

**Sodium Bicarbonate as an ergogenic aid in Acute
Moderate Hypoxic conditions: The Effect on Severe
Intensity Exercise**

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Abstract

Sodium bicarbonate (NaHCO_3) is a pre-exercise alkalotic buffering agent that is ingested to alleviate accumulation of hydrogen anions during exercise. As such, this supplement has been extensively used in scientific literature to assess NaHCO_3 ergogenic properties during high intensity exercise. These ergogenic properties are likely to be apparent when exercise perturbs the acid-base balance with excessive H^+ accumulation; therefore, the lowest intensity at which NaHCO_3 may exert an ergogenic effect is during exercise performed within the severe intensity domain. The physiological characteristics of severe intensity exercise include exacerbated rise in [bla], and therefore acid-base perturbations, until the termination of exercise. The environmental conditions can also have an additive physiological stress to exercise; indeed, acute hypoxia increases the relative energy contribution of anaerobic glycolysis. The resultant effect is an exacerbated rise in H^+ during exercise, which may, at least in part, contribute to the ergolytic effect of acute hypoxia on exercise performance and capacity. As such, severe intensity exercise performed in acute hypoxic conditions may benefit from NaHCO_3 ingestion to alleviate acidic stress and mitigate for the ergolytic effect of acute hypoxia. The purpose of this thesis was to evaluate the effect of NaHCO_3 on severe intensity exercise performed in acute hypoxic conditions. Furthermore, this effect was evaluated through the parameter of the power-duration relationship (i.e. CP and W') during all-out, intermittent and constant load exercise to exhaustion. Together, this series of investigations are the first to demonstrate that NaHCO_3 may be an effective ergogenic aid in acute moderate hypoxic conditions. In particular, this effect was observed during exercise in the severe intensity domain, with NaHCO_3 enhancing the capacity of W' during all-out and constant load exercise; along with increasing volume of work that can be performed at this intensity during intermittent exercise. Indeed, Chapter six demonstrated that NaHCO_3 may accelerate the rate of W' recovery during intermittent exercise when applied to the W'_{bal} model. Interestingly, this thesis is the first to identify the presence of an intensity dependant effect, with the magnitude of NaHCO_3 ergogenicity diminishing as exercise intensity rises from the severe intensity domain to supra-maximal intensities. Further research should consider testing these hypotheses in alternative ambient conditions to determine the efficacy of NaHCO_3 (e.g. in normoxic conditions or in combined extreme environmental conditions).

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List of abbreviations

31p magnetic resonance spectroscopy (^{31}P MRS)
Acid dissociation constant (pKa)
Adenosine-triphosphate (ATP)
Ammonium chloride (NH_4Cl)
Analysis of variance (ANOVA)
Arterial oxygen saturation (PaO_2)
Bicarbonate anions (HCO_3^-)
Blood lactate concentrations [bla]
Capacity test 110% ($\text{CCT}_{110\%}$)
Carbonic acid (H_2CO_3)
Cardiac output (q)
 CO_2 partial pressure (PCO_2)
Confidence intervals (CI)
Critical power (CP)
Deoxyhemoglobin breakpoint ($[\text{HHb}]_{\text{bp}}$)
Differences between CP and power output (D_{CP})
End power output (EP)
End power output w prime (W'_{ep})
End tidal CO_2 (PETCO_2)
Fructose-6-phosphate (F-6-P)
Fractional inspired oxygen (FiO_2)
Grades of recommendation, assessment, development and evaluation working group (GRADE)
Hedge's g (g)
Hydrogen cation concentration ($[\text{H}^+]$)
Hydrogen cations (H^+)
Hypobaric hypoxia (HH)
Hypoxic inducible factor-1 (HIF1)
Individual anaerobic threshold (IAT)
Intermittent hypoxic training (IHT)
Kilo joules (kJ)
Kilograms (Kg)
Lactate anion (La^-)
Lactate threshold 1 (LT1)
Lactate threshold 2 (LT2)
Maximal rate of pulmonary oxygen consumption ($\dot{V}\text{O}_{2\text{max}}$)
Monocarboxylic transporters (MCT)
Normobaric hypoxia (NH)
Omnibus moderator test statistic ($Q_{\text{m,df}}$)
Oxyhaemoglobin saturation (SaO_2)
Peak heart rate (HR_{peak})
Peak power output (PPO)
Peak power output (W_{peak})
Phosphate ion concentrations ($[\text{Pi}]$)
Phosphocreatine concentrations (Pcr)
Phosphofructokinase (PKF)
Potassium cation (K^+)
Potential renal acidic load (PRAL)

Preferred reporting items for systematic reviews and meta-analyses (PRISMA)
Pyruvate dehydrogenase (PDH)
Rate of perceived exertion (RPE)
Rate of pulmonary oxygen consumption ($\dot{V}O_2$)
Ratio of means (ROM)
Repeated sprint exercise (RSE)
residual heterogeneity test statistic ($Q_{e_{df}}$)
Secondary lactate (LT2)
Sodium (Na^+)
Sodium bicarbonate ($NaHCO_3$)
Sodium chloride (NaCL)
Standard deviations (SD)
Standard error of estimate (SEE)
Strong ion difference (SID)
Time constant of W' reconstitution ($\tau_{W'}$)
Time to exhaustion (TTE)
Time trials (TT)
Total work done (TWD)
Ventilatory threshold 1 (VT1)
Ventilatory threshold 2 (VT2)
W prime (W')
Work balance (W'_{bal})

Chapter 1: Introduction and Review of Literature

1.0. Introduction

The study of exercise physiology has long concerned itself with the aetiology of fatigue, due to its importance in health, disease and athletic performance. Furthering our understanding of fatigue has the potential to allow for the development of therapeutic and ergogenic interventions to enhance health/disease and/ or athletic performance. Exercise induced fatigue refers to the acute attenuation of exercise performance, that includes the progressive increase in perceived exertions to exercise when performed at a constant intensity, which ultimately leads to the inability to produce the desired intensity to complete the task (Ament and Verkerke, 2009). This definition not only highlights the progressive development of fatigue during exercise but also that it is not simply a physiological phenomenon, as it encompasses an integrated process of psychology and physiology. Indeed, the development of fatigue is often considered to be binary, with a central and peripheral fatigue system acting as an integrative system (Ament and Verkerke, 2009). Central fatigue refers to the diminished neural activation of active skeletal muscles through the central nervous system; while peripheral fatigue represents the bioenergetic and ionic perturbations at or distal to the neuromuscular junction that may impair muscle contractile function in response to a neural input (Gandevia, 2001).

The central and peripheral mechanisms of fatigue refer to constructs that embody physiological mechanisms of fatigue that are activated by the disturbance of internal environment caused during exercise (Allen, Lamb and Westerblad, 2008, Fitts, 2008, Ament and Verkerke, 2009). These systems are often discussed in isolation, although theoretical constructs suggest they are entwined through neural feedforward and feedback networks (Hureau, Romer and Amann, 2018). Indeed, central fatigue is considered to be a response to the stimulation of group III and IV muscle afferents, which is caused by metabolic/ionic disturbances in the active skeletal muscle (Gandevia et al., 1990) This is suggested to act as a protective mechanism to prevent the attainment of a 'critical threshold' of metabolic and ionic disturbance and therefore, limiting peripheral fatigue (Hureau, Romer and Amann, 2018). It has been argued however, that current thinking ignores the importance of psychology in the aetiology of exercise induced fatigue (St Clair Gibson, Swart and Tucker, 2018); as an individual's previous experiences may also dictate a limit at which exercise intensity will not be exceeded. Together, this highlights the integrative nature of fatigue, although the relative balance between central and peripheral fatigue contributions is dependent on a series of contextual factors, such as exercise intensity

(Thomas, Goodall, et al., 2015, Black et al., 2017) and environmental stressors (Ament and Verkerke, 2009).

The relative contributions of central and peripheral fatigue are predominantly regulated by the intensity and duration of exercise (Thomas, Goodall, et al., 2015, Black et al., 2017). This is notable when categorising a cluster of exercise intensities into discrete domains that represent the moderate, heavy and severe intensity domains (Jones et al., 2010, Black et al., 2017). Each intensity domain characterises distinct physiological behaviour during exercise; for example, the onset of the severe intensity domain represents the greatest intensity at which a steady state in blood lactate concentrations [bla] and the rate of pulmonary oxygen consumption ($\dot{V}O_2$) can be attained (Poole et al., 1988, Black et al., 2017). Above this intensity, it has been proposed the severe intensity domain defines the point whereby skeletal muscle exercise efficacy deteriorates (Grassi et al. 2015); which is embodied by a substantial increase in the oxygen and energetic cost of exercise. This physiological behaviour can be viewed through a progressively increasing ‘excess’ $\dot{V}O_2$ during exercise at a fixed intensity; a phenomenon that is termed the $\dot{V}O_2$ slow component (Jones et al., 2011). Concurrently, a continuing fall in intramuscular phosphocreatine concentrations (PCr) and pH is evident; which continues until exercise is no longer tolerable (Hogan, Richardson and Haseler, 1999, Jones et al., 2008). Given, $\dot{V}O_2$, intramuscular pH and PCr present indirect biomarkers of an elevated oxidative, glycolytic and adenosine-triphosphate (ATP)/PCr metabolic pathways, respectively; constant load exercise in the severe intensity domain is associated with an uncompensated rise in the energy cost of exercise. The relevance of this is that a reduction in exercise efficiency is associated with a decreased exercise tolerance (Zoladz, Rademaker and Sargeant, 1995), which can also be portrayed by the power-duration relationship of high intensity exercise.

The power-duration relationship has been used to describe and understand the physiological behaviour of exercise tolerance and fatigue in the severe intensity domain (Jones et al., 2010, Vanhatalo, Jones and Burnley, 2011, Poole et al., 2016). This model depicts the hyperbolic relationship between power output (or locomotor speed) and the duration of exercise prior to exhaustion (Figure 1.1); and can be applied to constant load (Poole et al., 1988), all-out (Vanhatalo, Doust and Burnley, 2007a), self-paced (Chidnok, Dimenna, et al., 2013) and intermittent exercise (Chidnok et al., 2012, Skiba et al., 2012). Traditionally, this model has two parameters that are known as critical power (CP) and W' prime (W'). The CP threshold is suggested to identify with the secondary lactate (LT2) and ventilatory (VT2) thresholds of

exercise intensity, which are all suggested to occur at the onset of the severe intensity exercise domain (Figure 1.1; Jones et al., 2010). Whereas the work above CP results in the utilisation of W' , as it represents a fixed amount of work that can be performed in the severe intensity domain. The CP is thought to represent an exercise intensity that is predominantly oxidative (Dekerle, Mucci and Carter, 2012a, Simpson et al., 2015); while the mechanistic constructs of W' remain allusive, it has been attributed to both peripheral and central parameters of fatigue (Burnley, Vanhatalo and Jones, 2012, Poole et al., 2016). As such, the power-duration relationship can provide a framework to investigate the physiology of exercise induced fatigue, along with providing a quantitative method to assess the effect of ergogenic or ergolytic interventions on exercise tolerance in the severe intensity domain (Whipp and Ward, 2009).

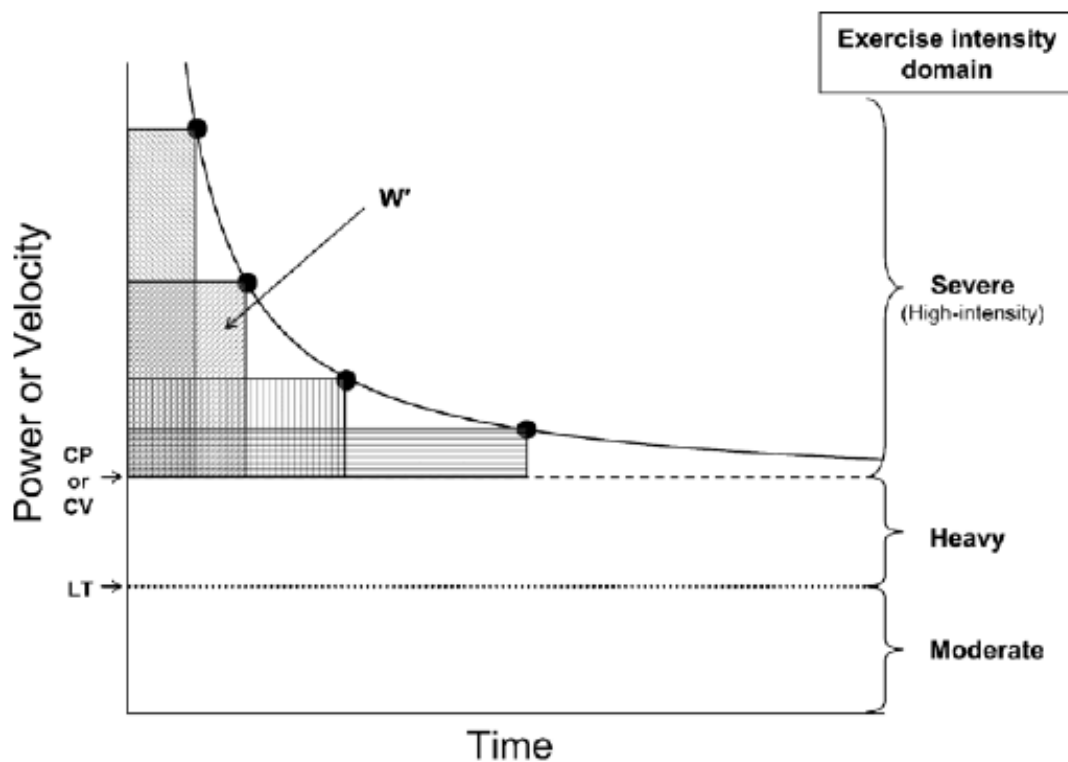


Figure 1.1. A graphical representation of the relationship between power/velocity and the duration that constant load exercise can be maintained prior to exhaustion, in accordance with the power-duration relationship. The shaded boxes above CP represent the fixed amount of work, denoted by the W' parameter, that can be undertaken in the severe intensity domain. Across the right-hand column, the location of exercise intensity domains in relation to the intensity thresholds of CP (heavy to severe intensity boundary) and the 1st lactate threshold (moderate to heavy intensity boundary) are presented. Adapted from Poole et al. (2016).

The power-duration relationship's sensitivity to exogenous interventions can be demonstrated through acute exposure to hypoxic conditions, which elicits a dose dependent ergolytic effect on CP (Dekerle, Mucci and Carter, 2012a, Simpson et al., 2015). Indeed, this response supports

the negative dose response observed between the magnitude of acute hypoxic exposure and the extent to which exercise performance and tolerance is impaired; with cycling time trials (TT) exhibiting a 7% decline in mean power output per 1000 m elevation (Clark et al., 2007) and time to exhaustion (TTE) tests reporting a decline by 9.4% in the first 500 m with a greater 14.3% per 1000 m thereafter (Wehrlin and Hallén, 2006). This impairment stems from a reduction in the availability of inspired oxygen, which subsequently has a deleterious effect on oxidative metabolism and enhances the relative contribution of anaerobic glycolysis (Horscroft and Murray, 2014, Scott, Goods and Slattery, 2016). The net effect, is an exacerbated accumulation in intramuscular glycolytic by-products, in lactate and hydrogen cations (H^+), compared to exercise undertaken at the same absolute intensity at sea level (Hogan, Richardson and Haseler, 1999, Romer et al., 2007). While fatigue remains an integrative phenomena of central and peripheral mechanisms under acute hypoxia (Amann et al., 2007, Romer et al., 2007, Billaut et al., 2013, Goodall et al., 2014), the elevated exercise-induced acidosis is likely to contribute, at least in part, to the diminished exercise performance and capacity (Amann et al., 2007).

Numerous nutritional interventions have been utilised to mitigate for the additive physiological stress elicited by acute hypoxia during exercise, which includes dietary nitrates (Shannon et al., 2017), carbohydrate ingestion (Fulco et al., 2005, O'Hara et al., 2017) and sodium bicarbonate ($NaHCO_3$) (Flinn et al., 2014, Saunders et al., 2014a). The latter of these interventions, $NaHCO_3$, has specific relevance as it acts as an alkalotic buffer that alleviates the heightened acidic stress associated with exercising in acute hypoxia. Previous work has predominantly investigated the ergogenic effect of $NaHCO_3$ in normoxic conditions and reported equivocal outcomes (McNaughton, Siegler and Midgley, 2008, Carr, Hopkins and Gore, 2011). There has however, been limited research attention on the effect of $NaHCO_3$ in acute hypoxic conditions and therefore, this will form the foundation of this literature review and the overall thesis. Furthermore, there is a paucity of research that has investigated the effect of $NaHCO_3$ within the severe intensity domain. Given this domain represents the lowest intensity at which intramuscular acidosis develops during exercise, it can be postulated as being the lowest intensity whereby acidosis may contribute to the fatiguing process. As such, this thesis will explore the ergogenic potential of $NaHCO_3$ during severe intensity exercise performed in acute hypoxic conditions. More specifically, this chapter will discuss and evaluate four distinct topic areas to provide a balanced scientific context to inform the subsequent experimental chapters. These sections include: 1) exercise intensity thresholds with a focus on

the power duration relationship; 2), the physiology of the acid-base balance at sea level and acute hypoxia; 3) the effect of acute hypoxia on exercise performance and capacity; and 4) the ergogenic effect of sodium bicarbonate at sea level and acute hypoxic conditions.

2.0 Review of Literature

2.1. Exercise Intensity Thresholds

The cardiopulmonary and metabolic response to a given exercise intensity can be clustered into three distinct domains that are referred to as moderate, heavy and severe intensity domains (Whipp, Ward and Rossiter, 2005; Burnley and Jones, 2007). These intensity domains have important implications for exercise physiologists in prescribing, testing and interpreting exercise response. Most notably these exercise intensity domains allow for the inter and intra individual normalisation of physiological stressors to exercise, thereby eliciting equivalent metabolic and cardiopulmonary kinetics, and a similar duration of exercise tolerance between each exercise bout (Lansley et al., 2011). The distinct response within exercise domains is evident through the observation of lactate/ H^+ and pulmonary $\dot{V}O_2$ kinetics. In addition to the presence of important physiological events that can be characterised through lactate and ventilatory response to exercise, which can be used to demarcate boundary between adjacent intensity domains.

Commonly used intensity thresholds in exercise physiology are represented by features of blood lactate and pulmonary $\dot{V}O_2$ kinetics; primary due to the ease of measurement and relatively simple interpretation. However, intensity thresholds also encompass the mathematical model of critical power and the deoxyhemoglobin breakpoint ([HHb]BP) (Keir et al., 2015). Through observing temporal lactate kinetics during incremental exercise tests, two distinct physiological events can be identified, which are known as the lactate threshold 1 (LT1) and the LT2. This lactate curve exhibits an exponential form, with the intensity at which the first sustained rise in [bla] occurs known as the LT1; whilst the intensity whereby an equilibrium between [bla] production and clearance cannot be maintained is known as LT2 (Billat et al., 2003). Therefore, above LT2, an inexorable rise in [bla] occurs to nadir until exercise is terminated. It is important to highlight however, that while the presence of two lactate thresholds are accepted, there remains a myriad of nonculture and methods to determine these thresholds. It is beyond the scope of this review to discuss all these available methods, and readers are guided to alternative sources for further information (Faude et al., 2009);

however, it is important to consider that the method used to determine lactate thresholds may affect the intensity at which exercise intensity thresholds are identified.

The corresponding pulmonary $\dot{V}O_2$ thresholds are known as the ventilatory threshold 1 (VT1) and the VT2. Similar to the lactate derived threshold, the ventilatory thresholds can be identified during cardiopulmonary exercise testing through detecting changes in expired CO_2 , O_2 and minute ventilation (\dot{V}_E) (Beaver, Wasserman and Whipp, 1986). The intensity at which these exercise thresholds reside is however, subject to large degree of between individual variability depending on health or training status of a participant (Poole et al., 2016). The LT1 and VT1 are typically identified at 50-65% and 70-80% of $\dot{V}O_{2max}$, in healthy and well-trained individuals, respectively. The CP and equivalent thresholds (i.e. VT2 and LT2) are on average found approximately equidistant between the LT1/VT1 thresholds and the maximum power attained during an incremental exercise test to exhaustion (Souza et al., 2016). However, these thresholds can vary between individuals at 70-80% $\dot{V}O_{2max}$ in young healthy participants and 80-90% $\dot{V}O_{2max}$ in well trained participants (Poole et al., 2016). Consequently, when exercising at equivalent percentage $\dot{V}O_{2max}$, two participants may display considerably different physiological responses to exercise as the variability in physiological thresholds may result in performing exercise within different exercise intensity domains.

When applied to the exercise domains, the LT1 and VT1 are suggested to denote the boundary between the moderate and severe domain, while the LT2 and VT2 are suggested to denote the partition between the heavy and severe domains (Burnley and Jones, 2007). Although, these pulmonary and lactate thresholds are most prevalent within research and applied physiology, CP, a parameter that describes the power-duration relationship of high intensity exercise, is also proposed to demarcate the heavy-severe domain boundary (Poole et al., 2016).

The VT2, LT2 and CP are suggested to possess a synonymous relationship due to their identification as markers of the lower boundary of the severe intensity domain, although this has not been apparent across scientific literature (Pringle and Jones, 2002, Dekerle et al., 2003, Bergstrom et al., 2013). A number of investigations have examined this assumption that these indices of exercise intensity are uniform amongst exercising individuals (Pringle and Jones, 2002, Dekerle et al., 2003, Bergstrom et al., 2013, Keir et al., 2015). Amongst these investigations, CP has been subject to criticism as the LT2 power output is reported to occur at an intensity up to 16% lower (Jenkins and Quigley, 1990, Dekerle et al., 2003). Although, on

average, CP and VT2 maintain a synonymous relationship, when expressed as an external marker of intensity (e.g. speed or power output) an intra-individual variance between the indices is evident; however, when expressed as an absolute measure of pulmonary $\dot{V}O_2$ they have been reported to be equivalent (Keir et al., 2015). While external intensity offers simplicity in application, there does appear to be a dissociation between metabolic activity and external intensity. For example, the detection of VT2 can vary depending on the intensity of increments of an exercise protocol (Scheuermann, Tripsse McConnell and Barstow, 2002). As such, the synonymy of these thresholds may be more accurate when expressed as a measure of pulmonary $\dot{V}O_2$. Indeed, Keir et al., (2015) reported limits of agreement within clinically meaningful ranges for comparisons between CP, VT2 and LT2; with a bias range of between -0.01 and 0.12 L·min⁻¹. While this is indicative of parameters that manifest at similar pulmonary $\dot{V}O_2$ intensities, it does not differentiate if these thresholds are coincidental or if a physiological association is evident. **Given CP does not represent a single physiological marker of exercise but rather an interplay of bioenergetic determinant of exercise, CP may be understood to represent a multi-factorial physiological marker at the onset of the severe domain, which functionally operates equivalently VT2 and LT2 as represented through $\dot{V}O_2$ kinetics.**

The CP presents an interesting concept, as it is proposed to represent a maximal metabolic state that is predominantly oxidative and greatest intensity at which a steady state can be attained (Poole et al., 1988). In support of this description, Poole et al., (1988) reported that the metabolic and pulmonary profile of constant load exercise performed at CP and an intensity 5% above CP, demonstrated a distinct profile. At CP, a steady state in $\dot{V}O_2$ was attained within 2 min, while [bla] and pH steady states were attained within 6 min (Poole et al., 1988). Whereas, the metabolic and pulmonary profile during exercise 5% above CP, a steady-state was not attained with $\dot{V}O_2$ progressively rising to the point of $\dot{V}O_{2max}$ and [bla] increasing inexorably until exhaustion. These observations support typical profiles observed with $\dot{V}O_2$ and lactate kinetics during constant load exercise the heavy-severe domain threshold (Rossiter, 2010).

Constant load exercise in the moderate intensity domain is typically described as sub-maximal, whereby a steady state of $\dot{V}O_2$ and [bla] is attained, typically within 3 min (Burnley and Jones, 2007, Rossiter, 2010). The pulmonary $\dot{V}O_2$ response undergoes an initial rapid rise known as the cardiac dynamic phase, which is followed by an exponential rise until a steady state is attained. This however, is not accompanied with a rise in [bla] during exercise (Burnley and

Jones, 2007). Consequently, the equilibrium between ATP utilisation and resynthesis is maintained predominantly via aerobic energy contribution. During the heavy domain, a secondary slower exponential rise in $\dot{V}O_2$ kinetics ensues, which is defined by the $\dot{V}O_2$ slow component (Burnley and Jones, 2007). The $\dot{V}O_2$ slow component is thought to manifest after 90-120 s of constant load exercise, with a continued rise as a function of time during a constant work rate until a steady state is typically attained within 10 mins (Ozyener et al., 2001). An increased but stabilised state is also exhibited in [bla], $[H^+]$ and intramuscular [PCr] (Jones et al., 2008), suggesting presence of a metabolic steady state.

Exercise intensities above CP reside in the severe intensity domain, during which cardiopulmonary and metabolic steady states cannot be attained (Poole et al., 1988, Jones et al., 2011). An important characteristic of the severe intensity domain is the progressive loss in metabolic homeostatic regulation (Jones et al. 2008) and exercise efficiency (Grassi, Rossiter and Zoladz, 2015), which contributes to the eventual termination of exercise. Indeed, constant load exercise within the severe domain leads to a continued $\dot{V}O_2$ rise until the $\dot{V}O_{2max}$ is attained, while [bla] transcends inexorably until exhaustion (Burnley and Jones, 2007, Jones et al., 2008). Notably, the severe domain is associated with a substantial $\dot{V}O_2$ slow component that is shown to account for a large volume of oxygen (over $1 \text{ L}\cdot\text{min}^{-1}$) of the total $\dot{V}O_{2max}$ volume (Ozyener et al., 2001). Therefore, it has been proposed that understanding the determinants of the $\dot{V}O_2$ slow component allows for greater insight into the association between physiology and performance, as this $\dot{V}O_2$ feature is attributed to reduced exercise efficiency and resultant exercise intolerance (Burnley and Jones, 2007).

