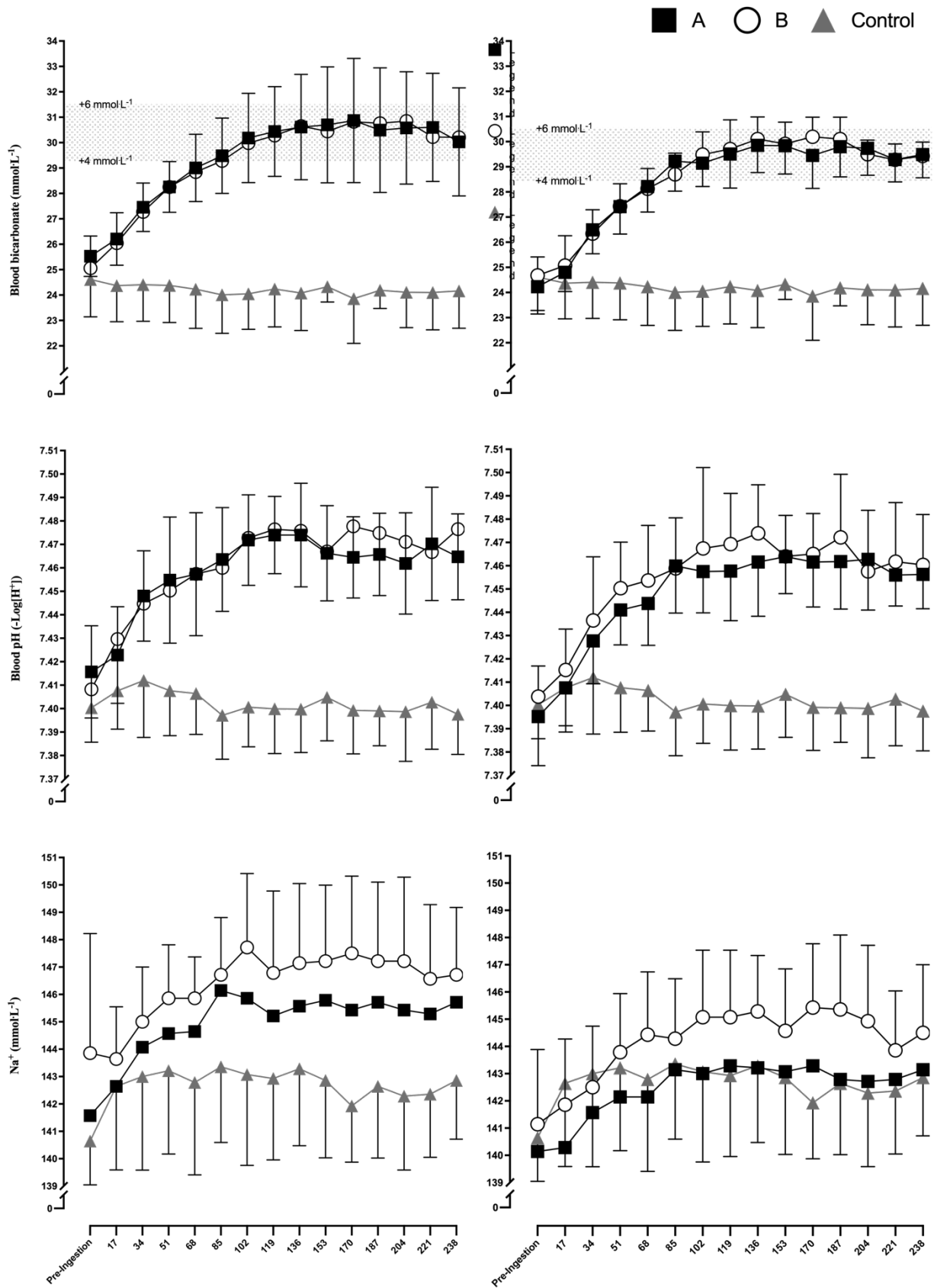
531 **Figure titles**

532 **Figure 1.** Mean blood analyte responses for bicarbonate (top), pH (middle) and sodium  
533 (bottom) following the ingestion of 0.5 (left) and 0.4 (right) g·kg<sup>-1</sup> BM sodium citrate (SC)  
534 (repeated 'A' and 'B') or 0.07 g·kg<sup>-1</sup> BM sodium chloride control (all). *Some error bars are*  
535 *omitted for clarity.*

