EFFECT OF INDUCED ACUTE METABOLIC ALKALOSIS BY SODIUM BICARBONATE ADMINISTRATION ON EXERCISE VENTILATORY EFFICIENCY IN HEALTHY ADULTS

by

JOSHUA BROADMAN

B.Sc., University of Ottawa, 2014

A THESIS SUBMITTED TO McGILL UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS OF THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF EDUCATION

(Department of Kinesiology & Physical Education)

McGILL UNIVERSITY
MONTREAL, QUEBEC, CANADA

July 2016

ACKNOWLEDGEMENTS

I would like to first and foremost express my gratitude and appreciation for my supervisor, mentor and friend, Dr. Jensen. The door to Jensen's office was always open whenever I ran into trouble, needed advice, or to have a friendly conversation. From day one he had the utmost confidence in me, allowing me to push myself everyday and to be the best version of myself. He constantly allowed this paper to be my own work, allowing me to make mistakes and to learn from them. He taught me how to be an independent researcher all while steering me in the right direction whenever he thought I needed it. There are no words to express how truly grateful I am. Thank you Dr. Jensen.

Thank you to the rest of my thesis committee: Drs. Benjamin Smith and Jean Bourbeau for guiding me along the way throughout the writing of my thesis and most importantly, during my various thesis presentations.

The past two years would have not been the same without Sara Abdallah, Courtney Wilkinson-Maitland, Kevin Pham, Kristina Muscat, Jared Ferguson, Steven Murray and Marcus Waskiw-Ford's friendship, support and generosity. Each and everyone one of you guys have helped me succeed in this journey and have had my back when I needed it the most.

I would like to thank my family and friends: my parents, David and Diane, for making me into the man I am today. My sister, Megan, who has been nothing less than the most amazing sister anyone could have ever asked for. I would like to give a special thanks to Lauren Zipkin for being my number one support system for the past two years, always there to listen to how my thesis is progressing without any science background

and still showing interest. Thank you for everything. Last but not least I would like to thank Russ Wolfe, Laurel Radin, AJ Rashkovan, Jon Cohen, Daniel Aintabi, Noah Zuckerman, Madi Shane and all of my friends for being there every step of the way.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background & Rationale. The ventilatory response ($\dot{V}_E$) to exercise-induced increases in the rate of CO_2 production ($\dot{V}CO_2$) depends on the regulated level of arterial PCO_2 ($PaCO_2$) and the dead space (V_D) to tidal volume (V_T) ratio, as described by the modified alveolar ventilation equation: $\dot{V}_E/\dot{V}CO_2 = 863/[PaCO_2 \times (1-V_D/V_T)]$. An abnormally high $\dot{V}_E$-$\dot{V}CO_2$ response to exercise, reflecting exercise ventilatory inefficiency and most often resulting from a high V_D/V_T, is a key pathophysiological feature of patients with chronic cardiopulmonary diseases like heart failure, pulmonary arterial hypertension, and chronic obstructive and restrictive pulmonary disease. In these patient populations, exercise ventilatory inefficiency is associated with several adverse clinical and patient-reported outcomes, including impaired exercise tolerance; increased physical activity-related breathlessness; and increased risk of hospitalization, major cardiac events and mortality. It follows that any intervention capable of decreasing the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise has the potential to improve clinical and/or patient-reported outcomes. Unfortunately, our ability to enhance exercise ventilatory efficiency is limited by the fact that ventilation-perfusion abnormalities reflecting a high V_D/V_T are often irreversible.

A largely unexplored approach to decreasing the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise is increasing the $PaCO_2$ equilibrium point by inducing a metabolic alkalosis via administration of an alkalizing agent such as sodium bicarbonate ($NaHCO_3$). The results obtained from relatively few small physiological studies concerning the effect of $NaHCO_3$ administration on the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise have been inconclusive and require further investigation.

Objective. To test the hypothesis that increasing the $PaCO_2$ equilibrium point via induced acute metabolic alkalosis by administration of $NaHCO_3$ improves exercise ventilatory efficiency and related physiological and perceptual responses high-intensity constant-load cycle exercise testing in healthy adults.

Methods. In a randomized, double blind, placebo controlled, crossover study of 18 healthy adults (12 men) aged 22.2 ± 0.5 yrs (mean ± SE), we compared the effect of single-dose administration of $NaHCO_3$ (0.3 g/kg) and sodium chloride (NaCl, 4 g) on arterialized venous blood gas and acid-base status at rest; and on detailed physiological and perceptual responses to symptom-limited constant-load cycle exercise testing performed at 80% of maximum incremental power output.

Results. None of the 18 participants reported any undue effects (e.g., gastrointestinal discomfort, belching) after treatment with either $NaHCO_3$ or NaCl. By design, ingestion of $NaHCO_3$ vs. NaCl induced a partially compensated metabolic alkalosis as evidenced by decreases in $[H^+]$ and increases in $PaCO_2$ and $[HCO_3^-]$ at rest (all $p<0.0001$). Compared with the NaCl control condition, treatment with $NaHCO_3$ decreased the $\dot{V}_E/\dot{V}CO_2$ ratio and increased end-tidal CO_2 tensions ($P_{ET}CO_2$) at rest and throughout exercise (all $p<0.05$). $NaHCO_3$-induced decreases in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise could not be easily explained by increased $\dot{V}CO_2$ but reflected statistically significant decreases in $\dot{V}_E$; for example, $\dot{V}_E$ was reduced by 5.8 ± 1.9 L/min, 5.0 ± 2.4 L/min and 4.5 ± 2.1 L/min at 2-min, 4-min and the peak of exercise after ingestion of $NaHCO_3$ vs.

NaCl, respectively (all $p<0.05$). The $\dot{V}_E/\dot{V}CO_2$ nadir was lower after treatment with $NaHCO_3$ vs. NaCl ($p<0.0001$). Mean values of $P_{ET}CO_2$, $\dot{V}_E$ and $\dot{V}CO_2$ corresponding to the $\dot{V}_E/\dot{V}CO_2$ nadir were higher (by 4.5 ± 0.3 mmHg, $p<0.0001$), lower (by 4.7 ± 1.8 L/min, $p=0.019$) and not significantly different in the $NaHCO_3$ vs. NaCl condition, respectively. Compared to the NaCl control condition, ingestion of $NaHCO_3$ had no effect on cardiometabolic, operating lung volume and symptom responses to exercise and thus was not associated with improved exercise endurance time.

Conclusion and implications. Induced acute metabolic alkalosis by ingestion of $NaHCO_3$ increased the $PaCO_2$ equilibrium point and improved exercise ventilatory efficiency as evidenced by a decrease in the $\dot{V}_E$-$\dot{V}CO_2$ response to high-intensity constant-load cycle exercise testing in healthy adults. The results of this study provide a physiological rationale to examine the potential benefits of induced acute metabolic alkalosis by $NaHCO_3$ administration on exercise ventilatory efficiency and related clinical- and patient-reported outcomes (e.g., exercise endurance, breathlessness) in selected patients with chronic cardiopulmonary disease.

RÉSUMÉ

Contexte et rationnel. La réponse ventilatoire ($\dot{V}_E$) pour l'augmentation induite par l'exercice du taux de production de CO_2 (VCO_2) dépend du niveau réglementé de PCO_2 artériel ($PaCO_2$) et l'espace mort (V_D) pour le ratio de volume courant (V_T), tel que décrit par l'équation modifiée alvéolaire de ventilation: $\dot{V}_E$ / $\dot{V}CO_2$ = 863 / [$PaCO_2$ x (1-V_D / V_T)]. Une réponse Vé-vco2 à l'exercice anormalement élevée, ce qui reflète l'exercice ventilatoire inefficace et qui résulte le plus souvent d'une haute V_D / V_T, est une caractéristique physiopathologique clé de patients atteints de maladies chroniques cardio-pulmonaires comme les arrêts cardiaques, l'hypertension artérielle pulmonaire, et la broncho-pneumopathie chronique obstructive. Dans ces populations de patients, l'inefficience ventilatoire liée à l'exercice est associée à plusieurs résultats cliniques et rapportés par les patients indésirables, y compris la tolérance à l'exercice avec facultés affaiblies; une dyspnée accrue liée à l'activité physique; et le risque d'hospitalisation, d'événements cardiaques majeurs et une mortalité accrue. Il en résulte que toute intervention capable de diminuer la réponse $\dot{V}_E$-$\dot{V}CO_2$ à l'exercice a le potentiel d'améliorer les résultats cliniques et / ou rapportés par les patients. Malheureusement, notre capacité à améliorer l'efficacité ventilatoire d'exercice est limité par le fait que les anomalies de ventilation-perfusion reflétant un haut V_D / V_T sont souvent irréversibles.

Une approche largement inexplorée pour la diminution de la réponse $\dot{V}_E$- $\dot{V}CO_2$ à l'exercice augmente le point d'équilibre $PaCO_2$ en induisant une alcalose métabolique par administration d'un agent alcalinisant tel que le bicarbonate de sodium ($NaHCO_3$). Les résultats obtenus à partir de relativement peu de petites études physiologiques

concernant l'effet de l'administration $NaHCO_3$ sur la réponse $\dot{V}_E$- $\dot{V}CO_2$ à l'exercice n'ont pas été concluants et nécessitent une enquête plus approfondie.

Objectif. Pour vérifier l'hypothèse que l'augmentation du point d'équilibre de $PaCO_2$ via alcalose métabolique aiguë induite par l'administration de $NaHCO_3$ améliore l'efficacité de l'exercice ventilatoire et physiologiques connexes et les réponses perceptives aux tests d'exercice à haute intensité avec cycle de charge constant chez les adultes en bonne santé.

Méthodes. Dans une étude randomisée en double aveugle, contrôlée par placebo, étude croisée de 18 adultes en bonne santé (12 hommes) âgés de 22,2 ± 0,5 ans (moyenne ± SE), nous avons comparé l'effet de l'administration d'une dose unique de $NaHCO_3$ (0,3 g / kg) et de sodium chlorure (NaCl, 4 g) sur le gaz de sang veineux et sur l'état de l'acide-base artérialisé au repos; et sur les réponses physiologiques et perceptifs détaillées à l'épreuve d'exercice avec cycle de charge constant limitée par les symptômes effectué à 80% de la puissance maximale incrémentale.

Résultats. Par sa conception, l'ingestion de $NaHCO_3$ contre NaCl a provoqué une alcalose métabolique partiellement compensée comme le confirme les diminutions de [H +] et l'augmentation des $PaCO_2$ et [HCO_3-] au repos ($p < 0,0001$). Par rapport à la condition de contrôle NaCl, le traitement avec $NaHCO_3$ a diminué le $\dot{V}_E$ / rapport $\dot{V}CO_2$ et des tensions accrues de CO_2 en fin d'expiration ($PETCO_2$) au repos et tout au long de l'exercice ($p < 0,05$). Une provocation de $NaHCO_3$ qui diminue la réponse $\dot{V}_E$-$\dot{V}CO_2$ à

l’exercice ne pouvaient pas être facilement expliquées par une augmentation de $\dot{V}CO_2$ mais reflètent une diminution statistiquement significative en $\dot{V}_E$; par exemple, $\dot{V}_E$ a été réduite de 5,8 ± 1,9 L / min, 5,0 ± 2,4 L / min et 4,5 ± 2,1 L / min à 2 min, 4 min et le pic de l'exercice après l'ingestion de $NaHCO_3$ vs. NaCl, respectivement ($p < 0,05$). Le nadir $\dot{V}_E$ / $\dot{V}CO_2$ était plus faible après le traitement avec $NaHCO_3$ vs NaCl ($p < 0,0001$). Les valeurs moyennes de $PETCO_2$, $\dot{V}_E$ et $\dot{V}CO_2$ correspondant au nadir $\dot{V}_E$ / $\dot{V}CO_2$ étaient plus élevés (de 4,5 ± 0,3 mmHg, $p < 0,0001$), inférieure (de 4,7 ± 1,8 L / min, $p = 0,019$) et non significativement différent dans le $NaHCO_3$ vs. NaCl condition, respectivement. Par rapport à la condition de contrôle NaCl, l'ingestion de $NaHCO_3$ n'a eu aucun effet sur le cardio-métabolique, l’exploitation des réponses de volume pulmonaire et les symptômes de l'exercice n'a donc pas été associée à une amélioration du temps d'exercice d'endurance.

Conclusion et implications. Une provocation d’alcalose métabolique aiguë par ingestion de $NaHCO_3$ a augmenté le point $PaCO_2$ d'équilibre et l'amélioration de l'efficacité ventilatoire d'exercice comme le confirme la diminution de la réponse $\dot{V}_E$-$\dot{V}CO_2$ à l’exercice à haute intensité avec cycle de charge constant chez les adultes en bonne santé. Les résultats de cette étude fournissent une justification physiologique afin d'examiner les avantages potentiels de la provocation d’alcalose métabolique aiguë par administration $NaHCO_3$ sur l'efficacité d’exercice ventilatoire et clinique connexes et les résultats rapportés par les patients (par exemple, l'exercice d'endurance, dyspnée) chez certains patients souffrant d'une maladie cardio-pulmonaire chronique.

PREFACE AND CONTRIBUTION OF AUTHORS

Joshua Broadman was the principal contributor to the collection, analysis, and interpretation of data; and was primarily responsible for thesis/manuscript preparation.

Daniel Gornitsky, Marcus Waskiw-Ford, and Courtney Wilkinson-Maitland contributed to the collection and analysis of data.

Drs. Benjamin Smith and Jean Bourbeau served as medical supervisors, and contributed to the review of the protocol, interpretation of data and review of the thesis/manuscript.

As principal investigator, **Dr. Dennis Jensen** secured financial support of the experiments, and contributed to all aspects of the study. He helped prepare the final draft of the thesis/manuscript. He is the guarantor of the thesis/manuscript and takes responsibility for the integrity of the data and accuracy of the data analysis.

CHAPTER 1: REVIEW OF LITERATURE

1.1. Ventilatory Challenges to Exercise in Health.

During progressive exercise in human subjects, the respiratory system (airways, lungs and respiratory musculature) is faced with the challenge of optimizing pulmonary gas exchange while the mixed-venous blood returning to the lungs from the peripheral locomotor muscles gets progressively more hypoxic and hypercapnic. It follows that exercise-induced increases in the metabolic rates of O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) have the potential to disturb acid-base balance and impair exercise tolerance by compromising peripheral locomotor muscle metabolic and contractile function (i.e., fatigue).