The $\dot{V}O_2$ slow component provides an interesting insight into the response to exercise in the severe intensity domain. Indeed, research has implicated the $\dot{V}O_2$ slow component with the parameters of the power-duration relationship (i.e. CP and W') (Murgatroyd et al., 2011), which itself describes exercise tolerance in the severe intensity domain (Poole et al., 2016). The power-duration relationship is a hyperbolic function of exercise intensity (e.g. speed or power output) and is comprised by two distinct parameters, the asymptote of the hyperbola that is termed as critical power, which is proposed to denote the lower boundary of the severe intensity domain. The second parameter is the curvature constant, which is known as the W' ; and quantifies the work that can be performed above CP (i.e. within in the severe intensity domain) prior to exhaustion. Indeed, the magnitude of W' and that of the $\dot{V}O_2$ slow component are positively correlated ($r = 0.87$) (Murgatroyd et al., 2011); as such, providing an association

between $\dot{V}O_2$ kinetics, the power-duration relationship and the exercise tolerance during severe intensity exercise.

2.1.1 The power-duration relationship

The power-duration relationship emerged in the early 20th Century, when velocity-time¹ curves were created with the then standing world records plotted on a graph of distance against time (Hill, 1925). Across various exercise modalities (e.g. running, cycling and skating) the world records depicted a uniform relationship, which was curved in nature. This curvature is still evident in present day when plotting current running world records but it is not limited solely to elite populations (Poole et al., 2016). Indeed, laboratory based investigations have supported the notional link between power and duration, with similar curves fitted for healthy (Poole et al., 1988), adolescent (Barker et al., 2012), elderly (Neder et al., 2000) and patient populations (Malaguti et al., 2006). Given the curvature of the power-duration relationship, Whipp et al., (1982) computed a geometric hyperbolic function to the curve which allows the determination of two parameters; the asymptote and curvature constant, which are referred to as CP and W'^2 . In concert, the CP and W' parameters depict the hyperbolic framework of the power duration relationship, which can be presented formulaically as:

$$(P - CP) t = W' \quad \text{[equation 1]}$$

Whereby, P represents power output during cycling, t is the duration a given power output is maintained (in secs). This formula can be rearranged to demonstrate the linear form of the relationship, which can calculate the required power output for exercise exhaustion at a pre-determined time (equation 2) and the determination of the time exercise can be maintained at a given intensity (equation 3).

$$P = (W' / t) + CP \quad \text{[equation 2]}$$

$$t = W' / (P - CP) \quad \text{[equation 3]}$$

Therefore, the graphical and formulaic depiction of the power-duration hyperbola offer a

¹ Reference is made to the velocity-time curve due to the nature of the analysis conducted by Hill (1925), this is synonymous with the power-duration relation which is referred to throughout the thesis.

² The terms CP and W' are typically used for cycling, while in other sports (such as running) the terms critical speed (CS) and distance (D) are used to express CP and W' , respectively.

mathematical method to describe tolerance to constant load severe intensity exercise (Poole et al. 2016).

Due to the identification of CP as the hyperbolic asymptote, from a pure mathematical premise, exercise performed at or below CP intensity can be maintained indefinitely. However, from a physiological perspective it is known exercise does reach an intolerable point at any given intensity due to a number of reasons, such as limited substrate availability, central regulators of exercise and thermoregulatory stresses (Ament and Verkerke, 2009). The applicability of the CP concept to exercise is therefore limited to intensities that reside above the CP threshold. However, the CP is suggested to represent the greatest metabolic rate that is predominantly oxidative in nature (Poole et al., 1988) and thus it is a useful index of aerobic capacity (Jones et al. 2010). Indeed, estimations of CP increase when determined under hyperoxic conditions (Vanhatalo, Fulford, et al., 2010a) and decrease when determined under hypoxic conditions (Dekerle, Mucci and Carter, 2012, Parker-Simpson et al., 2014, Shearman et al., 2016), demonstrating CP's sensitivity to oxygen availability during exercise (discussed further in section 3.0.). While exercise above CP is defined by the W' , which is deemed to represent the fixed finite energetic availability (in kilojoules) for exercise that can be performed above CP, and thus denotes the range of exercise intensities that reside within the severe intensity domain.

2.1.2. Critical power concept: practical application and intermittent exercise

The potential impact of the CP concept is evident through the wide reaching applications of the model from patient to elite populations (Vanhatalo, Jones and Burnley, 2011, Poole et al., 2016), for purposes including normalisation of constant duration and intermittent bouts (Ferguson, Wilson, Birch, Kemi, et al., 2013), and indication of exercise tolerance (Housh, Housh and Bauge, 1989) and performance (Smith, Dangelmaier and Hill, 1999, Black et al., 2014), and inform athletic pacing strategies (Chidnok et al., 2013). It is important to highlight the CP concept in these scenarios only offers a description of exercise that occurs at intensities equivalent to CP or higher (i.e. severe intensity domain); therefore, the application of the model is only appropriate for exercise that taxes W' . The W' parameter is fixed energy of work that maybe performed above CP, with the depletion of W' associated with exercise exhaustion (Fukuba et al., 2003, Chidnok et al., 2013). Indeed, the association between W' depletion and exercise tolerance prediction during constant intensity bouts is suggested to be relatively robust

for exercise ranging between 3-20 mins (Fukuba et al., 2003, Chidnok et al., 2013, Dekerle et al., 2015).

Constructed on the association between W' and exercise exhaustion, the direct application to sport and exercise training is likely to be limited to forms that tax the severe intensity domain. To date, this CP construct has been applied to running (Kolbe et al., 1995), cycling (Skiba et al., 2014), rowing (Cheng et al., 2012) and swimming (Dekerle et al., 2002), although the potential for application to endurance based and high intensity intermittent has not been evaluated. The CP concept for example, has been posited as a potential tool to break the elusive 2 hr marathon barrier (Joyner, Ruiz and Lucia, 2011) as it requires a relatively high speed to be maintained without the use of W' ; which therefore necessitates an equivalently higher critical speed (i.e. CP). Furthermore, knowledge of W' availability during endurance events may allow athletes to appropriately pace intense spurts during a race and/or appropriately time end-spurts to maximise performance (Noordhof et al., 2013). Recently, the CP concept has been successfully applied to high intensity intermittent exercise, with the work balance model (W'_{bal}), which accounts for the discharge and reconstitution of W' during severe intensity exercise and the interspersed recovery intervals, respectively (Chidnock et al., 2012; Skiba et al., 2012; Ferguson et al., 2013). Theoretically this allows for the determination of the remaining W' available at any given point during exercise, a value denominated as W'_{bal} (Skiba et al., 2012). Such a model has promising application to intermittent exercise training and other intermittent sports, such as football.

The application of CP to the W'_{bal} model was initially constructed on the notions presented by Coats et al., (2003) and Ferguson et al., (2010). In the earlier investigation, Coats et al. (2003) found that following 6 min of W' depleting exercise, work could still be performed at intensities below CP but was quickly terminated when intensity was reduced but remained above CP. During the severe intensity trial, where exercise was reduced to 110% of CP, following W' depletion, exercise maintenance was significantly lower (30 ± 12 sec) than the corresponding trials with subsequent intensities below CP. When workload was lowered abruptly to 80% of VT1 (i.e. moderate intensity domain) compared to 90% of CP (i.e. heavy intensity domain) a greater amount of work was performed, with all participants completing the set 20 min (1200 ± 0 sec) during moderate exercise but only complete 785 ± 400 sec during heavy exercise. Consequently, this study indicates following W' depletion, exercise can still be maintained for prolonged periods at intensities below CP, while the lower the intensity the

greater the volume of work that can be performed. As such, utilising recovery bouts of varying intensities may have implications for intermittent exercise when high intensity intervals are performed above CP (Coats et al., 2003). The second notion presented by Ferguson et al. (2010), questioned an original assumption that W' reconstitution was linear (Morton and Billat, 2004) and suggested the reconstitution was in fact exponential. Six recreationally trained participants performed nine experimental trials, following the determination CP and W' using four constant load tests to exhaustion. During each of the subsequent experimental trials, participants completed an exercise bout to exhaustion, with an intensity prescribed to deplete W' at 6 min (i.e. $W' = 0$). Three different active recovery (at 25 W) periods of 2, 6 and 15 min were then completed prior to the re-evaluation of CP and W' using three different constant load trials to exhaustion. Assuming W' equalled zero following the initial 6 min exhaustive bout in the experimental trials, the recalculation of W' were found to be progressively and significantly different with duration of active recovery from 7.8 ± 1.4 KJ at 2 min, 14.1 ± 3.7 KJ at 6 min and 18.5 ± 4.6 KJ at 15 min. Through plotting the recovery kinetics, a curvilinear profile was distinct with interpolation of time profile suggesting a half-life ($t_{1/2}$) of W' at 234 ± 32 sec. Although, the authors did not apply a more complex exponential analysis, due to the limited data points, it was evident that the original assumption of a linear W' recovery may not be correct.

Constructed on this *priori* knowledge of W' kinetics and intensity dependent nature of exercise tolerance following W' depletion, Skiba et al. (2012) created the W'_{bal} model. This can be depicted in a continuous integral equation:

$$W'_{bal} = W' - \int_0^t W'_{exp} \cdot e^{-(t-u)/\tau_{W'}} \quad [\text{equation 4}]$$

Whereby, W' represents *priori* determination of W' from two-parameter CP test, W'_{exp} represents the expended W' during work above CP ((PO – CP) *duration of work), (t - u) represents the time in seconds between exercise intervals which deplete W' , and $\tau_{W'}$ represents the time constant of W' reconstitution (in sec). Therefore, this equation illustrates that the amount of W' remaining at any time (W'_{bal}) is a function of the difference between the known W' and the sum W' expended (in joules) over time during work above CP; along with the recovery of W' during work below CP; which recovers exponentially. While, CP and W' can be calculated prior to the application of the W'_{bal} model; the $\tau_{W'}$ parameter was however, unknown and therefore, Skiba et al. (2012) derived the following exponential equation:

$$\tau_{W'} = 546 \cdot e^{(-0.01D_{CP})} + 316 \quad \text{[equation 5]}$$

The time constant of W' kinetics is therefore an exponential function related the D_{CP} , which itself represents the difference in power output between CP and the recovery power output. The validity of the overall regression equation and the determination of the $\tau_{W'}$, was established using three different intermittent exercise bouts to exhaustion, with varying recovery intensities across the spectrum of exercise intensity domains. These intermittent trials included 60 sec work performed within the severe intensity domain, which were normalised to an intensity that would elicit exhaustion at four min. While recovery power output was held for 30 sec and performed at either: 1) 20 W (light recovery); 2) 90% of the power output of VT1 (moderate recovery); or 3) 50% of the difference between VT1 and CP (heavy recovery). An iterative process was then applied to alter $\tau_{W'}$ until the W'_{bal} equalled zero at the point of fatigue during each intermittent bout. The $\tau_{W'}$ and D_{CP} were then plotted with an exponential regression applied to determine equation 5. This therefore, applied the finding of Coats et al. (2003) and Ferguson et al. (2010); in that, W' recovery kinetics is exponential and is altered as a function of recovery intensity.

Following the inception of the W'_{bal} model, research has tested the validation and robustness of the model in during field based cycling training (Skiba et al., 2014) and isolated muscular exercise (e.g. handgrip exercise) (Broxterman et al., 2016). However, the accuracy of the model when applied to intermittent exercise under hypoxic conditions has been questioned, as W' surpasses zero at the onset of exhaustion (Shearman et al., 2015, Townsend et al., 2017). This overestimation of W' could be due to the model's reliance on accurate *priori* determination of CP and W' , which is suggested to be 5% error for CP and 12% error with W' (Poole et al., 2016). Furthermore, the original determination of $\tau_{W'}$ is based on mean kinetics of seven healthy but untrained participants ($\dot{V}O_{2max}$: $4.1 \pm 0.78 \text{ L}\cdot\text{min}^{-1}$; CP: $240 \pm 56 \text{ W}$). Skiba et al., (2012) did not however, identify a narrow inclusion criterion, given one participant had a substantially greater $\dot{V}O_{2max}$ and CP ($5.59 \text{ L}\cdot\text{min}^{-1}$ and 351 W , respectively), which is over two-fold larger than the standard deviation of the mean. The individual data presented identifies that the highly trained participant did not exhibit any differences in $\tau_{W'}$ between the light and moderate recovery intensities, which consequently alludes to a faster W' recovery kinetics. Furthermore, recent evidence in four elite endurance trained athletes ($\dot{V}O_{2max}$: $83.2 \pm 2 \text{ ml}\cdot\text{kg}\cdot\text{min}^{-1}$) has demonstrated that the equation to establish $\tau_{W'}$ should be adjusted in highly trained individuals (Bartram et al., 2017). Consequently, this indicates that $\tau_{W'}$ may depend on

training status and thus be a dynamic feature of intermittent exercise, which can be altered through training and/ or nutritional interventions. Therefore, it is plausible that the trained participants used during both hypoxic investigations may possess a $\tau_{W'}$ that differs from originally determined constant by Skiba et al. (2012); which may confound research that suggest the W'_{bal} model is inaccurate in hypoxic conditions (Shearman et al., 2015, Townsend et al., 2017). As such, accurate application of the W'_{bal} model in research and practise should include a pre-determined $\tau_{W'}$ equation specific to the population.

2.1.3. Effects of acute hypoxia on the critical power model

The CP threshold also exhibits a similar trend to the equivalent VT2 and LT2 thresholds under acute hypoxia; in that, despite absolute intensity falling, the relative intensity as a percentage of $\dot{V}O_{2max}$ remains unchanged to normoxia (Dekerle, Mucci and Carter, 2012a, Shearman et al., 2015, Parker-Simpson et al., 2015). However, the CP concept also demonstrates that the amplitude of the severe intensity domain, on average, remains unchanged with acute moderate hypoxia, as depicted by the W' parameter (Dekerle, Mucci and Carter 2011; Parker-Simpson et al. 2015; Shearman et al. 2016). Parker-Simpson et al., (2015), highlighted changes in W' were variable, depending on the relative change in $\dot{V}O_{2max}$ and CP change with acute hypoxia. Due to the observation of a significant ($r = 0.83$; $p < 0.01$) relationship between change in W' and change in the gap between CP and $\dot{V}O_2$, it suggests the magnitude of W' and therefore the severe intensity domain is dependent on the CP and $\dot{V}O_2$ response, rather than an alteration in anaerobic energy supply per se. Acute hypoxia effects CP in a dose dependant manner, with increasing hypoxic magnitudes eliciting a greater ergolytic effect on CP (Townsend et al., 2017). The relationship between acute hypoxia and CP has been presented by a curvilinear cubic model, however, W' only changes from sea level under extreme hypoxic exposures (equivalent to 4000 m). This conforms with the only investigation undertaken in acclimatised participants at extreme terrestrial altitudes (5050 m), which also depicted a reduction in W' (Valli et al., 2011). Given W' was unaffected by O_2 availability at lower magnitudes of hypoxia, it is likely that alternative factors may influence W' at extreme hypoxic levels. Indeed, it has been shown that cerebral hypoxia may exert an inhibitory effect upon central motor drive, which is observed with severe hypoxic exposure (Millet et al., 2012). In addition, the magnitude of peripheral fatigue for a given task is significantly diminished at severe hypoxia compared to moderate hypoxia (Amann et al., 2007). Together this highlights that CP is sensitive to O_2 manipulation, whereas the factors that determine W' at hypoxia may be a

function of enhanced central fatiguing mechanisms and/ or an attenuation of peripheral fatigue mechanisms.

2.1.4. Physiological composites of CP and W'

Critical power is proposed to represent the highest intensity at which a metabolic and cardiopulmonary steady state is observed (Poole et al. 1988), with the energetic contribution proposed as being predominantly oxidative (Poole et al. 2016). This supposition is supported in the observation of CP response to the manipulation of oxygen availability. Accordingly, exposure to acute hypoxia lowers CP (Derkele et al 2013; Simpson et al. 2015), while hyperoxic exposure results in an enhanced CP (Vanhatalo et al., 2010). Furthermore, the CP parameter has been identified as a sensitive marker to indicate changes in aerobic fitness following continuous and interval based training interventions (Jenkins and Quigley, 1992, 1993, Vanhatalo, Doust and Burnley, 2007b); therefore, highlighting the use of CP as an indicator of oxidative capacity.

When exercise intensity surpasses CP, the utilisation of W' commences in the severe intensity domain; however, the physiological proponents of this parameter remain elusive (Poole et al., 2016). Historically, W' was purported to represent the finite anaerobic work capacity but this presents an over simplistic binary view to the energetic contribution to exercise limited to aerobic and anaerobic energy systems. A contemporary view on the subject provides a more holistic interpretation, as the determinants of W' cannot be attributed to a single physiological phenomenon but rather an integrative bioenergetic phenomena (Jones et al., 2010; Pool et al., 2016). This includes several metabolic and cardiopulmonary factors that have been linked to W' . In relation with pulmonary $\dot{V}O_2$, the amplitude of the slow component is positively correlated with the magnitude of the W' (Murgatroyd et al., 2011, Vanhatalo et al., 2011). While hyperoxic exposure exhibits a diminishing effect on W' , as the elevated O_2 availability increases CP and consequently reduces the gap between CP and $\dot{V}O_{2peak}$ (i.e. the severe intensity domain and W'). As such, W' is suggested to have an intrinsic relationship to $\dot{V}O_2$ kinetics; in that, the amplitude of the $\dot{V}O_2$ slow component and W' are closely aligned (Murgatroyd et al., 2011). While, W' is also closely aligned with muscle metabolic perturbations during exercise, which is similar metabolic characteristics associated with the $\dot{V}O_2$ slow component (Burnley and Jones, 2007). Muscle metabolic assessment utilising ^{31}P magnetic resonance spectroscopy (^{31}P MRS), demonstrated single leg exercise extension performed at a work rate 10% above CP resulted in a continuous increase to inorganic

phosphate ion concentrations [Pi] and a decrease in muscle [PCr] content and pH (Jones et al., 2008). Whereas during exercise 10% below CP a steady state in the aforementioned muscle metabolites were maintained. More recently, whole body exercise has supported these observations through obtaining muscle biopsies following cycling exercise to exhaustion 5% above and below CP. Below CP, muscle pH (7.10 ± 0.11), lactate ($35.5 \pm 13.2 \text{ mmol}\cdot\text{kg d}\cdot\text{w}^{-1}$) and [PCr] ($49.4 \pm 6.9 \text{ mmol}\cdot\text{kg d}\cdot\text{w}^{-1}$) remained stable, while above CP a fall in muscle pH (6.84 ± 0.06), increase muscle lactate ($95.6 \pm 14.1 \text{ mmol}\cdot\text{kg d}\cdot\text{w}^{-1}$) and a reduced [PCr] ($24.2 \pm 3.9 \text{ mmol}\cdot\text{kg d}\cdot\text{w}^{-1}$); all of which were significantly different between conditions (Vanhatalo et al., 2016). Furthermore, ^{31}P MRS research has also identified, a recovery interval, following period of exercise above CP, allows the restoration intramuscular metabolic homeostasis, with the degree of recovery dependent on the duration of recovery (Chidnok et al., 2013). This restoration towards metabolic homeostasis was subsequently identified as the recovery of W' (Skiba et al., 2012), thus further associating muscle metabolic perturbations to W' . Together these investigations allude to a more encompassing definition of W' , which identifies an interacting relationship with the amplitude of the $\dot{V}\text{O}_2$ slow component, a state intramuscular store depletion and metabolite accumulation and a reduced muscular efficiency (Poole et al., 2016).

Despite the proposed physiological constituents that can be attributed to W' , a causal mechanistic relation cannot be affirmed, as these parameters may preside coincidentally. As such, to identify the contributing factors of work performed above CP before exhaustion, it is appropriate to manipulate the aforementioned physiological parameters through exogenous environmental, nutritional and training interventions to ascertain their involvement in W' determination. Indeed, the prior depletion of muscle glycogen stores exhibited a significant 20% reduction in W' to $10.22 \pm 2.41 \text{ kJ}$ from $12.83 \pm 2.21 \text{ kJ}$ under normal muscle glycogen conditions (Miura et al., 2000). While, increasing muscle [PCr] concentrations, through creatine monohydrate supplementation has been demonstrated to enhance W' by 4% and 10% (Smith et al., 1998, Miura et al., 1999, respectively), although no change in CP was observed. The investigations by Miura et al., (1999 and 2000) and Smith et al., (1998) utilised the multiple exercise tests establish CP and W' to determine the effect of metabolic manipulation on the CP parameters. Succeeding investigations however, found no effect when using the 3 min all-out critical power test, to assess the influence of manipulating muscle PCr and blood pH, through exogenous supplementation of creatine monohydrate and NaHCO_3 , respectively (Vanhatalo and Jones, 2009, Vanhatalo et al., 2010). This raises concerns of the 3 min all-out test to detect

changes in W' , particularly given the CV of 10% for W' estimation (Vanhatalo, Doust and Burnley, 2007a). As such, for interventions to be deemed effective through this model, the magnitude of the intervention should be larger than 10% to detect a meaningful effect. Nonetheless, this body of research indicates that intramuscular energy stores act as a determinant of W' parameter.

Much of the scientific literature and the current thesis has focused on the peripheral entity of fatigue in relation to the power-duration relationship; however, it is likely that an interdependent effect with central mediators are also present. Indeed, an equivalent reduction in voluntary activation was evident during intermittent isometric contractions to exhaustion performed below and above critical torque (an analogous for CP) (Burnley, Vanhatalo and Jones, 2012). This consequently suggests central fatigue is evident when performing exercise above the CP threshold, and therefore, may have implications for the determination of W' . Furthermore, Salam, Marcora and Hopker, (2018) observed that a prior mental fatiguing task (i.e. modified Stroop word-colour task) had an ergolytic effect on the W' parameter of the power-duration relationship; which is indicative of central psychological factors that may mediate W' . Together, the reduction in voluntary action and the effect of mental fatigue on W' , indicate that work above CP is not solely a peripheral physiological phenomenon but rather an interplay of physiological and psychological factors related to the central and peripheral mechanisms of fatigue.

2.1.5. Limitations of the critical power model

The critical power model takes a reductionist view on the physiological characteristics of exercise, through compartmentalising the bioenergetics systems of exercise into two discrete domains (i.e. CP and W'). However, given the complexity of physiological process and the involvement of both central and peripheral contributors to fatigue, a number of assumptions are required in order for the concept to work (Morton, 2006, Jones et al. 2010). There are four-main assumptions that include:

- 1) Exercise intensity is a function of two energy systems, namely aerobic and anaerobic sources;
- 2) the aerobic energy supply is not capacity limited but is rate limited, in that when exercise intensity reaches a critical point (i.e. critical power) aerobic energy contribution is limited;

3) exercise continues while energetic supply and demand are matched. Therefore, indicating exercise in the 'severe' intensity domain can be maintained until W' is depleted, while exercise is 'indefinite' below CP, and

4) the anaerobic energy supply is capacity limited but not rate limited; in that, the volume of work performed above CP is fixed (i.e. W').

While these assumptions are required for a working CP model, they violate commonly accepted physiological knowledge. Assumption 1, simplifies the presence of three main energy systems, specifically the initial ATP/PCr energy system, glycolysis and oxidative phosphorylation. While assumption 2 implies that exercise duration can be infinite at exercise intensities below CP, which is not possible. Indeed, exercise tolerance at CP can be typically tolerated from approximately 20 – 40 min (McLellan and Cheung, 1992, Bull et al., 2000, Brickley, Doust and Williams, 2002). Furthermore, in direct contrast with assumption 3, Derkelele et al. (2015) demonstrated that that if exercise intensity is lowered, but remains above CP, exercise can be prolonged for greater durations than predicted by up to 19%, thus highlighting inaccuracies with the CP model. Assumption 4, however, provides a reasonable proposition that W' is capacity limited; in that, if the physiological correlates with W' are depleted (e.g. muscle glycogen or [PCr]) or there is an inexorable rise in fatigue metabolites (e.g. H^+ and K^+) or attainment of $\dot{V}O_{2max}$), then exercise in the severe intensity domain may not be able to continue. It also assumes however, that there is no physiological limit to the power or speed an individual can produce in a single intense burst; which is not plausible. This assumption was been rectified when using the three-parameter CP model, which includes maximal instantaneous power parameter to account for the limit an individual can produce in a single burst (Morton, 1996).

It has been argued that the introduction of a third parameter into the critical power concept, which represents maximal instantaneous power, provides a better description of physiological behavior (Morton, 1996). The three-parameter model involved the removal of the time asymptote as time approached zero and therefore, power at $t = 0$ was not identified as being infinite but rather adding an upper limit to the maximum power that can be produced instantaneously. The model also assumes that the maximal power produced in an instant is a function of the amount of W' remaining at any given moment. As a consequence, it is no longer assumed that exhaustion occurs when W' is depleted but rather when maximal instantaneous power can no longer attain the desired power output. This has been depicted during whole body

exercise, with exercise tolerance maintained at a lower intensity above CP despite the purported depletion of W' at a higher exercise intensity (Dekerle et al., 2015). While the three-parameter model accounts for the aforementioned limitations of the two-parameter model to describe the physiological behavior of exercise, it does not however, correct for the duration asymptote that assumed exercise below CP can be maintained indefinitely. As such, a number of other models have been developed to enhance the concepts description of physiological behavior; however, this is beyond the scope of the current review and readers are directed to more relevant publications (Bull et al., 2000, 2008, Morton, 2006, Busso, Gimenez and Chatagnon, 2010). Nonetheless, the simplicity of the mathematical modelling and practical applicability of the two-parameter model has been the main reason for the its prevalence in academic research and applied scientific practice.

