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Empirical modeling of metabolic alkalosis induced by sodium bicarbonate ingestion

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Abstract Biphasic responses of blood $[\text{HCO}_3^-]$ and $[\text{H}^+]$ following ingestion of three doses of NaHCO_3 (0.1, 0.2, 0.3 $\text{g}\cdot\text{kg}^{-1}$) were assessed in eight men. For $[\text{HCO}_3^-]$, there were significant effects of dose on maximum responses and timing, as well amplitudes, onsets and/or time constants of phases 1 and 2. Fewer significant effects of dose were observed for $[\text{H}^+]$ and additional data demonstrated differential effects of dose on $[\text{HCO}_3^-]$ and $[\text{H}^+]$ responses and underlying phases.

Key Words: alkali, dose, alkalosis, magnitude, timecourse, parameter estimation

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Introduction

Ingestion of sodium bicarbonate (NaHCO_3) to induce alkalosis and improve exercise performance is a common practice and has been studied extensively (Carr et al. 2011; Matson and Tran 1993). NaHCO_3 is usually ingested 60-90 minutes before exercise in varied doses ($0.1\text{-}0.5\text{ g kg}^{-1}$) as a single bolus or smaller multiples over a longer period (Carr et al. 2011). There is no consensus about the effect of NaHCO_3 ingestion on performance (Peart et al. 2012) and, for reasons not understood, the response varies considerably between individuals (Saunders et al. 2014).

Factors which contribute to this variation include technical error, dosing strategy and physiological processes such as absorption, distribution and buffering of the alkali. The rates of these physiological processes should influence peak levels and temporal responses of alkalosis (i.e. $[\text{H}^+]$) and related humoral variables (e.g., $[\text{HCO}_3^-]$). We showed that peak levels of blood $[\text{H}^+]$ and $[\text{HCO}_3^-]$ were affected by NaHCO_3 dose (Siegler et al. 2010) but, despite the biphasic response of these variables, did not examine dynamic, or time-dependent, features of the responses. Dynamic features are important to study because they influence the size and timing of peak responses and provide insight into the timing and rates of physiological processes linked to the temporal behaviour of $[\text{H}^+]$. Such knowledge is important from theoretical and practical perspectives, including the optimisation of alkali dosing strategies.

‘Empirical modeling’ provides insight into temporal dynamics of physiological responses and underlying processes by describing such responses in terms of underlying phases and parameters which define them (Green et al. 2015; Lamarra 1990; Reeder and Green 2012).

This approach has not yet been used in studies of induced alkalosis and might provide insight

into the dynamic behaviour of $[H^+]$. Therefore, we applied empirical modeling to previous data (Siegler et al. 2010) to quantify amplitudes and temporal features of phases underlying $[H^+]$ and $[HCO_3^-]$ responses (Fig 1) and tested the effects of dose on them.

Materials and Methods

Experimental Procedures

Data were obtained from eight male subjects (mean $\pm$ SD: age = 22.4 ± 5.7 y; height = 179.8 ± 9.6 cm; body mass = 76.3 ± 14.1 kg) involved in an alkali dosing study (Siegler et al. 2010). Subjects ingested three doses of $NaHCO_3$ (0.1 , 0.2 and $0.3 \text{ g}\cdot\text{kg}^{-1}$) and a placebo ($0.045 \text{ g}\cdot\text{kg}^{-1}$ of $NaCl$) diluted into 100 ml of low-calorie, flavored cordial. Each dose of $NaHCO_3$ and placebo was consumed one week apart in a counterbalanced, single-blinded manner. Ingestion (bolus) occurred within 10 minutes and arterialized capillary blood samples (fingertip) were collected before ingestion and each 10 minutes for 120 minutes after ingestion. Blood was collected in heparinized capillary tubes, capped, placed on ice and analysed for $[HCO_3^-]$ and $[H^+]$ (OMNI 4 Blood Gas Analyzer, Roche Diagnostics Ltd, Sussex, UK).