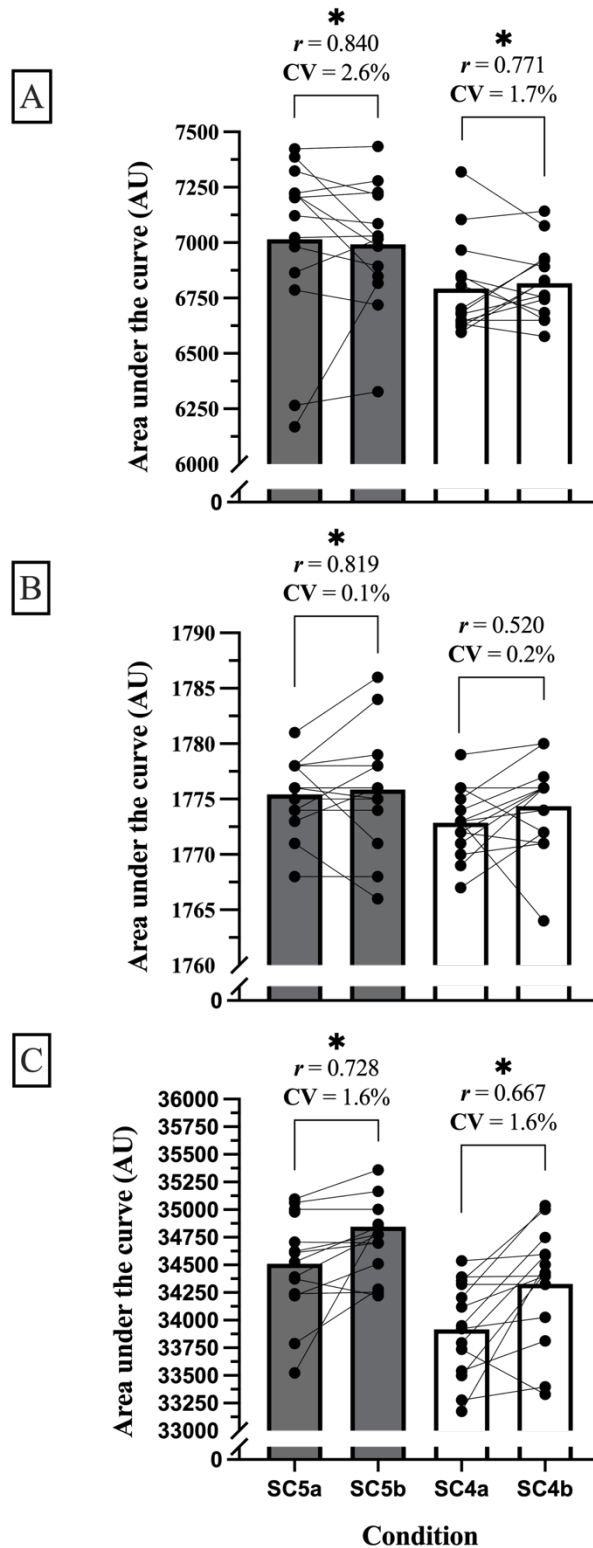
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537 **Figure 2.** Mean ( $\pm$ SD) area under the curve (AUC) for blood bicarbonate (HCO<sub>3</sub><sup>-</sup>) (A), pH (B)  
538 and sodium (Na<sup>+</sup>) (C) responses, following the ingestion of either 0.5 g·kg<sup>-1</sup> (SC5) or 0.4 g·kg<sup>-1</sup>  
539 (SC4) body mass (BM) sodium citrate (SC). Where 'r' represents the intraclass correlation  
540 coefficient (ICC), '\*\*' denotes a significant correlation between conditions and 'CV' illustrates  
541 the technical error, expressed as a coefficient of variation (%).

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**Figure 1.** Mean blood analyte responses for bicarbonate (top), pH (middle) and sodium (bottom) following the ingestion of 0.5 (left) and 0.4 (right) g·kg<sup>-1</sup> BM sodium citrate (SC) (repeated 'A' and 'B') or 0.07 g·kg<sup>-1</sup> BM sodium chloride control (all). Some error bars are omitted for clarity.



**Figure 2.** Mean ( $\pm$  SD) area under the curve (AUC) for blood bicarbonate ( $\text{HCO}_3^-$ ) (A), pH (B) and sodium ( $\text{Na}^+$ ) (C) responses, following the ingestion of either  $0.5 \text{ g}\cdot\text{kg}^{-1}$  (SC5) or  $0.4 \text{ g}\cdot\text{kg}^{-1}$  (SC4) body mass (BM) sodium citrate (SC). Where 'r' represents the intraclass correlation coefficient (ICC), '\*' denotes a significant correlation between conditions and 'CV' illustrates the technical error, expressed as a coefficient of variation (%).