The practical difficulty of determining CP and W' , using either the two- or three-parameter model, is the requirement of up to five exhaustive exercise bouts performed at approximately 75% to 105% of the maximal power output attained during an incremental exercise test; which yield exercise durations between 2-15 min (Vanhatalo, Jones and Burnley, 2011). Although, there has been disputes over the number, intensity and duration of exercise bouts required to accurately determine CP and W' (Maturana et al., 2017). Comparison of CP and W' when determined across a number of different exhaustive trials (ranging 1-20 min), highlighted the requirement of at least two bouts that exceeded 10 mins to obtain an accurate representation of W' . Whilst also including multiple exercise bouts to accurately depict the graphical hyperbola and thus, enhance the precision of CP. The requirement of multiple bouts can however, be logistically difficult in an applied sport setting and for researchers, when using this method to assess the efficacy of an intervention, as it would at least double the number of laboratory visits required. As such, researchers have aimed to identify methods to limit the time commitment in accurately assessing CP and W' , such as the development of the three min CP test (Vanhatalo, Doust and Burnley, 2007a).

The idea of the three min all-out test was first presented when a steady state in cycling power output was consistently observed following 2.5 min of the three min all-out exercise test (Burnley, Doust and Vanhatalo, 2006). This test took the form of an initial maximal power output, following which participants are asked to maintained the highest possible power output for the duration of the test. When graphically depicted the power output displays a hyperbolic form, which begins to plateau towards the end of the test, hence the observed steady state during

the last 30 sec. Theoretically, the maintenance of highest possible power out would deplete the W' and thus empirically reach zero, at which point the highest sustainable power output would represent CP. Consequently, Vanhatalo et al. (2007a) tested the assumption that the last 30 sec average power output represents CP and the work performed in the preceding 2.5 min represents W' . In comparison to the 'gold standard' multi-trial method, the three min is shown to provide a valid estimate for CP ($r = 0.99$; standard error of estimate (SEE) = 6 W) and W' ($r = 0.84$; SEE = 2.8 kJ). While the three min all-out test also possess a strong re-test reliability for CP ($r = 0.99$; SEE = 7 W) and W' ($r = 0.97$; SEE = 1.29 kJ). Moreover, the validity of the three min protocol to determine CP, against the multi-trial method, is maintained under hypoxic conditions ($r = 0.81$; Parker-Simpson et al., 2015). Hence, the three min 'all-out' protocol is suggested to represent a valid method to determine CP under both normoxic and hypoxic conditions. The three min 'all-out' protocol, however has received criticism, as it may overestimate CP (Shearman et al. 2015). To offset possible over estimation of CP, a minimum 30 sec of moving average was calculated, rather than the power output from the last 30 sec of the exercise bout. This allows the calculation of the minimum CP, as previously used by Shearman et al. (2015), with W' calculated from the power-time integral above CP.

Despite the suggested inaccuracies of the previously discussed tests and models and the assumptions of physiological behavior, the critical power concept provides a relatively robust model in relation to exercise performed in the severe intensity domain. Specifically, this includes the application to intermittent exercise (Chidnock et al., 2012; Ferguson et al., 2013), the physiological response to constant load exercise (Poole et al., 1988) and the application to stochastic field-based training (Skiba et al. 2014). Furthermore, the CP has been closely associated with the LT2 and VT2, when determined as a percentage of $\dot{V}O_2$, which identify as two distinct physiological events that depict the severe intensity domain (Kier et al., 2015). Therefore, when taken in consideration as a representation of the severe intensity domain the concept remain valid.

2.1.6. Summary

The grouping of the physiological response into discrete intensity domains provides practical value for athletes, coaches and scientists. Indeed, these domains can be effectively used to prescribe and normalize exercise intensities, inform athletic pacing strategies and allow the prediction of exercise tolerance (Burnley and Jones, 2007). This is particularly evident to exercise in the severe intensity domain, which can be simply described by the W' parameter of

the CP concept. Despite the robustness of the concept, the physiological constituents of the parameter remain allusive. Although, reductions of exercise efficiency, the development of a $\dot{V}O_2$ slow component and the substantial metabolic perturbations in the myofibrillar milieu (such as the development of exercise induced acidosis), have all been implicated. These factors are suggested to contribute to reduced exercise performance and exhaustion within the severe domain. As such, further investigation to elucidate the determinants of W' may better improve the application of the CP model and improve understanding of fatigue development in the severe intensity domain.

2.3. Human Physiology of Acid-Base Balance

The acid-base balance represents the homeostatic regulation of pH *in vivo*, which in the extracellular plasma, oscillates around 7.38 – 7.42 to facilitate metabolic and physiological process (e.g. enzyme activity; Atherton, 2003). The concept of pH was developed as a means of quantifying acidity through determining the concentration of hydrogen anions ($[H^+]$), as represented by the following logarithm:

$$pH = -\log (10) [H^+] \quad \text{[equation 6]}$$

Given the inverse log function, $[H^+]$ and pH are inversely related, with elevations in $[H^+]$ resulting in a lower pH, a condition commonly referred to as acidosis. The acid-base balance undergoes high levels of daily flux, with approximately 70-100 milliequivalents day^{-1} of H^+ generated metabolically or obtained exogenously (Poupin et al., 2012). Metabolically derived H^+ can be substantial, depending on the volume and intensity of physical activity, whilst the composition of dietary intake determines the magnitude of exogenous H^+ . Dietary acidic load is quantified by the potential renal acidic load (PRAL), a sum of acidic and alkalotic food intake (Remer, 2001). High PRAL for example, is characterised by a diet rich in cheese, red meats and grains, whereas low PRAL diets are comprised of dark leafy vegetables and fruits, such as bananas and apples (Remer and Manz, 1995). Endogenous defence systems are in place to protect the body against high acid loads, through buffering systems that involves the base components, such as bicarbonate, to regulate pH. The role of the buffering system is to remove free H^+ from the body through chemical reactions involving an un-dissociated acid and its base, forming a stabilised molecule (Atherton, 2003). In this process the acid is a positively charged molecule that is referred to as a proton donor, whilst a base is a negatively charged molecule that is referred to as a proton acceptor, thereby accepting an H^+ . A number of systems operate to regulate acid-base balance, including physiochemical buffering, respiratory and renal

compensation. These systems operate over various timeframes with differing responsibilities to maintain an alkaline environment in the face of endogenous and exogenous acidic stresses introduced to the body (Atherton, 2003; Poupin et al., 2012).

The physiochemical buffering system presents the first line of defence to elevations in plasma $[H^+]$ and involves the removal of H^+ through several chemical reactions (Atherton, 2003). These reactions however, can only attenuate the rate of pH decline rather than compensate for disturbances to the acid-base balance, which is mediated by the respiratory and renal compensation systems. Similar to physiochemical buffering, the respiratory compensation is immediate and can be viewed as the second line of defence against acidosis, whilst renal compensation is delayed, lasting several hours or days (Atherton, 2003). Both compensatory mechanisms mediate the bicarbonate buffering reactions, which will be discussed briefly in the following section. Due to the rapid nature the physiochemical buffering and respiratory compensation, they are central to acid-base regulation during exercise. For that reason, they will be discussed in greater detail in the proceeding sections. In particular, the role of these systems on the bicarbonate buffering reactions will be discussed, due to the pertinence to this thesis. For a detailed overview of the acid-base balance readers are directed to alternative reviews (Atherton, 2003, Goel and Calvert, 2012; Poupin et al., 2012).

2.3.1. Buffering systems

The primary purpose of physiochemical buffering is to attenuate elevations in H^+ and consequential pH decline, through chemical reactions to remove H^+ by either proteins, haemoglobin, phosphates or bicarbonate (Atherton, 2003, Poupin et al., 2012). The substantial daily acidic load requires an abundant and effective buffering system to mediate acid-base balance homeostasis. Of the physiochemical processes, endogenous bicarbonate buffering is prominent, representing 86% of total buffering capacity in extracellular space and 34% of total intracellular buffering capacity (Poupin et al., 2012). Other non-bicarbonate related chemical reactions in the extracellular space include plasma protein and haemoglobin, which represent 14% of extracellular buffering capacity. In contrast proteins and phosphate have a greater role in the intracellular compartments (66%: Atherton et al., 2003; Poupin et al., 2012). An additional consideration is the effectiveness of a buffering process, which is reliant on the environment in which it is situated. This is determined by the acid dissociation constant (pKa). The pKa represents the pH at which a dynamic equilibrium between the proton detachment and

re-attachment to the acid functional group of a molecule occurs (Robergs, Ghiasvand and Parker, 2004). The pKa of the bicarbonate buffering system is 7.4. This means a pH close to 7.4, presents the environment in which, bicarbonate buffering has the greatest proton binding affinity, thereby attaining the bicarbonate system's 'optimal' buffering capacity. The abundance and pKa within physiological pH ranges, suggests bicarbonate buffering is a pivotal physiochemical buffer, providing instantaneous protection to disturbances in acid-base balance.

The main components of the bicarbonate buffering process are bicarbonate anions (HCO_3^-) which couple with H^+ , to reduce $[\text{H}^+]$, and form carbonic acid (H_2CO_3). Carbonic acid possesses a pKa of 3.7, and therefore easily disassociates into carbon dioxide (CO_2) and water (H_2O). This reaction is reversible and is catalysed by *carbonic anhydrase*, which accelerates the formation of H^+ and HCO_3^- . The following equation outlines this reaction:



The nature of a reversible reaction necessitates a continuous process until a dynamic equilibrium prevails between both sides of the equation. Therefore, an increase in either $[\text{H}^+]$ or CO_2 drives the reaction in the opposite direction. Elevations in plasma CO_2 partial pressure (PCO_2) for example will stimulate production of H_2CO_3 and consequently augment $[\text{H}^+]$. Conversely, acidosis will result in a leftward shift of the equation, increasing the coupling of H^+ and HCO_3^- , and subsequent PCO_2 concentration. The direction of the reaction is however dependent on the finite availability of HCO_3^- , therefore once utilised the reaction cannot be maintained. Consequently, the maintenance of pH through this system is reliant on the respiratory and renal compensatory mechanism to release HCO_3^- (Atherton, 2003).

Respiratory compensation operates within minutes and acts to remove CO_2 through the exponential rise in respiratory rate and VCO_2 . Peripheral chemoreceptors are sensitive to changes in PCO_2 and are responsible for stimulating nerve firing rates as feedback response to enhance ventilatory response (Pittman, 2011). Therefore, eliminating CO_2 and thus reducing plasma PCO_2 , stimulates afferent feedback from the chemoreceptors to return ventilatory response towards resting levels. Accordingly, the bicarbonate buffering reaction, will continue to couple H^+ and HCO_3^- , allowing the further removal of H^+ to elevate pH. To quantify this process, a doubling of ventilatory rate will induce an approximate 0.23 rise in extracellular pH. This large compensatory action on pH demonstrates the importance of the respiratory system

on acid-base regulation (Guyton and Hall, 1996), particularly during exercise where an immediate response may be required. The renal system also has a major role in pH regulation, although this system operates over a number of days, and therefore may have a limited role in regulating acute exercise-induced disturbances in acid-base balance. In contrast, the physiochemical buffering and respiratory systems are pivotal during exercise due to their rapid action. Indeed, an exponential rise in $V\dot{C}O_2$ is observed during exercise, as depicted by the ventilatory thresholds of exercise intensity (Beaver, Wasserman and Whipp, 1986).

2.3.2. Exercise induced acidosis and fatigue

Exercise upregulates metabolic flux, with the purpose of generating sufficient ATP to match the energy output of exercise. It is well established that the elevated metabolic flux gives rise to H^+ accumulation, however the magnitude is largely dependent on the intensity, duration (Yoshida and Watari, 1993), type (Mannion, Jakeman and Willan, 1995) and presence of environmental stressors (e.g. hypoxia) (Hogan, Richardson and Haseler, 1999). Intramuscular acid-base balance is perturbed markedly during exercise, as pH can fall from 7.0 to 6.5 (Cairns, 2006) dependant on the type of exercise, whilst extracellular pH also falls but typically from 7.4 to 6.9-7.0 (Hermansen and Osnes, 1972, Sahlin, 1978). Fluctuations in pH are likely to be observed during all forms of exercise; however severe acidosis is anticipated during high intensity exercise lasting 1-10 min (McNaughton, 1990, 1992a, Cairns, 2006). Despite the unequivocal support for the presence exercise-induced acidosis, there is considerable scientific debate regarding the mechanism by which acidosis occurs (Robergs, Ghiasvand and Parker, 2004, Böning et al., 2005, Kemp, 2005, Kemp et al., 2006).

The traditional theory proposes that H^+ accumulation is a result of increased lactic acid formation during exercise, which is a by-product formed by glycolysis (Hultman and Sahlin, 1980). This theory initially came to light due to the strong correlations between lactic acid and pH changes following dynamic ($r = 0.92-0.93$) and isometric ($r = 0.89$) exercise (Sahlin, Harris and Hultman, 1975, Sahlin et al., 1976). Furthermore, lactic acid has a pK_a of 3.87, therefore under normal physiological conditions (i.e. pH 7.4) lactic acid will fully dissociate to form a lactate anion (La^-) and H^+ . Leading to a 1:1 ratio between La^- and H^+ production in active skeletal muscle (Lindinger, 1995). The assumption that all H^+ produced during exercise originates from lactic acid has been contested by Robergs, Ghiasvand and Parker, (2004), and described as an over simplification of the issue. Robergs et al. (2004) suggested that lactic acid

holds a carboxylic structure and consequently it is unable to disassociate fully, thereby implying the 1:1 ratio between La^- and H^+ produced during exercise may be coincidental, with other mechanisms contributing to H^+ production (Robergs, Ghiasvand and Parker, 2004). Furthermore, the production of lactate from pyruvate involves the consumption of H^+ (Toffaletti, 1991), therefore adding further weight to support the theory that lactate may not be a positive net contributor to exercise induced H^+ accumulation.

The alternative theory suggests H^+ are generated through the process of ATP hydrolysis and non-mitochondrial ATP resynthesis during exercise (Robergs, Ghiasvand and Parker, 2004). The ATP hydrolysis is the breakdown of ATP to provide energy for muscular contractions, during which one H^+ is released per reaction. It has been purported that ATP hydrolysis is a principle source of exercise induced acidosis and is deemed more crucial than lactate per se (Robergs, Ghiasvand and Parker, 2004). Despite this, modelling of ATP metabolic response during a high intensity burst of exercise has illustrated phosphate ions, also produced during ATP hydrolysis, may buffer H^+ , whilst creatine kinase also consumes the H^+ produced during ATP hydrolysis (Arthur et al., 1992). Therefore, indicating that the H^+ produced during ATP hydrolysis are removed via other by-products of the reaction. Moreover, the release of H^+ from ATP hydrolysis is thought to diminish as pH decreases, for example 0.52-0.73 H^+ molecules per ATP hydrolysis reaction are released at pH 7.4 and 0.03 – 0.34 H^+ molecules are released at pH 6.8 (Hultman and Sahlin, 1980, Kemp, 2005). Together, this evidence suggests ATP hydrolysis may have minimal influence on exercise induced acidosis despite the assertions of Robergs and colleagues (Robergs, Ghiasvand and Parker, 2004).

Conversely, the resynthesis of ATP may provide a more viable source of H^+ of production. In particular, during intense exercise, when ATP resynthesis is predominantly derived via anaerobic glycolysis and the phosphate system rather than mitochondrial based ATP resynthesis (Robergs, Ghiasvand and Parker, 2004). Basic exercise metabolism suggests that ATP turnover via glycolysis can result in a net production of one or two H^+ per unit of glycogen or blood glucose derived reactions, respectively (McArdle, Katch and Katch, 2015). Consequently, elevations in glycolytic flux, via increased exercise intensity, may be a substantial contributor to exercise induced acidosis. It is worth noting that lactic acid is a by-product produced from glycolysis, therefore it is unclear whether a combined and/or independent contribution of glycolytic chemical reactions and lactic acid dissociation are responsible for H^+ production. Nonetheless, it is apparent that glycolysis is central to the

development of exercise induced acidosis and the magnitude is primarily influenced by the intensity of exercise.

Early work studying the aetiology of fatigue proposed that acidosis was a major cause of fatigue (Hultman and Sahlin, 1980, Fitts, 1994). Research has depicted a close temporal relationship between a fall in intramuscular pH and peak tetanic force, with pH levels below 6.7 suggested to substantially impair the force produced (Spriet et al., 1987, Cady et al., 1989). This magnitude of acidosis (i.e. pH = 6.7) is not uncommon during intense exercise (Cairns, 2006), and therefore may contribute to force impairment during whole body exercise. Despite this, the recovery of power output, subsequent to a maximal 30 s cycling sprint, is shown to occur with three min without a recovery in pH ($p > 0.05$; Bogdanis et al., 1995). This suggests that pH is not the only factor that contributes to fatigue but rather an interplay of several fatigue inducing factors (Allen, Lamb and Westerblad, 2008, Fitts, 2008).

Various mechanisms have been implicated in the relationship between acidosis and fatigue, which predominantly include muscle contractile and metabolic functions (Cairns, 2006, Allen, Lamb and Westerblad, 2008, Fitts, 2008). More specifically, H^+ accumulation has been associated with dysfunction of the sarcoplasmic reticulum due to altered calcium ion sensitivity and handling (Fabiato and Fabiato, 1978), a reduced myosin-actin cross-bridge cycling activity (Mainwood and Renaud, 1985) and increased potassium ion release (Bangsbo et al., 1996), which together can impede muscular myofilament function and excitation-contraction coupling. Whereas, metabolic function is effected through the inhibition of glycolytic flux (Bishop et al., 2004), due to the attenuation of two key regulatory enzymes, phosphorylase and phosphofructokinase (PFK) activity (Trivedi and Danforth, 1966, Hultman and Sahlin, 1980). Hollidge-Horvat et al. (1999) investigated the effect of acidosis on regulation of glycolytic flux during a fifteen min cycling bout at 75% $\dot{V}O_{2max}$, with and without an acidosis inducing supplement, ammonium chloride (NH_4Cl). Phosphorylase activity was significantly lower with NH_4Cl supplementation (21.6 ± 4.5 vs. control: 29.8 ± 5.9 $mMol \cdot Kg^{-1}$ dry wt⁻¹; $p < 0.05$), whilst muscle glycogen sparing was 50% higher under enhanced acidosis (103 ± 16 vs. 157 ± 18 $mMol \cdot Kg$ drywt⁻¹; $p < 0.05$). Furthermore, the concentration of glucose-6-phosphate and fructose-6-phosphate (F-6-P) was significantly elevated ($p < 0.05$) with NH_4Cl compared to exercise alone, suggesting PFK activity was also attenuated, as it is key regulatory enzyme that facilitates the conversion of F-6-P during the glycolytic process (Berg, Tymoczko and Stryer, 2002a) The aforementioned study (Hollidge-Horvat et al., 1999), presents *in vivo* evidence that

acidosis can disturb metabolic functioning during exercise, and together with the proposed impairment of contractile function, may contribute to the development of fatigue and diminished exercise performance.

2.3.3. Metabolic implications of acute hypoxia: effect on acid-base balance

The availability, delivery and utilisation of O₂ is well established as a critical determinant of $\dot{V}O_{2max}$, which can be depicted as a stepwise process, known as the oxygen cascade. This cascade begins with inspired PO₂ during exercise and includes pivotal steps, which if disturbed may attenuate $\dot{V}O_{2max}$. These steps include: 1) pulmonary diffusive capacity, 2) maximal cardiac output, 3) blood flow distribution and haemoglobin content, and 4) skeletal muscle oxidative properties (Bassett and Howley, 2000). A prominent challenge of altitude is the hypoxic environment, representing a lower availability of inspired PO₂ and may subsequently disrupt the oxygen cascade at the initial step. The impact of this is clearly demonstrated through the concomitant decline in arterial oxygen saturation (PaO₂) to 92-95% at moderate altitudes (up to 3000m; Mazzeo, 2008) and consequently, the cardiopulmonary system must compensate for the reduced O₂ availability via delivery processes in the O₂ cascade. Despite this, pulmonary diffusive capacity is impaired. Thereby limiting O₂ movement into the capillaries, due to the narrowing of the oxygen gradient between alveoli and capillary beds in the pulmonary system. A response that is accentuated in highly trained individuals (Martin and O’Kroy, 1993, Calbet, Boushel, et al., 2003). Moreover, there is ambiguity on the effect on cardiac output (Q), with Q either reducing which may further impair delivery (Peltonen, Tikkanen and Rusko, 2001, Fukuda et al., 2010) or Q remains unchanged (Hartley, Vogel and Landowne, 1973, Wagner, Miles and Horvath, 1980) during exercise under moderate acute hypoxia, resulting in a potential negative effect on blood flow distribution (Calbet et al., 2009). Calbet et al. (2009) assessed the delivery of O₂ to exercise leg muscles in nine physically active individuals ($\dot{V}O_{2max}$: 59 ± 2 ml·kg⁻¹·min⁻¹) during incremental cycling exercise at a fractional inspired O₂ (FiO₂) equivalent to 5260 m altitude. The results demonstrated O₂ delivery to the exercising leg fell by 47% and also a corresponding decline in $\dot{V}O_{2peak}$ by 47%, therefore implicating reduction in blood flow distribution to working muscles as a contributing factor to $\dot{V}O_{2max}$ decrease. Together, this evidence offers support that hypoxia disturbs the O₂ delivery aspects of the oxygen cascade, which is linked to the reduction in PaO₂, impairment of pulmonary diffusive capacity, an unresponsive maximal cardiac output and altered blood flow distribution

(Bassett and Howley, 2000). As a result, the mismatch of oxygen availability and the oxidative demands of exercising muscles can disturb metabolic systems.

Skeletal muscle requires an abundant supply of O₂ to maintain energetic and metabolic homeostasis, therefore conditions of low O₂ availability can disturb homeostatic control, particularly to oxygen dependant mechanisms (Horscroft and Murray, 2014). Exposure to acute hypoxia upregulates transcriptional factor hypoxic inducible factor-1 (HIF1). This gene is postulated to operate as a metabolic fuel switch, acting to impair mitochondrial ATP resynthesis, whilst non-mitochondrial ATP resynthesis is maintained, and thus increasing the relative contribution of non-mitochondrial ATP resynthesis (Kim et al., 2006, Papandreou et al., 2006, Murray, 2009). Isolated cell culture work has identified the mechanism by which this phenomenon develops, whereby HIF-1 attenuates pyruvate dehydrogenase (PDH) complex activation and the subsequent oxidation of pyruvate in the aerobic metabolism (Kim et al., 2006; Papandreou et al., 2006). Concurrently, HIF-1 expression stimulates glycolytic gene expression (Berg, Tymoczko and Stryer, 2002; Papandreou et al., 2006) and when considered with the increased translocation glucose transporter, GLUT4, in resting skeletal muscle with hypoxia (Cartee et al., 1991); it offers evidence of an enhanced glycolytic flux with hypoxia. Congruently, research has also demonstrated enhanced glucose utilisation and greater glycolytic flux during submaximal exercise in healthy individuals at 4300 m altitude when compared to the same absolute intensity at sea level (Green et al., 1992, Roberts et al., 1996). The enhanced glycolytic flux however, could be explained by the increased relative intensity under hypoxic conditions compared to sea level, due to the deleterious effect acute hypoxia has on $\dot{V}O_{2max}$ (Wehrlin and Hallén, 2006). During the investigation conducted by Roberts et al., (1996), for example, the same absolute cycling exercise intensity was used in both normoxic and hypoxic trials, which was equivalent to 49% of sea level $\dot{V}O_{2max}$. This however, corresponded to a higher relative intensity at 4300 m, which was equivalent to 65% $\dot{V}O_{2max}$ of hypoxic $\dot{V}O_{2max}$. It is well established that increasing exercise intensities upregulates glycolysis and reduces aerobic energy contribution (Van Loon et al. 2001), hence it is difficult to ascertain whether the accelerated glycolytic flux reported at 4300 m altitude can be attributed to hypoxia or the exercise intensity (Green et al. 1992; Roberts et al. 1996).

Lundby and Van Hall, (2002) identified the limitations of the previous research and designed an investigation to determine the metabolic difference during absolute and relative exercise intensities under acute hypoxia compared to sea level. Eight trained cyclists participated in

three experimental trials involving sixty min of constant load exercise at an intensity equivalent to 60% sea level $\dot{V}O_{2\max}$ (workload: 154 ± 13 W), which included one normoxic and two acute hypoxic trials (4200 m). One hypoxic trial was performed at the same absolute intensity (workload: 154 ± 13 W) to sea level and the other hypoxic trial at a lower intensity (130 ± 15 W) equal to 60% of hypoxic $\dot{V}O_{2\max}$. The authors calculated carbohydrate and fat oxidation as a representation of glycolytic and aerobic contribution, respectively. When exercise was performed at the same relative intensity, determined by a percentage of $\dot{V}O_{2\max}$ at the respective environmental condition, carbohydrate oxidation rates were equivalent at normoxia and acute hypoxia (1.7 ± 0.1 g·min⁻¹), whereas fat oxidation decreased at hypoxia (SL: 0.3 ± 0.1 Vs. Hyp: 0.2 ± 0.1 g·min⁻¹). Therefore, supporting previous research (Green et al. 1992; Roberts et al., 1996). In contrast, carbohydrate oxidation rates were significantly greater when the same absolute intensity was used (2.5 ± 0.2 g·min⁻¹; $p < 0.05$), whilst fat oxidation significantly decreased (0.2 ± 0.1 g·min⁻¹; $p < 0.05$). Consequently, suggesting exercise intensity was primary driver of increased glycolytic flux observed in previous studies (Green et al., 1992; Roberts et al., 1996). Based on the evidence presented it is prudent to question the belief that glycolysis is upregulated under hypoxic conditions, but rather the oxidative metabolism is hindered, and glycolysis consequently provides a greater relative contribution to total energy expenditure during exercise.