In order to adequately meet the increased metabolic demands of exercise and prevent excessive changes in arterial blood gas and acid-base balance, alveolar ventilation ($\dot{V}_A$) must increase in direct proportion to increases in $\dot{V}O_2$ and $\dot{V}CO_2$ so as to (1) replenish the O_2 extracted from the blood and (2) eliminate the CO_2 added to the blood.[10] This precise matching of $\dot{V}_A$ to muscle metabolic demands must be accomplished while simultaneously minimizing the work and O_2 cost of breathing.[11,12] Briefly, during progressive exercise in healthy adults, tidal volume (V_T) expands by increasing end-inspiratory lung volume and decreasing the end-expiratory lung volume.[13] These changes in dynamic operating lung volumes help to ensure that V_T expansion occurs within the linear (compliant) portion of the respiratory systems sigmoid pressure-volume relation where (1) the work breathing is minimized; (2) length-tension relationships of the diaphragm and accessory inspiratory muscles are optimized, i.e., prevent excessive shortening, elastic loading and functional weakening

of inspiratory pump muscles; and (3) individuals do not experience undue increases in respiratory discomfort (breathlessness).[13]

$\dot{V}_A$ is the volume of gas per minute that reaches the alveoli and participates in gas exchange; and is calculated by subtracting dead space ventilation ($\dot{V}_D$ = anatomic + physiologic dead space) from minute ventilation ($\dot{V}_E = V_T$ x breathing frequency (f_R)): $\dot{V}_A = \dot{V}_D - \dot{V}_E$. With the consequent increase in $\dot{V}_E$ and $\dot{V}_A$ due to the increase in metabolic demands during exercise, differentiating $\dot{V}_E$ from $\dot{V}_A$ is compulsory, as the two do not always reflect one another. Unlike $\dot{V}_E$, $\dot{V}_A$ depends on $\dot{V}_D$ which, in turn, depends on f_R.[14] As illustrated in Table 1.1, adoption of a rapid and shallow breathing pattern serves to increase $\dot{V}_D$, decrease $\dot{V}_A$, and widen the disparity between $\dot{V}_E$ and $\dot{V}_A$. By contrast, adoption of a deep and slow breathing pattern serves to decrease $\dot{V}_D$, increase $\dot{V}_A$, and minimize the disparity between $\dot{V}_E$ and $\dot{V}_A$. It follows that adopting a rapid and shallow breathing pattern during exercise has the potential to compromise $\dot{V}_A$ and pulmonary gas exchange efficiency. Fortunately, in healthy adults, exercise-induced increases in $\dot{V}_E$ are due primarily to progressive increases in V_T rather than f_R; that is, optimization of breathing pattern during exercise serves to minimize and maximize increases in $\dot{V}_D$ and $\dot{V}_A$, respectively.[13]

Table 1.1. Impact of breathing pattern on dead space ventilation and alveolar ventilation.

Breathing Pattern	**V_T (L) x f_R (bpm) =**		**$\dot{V}_E$ (L/min) -**	**$\dot{V}_D$ (L/min) =**	**$\dot{V}_A$ (L/min)**
Rapid and Shallow	0.15	50	7.5	(0.15 x 50)	0
Normal	0.50	15	7.5	(0.15 x 15)	5.25
Deep and Slow	1.5	5	7.5	(0.15 x 5)	6.75

V_T = tidal volume; f_R = breathing frequency; $\dot{V}_E$ = minute ventilation; $\dot{V}_D$ = dead space ventilation, where 0.15 L represents the sum of anatomic and physiologic dead space; $\dot{V}_A$ = alveolar ventilation.

Exercise-induced increases in $\dot{V}_A$ are determined by concomitant increases in $\dot{V}CO_2$ and the regulated level of CO_2 in the arterial blood (P_aCO_2), as defined by the alveolar ventilation equation: $\dot{V}_A = 863 \text{ X } \dot{V}CO_2/P_aCO_2$, where 863 is the constant that corrects for different conditions of reporting the gas volume (for a body temperature of 37^{o}C) and also the transformation of fractional concentration to partial pressure.[15] This equation predicts that the $\dot{V}_A$ response to any given increment in $\dot{V}CO_2$ during exercise is inversely related to the regulated level of P_aCO_2. Thus, as the regulated level of P_aCO_2 increases, the relationship between increasing $\dot{V}_A$ and increasing $\dot{V}CO_2$ during exercise decreases, reflecting increased exercise ventilatory efficiency. By contrast, as the regulated level of P_aCO_2 decreases, the $\dot{V}_A$-$\dot{V}CO_2$ relationship during exercise increases, reflecting increased exercise ventilatory inefficiency.

Determination of $\dot{V}_A$ requires calculation of the physiologic dead space (V_D) to V_T ratio using the Bohr Equation: $V_D/V_T = (P_aCO_2-P_ECO_2)/P_aCO_2$, where P_ECO_2 represents the partial pressure of CO_2 in the expired air.[16] Determination of V_D/V_T, in turn, requires direct and serial measurement of P_aCO_2 either *via* catheterization of an artery or arterialization of venous blood.[17] Due to the relatively invasive nature of measuring P_aCO_2 to determine V_D/V_T and $\dot{V}_A$, most researchers and healthcare professionals have adopted use of the relationship between increasing $\dot{V}_E$ and increasing $\dot{V}CO_2$ during exercise as a non-invasive and readily available index of exercise ventilatory efficiency. To this end, the relationship between exercise-induced increases in $\dot{V}_E$ and $\dot{V}CO_2$ depend on the regulated level of $PaCO_2$ and V_D/V_T, as defined by the modified alveolar ventilation equation: $\dot{V}_E/\dot{V}CO_2 = 863/[PaCO_2 \text{ x } (1-V_D/V_T)]$. As illustrated in Fig. 1.1 and presented in Table 1.2, this equation predicts that (1) at a constant V_D/V_T, the $\dot{V}_E$ at any

given $\dot{V}CO_2$ during exercise will decrease as the regulated level of P_aCO_2 increases, with the opposite being true; and (2) at a constant $PaCO_2$, the $\dot{V}_E$ at any given $\dot{V}CO_2$ during exercise will increase as the V_D/V_T increases, with the opposite being true.

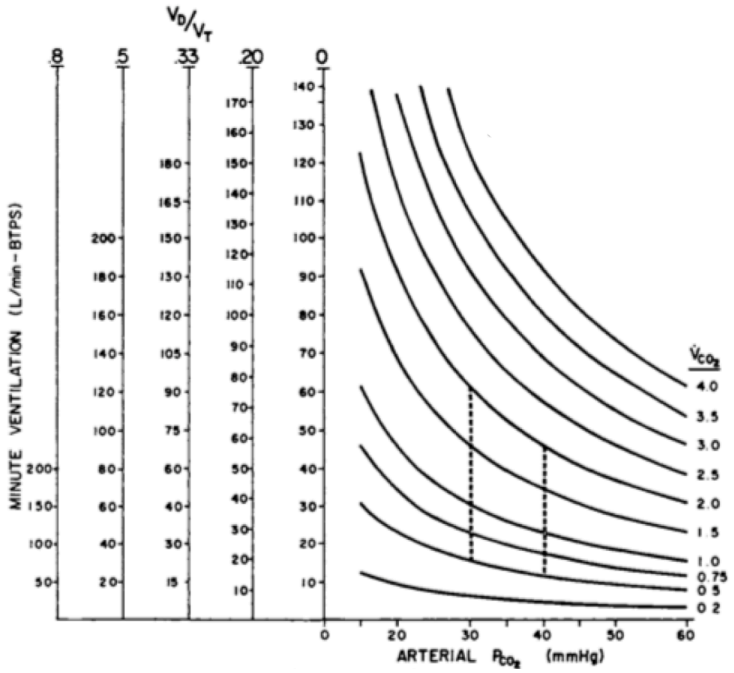

Figure 1.1. The effect of V_D/V_T and P_aCO_2 on $\dot{V}_E$ at various levels of $\dot{V}CO_2$ from rest (0.2 L/min) to maximal exercise (4.0 L/min). V_D/V_T = physiologic dead space to tidal volume ratio; P_aCO_2 = arterial CO_2 partial pressure; $\dot{V}CO_2$ = rate of CO_2 production. Refer to text for use of this graph. Adapted from Wasserman et al.[5]

Table 1.2. The effects of changing P_aCO_2 and V_D/V_T on exercise ventilatory efficiency.				
a) Effect of increasing P_aCO_2 equilibrium point from 30 to 40 mmHg on $\dot{V}_E/\dot{V}CO_2$ at a constant V_D/V_T				
P_aCO_2 (mmHg)	$\dot{V}CO_2$ (L/min)	V_D/V_T (%)	$\dot{V}_E$ (L/min)	$\dot{V}_E/\dot{V}CO_2$
30	2.0	0.33	85.8	42.9
40	2.0	0.33	64.4	32.2
b) Effect of increasing V_D/V_T from 0.33 to 0.50 on $\dot{V}_E/\dot{V}CO_2$ at a constant P_aCO_2				
P_aCO_2 (mmHg)	$\dot{V}CO_2$ (L/min)	V_D/V_T (%)	$\dot{V}_E$ (L/min)	$\dot{V}_E/\dot{V}CO_2$
40	2.0	**0.33**	64.4	32.2
40	2.0	**0.50**	86.4	43.2
P_aCO_2 = CO_2 tension in the arterial blood; $\dot{V}CO_2$ = rate of CO_2 output; V_D/V_T = dead space to tidal volume ratio; $\dot{V}_E$ = minute ventilation; $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for CO_2, an index of exercise ventilatory efficiency.				

Available evidence suggests that P_aCO_2 is relatively similar between-subjects with normal resting values ranging from 35-45 mmHg; is relatively unaffected by age, sex and cardiopulmonary diseases like chronic obstructive pulmonary disease (COPD) and heart failure (HF); and remains relatively unchanged from its resting value through moderate intensity exercise in healthy adults and in patients with chronic cardiopulmonary disease (Fig. 2).[6] As a result of this relative constancy of P_aCO_2 at rest and during exercise in health and disease, alterations in the $\dot{V}_E$-$\dot{V}CO_2$ relationship during exercise are interpreted as reflecting concomitant alterations in V_D/V_T and, by extension, exercise ventilatory efficiency; that is, as $\dot{V}_E$-$\dot{V}CO_2$ relationships increase, V_D/V_T and exercise ventilatory efficiency worsen; and as $\dot{V}_E$-$\dot{V}CO_2$ relationships decrease, V_D/V_T and exercise ventilatory efficiency improves.

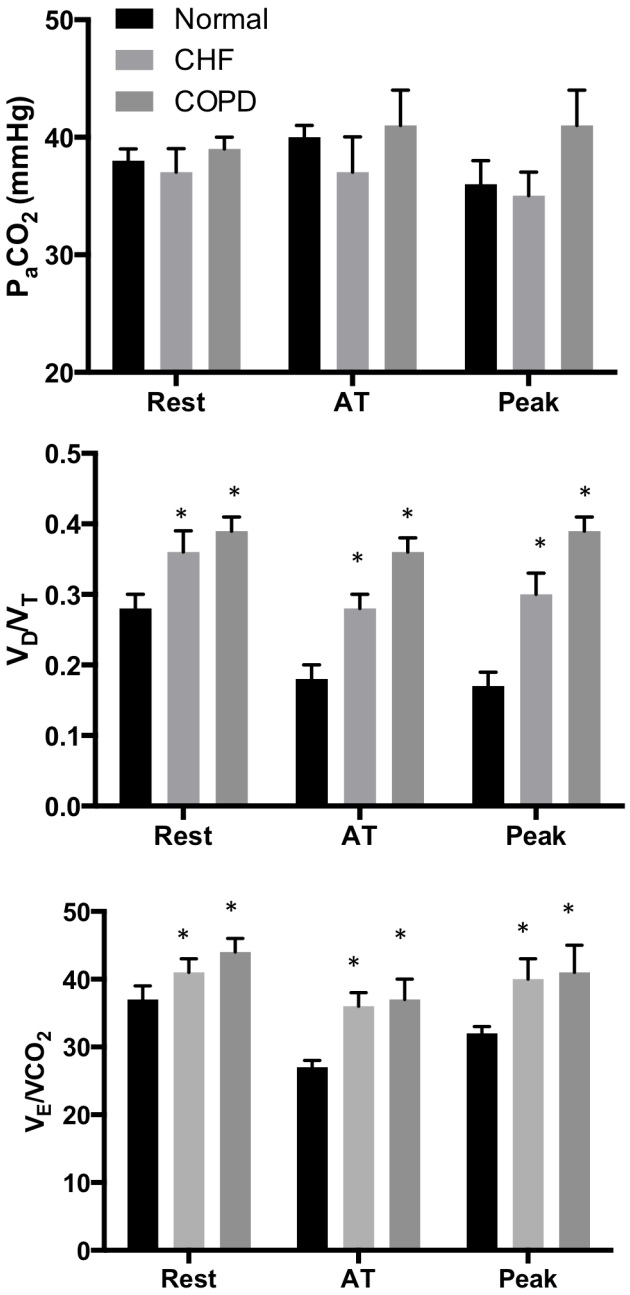

Figure 1.2. Effect of chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) on exercise ventilatory efficiency and its physiological determinants. $PaCO_2$ = partial pressure of CO_2 in arterial blood; V_D/V_T = ratio of physiologic dead space to tidal volume; V_E-VCO_2 = ventilatory equivalent for CO_2, an index of exercise ventilatory efficiency; AT = anaerobic threshold; Peak = end-exercise. Figure created using data from Kisaka et al.[6]

1.2. Exercise Ventilatory Efficiency: Methods of Assessment and Normal Values.

The most common methods used to quantify exercise ventilatory efficiency include: (1) the $\dot{V}_E$-$\dot{V}CO_2$ slope from rest to the respiratory compensation point for metabolic/lactic acidosis; (2) the $\dot{V}_E$-$\dot{V}CO_2$ slope from rest to peak exercise; (3) the $\dot{V}_E$-$\dot{V}CO_2$ ratio at the anaerobic threshold (AT); and (4) the lowest $\dot{V}_E$-$\dot{V}CO_2$ ratio during exercise, i.e., nadir.[18-22] Another less common parameter estimate is the y-axis intercept of the $\dot{V}_E$-$\dot{V}CO_2$ slope, where $\dot{V}_E$ in the absence of pulmonary gas exchange (i.e., $\dot{V}_E$ when $\dot{V}CO_2 = 0$) is theoretically equal to V_D.[3,18] Although there is some controversy in the literature about which of these methods should be used to estimate exercise ventilatory efficiency, a comprehensive study of 474 healthy adults aged 17-78 years by Sun et al.[18] reported that the $\dot{V}_E$-$\dot{V}CO_2$ nadir, which does not require determination of the AT and/or the respiratory compensation point, was not significantly different from the $\dot{V}_E$-$\dot{V}CO_2$ ratio at the AT; was less variable than the $\dot{V}_E$-$\dot{V}CO_2$ slope below the respiratory compensation point; and was unaffected by the type of ergometer (cycle vs. treadmill) and gas exchange measurement system used. Thus, it is both sensible and clinically practical to use the $\dot{V}_E$-$\dot{V}CO_2$ nadir to assess exercise ventilatory efficiency, at least in healthy subjects.