**Table 1.** Individual time to peak and peak absolute change from baseline in both blood pH and bicarbonate ( $\text{HCO}_3^-$ ) following 0.5 (SC5) and 0.4 (SC4)  $\text{g}\cdot\text{kg}^{-1}$  BM sodium citrate. 23

Participant	Time to peak (min)								Peak absolute change from baseline							
	pH				$\text{HCO}_3^-$ ( $\text{mmol}\cdot\text{L}^{-1}$ )				pH				$\text{HCO}_3^-$ ( $\text{mmol}\cdot\text{L}^{-1}$ )			
	SC5a	SC5b	SC4a	SC4b	SC5a	SC5b	SC4a	SC4b	SC5a	SC5b	SC4a	SC4b	SC5a	SC5b	SC4a	SC4b
1	170	170	204	187	170	102	153	136	0.08	0.7	0.08	0.06	7.5	5.9	5.0	4.9
2	136	153	204	119	170	170	187	136	0.11	0.09	0.09	0.08	7.6	7.3	7.5	6.1
3	170	238	153	136	102	204	85	153	0.07	0.10	0.03	0.05	6.0	7.2	5.7	4.5
4	102	85	187	102	136	136	153	170	0.05	0.07	0.07	0.09	3.8	4.9	5.1	5.7
5	119	119	136	136	221	204	136	136	0.11	0.13	0.11	0.09	6.6	5.4	4.9	4.9
6	136	136	204	136	170	136	204	170	0.08	0.07	0.09	0.07	6.2	6.2	7.2	5.8
7	119	204	119	85	119	204	102	153	0.03	0.06	0.07	0.08	1.8	2.9	5.4	5.8
8	68	136	85	102	119	170	102	187	0.10	0.14	0.07	0.13	1.5	5.4	4.6	5.0
9	238	238	153	170	187	187	238	170	0.06	0.10	0.08	0.10	5.9	7.0	6.1	7.1
10	85	238	187	187	136	136	187	187	0.09	0.10	0.10	0.14	7.0	8.2	5.0	7.4
11	153	187	136	136	187	187	153	119	0.07	0.08	0.08	0.07	8.3	8.3	6.3	7.0
12	136	187	187	187	102	136	170	187	0.03	0.05	0.09	0.08	4.8	4.6	6.7	5.5
13	153	238	204	136	153	204	85	136	0.07	0.08	0.08	0.06	6.8	7.2	6.6	5.6
14	221	221	204	187	153	119	119	170	0.09	0.07	0.09	0.09	5.9	6.1	8.6	6.7
<b>Mean</b>	143	182	169	143	152	164	148	158	0.07	0.09	0.08	0.09	5.7	6.2	6.1	5.9
<b>Range</b>	170	153	119	102	119	102	153	68	0.08	0.09	0.08	0.09	6.8	5.4	4.0	2.9
<b>95% CI</b>	96-190	131-233	130-208	108-178	117-187	128-200	102-194	136-181	0.05-0.09	0.06-0.12	0.06-0.10	0.07-0.11	3.6-7.8	4.7-7.7	4.9-7.3	5.0-6.8
<b>SD</b>	47	51	39	35	35	36	46	23	0.02	0.03	0.02	0.02	2.1	1.5	1.2	0.9
<b>CV</b>	32.8	27.7	22.9	24.5	23.0	21.8	31.3	14.3	33.9	29.8	23.1	29	36.1	24.1	19.3	15.4
<b>SEM</b>	12.6	13.5	10.3	9.4	9.3	9.5	12.4	6.0	0.01	0.01	0.01	0.01	0.5	0.4	0.3	0.2

**CI** = Confidence interval, **SD** = Standard Deviation, **CV** = Coefficient of Variation, **SEM** = Standard Error of Mean



**Table 2.** Individual gastrointestinal symptoms experienced following ingestion of sodium citrate 0.5 (SC5) and 0.4 (SC4) g kg<sup>-1</sup> BM sodium citrate (SC).

Participant	SC5a		SC5b		SC4a		SC4b	
	Total symptoms (AU)	Peak symptom	Total symptoms (AU)	Peak symptom	Total symptoms (AU)	Peak symptom	Total symptoms (AU)	Peak symptom
1	47	Stomach bloating	10	Nausea	14	Nausea/stomach ache	32	Nausea
2	8	Nausea/stomach ache	None	None	40	Nausea	2	Nausea/stomach ache
3	None	None	None	None	None	None	None	None
4	None	None	None	None	None	None	None	None
5	None	None	None	None	None	None	None	None
6	None	None	None	None	None	None	None	None
7	8	Nausea	7	Nausea	None	None	None	None
8	23	Vomiting	12	Diarrhoea	2	Flatulence	None	None
9	None	None	None	None	4	Bowel urgency	None	None
10	None	None	None	None	None	None	None	None
11	None	None	None	None	None	None	None	None
12	None	None	None	None	None	None	None	None
13	None	None	None	None	None	None	None	None
14	49	Stomach bloating	54	Nausea	16	Bowel urgency	238	Bowel urgency

*Where more than one symptom of equally high severity occurred at the same time point, both symptoms are noted.*

*Where more than one symptom of equally high severity occurred at different time points, only the symptom which occurred earliest is noted.*

DT, LM and AS contributed to the study conception and design. DT, BD and NH aided with data collection. DT, BD and AS worked on the analysis and interpretation of results. DT, BD, NH, LM and AS were all involved in manuscript preparation

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