In reference to acid-base balance, the diminished activity of oxidative metabolism prompts a greater non-mitochondrial ATP resynthesis which may be responsible, at least in part, for H⁺ accumulation during exercise. In addition, the multi-functional role of HIF-1 regulates multiple processes of H⁺ generation during exercise. This includes the deactivation of PDH enzyme activity (Kim et al., 2006; Papandreou et al., 2006), thereby increasing pyruvate availability for the conversion to lactic acid during exercise. It is also suggested HIF-1 augments the activity of *carbonic anhydrase*, a catalytic enzyme that accelerates reversible bicarbonate buffering reaction to produce H⁺ and HCO₃⁻ (Solani et al., 2010). Consequently, increasing [H⁺] due to the enhanced disassociation of carbonic acid to H⁺ and HCO₃⁻.

Taken together, the metabolic perturbations observed under acute hypoxia may be central components to the accelerated rate of exercise-induced acidosis (Hogan et al., 1999). In well trained individuals, the rate of lactate accumulation is progressively aggravated with increasing levels of hypoxia during sub-maximal exercise, with significant differences arising from 1000 m ($p < 0.05$; Clark et al., 2007). Comparably, under a hypoxic stress, equivalent to 3000 m, the

rate of lactate production is four-fold greater in comparison to normoxia (Romer et al., 2007). In a well-designed experiment, Romer et al. (2007) used three experimental trials during which participants cycled at a constant load equivalent to 92% normoxic W_{\max} , under acute hypoxic and normoxic conditions. The initial trials were performed to exhaustion, with exercise duration $70 \pm 3\%$ longer under normoxia compared to hypoxia (13.4 ± 0.8 min vs. 4.2 ± 0.5 min, respectively; $p < 0.01$) but end-point [bla] were similar between trials (Normoxia: 10.1 ± 0.6 mMol \cdot l $^{-1}$ vs. Hypoxia: 10.07 ± 0.9 mMol \cdot l $^{-1}$). The participants then completed a normoxic control trial that involved a constant load exercise for the duration equivalent to the hypoxic exhaustion trial (4.2 ± 0.5 min) and observed end-point [bla] to be 5.7 ± 0.3 mMol \cdot l $^{-1}$, which corresponds to a 43% ($p < 0.05$) lower blood lactate accumulation compared to end-point [bla] at exercise exhaustion at normoxia to hypoxia. As [bla] and H⁺ appearance exhibit a 1:1 ratio during exercise (Lindinger, 1995), it can be postulated that the rate of H⁺ accumulation, and thereby exercise-induced acidosis, develops at a greater rate under hypoxia and may consequently contribute to an early on-set of fatigue and diminished exercise performance at altitude.

2.4. The effect of acute hypoxia on exercise tolerance and performance

Sojourns to terrestrial high altitudes have grown in popularity in recent years, with the World Health Organisation reporting that approximately 35 million people visit terrains greater than 3000 m every year. Furthermore, there is a greater prevalence of altitude and hypoxic training camps amongst elite athletes in preparation for major competition. This has necessitated a greater understanding on the effect of altitude on exercise performance. A predominant environmental stressor for human physiology at altitude is the lower partial pressure of oxygen with progressive elevations. As such, the recent commercialisation of hypoxic simulation chambers and portable devices has increased the accessibility to acute hypoxic training strategies for recreational athletes and individuals predisposed to health issues. Intermittent hypoxic training (IHT) is one ergogenic training strategy commonly used; whereby isolated acute hypoxic training bouts are interspersed within a training programme. These acute training bouts; however, present a substantially negative impact on exercise capacity (Wehrlein and Hallén, 2006) and performance (Clark et al., 2007, Goods et al., 2014). Therefore, quantifying the negative effect of hypoxia is important to inform exercise prescription and performance management during IHT training and other forms of acute hypoxic exercise.

The magnitude of acute hypoxia's ergolytic effect is dependent on the type of exercise and the duration (Wyatt, 2014). Indeed, mean power output during 5 min TT reduces by 7% every 1000 m (Clark et al., 2007) and exercise capacity is reported to decline by 9.4% in the first 500 m with a greater 14.3% per 1,000 m thereafter (Wehrlin and Hallén, 2006). However, mean power output and work completed during repeated sprint exercise (RSE) is only impaired from hypoxic conditions equivalent to 4000 m (Bowtell et al., 2014, Goods et al., 2014). This difference in effect may be attributed to the shorter duration of activity during RSE tests; given the suggestion that high intensity exercise lasting less than 2 min is largely unaffected by hypoxia (Wyatt, 2014). Furthermore, acute hypoxia is shown to enhance the relative anaerobic energy contribution and concurrently lower the relative and absolute aerobic contribution (Horscroft and Murray, 2014, Scott, Goods and Slattery, 2016). Therefore, the magnitude of decline is likely to be dependent on the bioenergetic demand of the exercise bout, which is determined by duration and the required intensity. Despite current evidence from experimental investigations, a pooled effect from all available evidence is required for a more generalisable understanding of the effect of acute hypoxia on exercise performance.

The influence of acute hypoxia during exercise is subject to large inter-individual variability, with training status (Macinnis, Nugent, Macleod, & Lohse, 2015) and an individual's ability to maintain oxyhaemoglobin saturation (SaO₂) during exercise (Chapman et al., 2011), are all cited as the primary reasons for this variability. Indeed, a meta-analysis identified that the reduction of $\dot{V}O_{2max}$ under acute hypoxia was greater in those that possessed a superior $\dot{V}O_{2max}$ (Macinnis et al., 2015). Thereby, suggesting that athletes of a higher training status may be subject to a greater decrement in performance compared to their untrained counterparts. While, susceptibility to SaO₂ reductions is reported to be a more robust predictor of exercise performance under hypoxia, given the preservation of SaO₂ during exercise is linked to the improved maintenance of 3000 m running performance under acute moderate hypoxic conditions (Chapman et al., 2011). Therefore, reducing peripheral oxygen delivery to active musculature, as inferred through a lower SaO₂, is suggested to be a primary moderator of exercise performance within acute hypoxic conditions. With the resultant effect presenting an increased development of peripheral fatigue (Amann et al., 2006), particularly under moderate acute hypoxic conditions, due to the enhanced relative contribution of anaerobic energy sources (discussed in section 3.3).

2.5. The Ergogenic Effect of Sodium Bicarbonate

Sodium bicarbonate is an exogenous alkalising agent, which acts to increase extracellular blood $[\text{HCO}_3^-]$, which consequently induces blood alkalosis (i.e. increase blood pH) (Carr et al., 2011, Jones et al., 2016); whilst also strengthening extracellular HCO_3^- buffering capacity and altering muscle ionic membrane potential (Siegler et al., 2016). Supplementation of NaHCO_3 is prescribed in doses relative to body mass and have ranged from 0.1 to 0.5 $\text{g}\cdot\text{Kg}^{-1}$ body mass in scientific investigations (McNaughton, 1992b, Stannard et al., 2016). Accordingly, the temporal rise in blood $[\text{HCO}_3^-]$ is relative to the prescribed dose, with absolute increases of up to approximately 6 $\text{mmol}\cdot\text{L}^{-1}$ observed for doses of 0.3 $\text{g}\cdot\text{kg}^{-1}$ (Jones et al., 2016). Increases of such magnitude ($\geq 6 \text{ mmol}\cdot\text{L}^{-1}$) are purported to represent a threshold whereby the ergogenicity of NaHCO_3 is 'almost certain' (Matson and Tran, 1993, Carr et al., 2011). Indeed, the ergogenic effect of NaHCO_3 is mediated through the reinforcement of extracellular blood $[\text{HCO}_3^-]$, which facilitates extracellular removal of a substantial acidic load (i.e. H^+) produced during exercise. Accordingly, the emphasis of academic research is placed on supra-maximal, all-out and repeated sprint exercise bouts (Carr et al. 2011; McNaughton et al. 2008; 2016) which are exercise modalities that elicit the greatest metabolic acidosis (Cairns, 2006) and therefore, are postulated to exhibit the most efficacious ergogenic response from NaHCO_3 .

The effect of NaHCO_3 on short duration all-out and supra-maximal exercise has shown a large degree of variability, with investigations reporting both an improvement in performance (McNaughton, 1992b, Bellinger et al., 2012, Driller et al., 2012, Thomas, Delfour-Peyrethon, et al., 2015) and no effect (Vanhatalo, McNaughton, et al., 2010, Sale et al., 2011a, Higgins, James and Price, 2013, Kirk et al., 2014, Saunders et al., 2014b). Early research, demonstrated the ergogenicity of NaHCO_3 is observed during all-out cycling exercise of 120 sec and 240 sec in duration but not shorter 10 sec and 30 sec exercise bouts (McNaughton, 1992a). This corroborates with previously reported improvements in sprint times of 400 m, 800 m and 1500 m running track performances (Wilkes, Gledhill and Smyth, 1983; Goldfinch, McNaughton and Davies, 1988; Bird, Wiles and Robbins, 1995). Together, this led to the proposition of an ergogenic window of high intensity exercise spanning between 1-7 min, during which NaHCO_3 was deemed to be most efficacious. Indeed, more recent investigations have demonstrated improvements in all-out exercise of 70 sec (Thomas et al., 2016) and 4 min (Driller et al., 2012; Bellinger et al., 2013) amongst trained individuals ($\geq 65 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Although, in a lesser trained cohort ($\leq 50 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) the ergogenic effect is not observed (Vanhatalo et al. 2010;

Peart et al. 2013). Similarly, constant duration supra-maximal exercise to exhaustion has also shown no change following NaHCO₃ ingestion in recreational participants (Sale et al. 2011; Higgins et al. 2013; Saunders et al. 2014a; Dias et al. 2015), despite substantial challenges to the acid-base balance (Saunders et al. 2013).

Due to the equivocal research outcomes, Dias et al. (2015) designed an intelligent investigation to quantify this variability and to identify if the ergogenicity of NaHCO₃ was a question of the presence of responder/ non-responder phenomenon. In this study, 15 recreationally active participants conducted six experimental exercise trials, with four trials administering a prior NaHCO₃ bolus and two involving a taste-matched placebo before performing the Cycling Capacity Test 110% (CCT_{110%}); a TTE test performed at 110% of a participant's maximum power output (W_{max}) attained during an incremental test to exhaustion. Across the four NaHCO₃ trials, blood acid-base response was consistent; that is, mean pH and [HCO₃⁻] did not differ in each NaHCO₃ condition. Despite the consistent blood response, performance across the four trials were not consistent following supplementation, with performance only significantly improved compared to placebo in one of the four trials. Despite not reporting any gastrointestinal issues from NaHCO₃, which is often cited as a reason for a null effect observed from NaHCO₃, this study observed an inconsistency in individual response to supplementation as 10 participants demonstrated improved performance in at least one of the four trials; however, five participants did not exhibit improved performance in any of the trials. This study therefore may allude to a responder/ non-responder effect to NaHCO₃ supplementation during constant load supra-maximal exercise to exhaustion and a large degree of within subject variability (Dias et al. 2015).

These findings are however, in stark contrast to a similar investigation evaluating NaHCO₃ effect during two separate 4 km TT performances amongst 11 trained cyclists (Gough et al. 2017). Across two scientific publications in the same participants, the authors demonstrated that NaHCO₃ was an effective ergogenic aid during 4 km TT performance compared to a taste matched placebo (Gough et al. 2017); whilst also reporting an excellent consistency in performance improvement ($r = 0.9$) across the two repeated TT's (Gough et al., 2017a). In addition to contradicting previous research that alluded to a large within participant variability (Dias et al., 2015); these outcomes also oppose previous research that reported NaHCO₃ had no ergogenic effect on 4 km TT performance (Callahan et al., 2017, Correia-Oliveira et al., 2017). These discrepancies in evidence could be explained by methodological differences

across investigations, which include the participants training status, timing of NaHCO₃ supplementation, the type and intensity of exercise test. These variables could also be used to explain some of the variability in the body of scientific literature investigating the ergogenic effects of NaHCO₃.

Training Status

Meta-analytic data has highlighted that training status may moderate the ergogenic effects of NaHCO₃, as trained individuals were found to experience a greater performance improvement $1.7\% \pm 2.0\%$ (mean \pm 90% confidence interval) compared to non-athletic populations ($-1.1\% \pm 1.1\%$) (Carr, Hopkins and Gore, 2011). The reason for this observation remains unclear, although it is reasonable to postulate that a greater athletic status of participants may enhance the sensitivity to detect the 'true' ergogenic effect of NaHCO₃, simply because they are able to replicate performance more reliably (Currell and Jeukendrup, 2008). Alternatively, from a physiological perspective, it is known that a period of RSE training can enhance the abundance of MCT protein content (McGinley and Bishop, 2016). Given, induced blood alkalosis can upregulate MCT protein activity due to the increased pH gradient between intramuscular and extracellular compartments (Mainwood and Worsley-Brown, 1975). Trained individuals may possess a larger abundance of MCT protein that could be stimulated and therefore, the effect of NaHCO₃ on the efflux of H⁺ may be greater in trained than untrained individuals, and subsequently mediate greater performance benefits. To establish this however, research is required to assess if an increase in MCT protein content following a period of RSE training, alters the efficacy of NaHCO₃ ergogenic effect.

It could also be speculated that the greater experience of trained riders may allow these participants to access their performance reserve; a reserve that refers to an exercise intensity, that is below an individual's true absolute maximal intensity, which individuals do not exceed to prevent the negative consequences associated with absolute maximal exercise (St Clair Gibson, Swart and Tucker, 2018). Stone et al., (2017) suggested that training experience may increase an individual's introspective sensitivity and physiological awareness, thus it could be speculated that trained individuals may be more willing, with the facilitation of NaHCO₃, to perform exercise in their metabolic reserve. This subsequently may offer an explanation for the discrepancy between (Gough et al. 2017) and (Dias et al., 2015), who used trained and recreational participants, respectively. Nonetheless, this discrepancy can only be inferred from

the available literature, as no study has empirically assessed the efficacy of NaHCO₃ supplementation between the two groups.

Timing of NaHCO₃ supplementation

The blood acid-base kinetics following the ingestion of NaHCO₃ displays an individual temporal response; with time course of peak [HCO₃⁻] to transpire varying between individuals and doses administered (Gough et al. 2017; Jones et al. 2016). The administration of NaHCO₃ is most typically prescribed as standardised ingestion time prior to exercise, as early research suggested blood alkalosis occurred at 60-90 min following ingestion (Renfree, 2007, Price and Singh, 2008, Siegler et al., 2010). However, these investigations employed a low sampling frequency (≥ 20 min), which neglected the temporal characteristics of acid-base kinetics. The ergogenicity of NaHCO₃ is suggested to be mediated by the availability of blood [HCO₃⁻] to facilitate extracellular buffering of H⁺ produced during exercise (Matson and Tran, 1993, Carr et al., 2011); therefore, individualising the timing of NaHCO₃ supplementation prior to exercise may be most appropriate to maximise the ergogenic potential. Indeed, Jones et al., (2016) mapped the time course of blood acid-base analytes in response to three different doses of NaHCO₃ administered using capsules; peak blood [HCO₃⁻] were observed between 75 to 180 min following 0.3 g·kg⁻¹, 40 to 165 min following 0.2 g·kg⁻¹ and 30 to 150 min following 0.1 g·kg⁻¹. This individual blood acid-base response to NaHCO₃ is also thought to be reproducible in the time taken for peak [HCO₃⁻] to transpire, when the same dose was ingested on two separate occasions using a single liquid bolus (Gough et al. 2017). The authors demonstrated that time to attain peak blood [HCO₃⁻] was highly reproducible ($r = 0.94$, $p < 0.001$) and time taken to attain peak blood pH, while demonstrating a good reproducibility ($r = 0.71$, $p < 0.016$), was found to be less reliable. Together, this large variance in individual acid-base kinetics presents a caveat to all prior research, as the magnitude of [HCO₃⁻] may not have been maximised prior to exercise given standardised ingestion times were used previously.

This consequently may explain the discrepancies between outcomes of 4 km TT performances found by Gough et al. (2017) who used an individualised NaHCO₃ timing strategy, and that of Callahan et al. (2017) and Correia-Oliveira et al. (2017) who prescribed NaHCO₃ at a standardised time prior to exercise. The resultant effect of blood acid-base balance is evident when comparing the blood [HCO₃⁻] prior to exercise, with individually timed supplementation elevating blood [HCO₃⁻] by 6 mmol·l⁻¹ compared to placebo (Gough et al. 2017). Whereas,

those reporting a null effect reported increase of 4 mmol·l⁻¹ (Correia-Oliveira et al., 2017) and 5 mmol·l⁻¹ (Callahan et al., 2017), which are below the purported threshold required to elicit an ergogenic benefit (Matson and Tran, 1993). This therefore, suggests adopting a standardised dose timing strategy is, in some cases, ineffectual at elevating blood [HCO₃⁻] sufficiently. The rise in blood [HCO₃⁻] was not, however, the concern when comparing the two NaHCO₃ reproducibility investigations, as both reported an equivalent (~ 6 mmol·l⁻¹) increases in blood [HCO₃⁻] (Gough et al. 2017; Dias et al. 2015). As such, the contrasting outcomes between investigations cannot not be solely attributed, if at all, to the method NaHCO₃ administrations (i.e. individualised or standardised timing strategy). Despite a plausible physiological rationale for personalised administration, empirical research has yet to establish if this method is superior to the standardised timing strategy from a performance enhancement perspective. Inferences of this nature should therefore, be viewed with caution.

Type and intensity of exercise

An apparent difference between the two NaHCO₃ reproducibility investigations was the use of TTE and TT exercise tests. Time to exhaustion tests are typically used to test and identify mechanistic implications of experimental interventions. Indeed, Dias et al., (2015) used the CCT_{110%}, a supramaximal TTE to exhaustion, which was designed to yield a substantial H⁺ load during exercise (Saunders et al., 2013). As such, exercise induced acidosis was deemed to be the predominant reason for the development of fatigue during this test and was therefore, hypothesised to possess the appropriate physiological conditions to test the efficacy of alkalotic buffering supplements. The ecological validity of TTE test has however, been questioned as athletes do not typically maintain a constant load to exhaustion during competition. Whereas TT tests offer an ecologically valid model to simulate athletic performance in laboratory conditions, which allows the participants to self-regulate exercise intensity in response to physiological stressors and interventions (Currell and Jeukendrup, 2008). In addition, TT performance possess less variability in performance outcomes, which is essential to detect small changes in performance brought about by experimental interventions (Currell and Jeukendrup, 2008). More specifically, the CCT_{110%} possess a coefficient of variation (CV) equal to 4.42% (Saunders et al., 2013) and a 4 km TT test has a CV of 1.6% (Altareki et al., 2009). This therefore highlights the experimental tests employed by Gough et al. (2017) would be more sensitive to detect a change in performance following NaHCO₃; which consequently may explain the variance between the two investigations.

The CCT_{110%} and the 4 km TT are not only different types of exercise testing, they are also different in their mean duration and intensity. Typically, the CCT_{110%} can be sustained for 2-4 min and is a supra-maximal exercise test; whereas a 4 km TT is approximately 6 min in duration, for trained cyclists, and fluctuates in intensity depending on athlete pacing strategy but on average resides approximately 90% of $\dot{V}O_{2\max}$ (Stone et al., 2011). The difference in mean exercise intensity could also explain the differing outcomes, as NaHCO₃ has been suggested to have an intensity dependent effect (Higgins, James and Price, 2013). Interestingly, the authors reported NaHCO₃ improved exercise tolerance by 17% (383 ± 44 sec vs. 327 ± 29 sec; $p < 0.01$) during constant load exercise performed at 100% W_{\max} ; however, no effect was reported at neither 110% or 120% W_{\max} TTE tests. Intuitively, the greater exercise intensity will result in a larger and faster rise in the rate of intramuscular H⁺ accumulation, which may provide the most appropriate physiological conditions for pre-exercise alkalosis to be beneficial. As this was not apparent, alternative physiological mechanisms should be considered. Indeed, rodent models have alluded to an intensity dependent effect on the expression of MCT transporters, with increasing exercise intensity enhancing the activity of MCT isoforms 1 and 4 (Hamada and Takimoto, 2013). The stimulation of these MCT transporters is passive (i.e. energy independent) and regulated by the size of the pH gradient between intramuscular and extracellular compartments; as such, it may be speculated that higher intensity exercise, which elicits a greater rate in intramuscular acidic development, may activate a greater proportion of available transporters. If this hypothesis remains true in exercising human models, it could be speculated that the null effect reported by Higgins and colleagues (2013) during supra-maximal exercise could be attributed to a greater saturation of the MCT transporters compared to the 100% W_{\max} test. As such, the induced alkalosis via NaHCO₃ may have a diminishing effect on MCT upregulation, and thus intramuscular H⁺ efflux, as the transporters may become saturated with increasing intensity. Despite the sound physiological rationale this hypothesis should be interpreted with caution, as research is yet to evaluate the effect of induced blood alkalosis on MCT expression and the subsequent role of exercise intensity. Therefore, the importance of exercise intensity on explaining the differing outcomes between the two reproducibility studies can only be speculated at present (Dias et al., 2015, Gough et al., 2017a). Nevertheless, given NaHCO₃ has predominantly focused on maximal/supra-maximal intensity exercise, it warrants investigations into the ergogenic effect of NaHCO₃ during lower intensity exercise where substantial acid-base perturbations remain evident.

2.5.1. The Ergogenic effect of Sodium Bicarbonate on Severe Intensity Exercise

The identification of the severe intensity domain is relative to the presence of exercise intensity threshold and $\dot{V}O_{2max}$ (Burnley and Jones, 2007, Rossiter, 2010). This includes physiological thresholds of LT2 and VT2, and the mathematical construct, CP. Whereas the quantification of the severe domain is associated with the amplitude of the $\dot{V}O_2$ slow component and the W' parameter of the power-duration relationship. At this intensity an inexorable rise in $\dot{V}O_2$ occurs to nadir until the point of exercise exhaustion. As such, this may be the lowest exercise intensity where exercise-induced acidosis may contribute to development of fatigue and therefore, presents physiological conditions that may benefit from $NaHCO_3$ supplementation. This section will therefore, review the literature that has assessed the effect of $NaHCO_3$ during exercise relative to the LT2, VT2 and CP physiological thresholds that delineates the onset of the severe intensity domain.

The most prominent early investigation assessing the influence of pre-exercise alkalosis on prolonged exercise performance reported a significant 14% improvement in total work complete ($NaHCO_3$: 950 ± 81.1 kJ vs. PLA: 839.0 ± 88.6 kJ) during a 60 min TT (McNaughton, Dalton and Palmer, 1999). However, subsequent investigations have not supported the initial observations during a similar duration 40 km TT (Northgraves et al., 2014), while $NaHCO_3$ was also deemed to have no effect on 30 min TT performance (Stephens et al., 2002). The use of time-based and distance-based TTs, although of similar duration, do exhibit discrete differences in an athlete's perception of judging power output distribution (Abbiss et al., 2016). Therefore, the methodological difference between 60 min and 40 km TT may explain the difference observed between the two investigations (McNaughton, Palmer and Dalton, 1999; Northgraves et al., 2014). Furthermore, the presence of a head to head competition between two randomly assigned participants used by McNaughton et al. (1999) may also provide an explanation to the conflicting findings (Williams et al., 2015). As head to head competition is demonstrated to increase motivation of participants and improve performance by increasing anaerobic energy expenditure (Corbett et al., 2012). This consequently, may increase the amount of work performed in the severe intensity domain during the 60 min time trial and thus explain the ergogenic benefit of $NaHCO_3$ over this duration (McNaughton, Palmer and Dalton, 1999). Although, *priori* physiological thresholds were not identified and therefore this can only be speculated.

Research explicitly prescribing intensities for constant work rate exercise, relative to physiological thresholds have elicited an ergogenic effect from NaHCO_3 (George and MacLaren, 1988, Egger et al., 2014). Egger et al., (2014) asked 21 trained cyclists ($67.3 \pm 9.8 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to perform a 30 min exercise bout at 95% of the individual anaerobic threshold (IAT) followed by exercise to exhaustion set at 110% of IAT; with the purpose of comparing $0.3 \text{ g}\cdot\text{kg}^{-1} \text{ NaHCO}_3$ and a placebo (4 g sodium chloride; NaCl) supplement. Overall exercise tolerance was reported to significantly improve from $45.0 \pm 9.5 \text{ min}$ with placebo to $49.5 \pm 11.5 \text{ min}$ with prior NaHCO_3 , representing a 10% improvement (Egger et al., 2014). Despite different determination methods of the IAT and LT2, there is appears to be a synonymous relationship as both threshold have been determined at similar intensities (De Barros et al., 2012). Therefore, it is appropriate to suggest Egger et al. (2014) presents evidence of the ergogenic effect of NaHCO_3 in the severe intensity domain. Caution should however be taken in this interpretation, as the sodium content between supplement treatments were not matched, given sodium possess ergogenic traits, the improvements in performance cannot be attributed to an improved HCO_3^- buffering potential alone (see section 5.3 for further discussion). However, George and Maclaren, (1988) earlier presented evidence that corroborates the observation of Egger et al. (2014). The authors demonstrated $0.2 \text{ g}\cdot\text{kg}^{-1}$ body mass of NaHCO_3 improved exercise tolerance by 17% ($p < 0.01$) at an intensity prescribed at the onset of blood lactate accumulation ($4 \text{ mmol}\cdot\text{L}^{-1}$). Therefore, an improved HCO_3^- may elicit performance improvement in the severe intensity domain, at intensities relative to lactate thresholds, although further experimental work is required to elucidate this suggestion.