The collective results of studies by Poulin et al.,[23] Hadebank et al.[24] and Sun et al.[18] suggest that mean values of the $\dot{V}_E$-$\dot{V}CO_2$ slope, the $\dot{V}_E$-$\dot{V}CO_2$ ratio at AT and the $\dot{V}_E$-$\dot{V}CO_2$ nadir are about 25-26 in healthy men and women, and increase progressively with normative aging (Table 1.3). In normal subjects, the $\dot{V}_E$-$\dot{V}CO_2$ ratio at peak exercise is typically ≤36.[23]

Table 1.3. Exercise ventilatory efficiency by age and sex in healthy normal adults.				
Groups	**Sample Size**	**$\dot{V}_E$-$\dot{V}CO_2$ @ AT**	**$\dot{V}_E$-$\dot{V}CO_2$ slope**	**$\dot{V}_E$-$\dot{V}CO_2$ nadir**
Male				
<20 yrs	46	23.5 ± 2.0	22.9 ± 2.8	23.2 ± 2.0
21-30 yrs	90	24.2 ± 2.1	23.6 ± 2.8	23.9 ± 2.1
31-40 yrs	49	25.3 ± 2.6	23.9 ± 3.1	25.0 ± 2.7
41-50 yrs	37	26.2 ± 2.2	25.2 ± 2.9	26.1 ± 2.2
51-60 yrs	54	28.2 ± 2.8	27.2 ± 3.0	28.0 ± 2.9
>60 yrs	34	29.4 ± 2.2	27.5 ± 3.1	29.4 ± 2.3
Average	316	25.7 ± 3.1	24.7 ± 3.4	25.5 ± 3.2
Female				
<20 yrs	29	25.5 ± 1.7	25.2 ± 2.7	25.4 ± 1.8
21-30 yrs	50	25.8 ± 2.3	24.1 ± 2.1	25.4 ± 2.2
31-40 yrs	27	27.9 ± 2.1	26.9 ± 3.2	27.7 ± 2.3
41-50 yrs	28	26.7 ± 2.6	25.8 ± 2.7	26.5 ± 2.6
51-60 yrs	20	28.5 ± 3.2	26.5 ± 3.4	28.0 ± 3.3
>60 yrs	10	29.4 ± 2.5	28.7 ± 3.1	29.3 ± 2.6
Average	164	26.8 ± 2.7	25.6 ± 3.0	26.5 ± 2.7
TOTAL	**474**	**26.1 ± 3.0**	**25.0 ± 3.3**	**25.9 ± 3.0**
Data are presented as mean ± standard deviation. $\dot{V}_E$-$\dot{V}CO_2$ = ventilatory equivalent for CO_2; AT = anaerobic threshold. Reproduced from Sun et al.[18]				

1.3. Exercise Ventilatory Inefficiency in Cardiopulmonary Disease: Clinical Impact and Underlying Mechanisms. Exercise ventilatory inefficiency is a key pathophysiological feature of patients with chronic cardiopulmonary disease, such as HF,[2,19,25-29] COPD,[30-32] pulmonary arterial hypertension (PAH)[33-35] and interstitial pulmonary fibrosis (IPF).[36,37] In these patient populations, the $\dot{V}_E$-$\dot{V}CO_2$ slope, $\dot{V}_E$-$\dot{V}CO_2$ nadir, $\dot{V}_E$-$\dot{V}CO_2$ ratio at AT and/or $\dot{V}_E$-$\dot{V}CO_2$ intercept are abnormally high[6,32,34] and associated with several important adverse clinical and patient-reported outcomes, including: disease severity and progression (Fig. 1.3);[2,3,38] symptom-limited peak $\dot{V}O_2$ ($\dot{V}O_{2peak}$) on cardiopulmonary exercise testing (Fig. 1.4);[26,28,29,39] exertional breathlessness;[3,40,41] and risk of hospitalization (Fig. 1.5),[2,26,42] major cardiac events (Fig. 1.6)[7,39,43] and mortality (Fig. 1.7).[2,31,36,37,39] In fact, a growing body of evidence suggests that an abnormally high $\dot{V}_E$-$\dot{V}CO_2$ during exercise (slope, nadir, ratio at AT) is

superior to $\dot{V}O_{2peak}$ at predicting all-cause, cardiovascular and respiratory mortality patients with HF and COPD.[18,19,31,44,45]

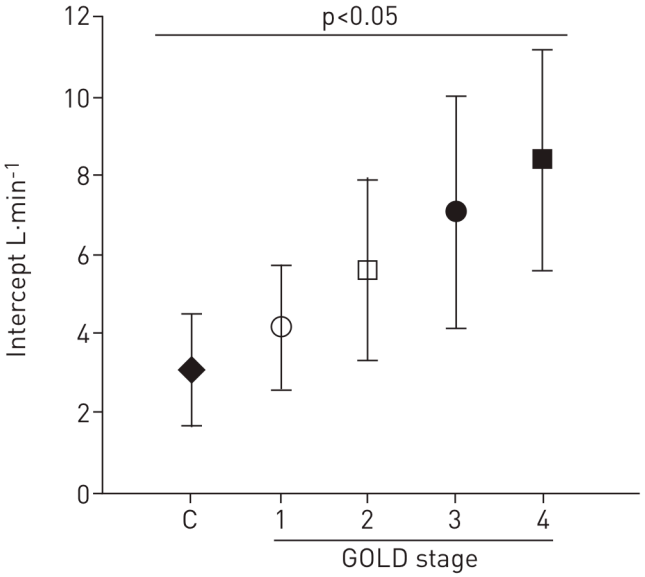

Figure 1.3. Relationship between V_E-VCO_2 intercept (an index of exercise ventilatory inefficiency) and chronic obstructive pulmonary disease (COPD) severity according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging criteria. C = healthy control subjects (n=69); GOLD stage 1 (n=81); GOLD stage 2 (n=112); GOLD stage 3 (n=84); and GOLD stage 4 (n=39). Adapted from Neder et al.[3]

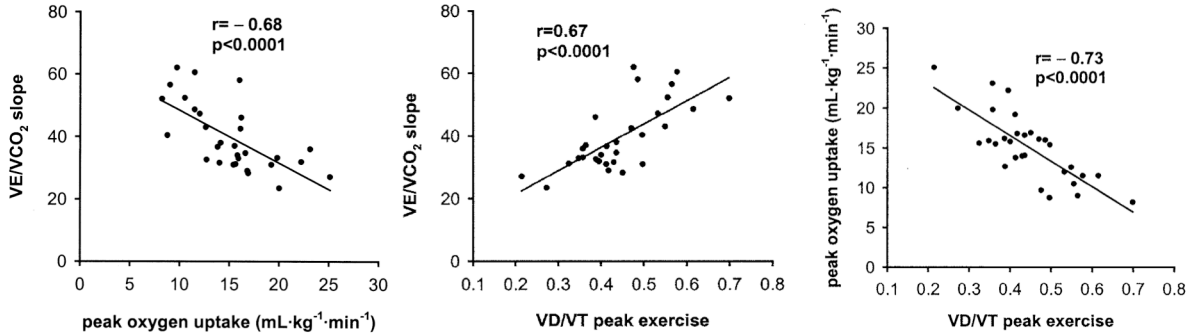

Figure 1.4. Inter-relationships between V_E-VCO_2 slope during exercise (i.e., exercise ventilatory efficiency), symptom-limited peak oxygen uptake and the dead space-to-tidal volume (V_D/V_T) ratio at peak exercise in 30 patients with chronic heart failure. Adapted from Wensel et al.[1]

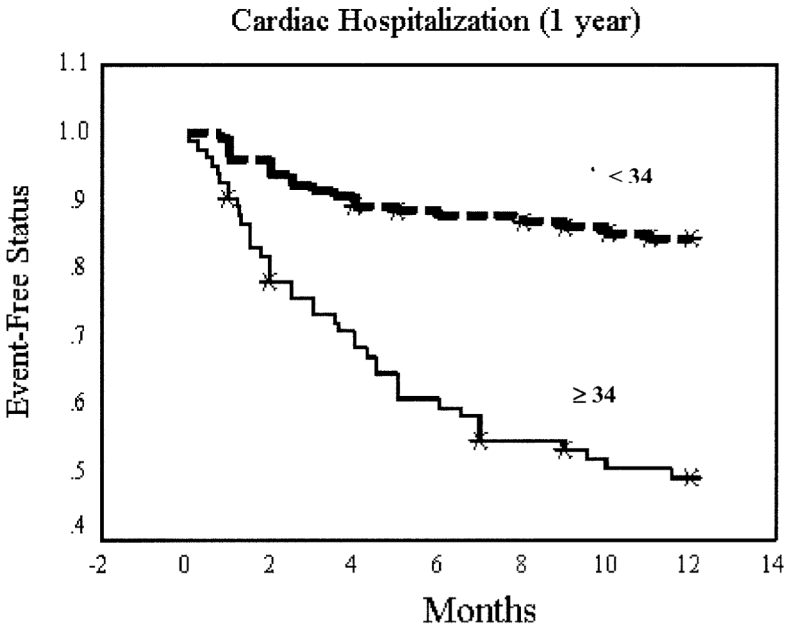

Figure 1.5. Kaplan-Meier analysis for 1-year cardiac-related hospitalization for heart failure patients (n-213) with V_E-VCO_2 slope threshold of 34 during exercise. Patients with V_E-VCO_2 slope <34 (n=130) were 84.6% event-free, whereas patients with V_E-VCO_2 slope ≥34 (n=83) were 50.6% event-free (p<0.0001). Adapted from Arena et al.[2]

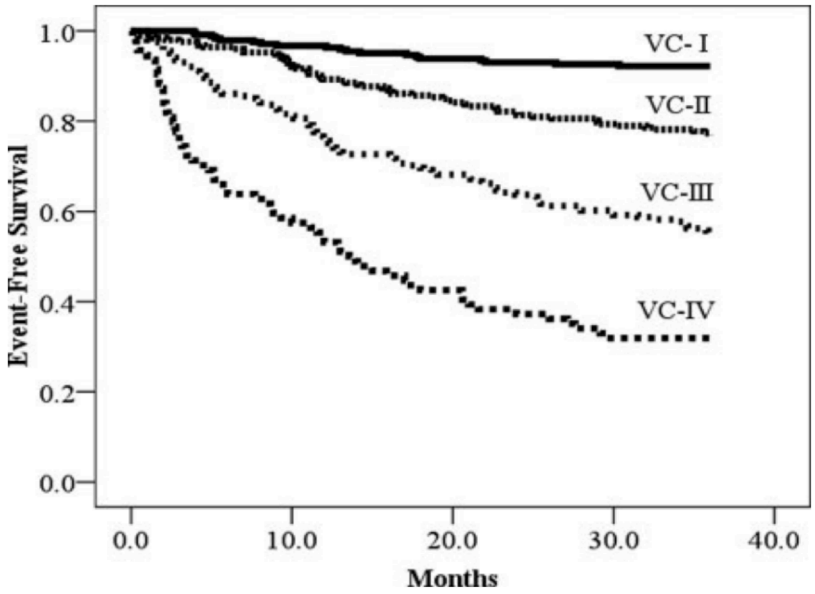

Figure 1.6. Kaplan-Meier analysis for 3-year major cardiac-related events for patients with heart failure divided by ventilatory class (VC). HF patients with V_E-VCO_2 slope during exercise: <29.9 (VC-I) were 92.2% event-free; between 30.0 and 35.9 (VC-II), were 77.0% event-free; between 36.0 and 44.9 (VC-III) were 55.2% event-free; and > 45.0 (VC-IV) were only 31.9% event-free. Adapted from Arena et al.[7]

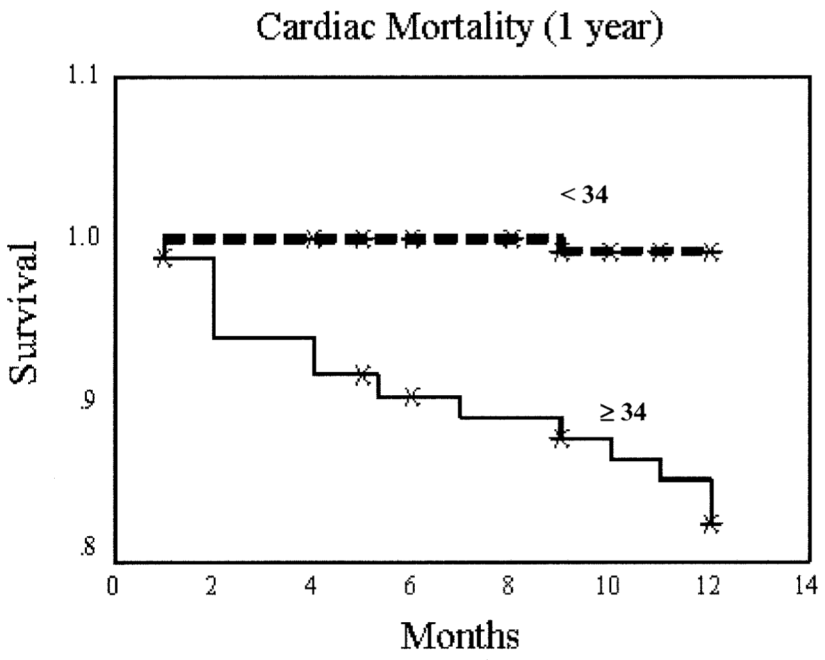

Figure 1.7. Kaplan-Meier analysis for 1-year cardiac mortality for heart failure patients (n-213) with V_E-VCO_2 slope threshold of 34 during exercise. Patients with V_E-VCO_2 slope <34 (n=130) were 99.2% event-free, whereas patients with V_E-VCO_2 slope ≥34 (n=83) were 83.1% event-free (p<0.0001). Adapted from Arena et al.[2]

In patients with HF and COPD compared to healthy subjects, the greater $\dot{V}_E$-$\dot{V}CO_2$ response to exercise cannot be readily explained by a lowering of the P_aCO_2 equilibrium point and thus primarily reflects the impact of a high V_D/V_T on ventilation-perfusion mismatching (Figs. 1.2 and 1.3).[1,6,15,46] In patients with PAH, the increased $\dot{V}_E$-$\dot{V}CO_2$ response to exercise reflects the combination of increased V_D/V_T (and ventilation-perfusion mismatching) and a lower P_aCO_2 equilibrium point by ~8-10 mmHg.[34,40,47,48] From the above, it is clear that V_D/V_T represents an important therapeutic target to improve exercise ventilatory efficiency and its associated clinical and patient-centered outcomes in adults with chronic cardiopulmonary disease. However, with the possible exception of surgical lung volume reduction techniques in COPD[49-52] and pulmonary vasodilator therapy in PAH[33] and HF,[53] our ability to enhance

exercise ventilatory efficiency is limited by the fact that ventilation-perfusion abnormalities as a result of high V_D/V_T are often irreversible.

1.4. Impact of Acid-Base Balance on Exercise Ventilatory Efficiency. A largely unexplored approach to decreasing the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise and improving exercise ventilatory efficiency and related physiological and perceptual outcomes (e.g., breathlessness) is increasing the P_aCO_2 equilibrium point by inducing a metabolic alkalosis. Briefly, induction of a strong positive ion (cation) alkalosis by administration of sodium bicarbonate (N_aHCO_3, i.e., baking soda) has been shown to decrease ventilatory chemoreflex responsiveness by decreasing the concentration of hydrogen ions ($[H^+]$) in the arterial blood and presumably also the cerebrospinal fluid.[54,55] The resultant effect would be a decrease in $\dot{V}_E$ and consequent increase in the P_aCO_2 equilibrium point.