Curve Fitting and Parameter Estimation

Blood $[HCO_3^-]$ and $[H^+]$ responses following $NaHCO_3$ ingestion (but not placebo) were fitted to the biexponential functions,

$$Y(t) = a + A_1(1 - e^{-\frac{(t-TD1)}{\tau1}}) - A_2(1 - e^{-\frac{(t-TD2)}{\tau2}}) \quad \text{Eq. 1}$$

or

$$Y(t) = a - A_1(1 - e^{-\frac{(t-TD1)}{\tau1}}) + A_2(1 - e^{-\frac{(t-TD2)}{\tau2}}) \quad \text{Eq. 2}$$

where Y is blood $[\text{HCO}_3^-]$ or $[\text{H}^+]$, a is the y-intercept and represents baseline $[\text{HCO}_3^-]$ or $[\text{H}^+]$ immediately before ingestion, and A_{1-2} , TD_{1-2} and τ_{1-2} are the amplitudes, time delays and time constants of the first and second phases, respectively (Fig. 1). Individual responses of blood $[\text{HCO}_3^-]$ and $[\text{H}^+]$ were fitted independently of each other and 48 individual responses ($2 \times 3 \times 8$) were fitted. Fitting was done in a three-step process (Green et al. 2015) using a weighted least squares nonlinear regression procedure and the Marquardt-Levenberg algorithm (TableCurve 2D, Systat Software Inc). Maximum $[\text{HCO}_3^-]$ and minimum $[\text{H}^+]$ values and their timing were calculated by differentiation of the functions.

Statistical Analyses

Effects of alkali dose ($0.1 \vee 0.2 \vee 0.3 \text{ g kg}^{-1}$) on parameter estimates and derived variables were analyzed using a one-way ANOVA for repeated measures. Normality was assessed (Shapiro-Wilk test) and, for non-normal data, a Friedman Rank test was used. Associations between variables were assessed using Pearson correlation coefficients. Significance was set at $P \leq 0.05$ and values are presented as means and standard deviations.

Results

Individual responses of blood $[\text{HCO}_3^-]$ and $[\text{H}^+]$ to three doses are shown as supplementary data (Fig. S1-S2). There was no significant change in these variables in response to placebo. Fitting of the mean blood $[\text{HCO}_3^-]$ and $[\text{H}^+]$ responses to biexponential functions are shown in Figure S3. Parameter estimates, derived variables and adjusted R^2 values related to the fitting of all individual responses are shown in Tables 1 and 2, as are statistical outcomes related to the effect of dose on them.

Peak responses of blood $[\text{HCO}_3^-]$ measured at 10 minute intervals were not significantly different from maximum responses predicted using Eq 1 (Table 1) at the low (27.5 ± 1.3 mM; $P > 0.05$), intermediate (30.3 ± 1.1 mM; $P > 0.05$) and high dose (32.1 ± 1.3 mM; $P > 0.05$). Likewise, the lowest measured values of blood $[\text{H}^+]$ were not significantly different ($P > 0.05$) from minimum values predicted using Eq 2 (Table 2) at these three doses (37.0 ± 1.7 ; 34.8 ± 1.7 ; 34.7 ± 1.6 mM). The maximum change in $[\text{HCO}_3^-]$ or $[\text{H}^+]$ for each response was calculated as the difference between a resting and maximum (Table 1), or minimum (Table 2), value and expressed as a proportion (%) of resting values. These proportional changes in $[\text{HCO}_3^-]$ and $[\text{H}^+]$ were significantly different at the highest (25.1 ± 3.8 vs 13.2 ± 2.6 %, $P < 0.001$) and intermediate dose (23.4 ± 5.5 vs 9.9 ± 2.2 %, $P < 0.001$) but not lowest dose (10.7 ± 2.0 vs 8.9 ± 2.6 %, $P = 0.14$). Timing of these maximum $[\text{HCO}_3^-]$ and $[\text{H}^+]$ responses was not significantly different at the three doses. There were no significant correlations between these maximum responses ($r = -0.04$ to 0.32) or timing ($r = 0.31$ to 0.63), or between amplitudes of the first phase of these responses ($r = -0.01$ to 0.28).

Discussion

This study provides the first description of dynamic response characteristics of $[\text{H}^+]$ and bioavailability of the alkali ($[\text{HCO}_3^-]$) after NaHCO_3 ingestion and effects of dose on them. For all doses both responses appeared biphasic. With respect to $[\text{HCO}_3^-]$, dose significantly affected the level and/or timing of the maximum response, amplitude and temporal parameters of the growth phase, as well as timing of the decay phase. There were fewer and smaller effects of dose on dynamic response characteristics of $[\text{H}^+]$. These preliminary observations are relevant to optimization of ingestion strategies and understanding physiological processes underlying the $[\text{H}^+]$ response.