The intensity of CP is equivalent to that of the lactate thresholds and has similarly demonstrated an improved exercise sustainability with pre-exercise NaHCO_3 at an intensity equivalent to CP (Mueller et al., 2013). The ergogenic effect of NaHCO_3 was assessed on five consecutive days, with performance greater on each day compared to placebo, which resulted in a significant mean improvement of 23.5% ($826.5 \pm 180.1 \text{ sec}$ vs. $669.0 \pm 167.2 \text{ sec}$; $p < 0.001$). It is important to note, however, that the average exercise duration during the placebo trial was $11.09 \pm 2.47 \text{ min}$, which is considerably less than in previous research (Poole et al., 1998; De Luca et al., 2012). De Luca et al. (2012) reported exercise sustainability at CP to be $22 \pm 7.5 \text{ min}$ in trained cyclist, whilst tolerance to an exercise intensity 5% above CP was maintained for $13.3 \pm 5.8 \text{ min}$. These findings corroborated earlier work conducted by Poole et al. (1998). Consequently, this may suggest that CP was overestimated by Mueller et al., (2013) given the 5% error associated with CP determination (Poole et al., 2016), or CP per se, overestimates the

maximal sustainable aerobic power and hence is affected by pre-exercise alkalosis. In contrast, the determination of CP using the three min all-out exercise protocol did not change with prior NaHCO₃ (Vanhatalo et al., 2010), which is indicative of an overestimation of CP by Mueller et al., (2013).

Exercise performed above CP is defined by the W' parameter, which itself is used as marker to quantify the volume of work that can be performed in the severe intensity domain (Jones et al., 2010). When considering the utilisation of W' is associated with accumulation of metabolites, including H⁺, pre-exercise alkalosis may theoretically increase the magnitude of W' . This was not, however, represented by Vanhatalo et al. (2010) during the three min all-out critical power test. This observation suggests that the H⁺ accumulation above CP is coincidental rather than a determining factor of W' . The reason for the difference is unclear, however, it could be associated with the previously discussed implications of aerobically fitter participants demonstrating greater performance benefits from NaHCO₃ (Carr et al. 2011b), as recreationally active participants were used in this study. Nonetheless, the results are opposed to the previously discussed research which indicates the alkalotic manipulation of the acid-base balance improves exercise capacity in the severe intensity domain. Furthermore, NaHCO₃ is thought to reduce the amplitude of the $\dot{V}O_2$ slow component (Berger et al., 2006), which itself is intrinsically associated with W' (Jones et al., 2010). As such, interventions that alter the magnitude of $\dot{V}O_2$ slow component should theoretically effect W' (Jones et al. 2010; Poole et al. 2016). On this premise, further work assessing the influence of pre-exercise alkalosis on W' in a trained cohort is warranted.

Despite the importance of exercise-induced acidosis in the severe intensity domain, relatively little research has focused on this range of intensities. Further to this, only a single investigation has tested the impact of alkalotic inducement on intermittent exercise, during which the work intervals were conducted within the severe intensity domain (Kozak-Collins, Burke and Schoene, 1994). Experimental trials were performed to exhaustion at 95% $\dot{V}O_{2peak}$ for 60 sec during work bouts and 60 sec recovery interval, with a non-significant 19% mean difference in exercise tolerance with prior NaHCO₃ ingestion. Despite the lack of significance, the difference could be interpreted as a practically meaningful change, while four of the seven participants were shown to elicit performance improvements. A low Statistical power may provide an explanation for the frequentist outcome and as such, further investigation is warranted to determine if NaHCO₃ elicits ergogenic effect.

2.5.2. Mechanism of action

The ergogenic effect of NaHCO_3 stems from the reinforcement of the extracellular bicarbonate buffer capacity, which enhances the buffering capacity to regulate of acid-base balance during intense exercise. Ingestion of NaHCO_3 gives rise to bicarbonate ions (HCO_3^-), thus contributing to an alkalotic environment in the extracellular fluid compartments (Carr et al. 2011a). Concurrently, the elevated HCO_3^- enlarges the gradient between extracellular and intracellular H^+ , which stimulates the lactate/ H^+ MCT co-transporters (Roth and Brooks, 1990). In turn, a greater efflux of H^+ from intramuscular regions into the extracellular fluid occurs; allowing for HCO_3^- and buffering compensatory systems to remove H^+ , and therefore increasing pH. The direct mechanism by which the inducement of alkalosis evokes an ergogenic response on exercise is however, unclear. Numerous propositions surrounding both peripherally and centrally driven mediators of fatigue and exercise performance have been investigated (Siegler and Marshall, 2015). Such mechanisms include the attenuation of exercise induce arterial oxygen desaturation allowing for enhanced O_2 delivery (Nielsen et al., 2002a), delaying the impairment muscular contractile properties during exercise (Verbitsky et al., 1997) and augmenting glycolytic enzyme activity (Hollidge-Horvat et al., 2000) and subsequent enhanced muscle glycogen utilisation (Percival et al., 2015). More recently, research is indicative of an altered neuromuscular response with pre-exercise NaHCO_3 administration (Hunter et al., 2009, Siegler et al., 2013). A neuromuscular response that is characterised by a reduced rate of force production decline during isometric contractions following a bout of sub-maximal exercise (Hunter et al., 2009) and repeated bouts of high intensity exercise (Siegler et al., 2013). Therefore, suggesting NaHCO_3 modifies peripheral indices of fatigue to improve exercise performance.

A physiological mechanism that is often ignored when discussing the ergogenic effect of NaHCO_3 is the strong ion difference (SID). The SID represents the balance the in ionic charge of blood plasma between cations (including Na^+ , K^+ , Ca^{2+} and Mg^{2+}) and anions (including Cl^- and lactate $^-$), which typically rest at a positive ionic charge between 40-45 mv. The supplementation of NaHCO_3 is accompanied with a substantial Na^+ load, which increases the SID and therefore, has an effect on increasing blood pH and reducing potassium cation (K^+) efflux from active skeletal musculature (Siegler et al., 2016). The latter has important implications on maintaining skeletal muscle resting membrane potential and thus sarcolemma excitability to prolong the sustainability of muscular contractions (Cairns and Lindinger, 2008).

However, only isolated small muscle mass exercise (i.e. finger flexion exercise) has been used to assess the effect of NaHCO₃ on the SID. The authors demonstrated an enhanced exercise tolerance, which was accompanied by an improved regulation of K⁺ and subsequently presented the evidence of the role of increasing SID on exercise performance. No study has yet however, investigated the relationship between NaHCO₃ and SID on whole body exercise performance; therefore, prominence of this mechanism is yet to be established.

There is also evidence that alludes to a central derived mechanism by which the ergogenic effect of NaHCO₃ is exerted. During a combination of ischemia and repeated maximal voluntary contractions, voluntary activation was preserved to a greater extent with prior alkalosis compared to control ($76 \pm 5\%$ vs. $57 \pm 8\%$, $p < 0.05$; Siegler et al., 2015). Voluntary activation is used as an indicator of descending central drive, which is hypothesised to be preserved with NaHCO₃ due to the reduced attenuation of group III and IV afferent firing under dampened acidic conditions (Pollak et al., 2014). The proposition of a centrally acting mechanism for NaHCO₃ is however not new, as early work by Swank and Robertson, (2002) introduced the concept of NaHCO₃ lowering the subjective perception of exercise intensity. Such an observation suggests NaHCO₃ may act centrally by altering the perception of exercise to prolong an individual's tolerance to exercise. Nonetheless, further work is required to elucidate the mechanism by which NaHCO₃ acts, although it is likely to be an interplay of peripheral and central components.

2.5.3. Limitations of Sodium Bicarbonate Supplementation

Gastrointestinal discomfort

The challenge in prescribing a NaHCO₃ dosage strategy to elicit maximal ergogenic potential is the attainment of a peak blood alkalotic environment while offsetting the onset and severity of gastrointestinal (GI) disturbances (Burke and Pyne, 2007, McNaughton et al., 2016). The most prevalent dose within scientific research is $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass NaHCO₃ preceding exercise, which is based on the early findings of McNaughton, (1992). Through the assessment of incremental doses from 0.1 to $0.5 \text{ g}\cdot\text{kg}^{-1}$ body mass, McNaughton, (1992) observed improvements to 60 sec maximal sprint performance plateaued beyond $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass, despite progressive rises in blood HCO₃⁻ as dose increased. A greater prevalence and increased severity of GI was observed with doses of 0.4 - $0.5 \text{ g}\cdot\text{kg}^{-1}$, compared to $0.3 \text{ g}\cdot\text{kg}^{-1}$, which is cited as the main reason for a plateau in performance (McNaughton, 1992). Nonetheless, ingestion of $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass also provokes instances of GI and are suggested to have a detrimental

effect on performance (Cameron et al. 2010; Saunders et al. 2014a). Indeed, Saunders et al., (2014a) reported a 4.7% improvement in total work done during a 110% peak power output to exhaustion but only when four participants that suffered from GI were removed from analysis (all participants (N=21): placebo = 45.6 ± 8.4 kJ, NaHCO_3 = 46.8 ± 9.1 kJ, $p > 0.05$; without GI (N=17): placebo = 46.2 ± 9.2 kJ, NaHCO_3 = 48.4 ± 9.3 kJ, $p < 0.05$). Nonetheless, Cameron et al., (2010) reported a weak relationship between GI occurrence and sprint performance ($p = 0.90$, $r = 0.34$), whilst other research has demonstrated performance improvements and GI occurrence can co-exist (McNaughton, 1992a, Miller et al., 2015); therefore, the impact of GI on performance may not be as detrimental as first proposed.

Sodium content

As the chemical formula suggests, NaHCO_3 is comprised of a sodium, hydrogen, carbon and three oxygen atoms; which holds a molecular mass of $84.00661 \text{ g}\cdot\text{mol}^{-1}$ of which 72.7% is formed by HCO_3^- and 23.3% of sodium (Na^+). The typical $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass NaHCO_3^- dose is therefore calculated to contain 0.081 g Na^+ and 0.216 g HCO_3^- and therefore, an example 70 kg individual would ingest 5.67 g Na^+ with the NaHCO_3^- dose. Consequently, the Na^+ content of NaHCO_3 has implications for health (Falkner and Kushner, 1990) and performance (Mora-Rodriguez and Hamouti, 2012). From a health perspective, a high daily Na^+ load ($> 10 \text{ g}\cdot\text{day}^{-1}$) above normal dietary intake is demonstrated to induce hypertension and increased cardiovascular risk (Falkner and Kushner, 1990, Wei et al., 2014). Interestingly, seven consecutive days of NaHCO_3 supplementation has been demonstrated to reduce blood pressure in hypertensive patients (Luft et al., 1990), therefore the action of Na^+ in NaHCO_3 may exert a different effect compared to alternative sources (e.g. sodium chloride (NaCl)). Although, further research is required to assess the safety of daily supplementation for athletes. Nevertheless, in the context of this thesis, NaHCO_3 is administered as an acute supplement and therefore, may not be deemed a substantial risk for participants if dietary Na^+ intake is regulated on the day of supplementation.

In relation to exercise performance, the Na^+ content may also contribute to the overall ergogenic effect of exogenous NaHCO_3 supplementation (Rodriguez and Hamouti, 2013). Sodium induces a state of hypervolemia, as fluid shifts from intra to extra-cellular fluid compartments to facilitate the attainment of a homeostatic Na^+ gradient across body water compartments (Luetkemeier, Coles and Askew, 1997). The ergogenic practice of ‘sodium

loading' with $164 \text{ mEq Na}\cdot\text{L}^{-1}$ is demonstrated to expand plasma volume and in turn improve exercise performance in temperate conditions (Greenleaf et al., 1997, Coles and Luetkemeier, 2005). This included a substantial 7.8% ($p < 0.05$) improvement in 15 min TT performance compared to a no-sodium experimental condition (Coles and Luetkemeier, 2005). The ingestion of $0.3 \text{ g}\cdot\text{kg}^{-1}$ body mass of NaHCO_3 by a hypothetical 70 kg athlete will include a Na^+ dose equivalent to $246.5 \text{ mEq Na}\cdot\text{L}^{-1}$, greater than the pre-exercise dose shown to elicit the ergogenic benefits of Na^+ . This necessitates the utilisation of a sodium-matched control beverage during experimental research assessing the improved physiochemical buffering potential determined by NaHCO_3 , so to discern the physiological mechanism responsible. Research that has not utilised a sodium-matched control, which includes that of Higgins, James and Price, (2013) and Dias et al., (2015), cannot assign the ergogenic effect of NaHCO_3 to the HCO_3^- buffering system alone but the combined action with Na^+ .

2.6. Sodium Bicarbonate and Exercise Performance Under Hypoxia

As discussed in section 2.3 performance limiting factors under hypoxia are postulated to operate through a number of mechanisms, including lowered levels of arterial O_2 saturation (Mazzeo, 2008), an exacerbated rate of H^+ accumulation (Hogan, Richardson and Haseler, 1999), an increased perception of exertion (Álvarez-Herms et al., 2015) and/or originate from central regions presiding a reduced central motor output (Noakes and Marino, 2007). Equivalently the ergogenic influence of NaHCO_3 has also been cited to operate through these means (see section 5.2). Sodium bicarbonate may therefore prove to be efficacious ergogenic aid to offset performance impairment under acute hypoxic conditions. At present, research investigating the use of exogenous buffering agents is limited, with only two investigations that have assessed the ergogenic effect of NaHCO_3 on performance under acute moderate hypoxic conditions within unacclimatised participants (Flinn et al., 2014, Saunders et al., 2014b).

An intermittent protocol modelled on peak power output at sea level was used by Flinn et al., (2014). This protocol involved cycling at $120\% W_{\text{max}}$ for 30 sec interspersed with 30 sec active recovery at $30\% W_{\text{max}}$, until volitional fatigue. The cumulative time spent cycling 120% of peak power output was no different between placebo ($133.3 \pm 28.7 \text{ sec}$) and NaHCO_3 ($127.8 \pm 27.9 \text{ sec}$) conditions. Performance was however greater in the normoxic control condition although NaHCO_3 did elicit a non-significant 8.3% difference compared to placebo in normoxia (183.8 ± 45 vs $199.1 \pm 62.3 \text{ s}$). A further consideration of this study (Flinn et al.,

2014), is that acute hypoxia impairs peak power output (Clark et al., 2007), thereby increasing the relative intensity of exercise under hypoxia, compared to normoxia for any given absolute power output. The authors did not mention accounting for this in the determination of the hypoxic exercise protocol, therefore the relative intensity of hypoxia may have been noticeably greater than 120% W_{\max} . Consequently, exacerbating the rate of fatigue development. As discussed earlier, the effect of NaHCO_3 may be dependent on exercise intensity, as increasing exercise intensities may saturate the MCT co-transporters (Hamada and Takimoto, 2013), thereby limiting the additive effect NaHCO_3 may have on H^+ efflux. This consequently may explain why a positive effect was noted at sea level but not hypoxia, due to the increased relative intensity of exercise. It is therefore unclear, whether the lack of improvement is due to the relative severity of the exercise bout or the ineffectuality of NaHCO_3 under hypoxic stress.

A more sport specific, ninety min football simulation protocol, with incorporated 5 x 6 sec maximal sprints, also reported no difference in exercise performance under acute hypoxia (Saunders et al., 2014b). Comparable to the aforementioned study, it is not known if this lack of change is due to hypoxia, as a normoxic control condition was not included to allow comparison. Despite this, a similar maximal repeated sprint test, without the extended football simulation, has previously shown to be improved with NaHCO_3 (Bishop and Claudius, 2005), indicating the performance protocol is appropriate to detect changes in response to NaHCO_3 . The key difference may lie in the methodological approach to NaHCO_3 administration. Saunders et al., (2014b) supplemented NaHCO_3 in a split dose, across a 4-hour period prior to exercise, which may not be 'optimal' given the individualised blood acid-base response to NaHCO_3 ingestion (Miller et al., 2015). An alternative personalised supplementation strategy to maximise the availability HCO_3^- , and therefore enhancing blood HCO_3^- buffering capacity, may enhance the likelihood of obtaining the ergogenic benefit under acute hypoxia. Further to this, the lack of improvement could be assigned to the potentially greater utilisation of muscle glycogen with a combination of hypoxia and NaHCO_3 . Both acute hypoxia and NaHCO_3 supplementation have been independently demonstrated to significantly enhance the rate of muscle glycogen use during exercise (Parolin et al. 2000, Percival et al. 2015, respectively). Despite the lack of data to support this assumption, it may be reasonable to infer that lower levels of muscle glycogen, particularly at the end of the prolonged football simulation, may have an adverse effect on performance and therefore mask any potential ergogenic effect of NaHCO_3 . Future research evaluating the use of NaHCO_3 under hypoxic condition should take this in to consideration.

To summarise, it is proposed that current literature has not assessed the effect of NaHCO_3 against exercise forms and intensities that are shown to benefit from prior alkalosis. In that, investigations have not been conducted on those activities that are demonstrated to elicit performance benefit under normoxic conditions. When applied to the intensity domains, it is evident that acute hypoxia lowers the intensity of the severe intensity domain (Shearman et al., 2015), with the exacerbated exercise induced acidosis cited as a primary contributor (Annam et al., 2007). As such, exogenous pre-exercise ingestion of NaHCO_3 may elicit the physiological conditions that can mitigate this consequence, and thus improve exercise tolerance in the severe domain. This however, has not been investigated and will therefore form the principal theme of this thesis.

2.7. Summary and Research Aims

This review of literature introduced numerous concepts and research themes, which together inform the experimental investigations of this PhD thesis. The principal theme of this thesis is grounded on the ergogenic features of NaHCO_3 supplementation, which acts as an alkalotic buffering agent to mitigate the rise in acidic cations (e.g. H^+) during exercise. The manifestation of exercise-induced acidosis is associated with the development of fatigue, which is suggested to contribute to eventual exhaustion during high intensity exercise. The intensity at which acidosis ensues is at the onset of the severe intensity domain, which is characterised by the physiological thresholds LT_2 and VT_2 , and mathematical construct CP. Together, these thresholds depict the intensity whereby the highest steady state in pulmonary $\dot{V}\text{O}_2$ and [bla] occur. Therefore, it is within the severe domain where the acid-base balance begins to be challenged. The ergogenic effect of NaHCO_3 has predominantly been investigated during supra-maximal exercise intensities, despite the ergogenic potential during sub-maximal exercise in the severe domain.

The power-duration relationship, has been presented as a valid model to describe constant load and intermittent exercise performed in the severe intensity domain. The power-duration concept is comprised of two key aspects, the CP that denotes the onset of the severe intensity and the W' parameter, which is proposed to describe the amount of work that can be performed in the severe intensity domain prior to exercise exhaustion. The W' parameter, therefore, presents an interesting insight in to fatigue; in that, understanding the physiological constitutes of W' may allow greater understanding of the determinates of exercise tolerance in the severe intensity domain. However, the physiological composites of W' remain largely elusive;

although the accumulation of H^+ is associated with the W' parameter. On this premise, it is appropriate to hypothesise that pre-exercise alkalotic inducement may improve the work that can be performed in the severe intensity domain. When modelled through the CP concept, $NaHCO_3$ may theoretically enhance the W' during constant load and intermittent exercise.

A novel and prominent component of this thesis is the supplementation of $NaHCO_3$ under acute hypoxic conditions. Research has been presented which indicates the ergolytic effect of hypoxia on exercise tolerance, performance and intensity of physiological thresholds. The lower O_2 availability is shown to diminish aerobic capacity and thus increase the relative contribution of anaerobic energy supply. Consequently, the rate at which exercise-induced acidosis ensues is exacerbated and may be an important contributor to the diminished exercise performance. Acute hypoxic exposure may therefore present the ideal physiological conditions, whereby $NaHCO_3$ may be more efficacious as an ergogenic aid. However, research with this focus is limited despite the important practical implications of improving exercise performance during training and competition under acute hypoxic conditions. This thesis will therefore address the following research aims in the proceeding five experimental chapters:

- 1) The aim of Chapter three is to quantify the ergolytic effect of acute hypoxic exposure on exercise capacity and performance through a systematic review and meta-regression.
- 2) The aim of Chapter four is to investigate the effect of pre-exercise $NaHCO_3$ supplementation on CP and W' during the 3 min critical power test under normoxic and acute hypoxic conditions
- 3) The aim of Chapter five is to assess the effect of $NaHCO_3$ supplementation on severe intensity intermittent exercise under acute hypoxic conditions
- 4) The aim of Chapter six was to assess if the ergogenic effect of $NaHCO_3$ is present during severe intensity intermittent exercise irrespective of the intensity of the recovery intervals. Furthermore, the study will assess the effect of alkalosis on the time constant on W' recovery kinetics in the W'_{bal} model during intermittent exercise.
- 5) The aim of Chapter seven is to assess the effect of $NaHCO_3$ on constant load exercise capacity on varying intensities and subsequently determine the effect of on CP and W' .

Chapter Two: General Methodology

The purpose of this section is to outline the procedures that are uniform across all the experimental trials in this thesis. Specific methodologies, statistical procedures and the experimental design will be discussed for each study within the relevant chapters.

1.0. Ethical Considerations

Ethical approval was obtained for all the studies in this thesis from the Sport and Physical Activity Department Research Ethics Committee at Edge Hill University. All participants provided their written informed consent prior to participation. Participants had to confirm they understood the procedures, benefits and risks of the respective research study. A participant information document detailing these factors was provided to allow each participant sufficient time to consider voluntary participation. A medical and pre-exercise screening procedure was also carried out to ensure the participant was fit and able to carry out maximal exercise, in accordance with Edge Hill University health and safety procedures.

2.0. Pre-experimental procedures

Before all experimental trials, participants undertook several standardised procedures to minimise the day to day physiological response and limit the confounding effect of nutrition and hydration on exercise performance. This included the within-subject standardisation of experimental time, dietary intake and hydration status. Each experimental trial was conducted at the same time of day to account for circadian rhythm influence on exercise (Reilly, 1990). Dietary intake was assessed prior to the initial experimental trial, using a 24-hour dietary log. This 24-hour dietary intake was replicated by the participants prior to each experimental trial, which was verbally confirmed before the commencement of testing. Participants were also required to arrive following a 4-hour post-absorptive state and avoid caffeine preceding 12 hours to the trial. Participants arrived in euhydrated state, which was achieved via the consumption of water (500ml) two hours leading up to the trials. Furthermore, participants were also asked to abstain from alcohol and strenuous exercise in the preceding 24-hours. Body mass was also recorded, ensuring the correct dose of NaHCO_3 was administered.

3.0. Supplement preparation

Experimental exercise trials were performed under two different experimental conditions, with the prior ingestion of either $0.3 \text{ g}\cdot\text{kg}^{-1} \text{ bm}$ of NaHCO_3 or a $0.21 \text{ g}\cdot\text{kg}^{-1} \text{ bm}$ of NaCl . Supplements were mixed with 400 ml of chilled water and 50 ml of sugar free cordial (blackcurrant squash,

Herritage, UK) to mask the experimental treatment. This dose of NaCl was chosen as it presents an equimolar composition of sodium to $0.3 \text{ g}\cdot\text{kg}^{-1} \text{ bm}$ of NaHCO_3 , which consequently mitigates for the ergogenic effects of sodium (Mora-Rodriguez and Hamouti, 2012). Prior to the experimental trials the individual time of NaHCO_3 administration was determined through identifying the time taken for peak blood $[\text{HCO}_3^-]$ to occur following a liquid bolus.

4.0. Identification of NaHCO_3 individualised administration time

During the initial visit, individual blood acid-base response to $0.3 \text{ g}\cdot\text{kg}^{-1} \text{ bm}$ of NaHCO_3 supplementation was established through measuring the time course of blood acid-base balance across a 90 min period following ingestion (Gough et al., 2017c). Fingertip capillary blood samples ($70 \mu\text{l}$) were drawn every 10 min for 60 min and then every 5 min from 60-90 min. Participants remained seated during the collection of blood into a capillary tube (Electrolyte balanced heparin clinitube, Radiometer, Denmark). Blood samples were analysed for $[\text{HCO}_3^-]$ using a blood gas analyser (Radiometer ABL800, Denmark). The individual time taken for peak $[\text{HCO}_3^-]$ to transpire was then used for the pre-ingestion timing for subsequent experimental exercise trials. This method controls for the intra-individual differences in acid-base kinetics following NaHCO_3 supplementation (Jones et al., 2016, Gough et al., 2017c) and thus enables individuals to exercise at their peak $[\text{HCO}_3^-]$ to maximise the HCO_3^- buffering potential. This timeframe in attaining peak $[\text{HCO}_3^-]$ following NaHCO_3 is shown to be reproducible ($r = 0.9$; $p < 0.001$) between ingestions within participants (Gough et al., 2017c) and thus, represents a reliable method to administer NaHCO_3 .

5.0. Environmental conditions

Exercise trials were all conducted within a normobaric environmental chamber (Model S016r-7-sp TISS, UK), with ambient temperature ($21 \text{ }^\circ\text{C}$) and humidity (40%) regulated throughout. Fractional inspired oxygen ($\text{FiO}_2\%$) was adjusted for normoxic ($\text{FiO}_2 = 20.93\%$) and hypoxic ($\text{FiO}_2 = 14.5\%$) environmental conditions, which are equivalent to sea level and 3000 m, respectively. Environmental conditions were single blind and randomised during experimentation. A ‘sham hypoxic’ condition was created during the normoxic trials to mask the environmental conditions. This involved maintaining the oxygen (O_2) controls to replicate auditory cues between conditions (Gallagher et al., 2014). Participants entered the chamber 10 min prior to exercise to allow for an equilibrium between atmospheric and body O_2 stores to develop (Andreassen and Rees, 2005).