While the effects of induced metabolic alkalosis by $NaHCO_3$ on exercise performance in athletic young adults are variable and relatively well described in the literature,[56-59] we are aware of only a few studies that have examined the effect of increasing the P_aCO_2 equilibrium point via N_aHCO_3 administration on $\dot{V}_E$ and gas exchange responses to exercise.[4,8,9,60]

A randomized, double blind, placebo-controlled, crossover study by Jones et al.[4] examined the acute effects of induced metabolic alkalosis and acidosis by oral administration of 0.3 g/kg of $NaHCO_3$ and of ammonium chloride (NH_4Cl), respectively, on cardiorespiratory and metabolic responses to constant load cycle exercise testing at 33%, 66% and 95% of peak incremental cycle power output (PPO) in 5 healthy men

aged 30.8 yrs. Compared with the calcium carbonate ($CaCO_3$) control condition, $NaHCO_3$ increased whereas NH_4Cl decreased arterialized venous pH, [HCO_3^-] and PCO_2 ($P_{a\text{-}v}CO_2$) at rest and during exercise (Table 1.4, Fig. 1.8). During exercise at 95% PPO, endurance time was higher after treatment with $NaHCO_3$ (438 ± 120 sec) and lower after treatment with NH_4Cl (160 ± 22 sec) compared with the $CaCO_3$ control condition (270 ± 13 sec). As illustrated in Fig. 1.8 and as predicted by the modified alveolar ventilation equation (refer to Fig. 1.1), $NaHCO_3$-induced increases in $P_{a\text{-}v}CO_2$ were associated with mean decreases in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise, whereas NH_4Cl-induced decreases in $P_{a\text{-}v}CO_2$ were associated with mean increases in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise. Unfortunately, in that small study, no data were given on the statistical significance (or insignificance) of the observed changes in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise with $NaHCO_3$ and NH_4Cl.

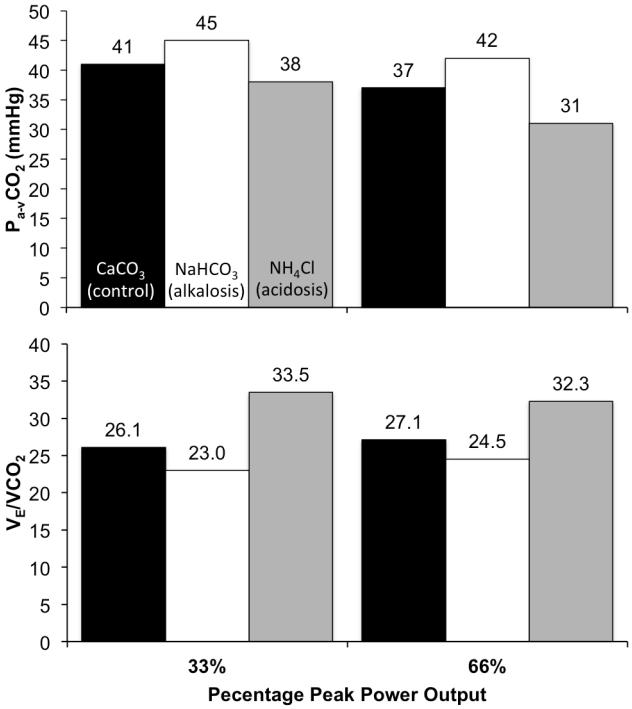

Figure 1.8. Effects of induced metabolic alkalosis by sodium bicarbonate administration ($NaHCO_3$, 0.3 g/kg) and induced metabolic acidosis by ammonium chloride administration (NH_4Cl, 0.3 g/kg) on arterialized venous CO_2 partial pressure ($P_{a\text{-}v}CO_2$) and the ventilatory equivalent for CO_2 (V_E-VCO_2) during constant-load cycle exercise at 33% and 66% of peak incremental power output in 5 healthy men. $CaCO_3$ = calcium carbonate control condition. Figure created using mean data from Jones et al.[4]

A subsequent randomized, double blind, placebo controlled, crossover study by Oren et al.,[61] examined the effect of induced chronic (3 days) metabolic alkalosis by $NaHCO_3$ administration (0.7 g/kg/day) and induced chronic metabolic acidosis by NH_4Cl

administration (0.3 g/kg/day) on $\dot{V}_E$-$\dot{V}CO_2$ responses to constant-load and incremental cycle exercise tests in 7 healthy men aged 22.4 yrs. During metabolic acidosis, $P_{a\text{-}v}CO_2$ was significantly lower than the $CaCO_3$ control condition and during metabolic alkalosis it was higher, although this difference was not statistically significant (Table 1.4).

Table 1.4. Effects of alkalinizing and acidifying salts on arterialized venous acid-base status.

	$NaHCO_3$ (Metabolic Alkalosis)	$CaCO_3$ (Control)	NH_4Cl (Metabolic Acidosis)
pH	7.43 ± 0.005*	7.38 ± 0.01	7.23 ± 0.02*
$[HCO_3^-]$, meq/l	32.5 ± 1.4*	24.4 ± 1.2	15.0 ± 0.8*
$P_{a\text{-}v}CO_2$, mmHg	47.1 ± 1.3	43.7 ± 2.9	36.3 ± 2.1*

Values are means ± SE. $NaHCO_3$ = sodium bicarbonate (0.7 g/kg/day x 3 days); $CaCO_3$ = calcium carbonate (0.1 g/kg/day x 3 days); NH_4Cl = ammonium chloride (0.3 g/kg/day x 3 days); $P_{a\text{-}v}CO_2$ = arterialized venous CO_2 partial pressure; $[HCO_3^-]$ = arterialized venous bicarbonate concentration. *$p<0.05$ versus $CaCO_3$ (control) values. Adapted from Oren et al.[9]

In keeping with the results of Jones et al.,[4] the significantly reduced $P_{a\text{-}v}CO_2$ levels caused by NH_4Cl administration were associated with increased $\dot{V}_E$-$\dot{V}CO_2$ responses to both constant-load (Fig. 1.9) and incremental (Fig. 1.10) cycle exercise testing compared with the $CaCO_3$ control condition. By contrast, administration of $NaHCO_3$, in the setting of an unchanged $P_{a\text{-}v}CO_2$, had no significant effect on the $\dot{V}_E$-$\dot{V}CO_2$ response to either constant-load (Fig. 1.9) or incremental (Fig. 1.10) cycle exercise testing relative to the $CaCO_3$ control condition.

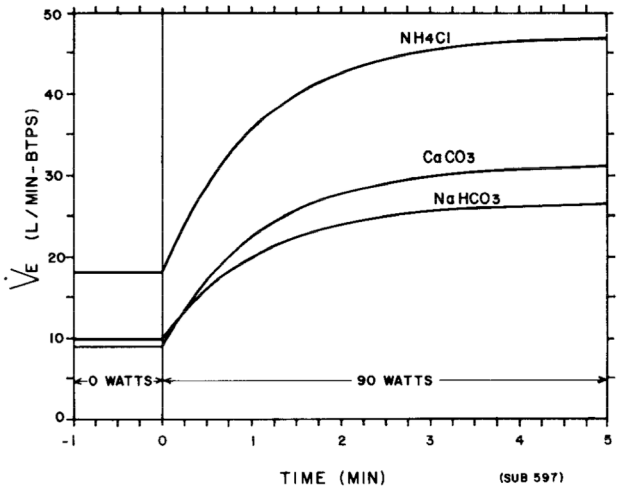

Figure 1.9. Best-fit first-order response of ventilation (V_E) during 3 chronic acid-base states in a representative subject. NH_4Cl = ammonium chloride-induced metabolic acidosis; $NaHCO_3$ = sodium bicarbonate-induced metabolic alkalosis; $CaCO_3$ = calcium carbonate control. The exercise transitions were from a baseline of unloading cycling (0 watts) to 90 watts. Reproduced from Oren et al.[9]

A randomized, double-blind, placebo controlled crossover study of 6 healthy men by Iwaoka et al.,[8] examined the effects of acute administration of $NaHCO_3$ (0.2 g/kg) on $\dot{V}_E$ and gas exchange responses to constant-load cycle exercise maintained at 40% of maximal incremental $\dot{V}O_2$ ($\dot{V}O_{2max}$) for 10-min, followed by 15-min at 12 watts above the respiratory compensation point, followed by an endurance test at 95% $\dot{V}O_{2max}$. In that study, $NaHCO_3^-$ decreased the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise above the respiratory compensation point (Fig. 1.11) coincident with a small but non-significant increase in $P_{a-v}CO_2$ at rest.

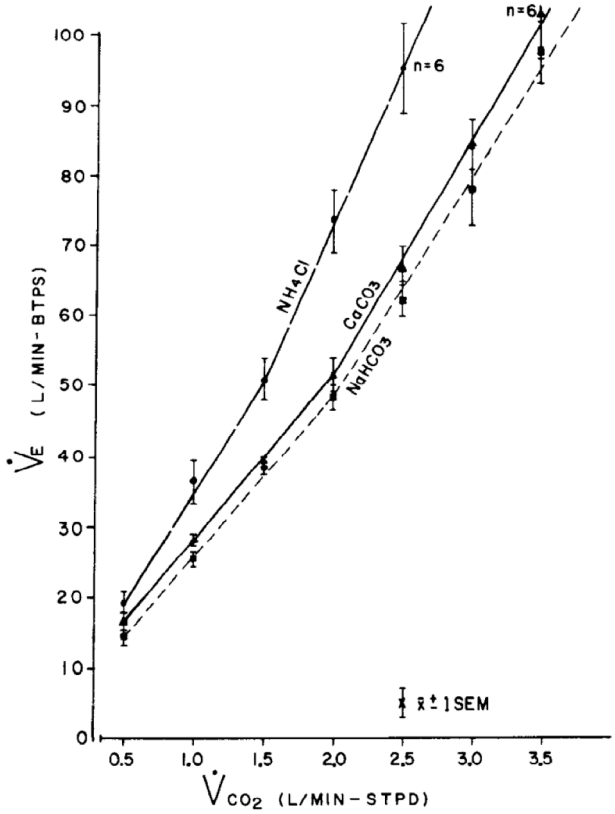

Figure 1.10. Effects of induced chronic metabolic alkalosis by sodium bicarbonate administration ($NaHCO_3$, 0.3 g/kg/day for 3 days) and induced chronic metabolic acidosis by ammonium chloride administration (NH_4Cl, 0.3 g/kg/day for 3 days) on the relationship between increasing ventilation (V_E) and increasing CO_2 production (VCO_2) during incremental cycle exercise testing in 7 healthy men, except where specified otherwise. $CaCO_3$ = calcium carbonate control condition. Reproduced from Oren et al.[9]

While the studies of Jones et al.,[4] Oren et al.[9] and Iwaoka et al.[8] employed a rigorous experimental study design, tests were performed in a combined total of just 18 men and the impact of induced acid-base states, particularly metabolic alkalosis, on exercise ventilatory efficiency could not be demonstrated with any level of certainty. Moreover, neither of these studies examined the effect of changes in the $PaCO_2$ equilibrium point on other relevant exercise physiological and

perceptual outcomes; for example, breathlessness and leg discomfort. Consequently, it remains unclear whether induced metabolic alkalosis by $NaHCO_3$ administration improves exercise ventilatory efficiency and related physiological and symptom responses to exercise by increasing the $PaCO_2$ equilibrium point.

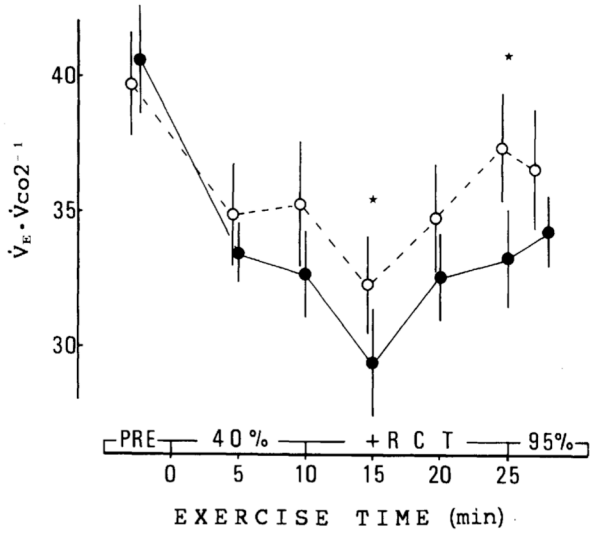

Figure 1.11. Effect on induced metabolic alkalosis (0.2 g of $NaHCO_3^-$/kg of body mass) on the ventilatory equivalent for CO_2 (V_E-VCO_2) at rest and during constant-load cycle exercise maintained at 40% of maximal incremental VO_2 (VO_{2max}) for 10-min, followed by 15-min at 12 watts above the respiratory compensation point, followed by an endurance test at 95% VO_{2max}. Open circles = placebo control condition; Closed circles = sodium bicarbonate ($NaHCO_3^-$) condition. *p<0.05 vs. placebo control condition. Adapted from Iwaoka et al.[8]

1.5. Objectives & Hypothesis

The *primary objective* of this randomized, double-blind, placebo-controlled crossover study was to examine the acute effects of induced metabolic alkalosis by oral administration of $NaHCO_3$ on exercise ventilatory efficiency, i.e., $\dot{V}_E$-$\dot{V}CO_2$ nadir.[18] Our *secondary objective* was to examine the effect of induced metabolic alkalosis on (i) exercise endurance and (ii) detailed physiological and perceptual responses to exercise. To this end, 18 healthy adults (12 men, 6 women) aged 18-40 years performed a symptom-limited constant-load cycle exercise test at 80% of their peak incremental power output following single-dose administration of either $NaHCO_3$ (0.3 mg/kg) or sodium chloride placebo (NaCl, 4 mg), randomized to order. Arterialized venous blood gases were measured at rest 90-min after administration of $NaHCO_3$ and NaCl. Exercise tests were performed ≥90 and ≤120-min after administration of $NaHCO_3$

and NaCl and included detailed evaluation of breathing pattern, dynamic operating lung volume, cardiometabolic, gas exchange and symptom parameters. We ***hypothesized*** that, compared to NaCl, induced metabolic alkalosis by single-dose administration of N_aHCO_3 vs. NaCl would: increase the $PaCO_2$ equilibrium point; decrease the $\dot{V}_E$-$\dot{V}CO_2$ nadir; increase exercise endurance time; and decrease intensity ratings of perceived breathlessness during exercise.