Empirical Modeling Optimization of NaHCO_3 ingestion requires knowledge of the extent and timing of phases of $[\text{H}^+]$ as it relates to bioavailability of the alkali (HCO_3^-). Empirical modeling helps describe these phases and provide insight into mechanisms influencing the distribution and effect of NaHCO_3 . Compared with placebo, all doses of NaHCO_3 induced significant changes in $[\text{HCO}_3^-]$ and $[\text{H}^+]$ (Siegler et al. 2010) and most responses appeared biphasic (Fig. S1-S2). We assumed each phase was exponential (Fig. 1 and Fig. S3), fitted a biphasic function to each individual response, and used parameters estimates to quantify the amplitude (A_1 or A_2), time delay (TD_1 or TD_2) and time constant (τ_1 or τ_2) of each phase.

$[\text{HCO}_3^-]$ Based on averaged measurements at 10 minute intervals, maximum responses of blood $[\text{HCO}_3^-]$ occur 60-90 minutes after ingestion (Price and Singh 2008; Renfree 2007; Siegler et al. 2010) and increase in a dose-dependent manner for doses of $0.1\text{-}0.3 \text{ g kg}^{-1}$ (Siegler et al. 2010). Present findings suggest that there is a saturation of effect of dose ($0.1\text{-}0.3 \text{ g kg}^{-1}$) on maximum $[\text{HCO}_3^-]$ and a dose-dependent slowing of this effect. These effects are influenced by the diminishing effect of dose on the growth phase amplitude (A_1), the dose-dependent reduction in the onset (TD_1) and slowing (τ_1) of this phase (TD_1), as well as an increase in the amplitude and time-delay of the ensuing decay phase at higher doses. Thus the diminishing effect of dose on maximum $[\text{HCO}_3^-]$ is a function of effects on amplitudes and timing of both phases indicative of dose-dependent changes in the temporal dynamics of the $[\text{HCO}_3^-]$ response.

$[\text{H}^+]$ Maximum and temporal responses of blood $[\text{H}^+]$ will be influenced by and somewhat mirror the dynamic response of blood $[\text{HCO}_3^-]$ (Price and Singh 2008; Renfree 2007; Siegler

et al. 2010). However, the complexity of mechanisms involved in $[H^+]$ regulation (Stewart 1981) suggests that some aspects of $[HCO_3^-]$ and $[H^+]$ will differ.

Like $[HCO_3^-]$, blood $[H^+]$ exhibited a biphasic response and its minimum was affected by dose with evidence of saturation. By contrast, proportional effects of dose on the maximum *change* in blood $[H^+]$ were smaller than for $[HCO_3^-]$ and there was a lack of effect of dose on timing and amplitude of the initial decay in $[H^+]$ at lower doses. These differential effects of dose on $[H^+]$ relative to $[HCO_3^-]$ suggest a dose-dependent influence on buffering mechanisms during the initial phase of alkalosis. Further support for this interpretation is the dose-dependent increase in amplitude of the growth phase of $[H^+]$. The lack of effect of dose on timing of this second phase differs from changes in timing of the coincident phase of $[HCO_3^-]$ and provides additional evidence of independence between $[H^+]$ and $[HCO_3^-]$ responses.

Methodological Limitations

Precision of parameter estimation depends on goodness of fit, data variability and temporal density, phase amplitude and observation period. Temporal responses of blood $[HCO_3^-]$ and $[H^+]$ were based on 13 measurements over ~2 hours, and increasing the replicates, measurement frequency and observation period should provide more accurate representations of individual responses. For $[HCO_3^-]$ responses, goodness of fit (R^2) was reasonably high given these limitations and did not differ significantly between doses. A lower goodness of fit was observed for blood $[H^+]$ responses and might be attributed to the smaller size and greater intra-individual variability of these responses (Tables 1-2, Fig. S1-S3). Poorer fit introduces greater imprecision and uncertainty of parameter estimates and caution should be applied to inferences based on comparisons between $[HCO_3^-]$ and $[H^+]$ responses.

Perspectives

Optimization is an important practical problem which has received little attention, and three interrelated aspects of optimization are the physiological variable, dosing strategy and individual variation in 'physiological responsiveness'. Use of a simple dosing strategy (bolus) revealed that dose affects the size and timing of dynamic response characteristics but which depended on the variable chosen. $[\text{HCO}_3^-]$ and $[\text{H}^+]$ responses varied considerably between individuals and between each other, evident in the substantial ranges of maximum responses and phase amplitudes between subjects (Tables 1-2) and the poor correlations between them. Optimization procedures must account for such variation, and the extent to which this variation contributes to variability of ergogenic effect warrants further investigation.