6.0. Determination of $\dot{V}O_{2\text{peak}}$ and VT1

The exercise protocol commenced with three min unloaded pedalling into a ramped increase of $2 \text{ W}\cdot\text{sec}^{-1}$, equivalent to $30 \text{ W}\cdot\text{min}^{-1}$. A preferred cadence was selected prior to the test, which participants were asked to maintain until volitional exhaustion. The test was terminated when this cadence could no longer be maintained within 10 rpm for 10 secs, despite strong verbal encouragement. Exercise tests were performed on an electrically braked ergometer (Lode Excalibur Sport, Groningen, The Netherlands), with the frame dimensions and pedals adjusted to participant preference and replicated for all subsequent exercise trials. Breath-by-breath pulmonary gas exchange was recorded throughout, and in all subsequent trials, using a metabolic analyser (Oxycon, Jaeger, Germany). Calibration was performed prior to every test in line with manufacturer's instructions. This included the turbine calibration with 3 L syringe, whilst the gas analysers were calibrated with gases of a known concentration. **The OxyconPro has been shown to be a valid and reliable online gas analysis system, as it possesses a low CV of < 7% (Carter and Jeukendrup, 2002).** Pulmonary gas exchange data was initially smoothed, by 4 standard deviations from the mean, to remove errant data points caused by coughing or swallowing. Data was then averaged to 10 s bins for the identification of VT1. The VT1 was detected through inflection points on gas exchange graphs using the following criteria: 1) the v-slope method through the breakpoint in $VCO_2/\dot{V}O_2$ against time; 2) an increase in $VE/\dot{V}O_2$ but no increase in VE/VCO_2 ; and 3) a fall in $PETCO_2$ (Beaver, Wasserman and Whipp 1986). Peak power output (PPO) was defined as the greatest power output attained at the termination of the test, whilst $\dot{V}O_{2\text{peak}}$ was defined as the highest 30 s rolling average of $\dot{V}O_2$. Peak power output (PPO) was defined as the greatest power output attained at the termination of the test, whilst $\dot{V}O_{2\text{peak}}$ was defined as the highest 30 s rolling average of $\dot{V}O_2$.

7.0. Determination of critical power using the three min CP test

The 'all-out' test involved an initial three min unloaded baseline pedalling at a preferred cadence followed by the commencement of the three min maximal sprint phase. On the sprint phase the ergometer was set on the linear mode which provides a fixed resistance. This linear factor (linear factor = power/cadence²) was calculated to determine a fixed resistance that enables the participants preferred cadence (used during the incremental ramp protocol) to be attained at a power output that corresponds to the mid-point of peak power output and the VT1 intensity. This linear factor was determined for the respective environmental condition to avoid

substantially larger determinations of W' under hypoxia (Simpson et al., 2015). During the last 10 sec of unloaded pedalling, participants were asked to increase cadence to 120 rpm, and given a countdown into the commencement of the sprint phase. Participants were instructed to attain a peak power on sprint phase initiation and hold the cadence as high as possible throughout test duration. Strong verbal encouragement was provided by the same researcher throughout the study and information of cycling cadence was given during the test, whilst information related to performance and time elapsed was withheld, to avoid pacing. The determination of CP and W' using the three min all-out test has been subject to criticism due to the suggested overestimation of the CP parameter (Bergstrom et al., 2013), therefore in Chapter three, a minimal 30 sec rolling average was taken as CP and work-integral above as W' . This replicates the analysis previously used by Shearman et al. (2015) who found a lower intensity than the original CP determination method, thus limiting the risk of overestimation. In addition, the original identification of CP through last 30 sec end power output and power-integral was calculated for comparative purposes and defined as EP and W' EP. Total work done across the 'all-out' trial will be determined in kilojoules (kJ), whilst the $\dot{V}O_{2peak}$ was established as the greatest values measured during a given 30 sec intervals.

In Chapter four and five, the experimental protocols were replicated with the addition of recording pulmonary $\dot{V}O_2$. The test was deemed valid in these chapters when there was no evidence of pacing; in that, the end 30 sec power output was the lowest recorded throughout the test. In addition, pulmonary $\dot{V}O_2$ had to reach 95% of maximum within 60 sec of the sprint phase and be maintained without downward drift for the remainder of the test (Jones et al. 2010). If these criteria were not attained, the test was repeated.

8.0. Blood acid-base and other physiological variables

In chapter four fingertip blood samples were collected in to a capillary tube immediately before supplementation, then immediately prior to and within 1 min of exercise termination, using the methods described earlier (Chapter two section 4.0). In the subsequent experimental trials, samples were taken immediately prior to and within 1 min of exercise termination. Samples were analysed for blood pH and $[HCO_3^-]$ (Radiometer ABL800, Denmark), with [bla] assessed using a portable measuring device (Lactate Pro 2, Arkray, Japan). Heart rate (Forerunner 15, Garmin, US) and SpO_2 using a fingertip pulse oximeter (Autocorr® Digital Pulse Oximeter, BCI, USA) were recorded at the end of every work stage and reported subsequently analysed as a test average.

Chapter Three: Quantifying the effects of acute hypoxic exposure on exercise performance and capacity: A systematic review and meta-regression

Parts of this chapter were published in the European Journal of Sport Science

1.0. Introduction

Acute hypoxic exposure is known to have an ergolytic effect on exercise capacity (Wehrlin and Hallén, 2006) and performance (Clarke et al. 2007), with the negative effect increasing linearly with the level of hypoxic exposure. However, more recent meta-analytic data suggests that $\dot{V}O_{2max}$ exhibits a curvilinear reduction with increasing hypoxic exposure (McInnis et al. 2015). As discussed in Chapter 1 (section 2.4), within the review of literature, current evidence is based on individual investigations on exercise capacity and performance and have only evaluated performance up to moderate hypoxic exposure. As such, the purpose of this section was to perform a systematic review and meta-regression to quantify the effect of varying magnitudes of hypoxia, from low to severe hypoxia, on exercise capacity and performance. Performance was further subdivided into continuous (i.e. TTE and TT), intermittent and sprint (i.e. Wingate test) exercise sub-groups; and each group assessed against the moderators of elevation equivalent to the hypoxic magnitude tested, mean SaO₂ reduction during exercise and training status. Furthermore, the ergolytic effect of hypoxia was assessed against exercise of different durations.

2.0. Method

This meta-analysis followed the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.1. Eligibility criteria

The research question was formulated using PICO method (Population, Intervention, Comparison and Outcomes) and used to inform the eligibility criteria of selected studies. The *population* of the review were healthy male and females (≥ 18 yrs old), including healthy to highly trained individuals. Samples that included acclimatised or altitude natives were excluded from the review. The *intervention* involved the assessment of exercise outcomes equivalent to sea level and an exposure to an acute hypoxic stress for less than 24 hrs prior to the assessment of performance. This timeframe was selected as a large degree of acclimatisation in exercise performance has been observed following 24 hrs of exposure (Wyatt, 2014). Investigations that utilised normobaric and hypobaric hypoxic exposures were included in this review. However, only laboratory simulations were included as equivalent power outputs elicit faster velocities at high terrestrial altitudes compared to sea level due to the lower air density, therefore mitigating performance decrements associated with the diminished O₂ availability (Garvican-Lewis et al., 2015). The *comparisons* for this review were

randomised controlled trials that involved a sea level exercise trial. Where a sea level trial was not performed (i.e. at 0 m elevation or a fractional inspired oxygen (FiO_2) equal to 21%) the difference between the lowest hypoxic exposure and experimental hypoxic exposure was used for analysis. The FiO_2 used during experimental trials were converted to the equivalent altitude elevation for analysis, however all outcomes are interpreted as the effect of acute hypoxia only. If room air was used as the sea level trial, the elevation of the testing laboratory was checked to ensure the correct elevation was tested. The *outcomes* included in this review involved exercise performance and exercise capacity. Exercise performance was defined as activities that were self-paced continuous (e.g. TT) or intermittent tasks, while exercise capacity referred to tests that required individuals to work to a point of volitional exhaustion at an established controlled intensity.

2.2. Search strategy and study selection

A literature search was conducted to identify all relevant original investigations that assessed the influence of acute hypoxic exposure on exercise performance, capacity and physiological thresholds of intensity. This involved two investigators independently inputting key search terms into three scientific data bases (Google Scholar, PubMed and SPORTDiscus). The search terms were combined to include a term referring to the environmental conditions ('altitude', 'hypoxia', and 'fractional inspired oxygen') with exercise performance ('time trial (TT)', 'repeated sprint exercise (RSE)', 'anaerobic exercise', 'Wingate' and 'sprint performance') or exercise capacity ('time to exhaustion (TTE)', 'exercise capacity'); with all searches restricted to the article titles. The articles were then all reviewed for relevance, which was assessed by the title, with all remaining articles downloaded for further screening and assessment against the eligibility criteria of this review. The reference lists of all retrieved articles and of relevant review articles were also screened for additional eligible articles. The abstracts of all studies were subsequently reviewed to narrow the pool the studies reviewed in full. This list of eligible studies obtained independently were then compared and amalgamated for data extraction. The last search was undertaken in April 2017.

2.3. Data collection process

The data from all eligible studies were extracted into a standardised excel template and checked for accuracy. The extracted data included author name, year, sample characteristics, $\dot{V}\text{O}_{2\text{max}}$, type of hypoxic exposure, arterial oxyhaemoglobin saturation (including SaO_2 obtained from blood samples, and SpO_2 obtained via pulse oximetry), exercise test description. Furthermore,

the mean data and standard deviation (SD) of control and experimental conditions were extracted, in addition to an exact p value or a value that indicated the variance in the intervention effect (e.g. 95% confidence intervals or SD of mean difference). Instances where mean \pm SD were displayed in figures only, a graph digitiser software was used to extract the data (Digitize, Germany). This extraction was performed independently by two researchers and compared for consensus, where this was not apparent a third researcher performed the extraction for agreement.

Data were primarily extracted as mean power output (or velocity) or total work done from the TT and intermittent exercise protocols, while exercise duration was extracted for all exercise capacity tests. Authors of studies where required data was missing, or outcomes were not reported appropriately for this review were contacted for further information. Where performance data was not reported in mean power output or work done, but rather test completion time, the available datum was converted into mean power (Carr, Hopkins and Gore, 2011). Investigations that included multiple exercise tests and varying magnitudes of hypoxia and experimental data from independent groups were extracted as separate outcomes.

Data were categorised into sub-groups based on exercise type and duration of exercise bout. The exercise subgroups reflected the outcomes outlined in the eligibility criteria: TT performance, intermittent exercise, TTE and sprint tests. Exercise was also categorised into three time based sub-groups (< 2 mins, 2 – 10 min and > 10 mins) as the ergolytic effect of hypoxia is proposed to be dependent on duration (Wyatt, 2014). The first category was chosen as exercise below 2 min is suggested to be unaffected by acute hypoxia (Wyatt, 2014); whereas the category between 2-10 min was chosen to include the range of exercises that are likely to require an anaerobic energy contribution (Duffield, Dawson and Goodman, 2005). Exercise beyond 10 min is included in this review to represent exercise intensities that predominantly require an aerobic energy contribution. Intermittent exercise, which involved controlled repetitions of work and recovery, were categorised on the total duration of high intensity activity periods. Furthermore, outcomes were categorised by training status with a sea level $\dot{V}O_{2\max} \geq 55 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ classified as trained and $< 55 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ as healthy untrained (De Pauw et al., 2013). Where $\dot{V}O_{2\max}$ was not reported, articles were not included in analysis to maintain objectivity.

2.4. Quality and bias assessment

The overall quality of evidence for each outcome was determined by two independent researchers, using the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) approach. The GRADE protocol offers a systematic method to evaluate the quality of research whilst considering methodological limitation, consistency of outcomes, reporting or publication bias and indirectness of evidence. Furthermore, to increase specificity to the current research question three discipline specific factors were considered under the category methodological limitation: 1) the control of prior altitude/hypoxic exposure to reduce any confounding effects of acclimatisation; 2) standardisation of dietary intake prior to experimental trials; and 3) familiarisation to exercise trials. In addition to the traditional quality control criteria to limit bias: 1) blinding of participants; 2) blinding of researcher; 3) blinding outcome assessment; and 4) complete outcome data. However, the indirectness of evidence was not considered in this review, due to inclusion criteria requiring the assessment of exercise performance directly; while a traditional funnel plot was not used to assess publication bias due to the natural negative skew expected in the data, given the strong physiological basis that exercise performance will not be enhanced under acute hypoxia.

2.5. Data analysis

The ratio of means (ROM) method was used to establish pooled effects and variances of hypoxic interventions. This method allows outcomes of different units to be pooled and compared, whilst also allowing for easy interpretation for practitioners, athletes, and coaches because outcomes can be expressed as a percentage change. The natural logarithm of each ROM (equation 1) and its variance (equation 2) were calculated using the mean values of sea level (\bar{x}_c) and hypoxia (\bar{x}_T), their respective standard deviations (SD), number of participants (N) and a correction (r) between sea level and hypoxic trial performance:

$$\log(RoM) = \left[\log \frac{\bar{x}_T}{\bar{x}_c} \right] \quad \text{[Equation 1]}$$

$$\text{Var}[\log(RoM)] = \frac{(SD_C)^2}{N_c \bar{x}_c^2} + \frac{(SD_T)^2}{N_T \bar{x}_T^2} + \frac{2rSD_CSD_T}{\bar{x}_c \bar{x}_T \sqrt{N_c N_T}} \quad \text{[Equation 2]}$$

The calculation of the variance of ROM requires knowledge of the correlation (r) between sea level and hypoxic trial outcomes, which is not commonly reported. Estimates from individual studies were obtained using reported t statistics as follows (equation 3):

$$r = \frac{(SD_c)^2 + (SD_T)^2 - t^{-2} N(\bar{x}_T - \bar{x}_c)^2}{2SD_cSD_T} \quad [\text{Equation 3}]$$

Appropriate information was only available for 23 studies; therefore, a pooled single estimate of the correlation r was calculated from the available data using the Meta package in R (R Foundation for Statistical Computing, Vienna Austria). The pooled correlation value ($r = 0.78$, 95% confidence interval: 0.62 to 0.87) was then applied to all studies. Sensitivity analyses using correlation values of $r = 0.68$ and $r = 0.88$ were also carried out to validate the primary model.

A three-level mixed effects meta-regression was used to analyse ROMs and variances whilst accounting for dependencies in the data set. The three levels can be described by regression equations at the sample (level 1), outcome (level 2) and study (level 3) level (Van den Noortgate et al., 2013). The fixed effects categorical moderators included exercise type (TT, intermittent, TTE and Sprint), exercise duration (< 2 min, 2-10 min and > 10 min) and training status (trained vs. healthy). The overall and interaction effects with altitude elevation in km equivalent to the FiO_2 exposure and end exercise mean difference in SaO_2 between normoxic and hypoxic conditions were also evaluated as continuous moderators. Furthermore, given the reported non-linear relationship between acute hypoxia and $\dot{V}\text{O}_{2\text{max}}$ (Macinnis et al., 2015) and critical power (Townsend et al., 2017), the review also assessed curvilinear effects of altitude elevation using quadratic models. Regression analyses were constrained to a zero intercept to enhance external validity. Pooled effects on the logarithmic scale were subsequently back transformed and multiplied by 100 to provide percentage change of effects. A normal distribution was assumed for log-transformed effects and therefore 95% confidence intervals were obtained from $\pm 1.96 \times$ standard error and back transformed. All outcomes are reported as percentage effect estimate \pm standard error and the corresponding 95% confidence intervals, unless otherwise stated. All analysis was performed using the metaphor package in R (R Foundation for Statistical Computing, Vienna Austria). Statistical significant was assessed through 95% confidence intervals, with estimates that cross the zero-boundary interpreted as non-significant.

3.0. Results

3.1. Study characteristics

Fifty-three studies met the inclusion criteria set for this review (Table 3.1), which provided effect statistics for 82 outcomes within 798 participants and ranged from 500-5700 m altitude

(mean \pm SD: 3000 \pm 1300 m). These studies were categorised into an exercise modality and an exercise duration category for analysis (Table 3.2). Training status was explicitly reported in 47 outcomes, with 33 cohorts classified as trained against 14 cohorts classified as untrained healthy participants; whilst SaO₂ was available in 54 outcomes (13.2% \pm 7.2%). Only five studies were performed utilising hypobaric hypoxia and therefore the type of hypoxic exposure was not considered as a moderator in this study.

3.2. Quality assessment

Under the GRADE research quality assessment, the overall quality is rated high due to the inclusion of only randomised control trials in this review and the limited evidence to warrant the downgrading of quality. Methodological limitations and bias in the included articles, were assessed against pre-determined criteria, with the percentage of studies demonstrating each criterion as follows: (1) the control of prior altitude/hypoxic exposure: 47%; (2) standardisation of dietary intake: 62%; (3) familiarisation to exercise trials: 87%; (4) blinding of participants: 43%; (5) blinding of researcher: 23%; (6) blinding outcome assessment: 0%; and (7) complete outcome data: 42%.

Table 3.1. Summary table of all outcomes by exercise type included in this review with effect and standard error of outcomes in this meta-analytic model.

Author	Participants [$\dot{V}O_{2peak}$] ($ml \cdot kg^{-1} \cdot min^{-1}$)	SaO ₂ (%)	Altitude elevation (NH or HH)	Exercise duration category	Exercise protocol	Effect (%) (95% CI)
Exercise performance – Continuous TT exercise						
Amann et al., 2000	8 [63.0 ± 1.3]	14.0	2700 m (NH)	2	5 km TT	-10.4 (-12.2 to -7.7)
Beidleman et al., 2014	6 [49.5 ± 5.0]	17.6	4300 m (NH)	3	Time to complete 72 J work	-25.9 (-31.6 to -19.7)
	6 [47.5 ± 4.3]	19.5	4300 m (HH)	3		-38.7 (-41.7 to -35.6)
Bourdillon, Fan, & Kayser, 2014	13	30.0	5000 m (NH)	3	15 km TT	-30.9 (-33 to -29.5)
Bourdillon et al., 2015	12	28.3	5000 m (NH)	3	15 km TT	-37.5 (-44.6 to -30.2)
Castellani et al., 2010	7 [44.1 ± 4.9]	20.0	3000 m (HH)	3	Total Work done during a 30 min TT	-12.2 (-19.7 to -3.9)
		4.0	1200 m (HH)		Total Work done during a 5 min TT	-5.8 (-10.4 to -1.0)
Clark et al., 2007	10 [67.7 ± 1.3]	13.0	2200 m (HH)	2		-10.4 (-14.8 to -5.8)
		12.0	3200 m (HH)			-19.7 (-23.7 to -15.6)
Dahlstrom et al., 2013	8 [52 ± 7.3]		2750 m (NH)	3	20 km TT	-16.5 (-18.1 to -13.9)

Deb et al., 2017	11 [59.2 ± 6.8]	10.5	3000 m (NH)	2	Total Work done during 3 min	-10.4 (-15.6 to -5.8)
Fan et al., 2013	10 [63.3 ± 6.6]	30.0	4600 m (NH)	3	15 km TT	-30.2 (-32.3 to -28.1)
Foss, 2015	10 [66.5 ± 5.2]	3.90	2500 m (NH)	3	20 km TT	-9.5 (-15.6 to -3.9)
Gore et al., 1997	10 [72.3 ± 2]	1.8	580 m (HH)	2	Total Work done during a 5 min TT	-3 (-3.9 to -2.0)
	10 [60.8 ± 2]	3.4	580 m (HH)			-3.9 (-4.9 to -3.0)
Jacobs et al., 2011	20 [56.5 ± 1.2]	21.0	3900 m (NH)	2	6 km TT	-20.5 (-21.3 to -18.9)
	15 [45.3 ± 1]	18.0		3	-28.8 (-29.5 to -28.1)	
Koelwyn et al., 2013	11 (58.3 ± 2.8)	10.8	1950 m (NH)	3	10 km TT	-10.4 (-13.1 to -7.7)
Kressler et al., 2011	21 [11 males: 55 ± 1.3] 10 females: [42.8 ± 0.6]	5.0	2100 m (NH)	3	15 km TT	-6.8 (-8.6 to -4.9)
		17.0	3900 m (NH)			-22.9 (-25.2 to -21.3)
MacLeod et al., 2015	11 [67.5 ± 5.8]	9.0	2500 m (NH)	3	10 km TT	-15.6 (-18.9 to -13.1)
Salazar-Martínez et al., 2017	16 [46.4 ± 8.7]		2500 m (NH)	2	Total Work done during a 10 min TT	-5.8 (-11.3 to 1.0)
Simpson et al., 2015	12 [41.6 ± 6.3]		3800 m (NH)	2	Total Work done during 3 min	-14.8 (-18.9 to -10.4)
Périard & Racinais, 2016	12 [59.5 ± 3.8]	13	3000 m (NH)	3	Time to complete 75 J work	-19.7 (-23.0 to -16.5)

Peltonen et al., 1995	6		2250 m (NH)	2	2.5 km rowing TT	-13.9 (-17.3 to -11.3)
	10 [55.1 ± 2.5]		3000 m (NH)			-14.8 (-17.3 to -13.1)
Puype et al., 2013	9 [53.3 ± 3.5]		3000 m (NH)	2	Total Work done during a 10 min TT	-15.6 (-16.5 to -14.8)
	10 [55.1 ± 1.7]		3000 m (NH)			-16.5 (-18.9 to -13.9)
Shearman et al., 2015	11 [61.5 ± 5.7]	11.4	2500 m (NH)	2	Total Work done during 3 min	-7.7 (-12.2 to -3.9)
Weavil et al., 2015	7 [61.5 ± 1.4]	9	1750 m (NH)	2	5 km TT	-7.7 (-11.3 to -4.9)

Exercise performance – Intermittent exercise

Aldous et al., 2016	12 [57.0 ± 2.0]		1000 m (NH)	3	90 min intermittent soccer performance test	-2.9 (-3.9 to -1.0)
Billaut & Buchheit, 2013	14		3800 m (NH)	1	10 x 10 sec sprints with 30 s rest	-7.6 (-13 to -2.9)
Billaut et al., 2013	10		3300 m (NH)	1	3 sets 5 x 5 s sprints with 25 s passive recovery	-8.6 (-18.1 to 2.0)
		20.7	2700 m (NH)			-3.9 (-8.6 to 1.0)
		26.2	3200 m (NH)			-8.6 (-12.2 to -3.9)
Bowtell et al., 2014	9		3800 m (NH)	1	10 X 6 sec sprints with 30 a rest	-8.6 (-13 to -5.8)
		13.6	3800 m (NH)			-8.6 (-13 to -5.8)
		18.1	4500 m (NH)			-14.8 (-18.1 to -10.4)

Brosnan et al., 2000	8 [61.0 ± 4.0]		1500 m (NH)	3	3 x max work in 10 min with 5 min active recovery (< 100w)	-7.7 (-13.1 to -3.9)
				2	3 sets 6 x 15 s sprints with 45 s recovery (< 100 w). 3 min recovery between sets	-7.7 (-10.4 to -2.0)
Girard et al., 2015	13	8.1	1800 m (NH)	1	8 x 5 s sprint with 25 s passive recovery	-1 (-2.9 to 1.0)
		15	3600 m (NH)			-1 (-5.8 to 3.0)
Girard et al., 2016	6		3600 m (NH)	1	5 x 5 s sprint with 25 s passive recovery	-3 (-4.9 to -1.0)
		5.4	2000 m (NH)			
Goods et al., 2014	10	10.9	3000 m (NH)	1	3 sets 9 x 4 sec max sprints non-motorised treadmill	-5.8 (-9.5 to -3.0)
		20.2	4000 m (NH)			-11.3 (13.9 to -7.7)
Goods et al., 2016	9					-19.7 (-22.9 to -17.3)
Kon et al., 2015	7		2000 m (NH)	2	4 x 30 s all out sprint with 4 min passive recovery	1.0 (0 to 2.0)
			3500 m (NH)			-3.9 (-4.9 to -2)
Morrison, McLellan, & Minahan, 2015	10		3800 m (NH)	1	4 sets of 4 x 4 sec sprints	-1.0 (-3.0 to 2.0)
Lovell, McLellan, & Minahan, 2015)	7		3800 m (NH)	1	10 x 26 sec sprint with 24 sec recovery	-5.8 (-11.3 to 0)

Smith & Billaut, 2010	13	12.1	3700 m (NH)	1	10 x 10 s sprint with 30 sec passive recovery	-7.7 (-10.3 to -4.9)
Smith & Billaut, 2012	10 male	12.5	3700 m (NH)	1	10 x 10 s sprint with 30 sec passive recovery	-7.7 (-13.1 to -3)
	10 female	14.7				-6.8 (-29.5 to -18.1)
Sweeting et al., 2017	7 [59.5 ± 5.1]		2000 m (NH)	3	26.4 min repeated sprint protocol	2.0 (-6.7 to 11.6)
			3000 m (NH)			-13.1 (-23.7 to -1.0)
Turner et al., 2014	9 [40.1 ± 4.6]	5	1600 m (NH)	3	80 min cycling intermittent sprint protocol	-4.9 (-13 to 3.0)
Witmer, 2011	14 [44.8 ± 8.0]	1.2	3000 m (NH)	1	10 X 6 sec sprints with 30 sec rest	-1.0 (-3.0 to 1.0)
Zinner et al., 2015	10 [72 ± 7.2]		2000 m (NH)	2	3 x 3 min 'all-out' double poling	-3.0 (-8.6 to 3.0)
<hr/>						
Anaerobic exercise – Sprint						
Calbet et al., 2015	11 [50.7 ± 4.0]		5300 m (NH)	1	30 s Wingate	-7.7 (-10.4 to -3.0)
	5 [62.0 ± 2.0]					-1.0 (-3.0 to 1.0)
Calbet et al., 2003			5300 m (NH)	1	30 s Wingate	-6.7 (-9.5 to -3.9)
	5 [72.0 ± 1.0]					
McLellan et al., 1990	12	15.7	5700 m (NH)	1	30 s Wingate	0 (-2.0 to 2.0)
		13.7			45 s Wingate	-1.0 (-3.0 to 1.0)

Morales-Alamo et al., 2012	10		5500 m (NH)	1	30 s Wingate	-4.9 (-9.5 to -1.0)
Ogura et al., 2006	7		2000 m (NH) 4000 m (NH)	1	40 s Wingate	0 (-5.8 to -5.1) -3.9 (-8.6 to 2.0)
Oguri et al., 2008	9 [62.5 ± 4.1]	8	2000 m (NH)	1	30 s Wingate	1.0 (-5.8 to 7.3)
	9 [49.9 ± 5.2]	6				-2.0 (-6.8 to 3.0)

Exercise capacity – time to exhaustion tests

Amann et al., 2007	8 [67.2 ± 2.5]	12	2700 m (NH)	2	81.4% normoxic W_{peak}	-57.7 (-60.1 to -55.1)
		27	5700 m (NH)			-81.0 (-82.1 to -79.6)
Billat et al., 2003	8 [57.3 ± 3.3]	13	3400 (NH)	2	Velocity at $\dot{V}O_{2max}$	5.1 (-7.7 to 19.7)
Flinn, Herbert, Graham, & Siegler, 2014	12 [53.5 ± 10.0]	2.7	3000 m (NH)	2	Intermittent 30 s work at 120% W_{peak} and 30 s recovery at 30% W_{peak}	-27.4 (-33.6 to -20.5)
Girard & Racinais, 2014	11	8	2500 m (NH)	3	66% normoxic $\dot{V}O_{2peak}$	-38.1 (-48.3 to -26.7)
Goodall et al. 2014	9 [61.1 ± 4.6]	17.4	3800 m (NH)	2	60% of the difference between the VT1 and $\dot{V}O_{2max}$	-55.5 (-62.1 to -47.8)

Heubert, Quaresima, Laffite, Koralsztein, & Billat, 2005	9	15	2200 m (NH)	2	90% Maximal aerobic power	-18.1 (-20.5 to -14.8)
Kelly et al., 2014	13 [58.3 ± 6.3]	14	3800 m (NH)	3	75% of the difference between the VT1 and $\dot{V}O_{2max}$	-54.2 (-58.9 to -48.8)
Romer et al., 2007	9 [56.5 ± 2.7]	17	3800 m (NH)	3	92 ± 1% of W_{peak}	-68.7 (-70.2 to -67.0)
		2.8	500 m (HH)			-13.1 (-16.5 to -9.5)
		4.8	1000 m (HH)			-14.8 (-17.3 to -12.2)
Wehrlin & Hallén, 2006	8 [66.0 ± 1.6]	7.2	1500 m (HH)	2	107% $\dot{V}O_{2peak}$	-25.9 (-28.8 to -22.9)
		9.8	2000 m (HH)			-29.5 (-31.6 to -27.4)
		12.4	2500 m (HH)			-35.6 (-37.5 to -34.3)

NH: normobaric hypoxia; HH: hypobaric hypoxia.