CHAPTER 2: EFFECT OF INDUCED ACUTE METABOLIC ALKALOSIS BY SODIUM BICARBONATE ADMINISTRATION ON EXERCISE VENTILATORY EFFICIENCY IN HEALTHY ADULTS

2.1. ABSTRACT

In a randomized, double blind, placebo controlled, crossover study of 18 healthy adults aged 22.2 ± 0.5 yrs (mean ± SE), we tested the hypothesis that increasing the arterial PCO_2 equilibrium point via induced acute metabolic alkalosis by sodium bicarbonate ($NaHCO_3$, 0.3 g/kg) administration would decrease the ventilatory equivalent for CO_2 ($\dot{V}_E$-$\dot{V}CO_2$) at its lowest point ("nadir") during high-intensity constant-load cycle exercise testing, reflecting improved exercise ventilatory efficiency. Compared to the NaCl control condition, administration of $NaHCO_3$: increased arterialized venous pH, HCO_3^- and PCO_2 at rest by 0.05 ± 0.01 units, 4.3 ± 0.7 mmHg and 6.4 ± 0.4 meq/L, respectively (all $p<0.0001$); decreased the $\dot{V}_E/\dot{V}CO_2$ nadir by 9.4% ($p<0.0001$) secondary to reduced $\dot{V}_E$ (by 4.7 ± 1.8 L/min, $p=0.019$); had no effect on cardiometabolic and symptom responses to exercise; and did not improve exercise tolerance. In conclusion, induced acute metabolic alkalosis by $NaHCO_3$ administration improved exercise ventilatory efficiency in healthy adults.

2.2. INTRODUCTION

The ventilatory response ($\dot{V}_E$) to exercise-induced increases in the rate of CO_2 production ($\dot{V}CO_2$), an index of exercise ventilatory efficiency, depends on the regulated level of arterial PCO_2 ($PaCO_2$) and the dead space (V_D) to tidal volume (V_T) ratio, as described by the modified alveolar ventilation equation: $\dot{V}_E/\dot{V}CO_2 = 863/[PaCO_2 \times (1-V_D/V_T)]$ (Fig. 1.1).[62,63]

An abnormally high $\dot{V}_E$-$\dot{V}CO_2$ response to exercise, reflecting exercise ventilatory inefficiency and consequent to a high V_D/V_T and/or low $PaCO_2$ equilibrium point,[62,63] is a key pathophysiological feature of patients with chronic cardiopulmonary disease, including heart failure (HF),[19,25] pulmonary arterial hypertension (PAH),[34] idiopathic pulmonary fibrosis (IPF)[36] and chronic obstructive pulmonary disease (COPD).[32] In these patient groups, exercise ventilatory inefficiency[6,32,34] is associated with: disease severity and progression;[2,3,34,38] exercise intolerance;[26,28,29,34,36,39] exertional breathlessness;[3,41] and increased risk of hospitalization,[26,42] major cardiac events[7,39,43] and mortality.[19,31,36,39,64] It follows that any intervention capable of decreasing the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise has the potential to improve clinical and/or patient-reported outcomes. Unfortunately, our ability to enhance exercise ventilatory efficiency is limited by the fact that, with the possible exception of lung volume reduction surgery in COPD[49-52] and pulmonary vasodilator therapy in PAH[33] and HF,[53] ventilation-perfusion abnormalities reflecting a high V_D/V_T are often irreversible.

A largely unexplored approach to decreasing the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise is increasing the $PaCO_2$ equilibrium point by inducing a metabolic alkalosis via administration of an alkalizing agent such as sodium bicarbonate ($NaHCO_3$). Oren et

al.[9] examined the effect of induced chronic metabolic alkalosis by 3 consecutive days of $NaHCO_3$ administration (0.7 g/kg/day) on $\dot{V}_E$-$\dot{V}CO_2$ responses to exercise in 7 healthy men. Compared to the calcium carbonate control condition ($CaCO_3$, 0.1 g/kg/day), $NaHCO_3$ increased $PaCO_2$ by ~3.5 mmHg at rest and decreased $\dot{V}_E$-$\dot{V}CO_2$ responses to (i) symptom-limited incremental cycle exercise testing and (ii) constant-load cycle exercise testing at a power output below the anaerobic threshold; however, none of these differences were statistically significant. A study of 6 healthy men by Iwaoka et al.[8] reported that, compared to the starch control condition, single-dose administration of $NaHCO_3$ (0.2 g/kg) significantly decreased $\dot{V}_E$-$\dot{V}CO_2$ ratios during cycle exercise above but not below the respiratory compensation point coincident with small, statistically non-significant increases in $PaCO_2$ at rest and during exercise. Based on the results of these small studies, it remains unclear whether increasing the $PaCO_2$ equilibrium point via induced metabolic alkalosis by $NaHCO_3$ administration has the potential to decrease $\dot{V}_E$-$\dot{V}CO_2$ responses to exercise in human subjects.

Therefore, the primary objective of this randomized, double blind, placebo controlled, crossover study was to test the hypothesis that increasing the $PaCO_2$ equilibrium point via induced acute metabolic alkalosis by single-dose administration of $NaHCO_3$ would improve exercise ventilatory efficiency, as evidenced by a decrease in the $\dot{V}_E$-$\dot{V}CO_2$ ratio at its lowest point ("nadir")[18] during high-intensity constant-load cycle exercise testing in healthy adults.

2.3. METHODS

2.3.a. Participants. Participants included healthy, non-smoking, non-obese (body mass index [BMI] <30 kg/m^2) men and women aged 18-40 years with normal spirometry: forced expiratory volume in 1-sec (FEV_1) ≥80% predicted[65] and a FEV_1-to-forced vital capacity ratio (FEV_1/FVC) >70%. Participants were excluded if they were taking doctor-prescribed medications other than oral contraceptives and/or had a history of gastrointestinal, cardiovascular, respiratory, kidney, liver, musculoskeletal, endocrine, neuromuscular and/or metabolic disease/disorder. Pregnancy in women was ruled out via standard (urine) pregnancy test prior to study enrolment. Participants were recruited from McGill University and the general population.

2.3.b. Study design. This was a randomized, double blind, placebo controlled, crossover study wherein participants visited the laboratory on three separate occasions over a period of 8-14 days. *Visit 1* included screening for eligibility, spirometry and a symptom-limited incremental cycle exercise test to determine peak power output (PPO). After randomization of treatments (*Visits 2 and 3*), participants received a single-dose of either 0.3 g/kg of $NaHCO_3$ (Arm and Hammer Baking Soda, Church and Dwight Co., Inc., Mississauga, ON, Canada) or 4 g of sodium chloride placebo (NaCl; Kalas Iodized Sea Salt, Piloros Inc., Laval, QC, Canada). Briefly, both $NaHCO_3$ and NaCl were dissolved in 700 mL of water mixed with 4 tablespoons of President's Choice® Extra Rich Chocolate Milk Mix (Loblaws, Inc., Toronto, ON, Canada) to mask the taste of $NaHCO_3$ and help ensure that participants were blinded to the treatments. The supplemented and chocolate flavored water was drunk in sips from 120- to 90-min prior

to each test, an administration strategy employed by Egger et al.[66] to obviate the potentially confounding effects of gastrointestinal discomfort and belching often associated with consuming $NaHCO_3$. Arterialized venous blood samples were obtained at rest exactly 90-min post-treatment. Immediately after blood sampling, participants completed a symptom-limited constant-load cycle exercise test at 80% of their PPO.

Visits were separated by ≥48-hr and conducted at the same time of day (±1 hr) for each volunteer. Participants were asked to avoid strenuous exercise as well as alcohol and xanthine-containing food and drinks (e.g., coffee, tea, cola) on each test day. The study protocol and consent form were approved by the Institutional Review Board of the Faculty of Medicine at McGill University (A02-M19-15B) and conformed to the ethical standards set by the *Declaration of Helsinki*. Each participant provided written, informed consent.

2.3.c. Randomization and blinding of treatments. The randomization scheme was generated using the Web site Randomization.com (http://randomization.com) by an unblinded third party of the Principal Investigator's research team that was not affiliated with either participant recruitment and/or data collection or analysis. This person also prepared the treatments so that neither the participant nor the research staff directly involved with the study were aware of the treatment allocation before or after randomization.

2.3.d. Blood biochemistry. Arterialized venous blood samples for the determination of $PaCO_2$ and of hydrogen ion ($[H^+]$) and bicarbonate ($[HCO_3^-]$) concentrations were drawn

from the earlobe at rest 90-min after administration of $NaHCO_3$ and NaCl. Briefly, the earlobe was warmed for 10-min prior to blood sampling using the rubefacient Finalgon® Cream (Boehringer Ingelheim GmbH); a puncture was made with a lancet so that a free flow of blood appeared; and blood was drawn into pre-heparinized capillary tubes (safeCLINITUBES, D957P-70-125; Radiometer Copenhagen, Denmark) and analyzed immediately using an Opti CCA-TS2 Portable Blood Gas Analyzer (OPTI Medical Systems, Inc., Roswell, Georgia, USA) at a standard temperature of 37°C.

2.3.e. Spirometry and cardiopulmonary exercise testing. Spirometry was performed with participants seated using automated equipment (Vmax Encore®; Carefusion, Yorba Linda, CA, USA) and according to recommended techniques.[67] Exercise tests were conducted on an electronically braked cycle ergometer (Ergoline 800s; Carefusion) using a Vmax Encore® cardiopulmonary exercise testing system. Incremental exercise tests consisted of a steady-state resting period of ≥6-min, followed by 25 watt increases in power output (starting at 25 watts) every 2-min: PPO was defined as the highest power output that the participant was able to sustain for ≥30-sec, while the peak rate of O_2 uptake ($\dot{V}O_{2peak}$) was taken as the average of the last 30-sec of loaded pedaling. Constant-load exercise tests consisted of a steady-state resting period of ≥6-min, followed by a 1-min warm-up at 25% of PPO and then a step increase in power output to 80% of PPO. During both incremental and constant-load tests, pedaling cadence was maintained between 60-80 rev/min and participants were verbally encouraged to exercise to the point of symptom-limitation (i.e., volitional fatigue).

Standard respiratory and gas exchange parameters were collected breath-by-breath while participants breathed through a rubber mouthpiece and low-resistance flow transducer with nasal passages occluded by a nose clip. Heart rate was monitored continuously by 12-lead electrocardiography. Inspiratory capacity (IC) maneuvers were performed at rest, within the last 30-sec of every 2-min interval during exercise, and at end-exercise. Assuming that total lung capacity does not change during exercise,[68] changes in IC and inspiratory reserve volume (IRV = IC - tidal volume [V_T]) reflect changes in dynamic end-expiratory and end-inspiratory lung volume, respectively. Using Borg's 0-10 category-ratio scale (Borg CR10),[69] participants rated the intensity of their perceived breathlessness and perceived leg discomfort at rest, within the last 30-sec of every 2-min interval during exercise, and at end-exercise. At end-exercise, participants verbalized their main reason(s) for stopping exercise; and quantified the percentage contribution of breathlessness and leg discomfort to exercise cessation.

2.3.f. Analysis of exercise end-points. Physiological parameters measured breath-by-breath were averaged in 30-sec intervals at rest and during exercise at 80% PPO. These parameters, collected over the first 30-sec period of every 2-min interval during exercise, were linked with symptom ratings and IC-derived measurements collected over the latter 30-sec of the same minute. Measured parameters were examined at rest (i.e., steady-state period after at least 3-min of breathing on the mouthpiece while seated at rest before the start of exercise); at standardized submaximal time points completed by all participants during all constant-load exercise tests (i.e., 2-min and 4-min); at the highest equivalent submaximal time completed by a given participant during

each of his/her two constant-load exercise tests (i.e., isotime); and at peak exercise, defined as the average of the last 30-sec of loaded pedaling. Exercise endurance time (EET) was defined as the duration of pedaling at 80% of PPO. Our primary outcome, the $\dot{V}_E$-$\dot{V}CO_2$ nadir, was identified for each participant and treatment period as the lowest 30-sec average data point during constant-load cycle exercise testing: corresponding values of $\dot{V}_E$, $\dot{V}CO_2$ and end-tidal CO_2 tension ($P_{ET}CO_2$) were also identified.

2.3.g. Statistical analysis. Two-tailed paired t-tests were used to compare the effects of treatment with $NaHCO_3$ and NaCl on: resting $PaCO_2$, $[H^+]$ and $[HCO_3^-]$; EET; $\dot{V}_E$-$\dot{V}CO_2$ nadir and corresponding measures of $\dot{V}_E$, $\dot{V}CO_2$ and $P_{ET}CO_2$; and the percentage contribution of breathlessness and leg discomfort to exercise cessation (SigmaStat; Systat Software Inc., San Jose, CA, USA). The effect of treatment ($NaHCO_3$ vs. NaCl), measurement time (rest, 2-min, 4-min, isotime and peak exercise) and their interaction on measured parameters was examined using a two-tailed, two-way repeated measures analysis of variance with correction for multiple comparisons using Tukey's HSD test. Fisher's exact test was used to compared the effect of treatment with $NaHCO_3$ and NaCl on reasons for stopping exercise. Statistical significance was set at $p<0.05$ and values are reported as mean ± SE.

2.4. RESULTS

2.4.a. Participant characteristics. Participants included 18 young (22.2 ± 0.5 yrs), non-obese (BMI, 24.2 ± 0.7 kg/m^2) men and women (n=12 and 6, respectively) with normal spirometry (FEV_1, 104 ± 3% predicted; FEV_1/FVC, 82.1 ± 1.8%) and a PPO of 219.4 ± 13.9 watts (108 ± 6% predicted[70]) and a $\dot{V}O_{2peak}$ of 51.8 ± 2.6 ml/kg/min (129 ± 6% predicted[70]).

2.4.b. Blood biochemistry. As illustrated in Fig. 2.1, single-dose administration of $NaHCO_3$ induced a partially compensated metabolic alkalosis with decreases in [H^+] (by 4.3 ± 0.5 meq/L) and increases in $PaCO_2$ and [HCO_3^-] (by 4.3 ± 0.7 mmHg and 6.4 ± 0.4 meq/L, respectively) compared with the NaCl control condition (all $p<0.0001$).

2.4.c. Exercise endurance time and symptom responses. None of the 18 participants reported any undue effects (e.g., gastrointestinal discomfort, belching) after ingestion of either $NaHCO_3$ or NaCl. As illustrated in Fig. 2.2, neither EET nor intensity ratings of breathlessness and leg discomfort were different after treatment with $NaHCO_3$ vs. NaCl. Similarly, $NaHCO_3$ had no effect on the number of participants stopping exercise due to leg discomfort (NaCl, 55.5% vs. $NaHCO_3$, 50%); breathlessness (NaCl, 5.6% vs. $NaHCO_3$, 11%); or a combination of leg discomfort and breathlessness (NaCl, 38.9% vs. $NaHCO_3$, 33.3%) (all $p>0.05$). Moreover, the percentage contribution of leg discomfort (NaCl, 58.1 ± 5.2% vs. $NaHCO_3$, 53.6 ± 5.8%; $p=0.451$) and breathlessness (NaCl, 41.9 ± 5.2% vs. $NaHCO_3$, 46.4 ± 5.8%; $p=0.451$) to exercise cessation were similar between NaCl and $NaHCO_3$ conditions.