Modeling physiological responses provides insight into underlying mechanisms and their interactions. Empirical modeling enables a description of the dynamic 'structure' of a physiological response and, with respect to induced alkalosis, provides a quantitative, temporal framework for understanding how $[\text{H}^+]$ is affected by the timing and rates of underlying mechanisms involved in absorption, distribution and buffering of the alkali. Further research is required to establish this dynamic structure of the $[\text{H}^+]$ response and contributions of these mechanisms to it.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Table 1. Parameter estimates, derived variables and statistical outcomes related to blood [HCO₃⁻] response to three doses of NaHCO₃. F = F ratio (one-way ANOVA). P = P value.

	Rest	Phase 1			Phase 2			Fit	Maximum	
	<i>a</i>	A ₁	TD ₁	τ ₁	A ₂	TD ₂	τ ₂	R ²	Level	Time
	(mM)	(mM)	(min)	(min)	(mM)	(min)	(min)		(mM)	(min)
Dose (g·kg ⁻¹)										
0.1	25.4 ± 0.8	2.8 ± 0.4	8.3 ± 10.4	8.6 ± 9.6	1.5 ± 1.0	49.2 ± 36.3	25.0 ± 17.9	0.84 ± 0.12	28.1 ± 1.2	39.4 ± 20.5
0.2	25.4 ± 1.0	7.2 ± 3.4*	4.8 ± 4.4	18.9 ± 25.2	3.6 ± 2.6	46.3 ± 13.9	23.4 ± 15.2	0.93 ± 0.03	31.5 ± 0.7	42.7 ± 16.4
0.3	26.0 ± 0.6	8.0 ± 1.4*	1.7 ± 3.2	39.9 ± 20.5*	3.7 ± 1.0	67.0 ± 9.0	23.7 ± 10.3	0.92 ± 0.08	32.6 ± 1.3*	67.0 ± 9.0†
F		9.4	FR	4.5	3.3	FR			33.3	6.9
P		<0.01	<0.05	<0.05	0.07	0.05			<0.001	<0.05

*different from 0.1

†different from 0.2

FR = Friedman Rank Test

Table 2. Parameter estimates and derived variables related to blood $[H^+]$ responses to three doses of $NaHCO_3$. F = F ratio (one-way ANOVA). P = P value.

	Rest	Phase 1			Phase 2			Fit	Minimum	
	a	A_1	TD_1	τ_1	A_2	TD_2	τ_2	R^2	Level	Time
		($\times 10^{-7}$ mM)	(min)	(min)	($\times 10^{-7}$ mM)	(min)	(min)		(mM)	(min)
Dose (g kg ⁻¹)										
0.1	39.7 $\pm$ 1.3	3.8 $\pm$ 1.7	4.5 $\pm$ 5.0	23.2 $\pm$ 23.2	2.1 $\pm$ 1.8	37.8 $\pm$ 22.3	80.4 $\pm$ 113.8	0.62 $\pm$ 0.21	36.2 $\pm$ 1.0	63.8 $\pm$ 45.8
0.2	38.4 $\pm$ 1.7	3.8 $\pm$ 0.8	6.2 $\pm$ 4.0	13.5 $\pm$ 13.5	4.1 $\pm$ 2.2	46.2 $\pm$ 12.9	54.4 $\pm$ 93.1	0.70 $\pm$ 0.17	34.6 $\pm$ 1.6*	54.1 $\pm$ 29.6
0.3	39.7 $\pm$ 1.3	5.7 $\pm$ 3.8†	11.0 $\pm$ 15.1	15.9 $\pm$ 10.3	4.5 $\pm$ 3.5	66.3 $\pm$ 9.8	135.0 $\pm$ 238.0	0.77 $\pm$ 0.08	34.3 $\pm$ 1.9	72.3 $\pm$ 36.1
F		6.8				6.5			6.6	
P		<0.05				<0.05			<0.05	

*different from 0.1

†different from 0.2

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Figure 1. Conceptual diagrams of biexponential responses of blood $[\text{HCO}_3^-]$ and blood $[\text{H}^+]$ after NaHCO_3 ingestion. Ingestion is completed at $t = 0$ min. Phases are described in terms of amplitudes (A_1 , A_2), delays from beginning of ingestion (TD_1 , TD_2), and time constants (τ_1 , τ_2).

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