Exercise duration categories are numerically defined as: (1) < 2min; (2) 2-10 min; and (3) > 10 min

Table 3.2. Mean \pm SD descriptive statistics for the categorical variables.

	Exercise type category				Exercise duration category			Training status	
	TT	Intermittent	Sprint	TTE	< 2 min	2-10 min	> 10 min	Healthy	Trained
Outcomes (N)	30 (313)	23 (271)	11 (87)	13 (127)	27 (297)	27 (266)	23 (235)	14 (138)	32 (320)
Mean altitude (range) (km)	2.9 \pm 1.1 (0.58-5.5)	3.0 \pm 1.1 (1-5.5)	4.3 \pm 1.6 (2- 5.7)	2.7 \pm 1.3 (0.5- 5.7)	3.7 \pm 1.2 (1.8-5.7)	2.3 \pm 0.97 (0.5- 3.9)	3.2 \pm 1.2 (1- 5.7)	3.2 \pm 0.7 (2-4.3)	2.6 \pm 1.3 (0.5-5.7)
Mean SaO ₂ (%)	14.01 \pm 8.25	14.2 \pm 6.9	11.7 \pm 6.6	10.9 \pm 4.6	13.9 \pm 6.3	9.8 \pm 5.4	16.0 \pm 8.4	13.1 \pm 6.7	12.7 \pm 7.9

3.3. Overall effect

The intercept only three-level mixed effects model identified a negative $17.1 \pm 3.7\%$ (95% CI -22.8% to -11%) effect on all categories of exercise capacity and performance with 20.8%, 62.5% and 16.7% of the variance explained by the sample, between study and between outcome variance, respectively. The outcomes from the sensitivity analysis found no substantive difference in effect or variance between models using $r = 0.67$, $r = 0.87$ and $r = 0.77$ correlation values. Acute hypoxic exposure was calculated to have a significant moderating effect that equates to a 6.5% reduction for every 1000 m elevated ($-6.5 \pm 0.9\%$; 95% CI -8.2% to -4.8%). No evidence was obtained for a non-linear effect of altitude on the overall dataset. Similarly, for a 1% reduction in SaO₂ a significant negative $2.0 \pm 0.4\%$ (95% CI -2.9% to -1.2%) effect was reported.

3.4. Moderating effects of exercise types

Exercise type was found to have a moderating effect on exercise performance under acute hypoxic conditions (Figure 3.1), with TT performance and TTE tests experiencing a significant $-16.2 \pm 4.3\%$ (95% CI -22.9% to -9.0%) and $-44.5 \pm 6.9\%$ (95% CI -51.3% to -36.7%) change. However, the overall effect on intermittent exercise ($-5.6 \pm 4.8\%$; 95% CI -13.9% to 3.5%) and sprint performance (-2.9 ± 8.0 ; 95% CI -16.5% to 12.8%) were non-significant. Moreover, interaction effects were reported between exercise type and magnitude of altitude elevation. Additionally, altitude² moderator improved model fit compared to the linear model when exercise type was included ($\chi_{(10)} = 8.0$; $p = 0.005$), indicating a curvilinear effect of acute hypoxia. The exercise type category was subsequently reduced to TT and TTE sub-groups to determine the interaction effects with linear and quadratic effects of altitude elevation (Table 3.3), which are depicted in Figure 3.2. The magnitude of SaO₂ decline was also determined to have the largest moderating effect on TTE exercise compared to the three other exercise types, with a $-4.5 \pm 0.5\%$ (95% CI -5.4% to -3.6%) for every 1% reduction in SaO₂. A lower $-1.3 \pm 0.4\%$ (95% CI -2.1% to -0.5%) moderating effect for every 1% reduction in SaO₂ was also evident on TT performance.

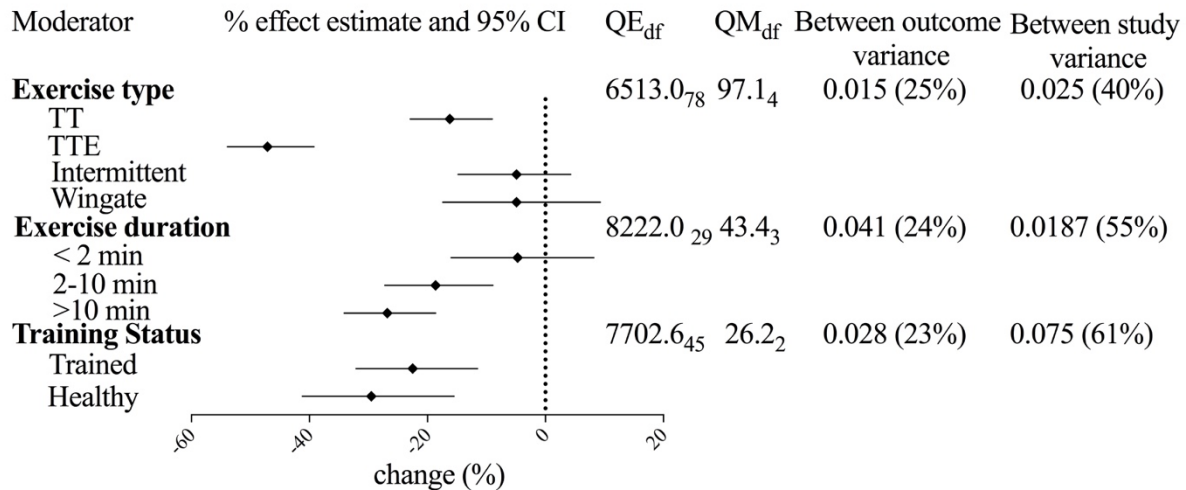


Figure 3.1. Results from categorical moderator analysis.

QE_{df}: residual heterogeneity test statistic; QM_{df}: omnibus moderator test statistic.

Between outcome and study variance are accompanied by a percentage showing the proportion of total variance in the model that they account for.

Confidence intervals crossing the zero-boundary show non-significant effects.

Table 3.3. Linear and quadratic interaction between altitude and subgroups within exercise type, with an illustrative example of percentage effect on performance at 3000 m.

Exercise Category	Model	Altitude	Altitude ²	Example performance effect at 3000 m
TT	Linear	-6.4 ± 0.4%*		-58.0%
	Quadratic	-1.7 ± 3.5%	-1.4 ± 0.3% *	-47.7%
TTE	Linear	-19.6 ± 2.0% *		-19.2%
	Quadratic	-10.2 ± 2.6% *	-1.9 ± 0.4% *	-17.7%

*Represents a statistically significant interaction determined through 95% confidence intervals

Data reported as mean ± standard error.

Intercept for all models are constrained to zero.

3.5. Moderating effects of exercise duration

Acute hypoxia had no effect on exercise of < 2 min duration (-6.3 ± 5.6%; 95% CI -16.1% to -3.8%), however exercise between 2-10 min and > 10 min had a significant -18.0 ± 6.0% (95% CI -25.8% to -8.2%) and -26.8 ± 5.5% (95% CI -33.2% to -18.2%) effect, respectively. A similar interaction effect with altitude was also found for exercise between 2 to 10 min and > 10 min, with a negative -13.6 ± 2.4% (95% CI -17.8% to 9.7%) and -18.2 ± 2.1% (95% CI -21.5% to -14.8%) per 1000 m, respectively. A similar moderating effect of SaO₂ was noted for the 2-10 min category at -2.4 ± 0.7% (95% CI -3.8% to -1.0%) and over 10 min category at -2.8 ± 0.6% (95% CI -3.9% to -1.6%) for every 1% reduction in SaO₂.

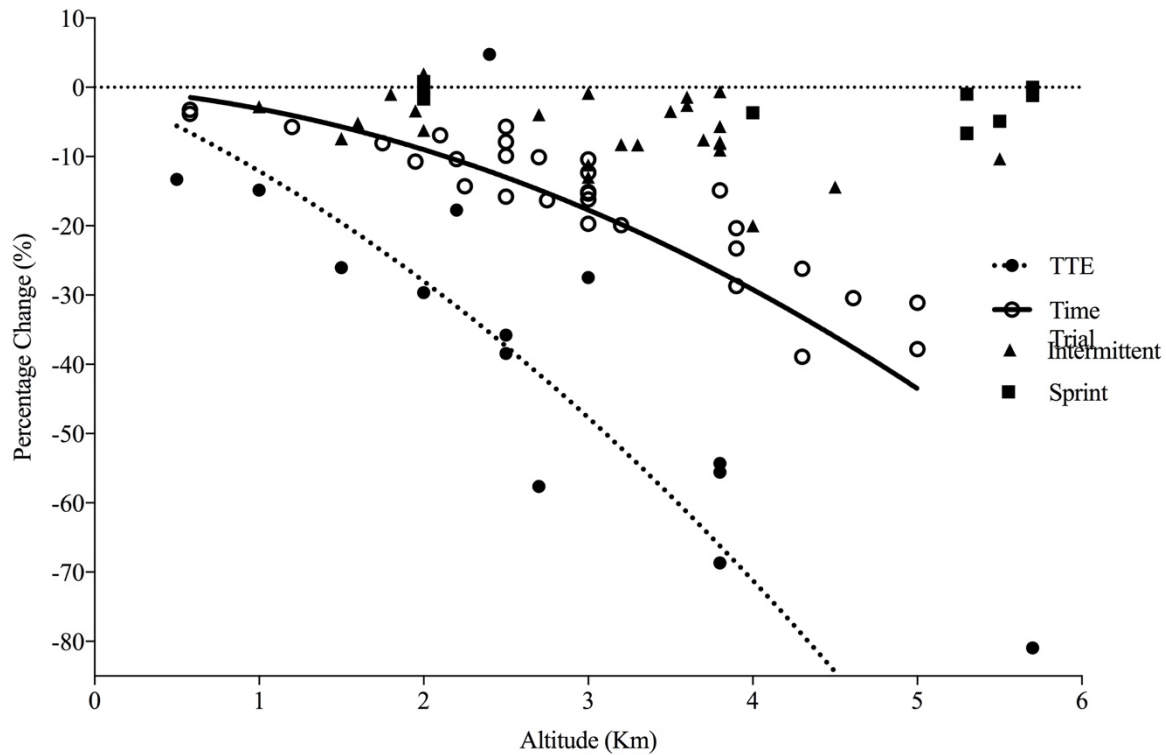


Figure 3.2. A scatterplot showing the outcomes included this meta-analysis categorised by exercise type, with quadratic regression lines shown for TTE and TT performance. Wingate, intermittent and TT performance are shown as a percentage change in mean power output, while TTE as a percentage change in exercise tolerance duration.

3.6. Moderating effect of training status

Trained and healthy individuals were found to have a pooled $-21.8 \pm 6.8\%$ effect (95% CI -31.2% to -11.1%) and $-29.5 \pm 9.6\%$ (95% CI -41.1% to -15.5%) decline in performance with acute hypoxia, respectively. Given the variance in the range of altitude elevations and greater mean elevation in the healthy cohort, further analysis that controlled for altitude found a non-significant effect between sub-groups. There was however, a difference in the moderating effect of SaO_2 between the sub-groups, with a significant moderating effect for every 1% reduction in SaO_2 apparent in trained ($-2.8 \pm 0.5\%$; 95% CI -3.8% to -1.7%) but not in untrained healthy participants ($-2.0 \pm 1.6\%$; 95% CI -5.1% to 1.1%).

3.7. Further analysis

Owing to the large proportion of outcomes in the intermittent exercise group also classified as < 2 min (17 of the 23), the main effect in the intermittent sub-group may have been skewed. Therefore, further analysis to determine the pooled effect on intermittent exercise bouts > 2 min were performed. An overall pooled estimate of $-4.7 \pm 1.3\%$ (95% CI -7.2% to -2.2%) was

observed, however acute hypoxia elevation was not found to be a significant moderator of intermittent exercise over 2 min (95% CI -7.7% to 3.1%).

4.0. Discussion

This is the first meta-analysis to study the effects of acute hypoxic exposure on exercise capacity and performance; and assess the effect against moderators of altitude elevation based on FiO_2 tested, SaO_2 , training status, exercise duration and type of exercise. This review is the first to show the curvilinear relationship between exercise and acute hypoxic exposure during TT and TTE exercise tests, and exercise activity > 2 min. In contrast, no ergolytic effect was found during intermittent exercise and sprint tests; and exercise < 2 min. When exercise < 2 min were removed from the analysis of intermittent exercise, a significant negative effect was seen, suggesting prolonged intermittent exercise is impaired under acute hypoxic conditions. Training status was demonstrated to be a significant moderator, with trained and healthy individuals exhibiting a similar negative effect. While reductions in SaO_2 displayed a negative moderating effect in the overall model, however these effects were more pronounced within trained participants. Together, these results highlight the magnitude dependent moderating effects of acute hypoxia, while also showing potential factors that are likely to influence exercise performance at acute hypoxia.

The curvilinear relationship between exercise and hypoxic exposure is described by a quadratic model. This is equivalent to the meta-analytic model previously used to describe the relationship with $\dot{\text{V}}\text{O}_{2\text{max}}$ (Macinnis et al., 2015). Furthermore, critical power (CP), a suggested marker of maximal sustainable aerobic power, has been fitted to a higher order cubic model to show the negative relationship within nine trained cyclists (Townsend et al., 2017). Nonetheless, this is the first study to describe a curvilinear relationship during TT performance and TTE tests, given previous experimental studies have reported a linear 7.0% reduction in TT performance per 1000 m (Clark et al., 2007) and TTE decline linearly by 14.5% per 1000 m up to a moderate 3000 m elevation (Wehrlin and Hallén, 2006). When comparing the quadratic models of the current dataset at a hypoxic exposure equivalent to 3000 m. TTE and TT performance can be predicted fall by 47.7% and 17.7%, respectively, whereas previous research would suggest a 43.5% reduction in TTE and 21.0% reduction in TT performance. The small but important difference in the magnitude of decline and the curvilinear model is likely to be explained by the greater range of acute hypoxic magnitudes, equivalent 500 m to 5700 m elevation, in the present model, which includes severe hypoxic exposures, whereas

previous experimental work only assessed low and moderate altitudes (< 3000 m) (Wehrlin and Hallén, 2006, Clark et al., 2007). Indeed, earlier articles that also reported a curvilinear relationship, also included severe hypoxic exposures (Macinnis et al., 2015; Townsend et al., 2017), which suggests alternative fatiguing mechanisms may be operating. Current evidence alludes to an exacerbated central fatigue action through diminished group III/IV afferent feedback with exposure to severe hypoxic conditions, whereas the central motor output is unchanged from sea level at moderate hypoxic exposures (Amann et al., 2007). This diminished central motor output may, in part, explain the exponential decline in performance observed with greater elevation.

The magnitude of the impairment with acute hypoxia is dependent on the type and duration of exercise, with TT performance and TTE tests found to elicit ergolytic effects, while sprint and intermittent tests found to be largely unchanged from sea level. This effect may be explained by the duration of exercise within these sub-groups, given sprint exercise and the repeated sprint exercise (RSE) within the intermittent group formed the < 2 min sub-group. Indeed, experimental studies assessing the various magnitudes of hypoxia on RSE have only reported performance decrements above 4000 m (Bowtell et al., 2014, Goods et al., 2014). However, the current model did not show this due to the assessment of performance against a continuous hypoxic moderator rather than at 1000 m categorical intervals used in experimental studies. Nonetheless, sprint and RSE performance, which is equivalent for the < 2 min duration category, are sustained with acute hypoxia; an effect that can be explained through greater reliance on anaerobic energy sources, which provides the greatest contribution to RSE and sprint performance (Scott, Goods and Slattery, 2016). The separation of exercise activity less than 2 min in the intermittent sub-group did however, suggest prolonged intermittent exercise is impaired under acute hypoxia, which may explain the decrement in physical output during team sports competition at altitude (Aldous et al., 2016). However, the moderating effect of acute hypoxia were not evident, which may be attributed to the lack of available outcomes; therefore, further research should aim to assess effects of several incremental magnitudes of acute hypoxia on prolonged intermittent performance.

The lack of effect during short duration (< 2 min) exercise bouts is also reflected in previous research assessing the impact of altitude on track athletes (Hamlin, Hopkins and Hoolings, 2015) and may also be mechanistically explained when viewed through the two parameter CP concept (Simpson et al. 2015; Sherman et al., 2016; Townsend et al., 2017). When analysing

track performances of major international competitions at varying degrees of altitude, Hamlin et al., (2015) reported track sprint events (100-400 m) did not exhibit a negative effect associated with hypoxia, but rather, a performance improvement due to the reduced aerodynamic resistance caused by the lower barometric pressure present at terrestrial altitudes. Whereas, longer track events (800 -10000 m) that require a larger relative aerobic energetic contribution exhibit a performance decrement at elevations ≤ 150 m. As such, demonstrating the outcomes of this meta-analysis are also reflected during athletic competition. Further to this, with hypoxic exposures, critical power exhibits a substantial decline in performance corresponding to the performance impairment noted during longer TT and TTE exercise that requires a greater aerobic contribution. Whereas, W' , the ability to perform work above CP is unchanged under moderate hypoxic conditions (Shearman et al., 2015, Simpson et al., 2015, Townsend et al., 2017). Traditionally, W' is purported to represent the anaerobic work capacity and as such, the lack of change reported during exercise < 2 min in the current study may be explained through the two parameter CP model.

There is evidence to suggest an individual variability in exercise response to acute hypoxic exposure, which is predominantly accounted by superiorly trained individuals exhibiting the largest decrement in $\dot{V}O_{2\max}$ (Macinnis et al., 2015) under acute hypoxic conditions, given their inability to maintain SaO_2 during exercise compared to untrained individuals (Chapman et al., 2011). Chapman et al., (2011) further identified that individuals that exhibited the greatest reductions in SaO_2 during a 3000 m running performance, experienced a greater impairment in running performance. In the current study, performance decrements between healthy and trained cohorts could not be differentiated when controlling for differing hypoxic exposures. However, the moderating effects of SaO_2 were more evident within trained individuals with a significant $2.8 \pm 0.5\%$ fall in performance for every 1% reduction in SaO_2 , while no significant moderating effect was noted in healthy individuals. This is however, presented with a caveat as fewer outcomes were included in the healthy cohort sub-group, which may have contributed to the null findings. Nonetheless, SaO_2 was demonstrated to have an overall moderating effect, which was most evident during TTE tests and TT performance.

In this review, the effects of the type of hypoxic exposure (i.e. normobaric vs hypobaric) could not be evaluated due to the lack of available data. Research has suggested the different physiological response to exercise between normobaria and hypobaria (Coppel et al., 2015); while it is important to highlight the reduced air density at terrestrial altitude, result in fast

velocities at equivalent power outputs (Garvican-Lewis et al., 2015), therefore the results of this study are not directly applicable to field based performance. Nonetheless, this review quantifies the non-linear relationship between acute hypoxia and both TTE and TT performance, whilst also highlighting the lack of effect during Sprint and RSE. Additional, noteworthy limitations to this study are apparent in the interpretation of the effect of SaO₂ and training status moderators. End exercise SaO₂ was used in the current study as opposed to mean SaO₂ due the much greater frequency in measurement of the former. The use of mean SaO₂ would take in to account the different rates of change in oxygen saturation during exercise and within exercise SaO₂ may have implications for pacing, therefore further experimental research should consider this effect. In the present study, training status was defined with a cut off in mean $\dot{V}O_{2max}$ to maintain objectivity of physiological fitness, however, this categorical approach is limited, in that, participant cohorts may not be homogenous with $\dot{V}O_{2max}$ of individuals ranging above and below the cut off. The moderating effects of $\dot{V}O_{2max}$ should therefore be interpreted with this caveat. Nonetheless, this review offers a useful practical interpretation for practitioners, coaches and athletes when planning training during a range of acute hypoxic levels. Furthermore, this review highlights the importance of mitigating the reduction of SaO₂ to maintain exercise performance under acute hypoxia, particularly within trained cohorts who are suggested to experience a larger moderating effect of SaO₂. The subsequent chapters will build on these findings, through evaluating if nutritional ergogenic aids can be used to mitigate the decremental effects of acute hypoxia on exercise performance. More specifically, this will look to address the principle aim of this thesis to determine if NaHCO₃ demonstrates ergogenic properties in acute hypoxic conditions and thus, mitigating the ergolytic effect of acute hypoxia on exercise performance.

Chapter Four: Determinants of curvature constant (W') of the power duration relationship under normoxia and hypoxia: the effect of pre-exercise alkalosis

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1.0.Introduction

Fatigue is determined by an array of factors that are suggested to originate from afferent/efferent feedback from the central nervous system (i.e. central fatigue), and/or metabolic and biochemical alterations in the intramuscular regions (Ament and Verkerke, 2009). The mediators of fatigue are, however, predominantly dependant on exercise intensity and as such, the physiological response and tolerance to exercise can be clustered into distinct domains (Burnley and Jones, 2007). Tolerance within the severe intensity domain can be described by a mathematical hyperbolic curve known as the power-duration relationship (Jones et al. 2010; Poole et al. 2016). This hyperbolic curve can be categorised into the asymptote and the curvature constant, which in the power-duration relationship are known as CP and W' , respectively. The CP signifies the greatest intensity where a physiological steady state can be maintained (Poole et al. 1988); in addition to defining the boundary between heavy and severe exercise intensity domains (Burnley and Jones 2007). The range of exercise intensities between CP and the power output at $\dot{V}O_{2peak}$ represent the W' . This quantifies a fixed work constant available for exercise within the severe exercise intensity domain (Jones et al. 2010; Poole et al. 2016); and therefore, enables the prediction of time to exercise exhaustion at any given power output above CP. Exercise within the W' range is associated with a distinct physiological response that are associated with fatigue (Poole et al. 1988; Burnley and Jones 2007; Jones et al. 2008). This includes, muscle metabolite perturbations, such as an exponential rise in muscle H^+ and PCr breakdown (Jones et al. 2008); as well as the development of a substantial $\dot{V}O_2$ slow component (Murgatroyd et al. 2011).