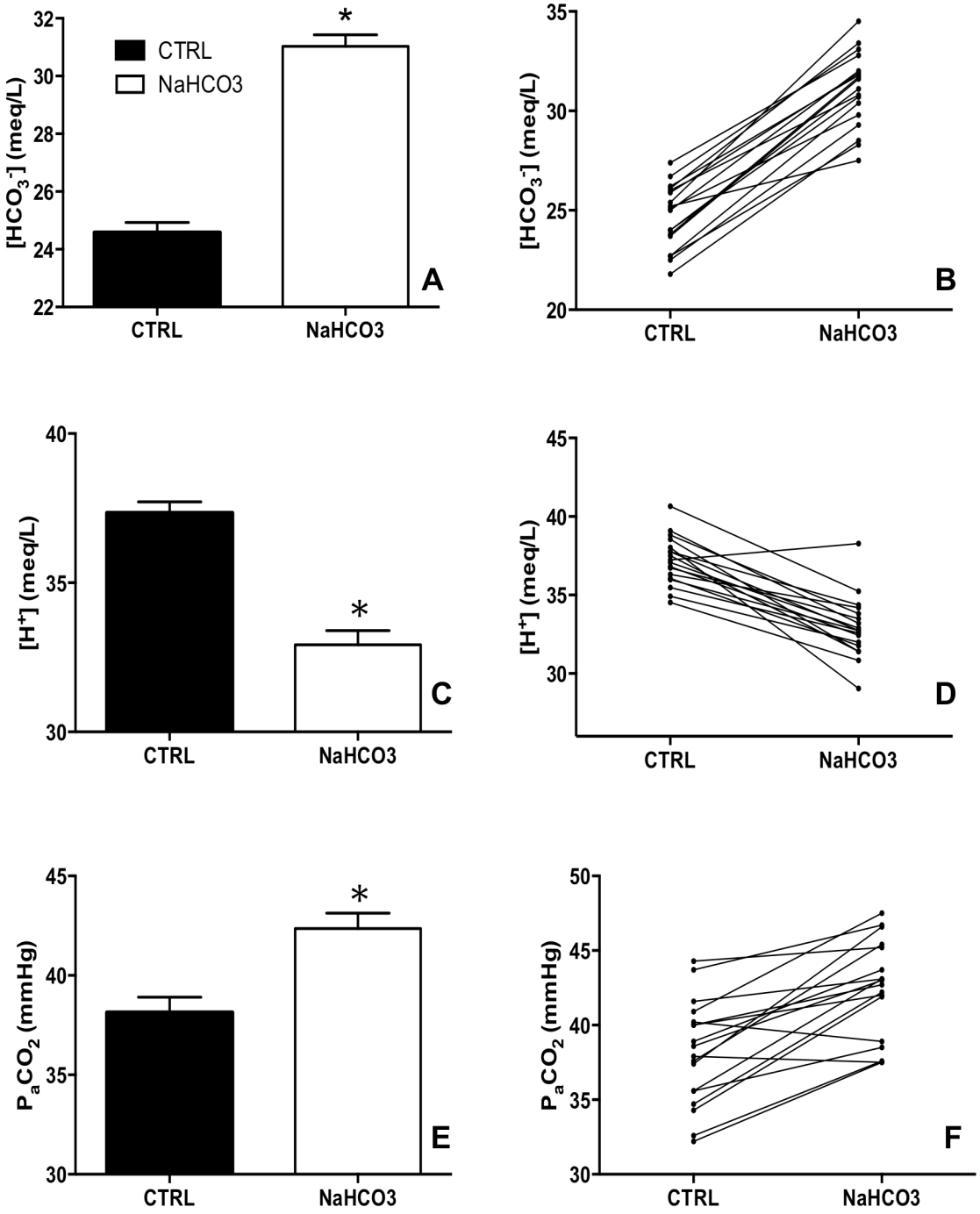

Figure 2.1. Effect of single-dose administration of sodium bicarbonate ($NaHCO_3$) compared with sodium chloride (CTRL) on blood biochemistry parameters at rest, with mean ± SE responses (A, C and E) and individual subject responses (B, D and F) presented. [H^+], arterialized venous hydrogen ion concentration; [HCO_3^-], arterialized venous bicarbonate concentration; $PaCO_2$, arterial venous CO_2 partial pressure. *p<0.05 vs. CTRL.

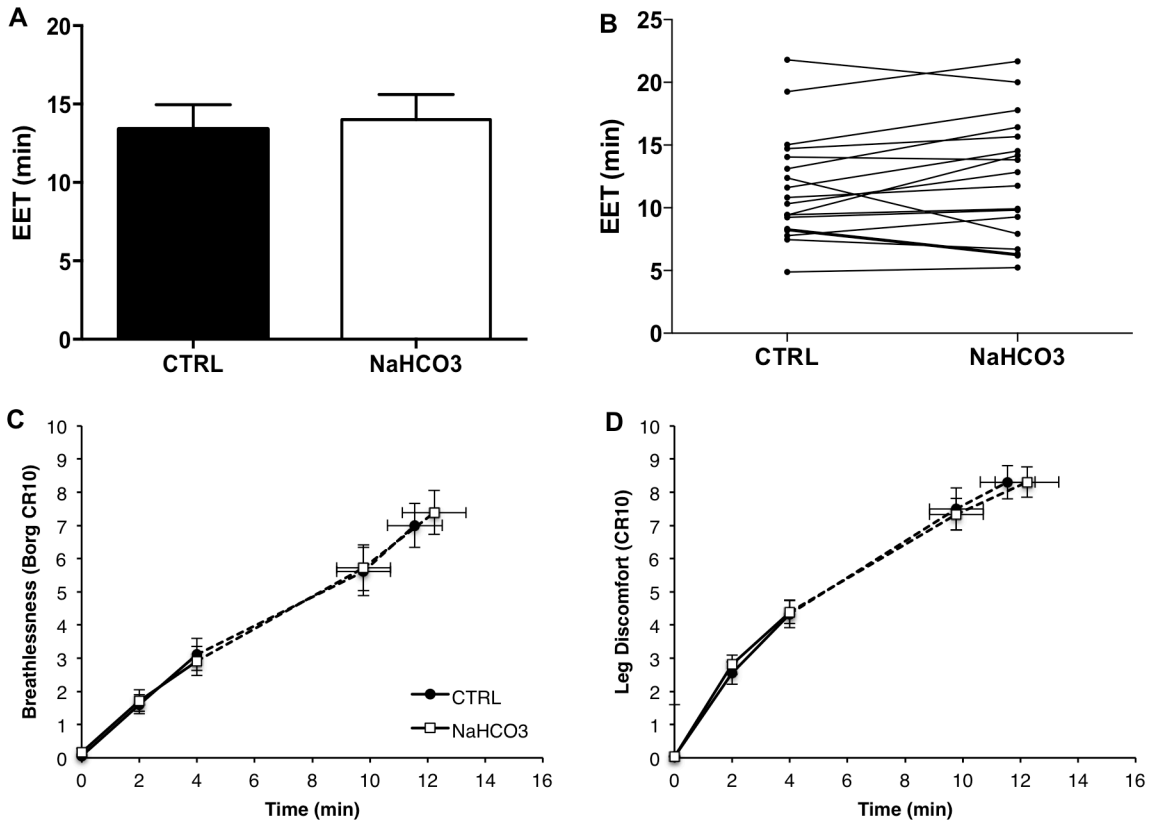

Figure 2.2. Effect of single-dose administration of sodium bicarbonate ($NaHCO_3$) compared with sodium chloride (CTRL) on exercise endurance time (EET) and Borg 0-10 category ratio scale intensity ratings of perceived breathlessness and leg discomfort during constant-load cycle exercise testing performed at 80% of peak incremental power output, equivalent to 176 ± 10 watts. A) Mean ± SE values after treatment with $NaHCO_3$ vs. CTRL. B) Individual subject responses in EET to treatment with $NaHCO_3$ vs. CTRL. C and D) Data points are mean ± SE values at rest, at standardized submaximal times of 2-min and 4-min, at isotime (9.78 ± 0.93 min), and at peak

2.4.d. Exercise ventilatory efficiency. Compared with NaCl, ingestion of $NaHCO_3$ decreased the $\dot{V}_E/\dot{V}CO_2$ ratio (Fig. 2.3A) and increased $P_{ET}CO_2$ (Fig. 2.3B) at rest and throughout exercise. The $\dot{V}_E/\dot{V}CO_2$ nadir was lower (by 2.34 ± 0.20 units, $p<0.0001$) after treatment with $NaHCO_3$ vs. NaCl (Figs. 2.3C-D). Mean values of $P_{ET}CO_2$, $\dot{V}_E$ and $\dot{V}CO_2$ corresponding to the $\dot{V}_E/\dot{V}CO_2$ nadir were higher (by 4.5 ± 0.3 mmHg, $p<0.0001$), lower (by 4.7 ± 1.8 L/min, $p=0.019$) and not significantly different in the $NaHCO_3$ vs. NaCl condition, respectively (Figs. 2.3E-J).

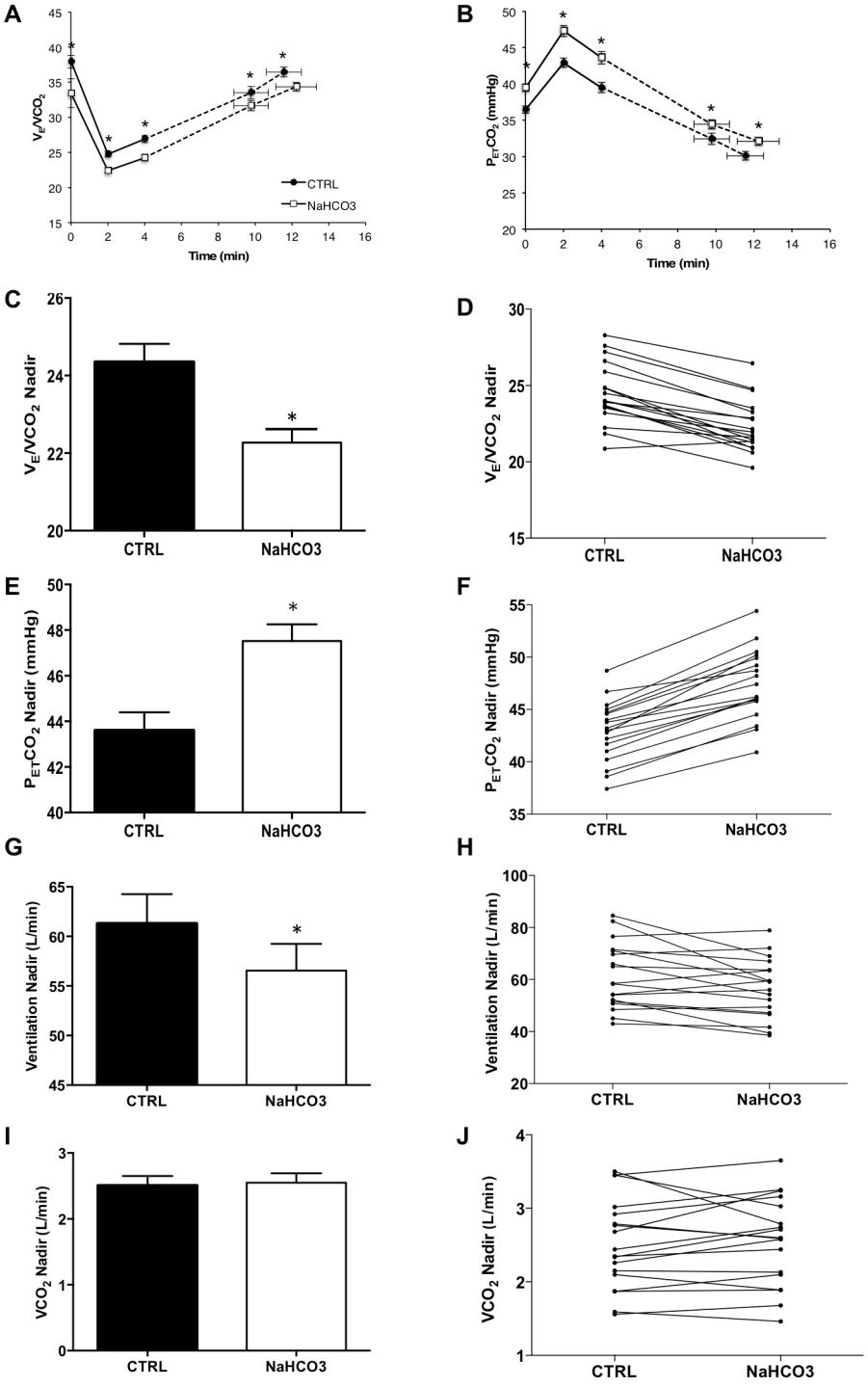

Figure 2.3. Effect of single-dose administration of sodium bicarbonate ($NaHCO_3$) compared with sodium chloride (CTRL) on the ventilatory equivalent for CO_2 (V_E/VCO_2), an index of exercise ventilatory efficiency, and related outcomes at rest and during constant-load cycle exercise testing at 80% of peak power output, equivalent to 176 ± 10 watts. A and B) Data points are mean ± SE values at rest, at standardized submaximal times of 2-min and 4-min, at isotime (9.78 ± 0.93 min), and at peak exercise. C, E, G and I) Mean ± SE values at the V_E/VCO_2 nadir after treatment with $NaHCO_3$ vs. CTRL. D, F, H and J) Individual subject responses at the V_E/VCO_2 nadir after treatment with $NaHCO_3$ vs. CTRL. $P_{ET}CO_2$ = end-tidal CO_2 partial pressure; VCO_2 = rate of CO_2 production. *$p<0.05$ vs. CTRL.

2.4.e. Cardiometabolic and ventilatory responses. With the exception of a 0.24 ± 0.06 L/min (p=0.002) increase in $\dot{V}CO_2$ during exercise at isotime after treatment with $NaHCO_3$ vs. NaCl, cardiometabolic responses to exercise were similar between treatments (Fig. 2.4). Compared with NaCl, ingestion of $NaHCO_3$ decreased $\dot{V}_E$ by 5.8 ± 1.9 L/min during exercise at 2-min, by 5.0 ± 2.4 L/min during exercise at 4-min, and by 4.5 ± 2.1 L/min at end-exercise (all p<0.05) (Fig. 2.5A). These differences in $\dot{V}_E$ were due to small but consistent decreases in V_T expansion (Fig. 2.5B) with no associated changes in breathing frequency (Fig. 2.5C) or the behavior of dynamic IC and IRV (Fig. 2.5D).

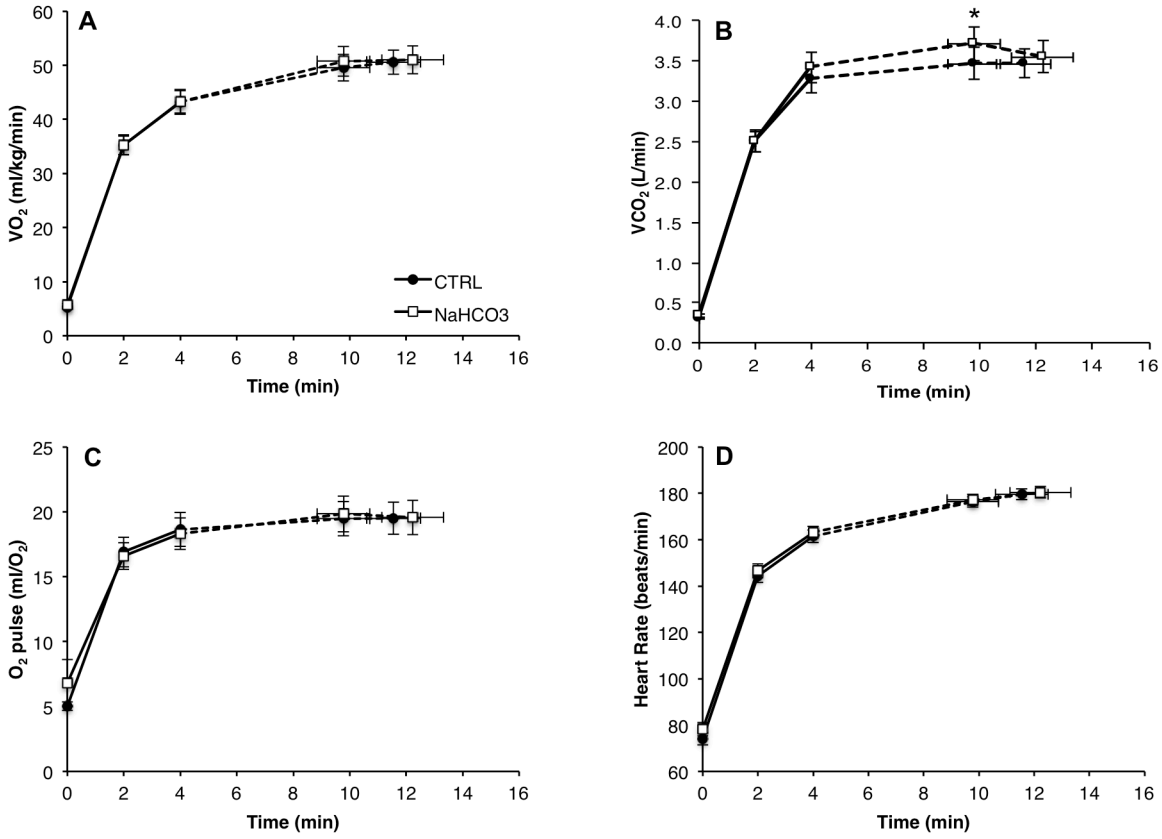

Figure 2.4. Effect of single-dose administration of sodium bicarbonate ($NaHCO_3$) compared with sodium chloride (CTRL) on cardiometabolic responses at rest and during constant-load cycle exercise testing at 80% of peak power output, equivalent to 176 ± 10 watts. Data points are mean ± SE values at rest, at standardized submaximal times of 2-min and 4-min, at isotime (9.78 ± 0.93 min), and at peak exercise. VO_2 and VCO_2 = rates of O_2 uptake and CO_2 production, respectively. *p<0.05 vs. CTRL.

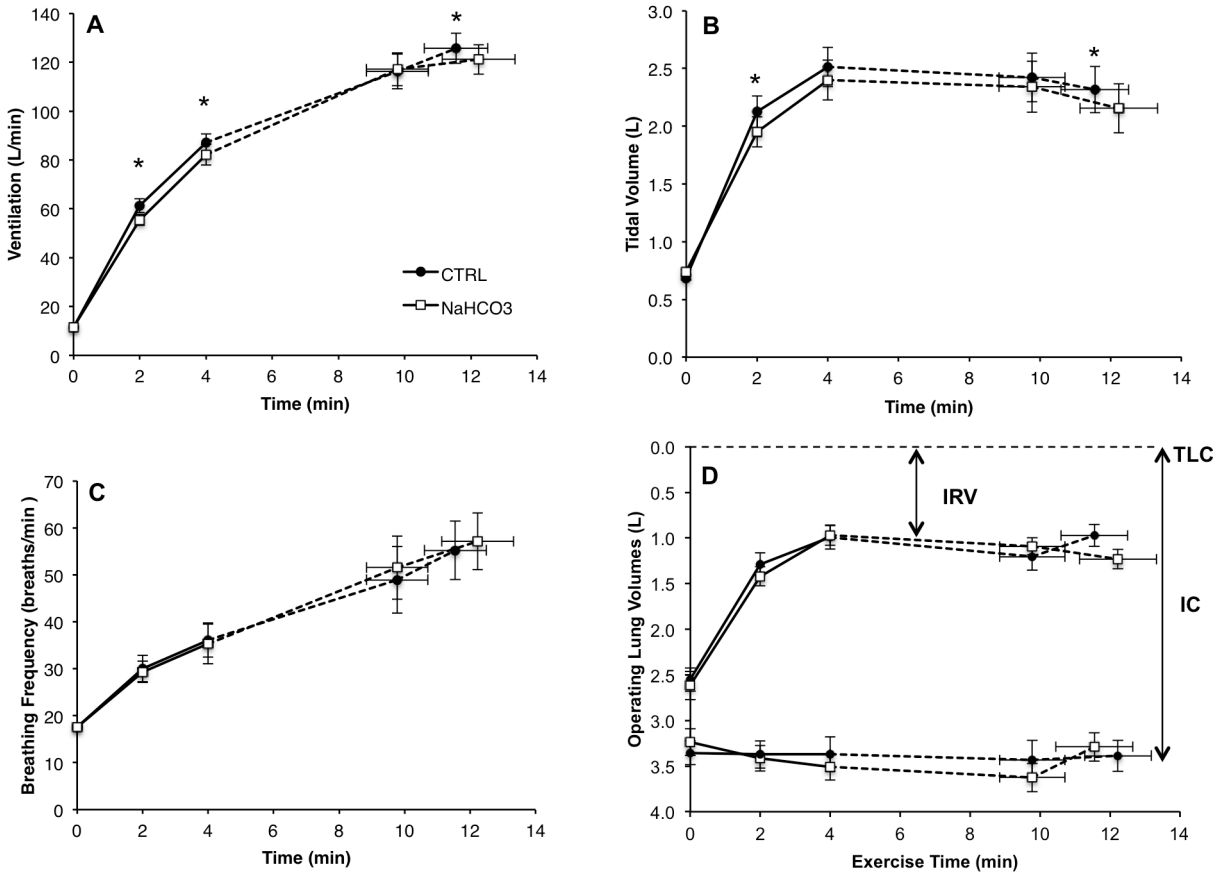

Figure 2.5. Effect of single-dose administration of sodium bicarbonate ($NaHCO_3$) compared with sodium chloride (CTRL) on ventilation, breathing pattern and dynamic operating lung volume response at rest and during constant-load cycle exercise testing at 80% of peak power output, equivalent to 176 ± 10 watts. Data points are mean ± SE values at rest, at standardized submaximal times of 2-min and 4-min, at isotime (9.78 ± 0.93 min), and at peak exercise. IRV = inspiratory reserve volume; TLC = total lung capacity; IC = inspiratory capacity. *p<0.05 vs. CTRL.

2.5. DISCUSSION

The primary finding of this randomized, double blind, placebo-controlled, crossover study is that increasing the $PaCO_2$ equilibrium point via induced acute metabolic alkalosis by ingestion of $NaHCO_3$ decreased the $\dot{V}_E$-$\dot{V}CO_2$ response to high-intensity constant-load cycle exercise testing in healthy adults.

The modified alveolar ventilation equation ($\dot{V}_E/\dot{V}CO_2 = 863/[PaCO_2 \times (1-V_D/V_T)]$) predicts that the $\dot{V}_E$ response to any given increment in $\dot{V}CO_2$ during exercise will decrease as V_D/V_T decreases and/or as the regulated level of $PaCO_2$ increases (Fig. 1.1).[62,63] To the best of our knowledge, there is no reason to believe that acutely increasing blood [HCO_3^-] via ingestion of $NaHCO_3$ vs. NaCl decreased V_D/V_T at rest or during exercise in our participants. It follows that increases in the $PaCO_2$ equilibrium point (by ~4.5 mmHg at rest and presumably also during exercise based on measured values of $P_{ET}CO_2$) were most likely responsible for the observed decrease in $\dot{V}_E$-$\dot{V}CO_2$ relationships at rest and during exercise after treatment with $NaHCO_3$ vs. NaCl. With the exception of measurements made during exercise at isotime, $NaHCO_3$-induced decreases in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise were accounted for by statistically significant decreases in $\dot{V}_E$; for example, the decrease in the $\dot{V}_E$-$\dot{V}CO_2$ nadir (by 9.4%) after ingestion of $NaHCO_3$ vs. NaCl reflected a 4.7 L/min (or 7%) decrease in $\dot{V}_E$ without a significant change in $\dot{V}CO_2$.

Relatively few studies have examined the effect of induced metabolic alkalosis on the ventilatory response to exercise in health and/or disease.[4,8,9,71,72] Jones et al.[4] studied the effect of induced acute metabolic alkalosis by ingestion of $NaHCO_3$ on the cardiorespiratory and metabolic responses of 5 healthy young men to constant-load

cycle exercise testing. In that study, single-dose administration of $NaHCO_3$ vs. $CaCO_3$ (both 0.3 g/kg) had no statistically significant effect on the $\dot{V}CO_2$ response to exercise, but was associated with a 4-5 mmHg increase in $PaCO_2$ and a 3.5-4.5 L/min decrease in $\dot{V}_E$ during exercise at 33 and 66% of PPO. However, the investigators did not report on whether these differences in $PaCO_2$ and $\dot{V}_E$ were statistically significant nor did they report on the effect of treatment with $NaHCO_3$ vs. $CaCO_3$ on $\dot{V}_E$-$\dot{V}CO_2$ relationships during exercise. A subsequent study from the same laboratory by Kowalchuk et al.[71] reported no change in $PaCO_2$, $\dot{V}_E$ and $\dot{V}CO_2$ responses at rest or during incremental cycle exercise testing to exhaustion in 5 healthy young men after single-dose administration of $NaHCO_3$ vs. $CaCO_3$ (both 0.3 g/kg). A study of 7 healthy young men by Oren et al.[9] found that chronic metabolic alkalosis induced by 3 consecutive days of treatment with $NaHCO_3$ (0.7 g/kg/day) vs. $CaCO_3$ (0.1 g/kg/day) increased $PaCO_2$ by ~3.5 mmHg at rest and decreased $\dot{V}_E$-$\dot{V}CO_2$ responses to both incremental and constant-load cycle exercise testing; however, none of these differences were statistically significant. Iwaoka et al.[8] observed that $\dot{V}_E$-$\dot{V}CO_2$ ratios were significantly lower during constant-load cycle exercise testing performed above but not below the respiratory compensation point following single-dose administration of $NaHCO_3$ vs. starch (both 0.2 g/kg) among 6 healthy young men. Moreover, Coppoolse et al.[72] found that induced acute metabolic alkalosis by ingestion of $NaHCO_3$ (0.3 g/kg) increased mean resting values of $PaCO_2$ by 2-7 mmHg, but did not alter the $\dot{V}_E$ response to symptom-limited incremental cycle exercise testing in 5 healthy young men or in 6 older adults (5 men) with severe COPD; however, no data were given on the effect of $NaHCO_3$ ingestion on $\dot{V}_E$-$\dot{V}CO_2$ relationships during exercise in either group.

The reasons for the discrepant results concerning the effects of $NaHCO_3$ administration on $\dot{V}_E$ and $\dot{V}_E$-$\dot{V}CO_2$ responses to exercise between the current and earlier studies are unclear, particularly in view of similarities in experimental study design (i.e., randomized, double blind, placebo controlled, cross over), study participants (i.e., healthy young adults, the majority of whom were male), exercise test modality (i.e., cycle ergometer) and dose of $NaHCO_3$ used (i.e., 0.3 g/kg). Notwithstanding these similarities, our sample size of 18 was 2-4 times larger than those of all earlier studies and thus less susceptible to a Type II statistical error. It is also possible that the lack of effect of induced metabolic alkalosis on $\dot{V}_E$ and $\dot{V}_E$-$\dot{V}CO_2$ responses to exercise in earlier studies[4,9] reflected their use of relatively lower exercise intensities. To this end, the metabolic hyperbola, which represents the curvilinear relationship between $\dot{V}_E$ and $PaCO_2$ at any given $\dot{V}CO_2$, is relatively flat at low levels of $\dot{V}CO_2$ and steepens with increasing $\dot{V}CO_2$ (Fig. 1.1).[63] Thus, an increase in the $PaCO_2$ equilibrium point on the order of magnitude reported in the current study and in earlier studies (i.e., 3-5 mmHg) after treatment with $NaHCO_3$ would have little effect on $\dot{V}_E$ during exercise at levels of $\dot{V}CO_2$ less than ~2.5 L/min. Indeed, neither Jones et al.[4] nor Oren et al.[9] were able to demonstrate a statistically significant effect of induced metabolic alkalosis by ingestion of $NaHCO_3$ on the $\dot{V}_E$ response to constant-load cycle exercise testing performed at mean levels of $\dot{V}CO_2$ ranging 1.13 to 2.42 L/min. In the current study, constant-load cycle exercise tests were performed at 80% of PPO, corresponding to mean levels of $\dot{V}CO_2$ ≥3 L/min (Fig. 2.4b). It follows that $NaHCO_3$-induced increases in the $PaCO_2$ equilibrium point by ~4.5 mmHg were associated with

statistically significant reductions of in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise, presumably reflecting enhanced exercise ventilatory efficiency.

Sue[19] has argued, on the basis of pulmonary gas exchange, that because $\dot{V}_E$ is the sum of alveolar ventilation ($\dot{V}_A$) and dead space ventilation ($\dot{V}_D$), true ventilatory inefficiency exists only if an abnormally high $\dot{V}_E$-$\dot{V}CO_2$ response to exercise results from increased $\dot{V}_D$. The corollary of this is that, in the current study, $NaHCO_3$-induced reductions in the $\dot{V}_E$-$\dot{V}CO_2$ response to exercise may not necessarily reflect enhanced exercise ventilatory efficiency since reductions in $\dot{V}_E$ (in the setting of a relatively unchanged $\dot{V}CO_2$) resulted from an increased $PaCO_2$ equilibrium point.

As reviewed in detail elsewhere,[59,73,74] the results obtained from numerous studies concerning the effects of $NaHCO_3$ on human exercise tolerance/performance have been conflicting and inconclusive. Under the experimental conditions of the current study, induced acute metabolic alkalosis by ingestion of $NaHCO_3$ had no meaningful effect on cardiometabolic, operating lung volume and perceptual responses to exercise and thus was not associated with improved EET.

2.5.a. Methodological considerations. Although there is some controversy in the literature about which method should be used to estimate exercise ventilatory efficiency, a comprehensive study of 474 healthy adults aged 17-78 years by Sun et al.[18] concluded that the $\dot{V}_E$-$\dot{V}CO_2$ nadir (our primary outcome) is the preferred noninvasive parameter estimate of exercise ventilatory efficiency, at least in healthy subjects.

Our participants were healthy, young, non-obese and non-smoking men and women with normal-to-above normal levels of cardiorespiratory fitness. It follows that the results of this study may not be generalizable to any one or combination of the

following: elderly men and women; obese men and women; physically inactive/deconditioned men and women; current or ex-smokers; and adults with chronic cardiovascular, metabolic, pulmonary and/or neuromuscular disease.

We examined the acute effect of induced metabolic alkalosis by ingestion of 0.3 g of $NaHCO_3$ per kilogram body mass on exercise physiological and perceptual responses. Thus, we cannot extrapolate our results to longer-term use of $NaHCO_3$ nor can we comment on the efficacy and/or tolerability of $NaHCO_3$ ingestion at doses >0.3 g/kg.

2.5.b. Clinical implications. It is relatively well established that any therapeutic intervention capable of decreasing exercise ventilatory requirements (e.g., exercise training, supplemental oxygen) has the potential to improve exercise endurance and decrease intensity ratings of physical activity-related breathlessness in patients with chronic cardiopulmonary disease. Although $NaHCO_3$-induced reductions in exercise $\dot{V}_E$ and $\dot{V}_E$-$\dot{V}CO_2$ responses were not associated with improved EET and/or relief of exertional breathlessness in our group of healthy young adults, the results of the current study nevertheless provide a physiological rationale to examine the potential benefits of induced acute metabolic alkalosis by $NaHCO_3$ administration on exercise ventilatory efficiency and related clinical- and patient-reported outcomes (i.e., EET, breathlessness) in selected patients with HF, PAH, COPD and IPF. A particularly interesting question is whether acute administration of $NaHCO_3$ prior to each bout of exercise performed in the context of a rehabilitative training program can enable such

patients to train at higher exercise intensities and thus derive greater physiological benefits/adaptations.

2.5.c. Conclusion. The results of our study provide new evidence to support the hypothesis that increasing the $PaCO_2$ equilibrium point via induced acute metabolic alkalosis with $NaHCO_3$ can enhance exercise ventilatory efficiency, at least in healthy young adults.

REFERENCES

1. Wensel R, Georgiadou P, Francis DP, et al. Differential contribution of dead space ventilation and low arterial pCO2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *The American journal of cardiology.* 2004;93(3):318-323.
2. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *American heart journal.* 2004;147(2):354-360.
3. Neder JA, Arbex FF, Alencar MC, et al. Exercise ventilatory inefficiency in mild to end-stage COPD. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology.* 2015;45(2):377-387.
4. Jones NL, Sutton JR, Taylor R, Toews CJ. Effect of pH on cardiorespiratory and metabolic responses to exercise. *J Appl Physiol Respir Environ Exerc Physiol.* 1977;43(6):959-964.
5. Wasserman K. Testing regulation of ventilation with exercise. *CHEST Journal.* 1976;70(1_Supplement):173-178.
6. Kisaka T, Cox TA, Dumitrescu D, Wasserman K. CO 2 pulse and acid-base status during increasing work rate exercise in health and disease. *Respiratory physiology & neurobiology.* 2015;218:46-56.
7. Arena R, Myers J, Abella J, et al. Defining the optimal prognostic window for cardiopulmonary exercise testing in patients with heart failure. *Circulation: Heart Failure.* 2010:CIRCHEARTFAILURE. 109.906446.
8. Iwaoka K, Okagawa S, Mutoh Y, Miyashita M. Effects of bicarbonate ingestion on the respiratory compensation threshold and maximal exercise performance. *Jpn J Physiol.* 1989;39(2):255-265.
9. Oren A, Wasserman K, Davis JA, Whipp BJ. Effect of CO2 set point on ventilatory response to exercise. *Journal of applied physiology: respiratory, environmental and exercise physiology.* 1981;51(1):185-189.
10. Forster HV, Haouzi P, Dempsey JA. Control of breathing during exercise. *Comprehensive Physiology.* 2012.
11. Dempsey JA, Adams L, Ainsworth DM, et al. Airway, lung, and respiratory muscle function during exercise. *Comprehensive Physiology.* 1996.
12. Tipton CM, American College of Sports M. *ACSM's advanced exercise physiology.* Vol 143: Lippincott Williams & Wilkins; 2006.
13. Sheel AW, Romer, L.M. Ventilation and Respiratory Mechanics. *Comprehensive Physiology.* 2012;2:1093-1142.
14. Petersson J, Glenny RW. Gas exchange and ventilation–perfusion relationships in the lung. *European Respiratory Journal.* 2014;44(4):1023-1041.
15. Wasserman K, Zhang YY, Riley MS. Ventilation during exercise in chronic heart failure. *Basic research in cardiology.* 1996;91(1):1-11.
16. Enghoff H. Volumen inefficax. *Bemerkungen zur Frage des schädlichen Raumes. Uppsala Läkareforen Forhandl.* 1938;44:191-218.
17. Siobal MS, Ong H, Valdes J, Tang J. Calculation of physiologic dead space: comparison of ventilator volumetric capnography to measurements by metabolic analyzer and volumetric CO2 monitor. *Respiratory care.* 2013;58(7):1143-1151.

18. Sun X-G, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *American journal of respiratory and critical care medicine.* 2002;166(11):1443-1448.
19. Sue DY. Excess ventilation during exercise and prognosis in chronic heart failure. *American journal of respiratory and critical care medicine.* 2011;183(10):1302-1310.
20. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *American journal of respiratory and critical care medicine.* 2003;167(2):211-277.
21. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology.* 2016;47(2):429-460.
22. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation.* 2010;122(2):191-225.
23. Poulin MJ, Cunningham DA, Paterson DH, Rechnitzer PA, Ecclestone NA, Koval JJ. Ventilatory response to exercise in men and women 55 to 86 years of age. *American journal of respiratory and critical care medicine.* 1994;149(2 Pt 1):408-415.
24. Habedank D, Reindl I, Vietzke G, et al. Ventilatory efficiency and exercise tolerance in 101 healthy volunteers. *European journal of applied physiology and occupational physiology.* 1998;77(5):421-426.
25. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart failure reviews.* 2008;13(2):245-269.
26. Arena R, Humphrey R. Comparison of ventilatory expired gas parameters used to predict hospitalization in patients with heart failure. *American heart journal.* 2002;143(3):427-432.
27. Wasserman K, Zhang Y-Y, Gitt A, et al. Lung function and exercise gas exchange in chronic heart failure. *Circulation.* 1997;96(7):2221-2227.
28. Ingle L, Goode K, Carroll S, et al. Prognostic value of the V E/V CO2 slope calculated from different time intervals in patients with suspected heart failure. *International journal of cardiology.* 2007;118(3):350-355.
29. Shen Y, Zhang X, Ma W, et al. VE/VCO2 slope and its prognostic value in patients with chronic heart failure. *Experimental and therapeutic medicine.* 2015;9(4):1407-1412.
30. Panagiotou M, Kastanakis E, Vogiatzis I. Exercise Limitation in COPD. *www. pneumon. org.* 2013;1(3):245.
31. Neder JA, Alharbi A, Berton DC, et al. Exercise Ventilatory Inefficiency Adds to Lung Function in Predicting Mortality in COPD. *Copd.* 2016:1-9.
32. Neder JA, Arbex FF, Alencar MCN, et al. Exercise ventilatory inefficiency in mild to end-stage COPD. *European Respiratory Journal.* 2015;45(2):377-387.
33. Oudiz RJ, Roveran G, Hansen JE, Sun XG, Wasserman K. Effect of sildenafil on ventilatory efficiency and exercise tolerance in pulmonary hypertension. *European journal of heart failure.* 2007;9(9):917-921.

34. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104(4):429-435.
35. Schwaiblmair M, Faul C, von Scheidt W, Berghaus TM. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC pulmonary medicine.* 2012;12(1):1.
36. Vainshelboim B, Oliveira J, Fox BD, Kramer MR. The Prognostic Role of Ventilatory Inefficiency and Exercise Capacity in Idiopathic Pulmonary Fibrosis. *Respiratory care.* 2016.
37. Triantafillidou C, Manali E, Lyberopoulos P, et al. The Role of Cardiopulmonary Exercise Test in IPF Prognosis. *Pulmonary medicine.* 2013;2013:514817.
38. Thirapatarapong W, Armstrong HF, Thomashow BM, Bartels MN. Differences in gas exchange between severities of chronic obstructive pulmonary disease. *Respiratory physiology & neurobiology.* 2013;186(1):81-86.
39. Poggio R, Arazi HC, Giorgi M, Miriuka SG. Prediction of severe cardiovascular events by VE/VCO 2 slope versus peak VO 2 in systolic heart failure: a meta-analysis of the published literature. *American heart journal.* 2010;160(6):1004-1014.
40. Sajkov D, Petrovsky N, Palange P. Management of dyspnea in advanced pulmonary arterial hypertension. *Current opinion in supportive and palliative care.* 2010;4(2):76-84.
41. Elbehairy AF, Ciavaglia CE, Webb KA, et al. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. *American journal of respiratory and critical care medicine.* 2015;191(12):1384-1394.
42. Arena R, Myers J, Abella J, et al. The ventilatory classification system effectively predicts hospitalization in patients with heart failure. *Journal of cardiopulmonary rehabilitation and prevention.* 2008;28(3):195-198.
43. Tabet J-Y, Beauvais F, Thabut G, Tartière J-M, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation.* 2003;10(4):267-272.
44. Myers J, Arena R, Oliveira RB, et al. The lowest VE/VCO 2 ratio during exercise as a predictor of outcomes in patients with heart failure. *Journal of cardiac failure.* 2009;15(9):756-762.
45. Barr RG. The epidemiology of vascular dysfunction relating to chronic obstructive pulmonary disease and emphysema. *Proceedings of the American Thoracic Society.* 2011;8(6):522-527.
46. Lewis NP, Banning AP, Cooper JP, et al. Impaired matching of perfusion and ventilation in heart failure detected by133xenon. *Basic research in cardiology.* 1996;91(1):45-49.
47. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. *Journal of the American College of Cardiology.* 2003;41(6):1028-1035.
48. Yasunobu Y, Oudiz RJ, Sun X-G, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *CHEST Journal.* 2005;127(5):1637-1646.

49. Geddes D, Davies M, Koyama H, et al. Effect of lung-volume–reduction surgery in patients with severe emphysema. *New England Journal of Medicine.* 2000;343(4):239-245.
50. Stirling GR, Babidge WJ, Peacock MJ, et al. Lung volume reduction surgery in emphysema: a systematic review. *The Annals of thoracic surgery.* 2001;72(2):641-648.
51. Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine.* 1999;160(6):2018-2027.
52. Armstrong HF, Dussault NE, Thirapatarapong W, Lemieux RS, Thomashow BM, Bartels MN. Ventilatory efficiency before and after lung volume reduction surgery. *Respiratory care.* 2015;60(1):63-71.
53. Kim KH, Kim HK, Hwang IC, et al. PDE 5 inhibition with udenafil improves left ventricular systolic/diastolic functions and exercise capacity in patients with chronic heart failure with reduced ejection fraction; A 12-week, randomized, double-blind, placebo-controlled trial. *Am Heart J.* 2015;169(6):813-822 e813.
54. Duffin J. Role of acid-base balance in the chemoreflex control of breathing. *Journal of applied physiology.* 2005;99(6):2255-2265.
55. Oren A, Whipp BJ, Wasserman K. Effects of chronic acid-base changes on the rebreathing hypercapnic ventilatory response in man. *Respiration; international review of thoracic diseases.* 1991;58(3-4):181-185.
56. McNaughton LR, Siegler J, Midgley A. Ergogenic effects of sodium bicarbonate. *Current sports medicine reports.* 2008;7(4):230-236.
57. Peart DJ, Siegler JC, Vince RV. Practical recommendations for coaches and athletes: a meta-analysis of sodium bicarbonate use for athletic performance. *The Journal of Strength & Conditioning Research.* 2012;26(7):1975-1983.
58. Schubert MM, Astorino TA. A systematic review of the efficacy of ergogenic aids for improving running performance. *The Journal of Strength & Conditioning Research.* 2013;27(6):1699-1707.
59. Carr AJ, Hopkins WG, Gore CJ. Effects of acute alkalosis and acidosis on performance: a meta-analysis. *Sports Med.* 2011;41(10):801-814.
60. Coppoolse R, Barstow TJ, Stringer WW, Carithers E, Casaburi R. Effect of acute bicarbonate administration on exercise responses of COPD patients. *Medicine and science in sports and exercise.* 1997;29(6):725-732.
61. Oren A, Wasserman K, Davis JA, Whipp BJ. Effect of CO 2 set point on ventilatory response to exercise. *Journal of applied physiology: respiratory, environmental and exercise physiology.* 1981;51:185-189.
62. Whipp BJ, Ward SA, Wasserman K. Ventilatory responses to exercise and their control in man. *The American review of respiratory disease.* 1984;129(2 Pt 2):S17-20.
63. Wasserman K. Testing regulation of ventilation with exercise. *Chest.* 1976;70(1 Suppl):173-178.
64. Schwaiblmair M, Faul C, von Scheidt W, Berghaus TM. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC pulmonary medicine.* 2012;12:23.

65. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *American journal of respiratory and critical care medicine.* 1999;159(1):179-187.
66. Egger F, Meyer T, Such U, Hecksteden A. Effects of Sodium Bicarbonate on High-Intensity Endurance Performance in Cyclists: A Double-Blind, Randomized Cross-Over Trial. *PloS one.* 2014;9(12):e114729.
67. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology.* 2005;26(2):319-338.
68. Stubbing DG, Pengelly LD, Morse JL, Jones NL. Pulmonary mechanics during exercise in normal males. *J Appl Physiol.* 1980;49(3):506-510.
69. Borg GA. Psychophysical bases of perceived exertion. *Medicine and science in sports and exercise.* 1982;14(5):377-381.
70. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *The American review of respiratory disease.* 1985;131(5):700-708.
71. Kowalchuk JM, Heigenhauser GJ, Jones NL. Effect of pH on metabolic and cardiorespiratory responses during progressive exercise. *Journal of applied physiology: respiratory, environmental and exercise physiology.* 1984;57(5):1558-1563.
72. Coppoolse R, Barstow TJ, Stringer WW, Carithers E, Casaburi R. Effect of acute bicarbonate administration on exercise responses of COPD patients. *Medicine and science in sports and exercise.* 1997;29(6):725-732.
73. Requena B, Zabala M, Padial P, Feriche B. Sodium bicarbonate and sodium citrate: ergogenic aids? *Journal of strength and conditioning research / National Strength & Conditioning Association.* 2005;19(1):213-224.
74. Peart DJ, Siegler JC, Vince RV. Practical recommendations for coaches and athletes: a meta-analysis of sodium bicarbonate use for athletic performance. *Journal of strength and conditioning research / National Strength & Conditioning Association.* 2012;26(7):1975-1983.