The power-duration relationship has varying applications to healthy, patient and athletic populations. More specifically this includes; the normalisation and prescription of exercise intensities (Ferguson, Wilson, Birch and Kemi, 2013), a method to predict exercise performance capabilities (Black et al., 2014) and inform athletic pacing strategies (Vanhatalo, Jones and Burnley, 2011). Furthermore, the CP concept has been cited as a method that can assess the effect of interventions by providing both functional exercise capacity data and associated physiological benefits (Whipp and Ward, 2009, Jones et al., 2010). Therefore, greater mechanistic appreciation of the physiological components that determine CP and W' may improve the practical application of this power-duration model. Critical power is sensitive to manipulation in O_2 availability with hypoxic exposure diminishing CP (Dekerle, Mucci and Carter, 2012a, Simpson et al., 2015, Townsend et al., 2017) and hyperoxic exposure increasing

CP (Vanhatalo, Fulford, et al., 2010b). As such CP is suggested to be predominantly comprised of oxygen dependant, aerobic energy sources (Poole et al. 2016). In comparison, the determinants of W' are less clear (Jones et al. 2010; Poole et al. 2016) as interventions that increase CP can concurrently reduce W' (Vanhatalo et al. 2010). This may indicate that W' may not only represent the finite anaerobic energy contribution, as originally proposed, but rather an interplay of aerobic and anaerobic energetic factors.

Muscle metabolite disturbances are closely linked with W' (Jones et al., 2008) and the exogenous manipulation of metabolite disturbances can enhance W' ; such as creatine ingestion to increase PCr resynthesis and thus W' (Miura et al., 1999). This, however, has not been consistently demonstrated, as pre-exercise alkalosis (through NaHCO_3 supplementation) was shown not to alter W' , despite the alleviation of H^+ accumulation during all-out exercise (Vanhatalo et al. 2010). Indeed, there is considerable debate regarding the involvement of acidosis in fatigue and exercise performance (Fitts, 2016, Westerblad, 2016), which may explain the lack of improvement reported in W' . Morales-Alamo et al. (2015) observed that sprint performance following exhaustive exercise recovered at a faster rate than muscular acidosis (i.e. removal of H^+). This suggests a close temporal relationship between acidosis and whole-body exercise performance may not coexist. Furthermore, performance recovery was faster with hypoxic exposure, with the authors suggesting central fatigue mechanisms may have a more prominent role in fatigue in comparison to normoxia. This is despite acute hypoxia eliciting an additive acidic stress during exercise (Hogan, Cox and Welch, 1983), which is identified as a factor contributing to the diminished exercise performance under this environmental stressor (Clarke et al. 2007). While, NaHCO_3 supplementation is shown to be an effective ergogenic aid by acting to delay the onset of acidosis during exercise (McNaughton et al., 2016), suggesting acid-base balance is implicated with exercise performance and fatigue. Furthermore, exercise above CP is associated with an increase in H^+ and therefore, the hypothesis identifying acidosis as a physiological determinant of W' utilisation cannot be dismissed.

Theoretically, NaHCO_3 may enhance W' by increasing the availability of blood HCO_3^- and strengthen the physiochemical buffering capacity, which acts to dampen the rate of H^+ accumulation during exercise (Carr et al. 2011). More recent methodological developments in NaHCO_3 administration suggest an inter-individual variability in extracellular peak blood alkalosis, which ranges from 10-140 min (Stannard et al. 2016; Miller et al. 2016).

Consequently, previous research utilising standard ingestion times across all participants may not have induced individual peak alkalosis, such as that used by Vanhatalo et al. (2010). Thereby limiting the potential to attain an accurate representation of the effect of alkalosis. The purpose of this study was therefore, to investigate the effect of individualised pre-exercise NaHCO_3 supplementation on CP and W' during the 3 min CP test under normoxic and hypoxic conditions

2.0. Methods

2.1. Participants

Eleven male trained cyclists volunteered to participate in this study with the following mean \pm SD physical characteristics, age 32 ± 7.2 yrs; body mass 77.0 ± 9.2 kg; $\dot{V}\text{O}_{2\text{peak}}$ 59.2 ± 7.4 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; peak power output 391.3 ± 43.7 W. Participant inclusion was determined by age (18-40 years), training history (minimum of two years cycling and a seven hrs \cdot week $^{-1}$ minimum training volume) and previous altitude exposure (not resided at altitude for the previous six months). Written informed consent was obtained from all participants after explanation of test procedures and associated risks. Ethical approval was obtained for the study from the Departmental Research Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Experimental overview

Participants visited the laboratory on seven separate days at the same time of day (± 1 hr), with visits separated by at least two, but no more than seven days. Pre-experimental procedures were performed as described in chapter two section 2.0 During the first visit, individual time to peak blood alkalosis was established using the methods described in chapter two section 4.0. This formed the timescale for individualised NaHCO_3 ingestion prior to exercise during subsequent experimental trials.

Both normoxic and hypoxic exercise trials were performed in this study, with environmental conditions described in chapter two section 5.0. The first two exercise trials consisted of an incremental ramp test assigned in a single-blinded, random order to either the normoxic or hypoxic environmental condition to determine $\dot{V}\text{O}_{2\text{peak}}$ and VT1 . This RAMP test and accompanying procedures are described in chapter two section 6.0. A randomised, cross-over

design was employed for the following four experimental trials under different environmental conditions. All exercise tests were performed to replicate the original ramp and 3 min all-out critical power test performed by Vanhatalo et al. (2007) to maintain the validity of the CP and W' measured. This test is described in chapter two section 7.0 and participants undertook a familiarisation prior to experimental trial. The four experimental conditions in this study were: alkalosis normoxia (ALN), placebo normoxia (PLN), alkalosis hypoxia (ALH), and placebo hypoxia (PLH). Supplements were administered in a double-blinded manner prior to exercise at the time to peak alkalosis identified in the initial trial. These supplements were prepared and administered as described in chapter two section 3.0; with capillary blood sample taken and analysed for blood acid-base variables, HR and SPO₂% taken during each experimental trial as described in chapter two section 8.0.

2.3. Statistical Analysis

The Shapiro-Wilk test provided no evidence to reject the hypothesis that all data was normally distributed. A two-way ANOVA (condition [normoxia vs. hypoxia] x time) was used to compare power outputs of VT1 and PPO during the incremental ramp test, whilst cardiopulmonary variables between environmental conditions were compared using a paired t-test. A two-way (treatment [alkalosis vs. placebo] x condition [normoxia vs. hypoxia]) repeated measures ANOVA was used to compare means for dependant variables within the 3 min CP test (CP, W' , total work done (TWD), PPO, and HR) and RPE. A three way (treatment [alkalosis vs. placebo] x condition [normoxia vs. hypoxia] x time [pre-supplementation vs. pre-exercise vs. post exercise]) repeated measures ANOVA was conducted to compare blood [HCO₃⁻] and [H⁺], whilst further comparison of change in blood [HCO₃⁻], [H⁺] and lactate during exercise were conducted through a two-way ANOVA. Furthermore, a comparison of CP to EP and W' to W'_{EP} was performed using a two-way ANOVA. Where significant main effects were found, a Bonferroni correction was used for *post-hoc* pair-wise analyses. Pearson correlations were performed to examine the relationship between the effect of NaHCO₃ on TWD and the effect on W' and CP, under both environmental conditions. Effect sizes and their 95% confidence intervals (CI) were calculated using Hedge's *g* for paired comparisons, with the effects interpreted and discussed against effects of the relevant prior literature (Thompson, 2007). These effect sizes can also be interpreted as trivial (<0.20), small (0.20-0.49), moderate (0.50-0.79) or large (≥0.80) (Cohen 1988). The Hedge's *g* correction was used to mitigate positive bias of the Cohen's *d* effect size when using sample sizes less than 20 (Lakens,

2013). Descriptive data is presented as mean \pm SD and statistical significance accepted at $p < 0.05$. Data were analysed using SPSS v22 for Windows (SPSS Inc., Chicago, IL, USA).

3.0. Results

During the preliminary trial, time to peak pH following 0.3 g·kg⁻¹ bm of NaHCO₃ ingestion ranged between 40-70 min (mean: 50 \pm 9.6 min). A significant interaction between environment was found ($p = 0.005$) on peak power during the ramp test (Table 4.1). This was represented in peak power output reducing by 10% from normoxia to hypoxia (mean difference: 40.1 \pm 20.5 W; $p < 0.001$); although power output at VT1 was similar between environmental conditions (9.6 \pm 2.0.2 W; $p = 0.38$). There was also a significant 18% reduction in $\dot{V}O_{2\text{peak}}$ between normoxic to hypoxic environment (10.8 \pm 6.0 ml·kg⁻¹·min⁻¹; W; $p = 0.001$).

Table 4.1. RAMP test result under normoxic and hypoxic conditions.

Variables	Normoxia	Hypoxia
$\dot{V}O_{2\text{max}}$ (ml·kg ⁻¹ ·min ⁻¹)	59.3 \pm 7.4*	48.5 \pm 6.0
PPO (W)	390.4 \pm 45.0*	351.5 \pm 40.1
VT1 _{power} (W)	176.4 \pm 18.2	166.8 \pm 19.4
HR _{peak} (bpm)	181 \pm 6.6	179 \pm 7.1

*denotes significantly different to Hypoxia ($p < 0.05$). Values reported as a mean \pm SD.

Pre-exercise alkalosis had a significant main effect on W' ($p < 0.001$) (Figure 4.1) and TWD ($p = 0.015$) (Figure 4.2). This represents a 14% increase in W' under normoxic ($p = 0.006$; $g = 0.38$, 95% CI: -0.5 to 1.3) and an 18% increase under hypoxic ($p = 0.001$; $g = 0.53$, 95% CI: -0.4 to 1.4) conditions with NaHCO₃ compared to placebo. Pre-exercise alkalosis also elicited a positive effect on TWD, with *post hoc* comparisons showing a 5.5% ($p = 0.048$; $g = 0.36$, 95% CI: -0.5 to 1.26) and 4.8% ($p = 0.001$; $g = 0.46$, 95% CI: -0.4 to 1.3) increase under normoxic and hypoxic environments, respectively. In contrast, there was no overall supplement effect on CP ($p = 0.41$).

Critical power was, however, effected by the environmental conditions ($p = 0.41$), with an overall mean reduction of 44.5 \pm 23.2 W (Table 4.2). Similarly, an overall significant environmental effect on TWD was found ($p < 0.001$; $g = 0.8$; -0.1 to 1.7) with hypoxia eliciting

a mean 10.7% reduction. Conversely, W' was not influenced by the environmental conditions ($p = 0.59$; $g = 0.01$; -0.9 to 0.9). Comparison of CP to EP demonstrated an overall significant main effect across conditions ($p = 0.004$), although pairwise comparisons were non-significant; while W' and W'_{EP} did not differ ($p = 0.210$). Pearson's correlation between the effect of alkalosis reported a significant relationship between the effect on TWD and the effect on CP under normoxic ($r = 0.92$; $p < 0.001$) and hypoxic environments ($r = 0.83$; $p = 0.001$). Whereas, the relationship between the effect on TWD and W' was not significantly different under normoxia ($r = 0.52$; $p = 0.09$) and hypoxia ($r = 0.2$; $p = 0.54$).

Table 4.2. Overview of three min all-out critical power test data

Variables	PLN	ALN	PLH	ALH
CP (W)	304.2 ± 40.0*	313.2 ± 48.5*	263.3 ± 34.3	264.8 ± 3
W' (kJ)	15.1 ± 6.2 [#]	17.4 ± 5.1	15.2 ± 4.9 [#]	17.9 ± 5.2
EP (W)	308.2 ± 43.3	314.2 ± 55.5	267.0 ± 31.7	267.1 ± 29.4
W'_{EP} (kJ)	14.1 ± 6.3	17.1 ± 5.0	14.5 ± 5.6	17.4 ± 5.2
TWD (kJ)	69.9 ± 10.2* [#]	73.8 ± 10.5*	62.6 ± 7.2 [#]	65.6 ± 6.0
PPO (W)	697 ± 91	694 ± 87	694 ± 90	695 ± 86
[BLA] (mmol·l ⁻¹)	13.9 ± 5.2	15.5 ± 7.0	14.7 ± 6.4 [#]	16.5 ± 5.4
HR _{peak} (bpm)	175.1 ± 7.1	175.3 ± 6.8	175.8 ± 7.4	176.1 ± 6.9
SpO ₂ (%)	94.0 ± 2.1*	93.7 ± 2.3*	83.5 ± 7.1	84.4 ± 3.9
RPE	18.8 ± 1.8	19.3 ± 1.6	19.0 ± 1.9	19.3 ± 1.6

PLN represents the placebo normoxia condition. ALN represents the alkalosis normoxia condition. PLH represents the placebo hypoxia condition. ALH represents the alkalosis hypoxia condition. [bla] represents blood lactate accumulation during exercise

*denotes significantly different to corresponding hypoxic trial ($P < 0.001$).

[#]denotes significance to corresponding alkalosis trial ($p < 0.001$).

Values reported as a mean ± SD.

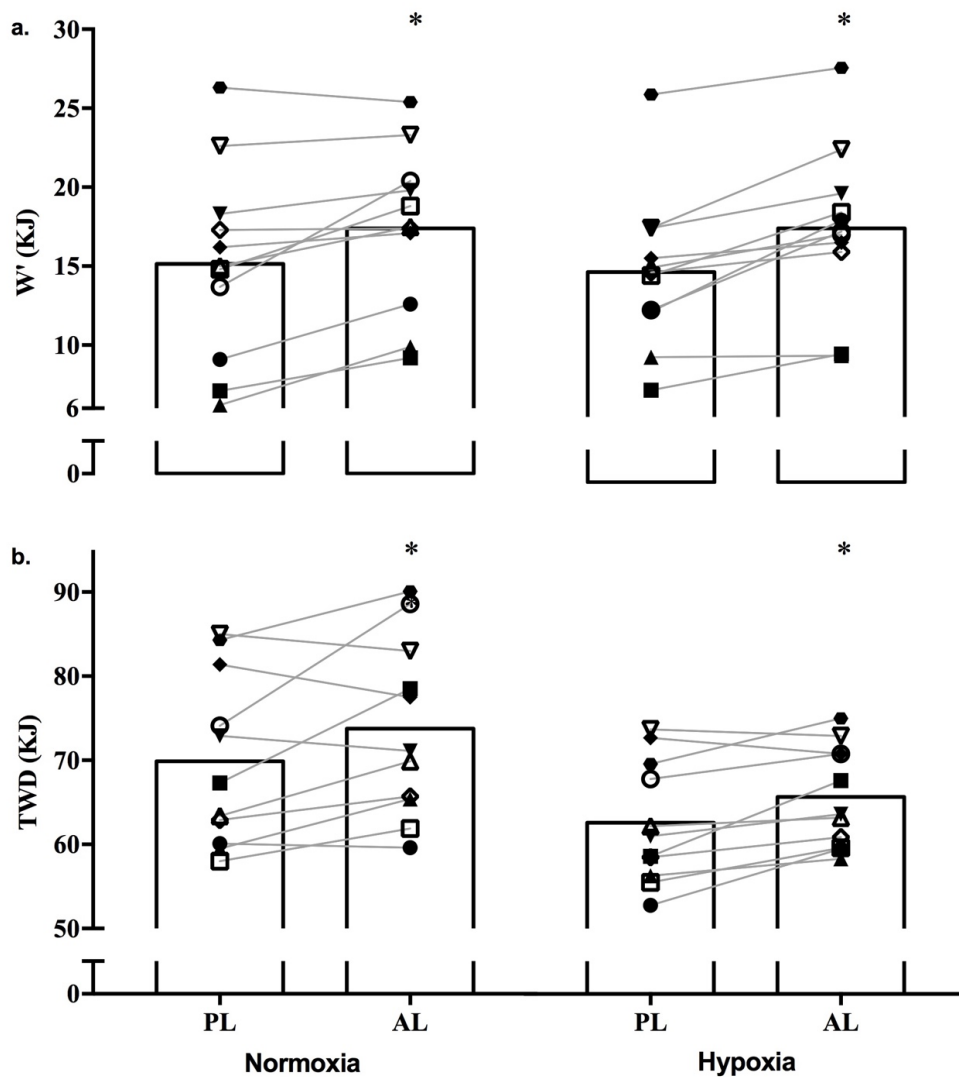


Figure 4.1. Graph (a) displays W' and graph (b) displays TWD. These figures represent the mean values in each experimental condition, while the individual points and connecting lines represent the individual response to alkalosis under the respective environmental conditions. * represents significantly different to placebo condition ($p < 0.05$).

A significant two-way [supplement x time] interaction was detected on $[\text{HCO}_3^-]$ ($p < 0.001$) and $[\text{H}^+]$ ($p < 0.001$), indicating NaHCO_3 supplementation had a significant effect on blood $[\text{HCO}_3^-]$ and $[\text{H}^+]$ ($p < 0.001$) as displayed in Figure 4.2. A significant main effect with alkalosis was evident on change in $[\text{HCO}_3^-]$ during exercise ($p < 0.001$), although the environmental effect was not significant ($p = 0.615$). Further, pairwise comparisons revealed a 28% ($p < 0.001$) and 27% ($p < 0.001$) greater increase in $[\text{HCO}_3^-]$ reduction with pre-exercise alkalosis in the respective normoxic and hypoxic trials, compared to placebo (Figure 4.2). Equivalently, $[\text{bl}a]$ change during exercise was significantly increased with alkalosis by 10% under normoxia and 15% under hypoxia (Table 4.2) ($p = 0.005$) but environmental conditions had no influence

($p = 0.41$). Despite this, the significant supplement effect on change in [bla] only manifested during hypoxic conditions (mean difference = - 2.22 nM; $p = 0.012$) but not during normoxic conditions (mean difference = - 1.58 nM; $p = 0.08$). In contrast, change in $[H^+]$ from pre to post- exercise did not change with neither a supplement ($p = 0.82$) nor environment ($p = 0.38$) effect (Figure 4.2).

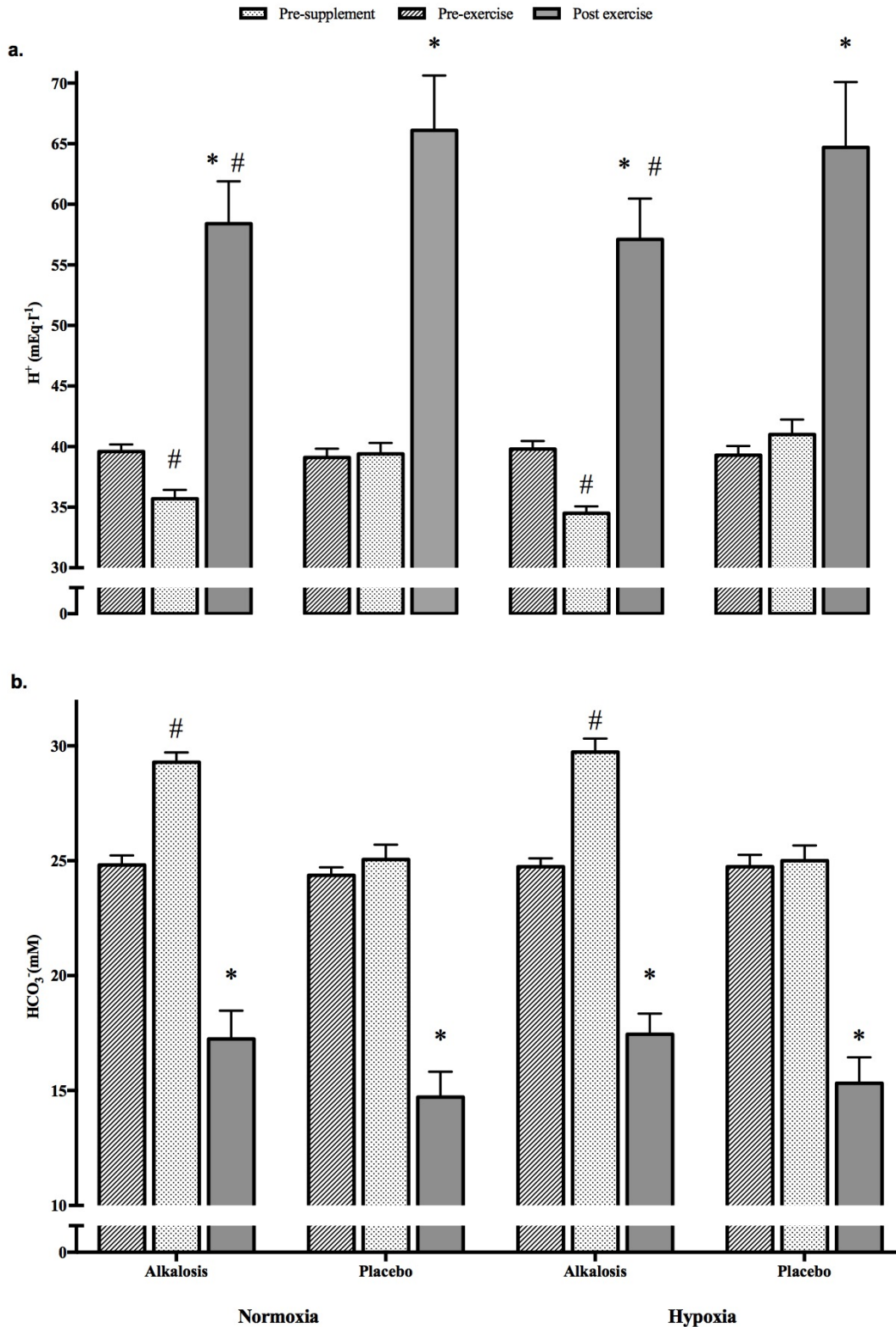


Figure 4.2. Graph (a) displays change in blood [H⁺] and graph (b) displays change in blood [HCO₃⁻] across three-time points during the four different experimental trials. Error bars are displayed as SEM. * represents significantly different from pre-supplement and pre-exercise time points ($p < 0.05$); # represents significantly different from placebo conditions at the same time point.

4.0. Discussion

This study was designed to determine the effect of NaHCO₃ on the W' parameter of power-duration relationship. The principle and novel finding was that attaining individualised peak blood alkalosis, appears to enhance the magnitude of W' under both normoxic and hypoxic conditions. Furthermore, an increase in total work done across the 3 min exercise period was evident; along with greater reduction in blood [HCO₃⁻] and increased [bla] during exercise with pre-exercise NaHCO₃ treatment. This investigation also revealed the magnitude of CP declines under moderate hypoxic exposure, supporting previous research (Dekerle et al. 2012; Simpson et al. 2015; Shearman et al. 2016). However, manipulation of acid-base status was deemed to have no effect on CP determination. Therefore, NaHCO₃ may be an effective ergogenic aid by increasing work performed above CP and, also, the total work performed in the severe intensity domain.

The primary finding of the study is in contrast with previous research by Vanhatalo et al. (2010), who, in a normoxic environment, reported no effect with NaHCO₃ ingestion on the W' parameter. The exercise protocols in both studies were matched, although the calculation of W' did however differ, with W' determined from the final 30 sec power outputs by Vanhatalo et al. (2010) whereas the present study used the lowest 30 s average power output. There were no significant differences in the current study, however, in W' between the methods of calculation and therefore this is not likely to explain the differences. There are, however, two main methodological differences that may explain the opposing finding. Recent research has identified exogenous NaHCO₃ ingestion is subject to inter-individual variance in blood pH and HCO₃⁻ (Miller et al. 2016, Stannard et al. 2016). The current investigation accounted for this varied blood analyte response through individualised NaHCO₃ administration prior to exercise, which ranged from 40 to 70 min and represented a significant increase in blood alkalinity and [HCO₃⁻] prior to exercise (figure 4.2). The only previous investigation to employ this NaHCO₃ administration protocol reported a larger variance between 10 to 90 min to peak alkalinity within in a recreationally active cohort (Miller et al. 2016). On this premise, it is reasonable to suggest that the standardised 60 min pre-exercise ingestion used by Vanhatalo et al. (2010) may not have induced maximal peak alkalosis within all participants; thereby masking the influence of alkalosis on W' . The differing results with the current study could also be attributed to the training status of participants used, as the ergogenicity of NaHCO₃ has been suggested to be greater in trained individuals (Carr, Hopkins and Gore, 2011; McNaughton et

al. 2016). Alternatively, the differing results could be attributed to the recently identified inter-individual variability in performance response to NaHCO₃ supplementation (Saunders et al. 2014a; Dias et al. 2015)

Comparison of the hedges *g* effect sizes suggests the ergogenic effect of NaHCO₃ may be larger under acute hypoxic conditions compared to normoxia, with an effect of 0.53 and 0.46 for *W'* and TWD in hypoxic conditions, respectively, compared to 0.38 and 0.36 for *W'* and TWD in normoxic conditions, respectively. The current investigation is the first to demonstrate a significant and meaningful improvement in performance from NaHCO₃ under acute hypoxic conditions, in contrast with as previous investigations reporting no effect (Saunders et al. 2014b; Flinn et al. 2014). The conflicting results to previous investigations may be attributed to the intensity and type of exercise, which were supra-maximal and intermittent in both previous studies, or the training status of participants, who were recreationally trained. Furthermore, it should be acknowledged that acidosis is suggested not to be an important contributor to fatigue at hypoxia; indeed, maximal repeated sprint performance is shown to be independent of the presence of muscular acidosis following exhaustive exercise (Morales-Alamo et al. 2015). While other investigations have reported findings in direct contrast by suggesting acidosis can better maintain performance at hypoxia (Schone et al. 1983; Fulco et al. 2006). Therefore, importance of alkalosis on exercise performance cannot be concluded from the observations of the current study and both acidosis and alkalosis may be beneficial to performance though differing mechanism of action. Interestingly, the larger effect sizes of NaHCO₃ under hypoxia compared to normoxia may be due to the greater acidic stress and the subsequent increased reliance on the HCO₃⁻ buffering system during exercise. However, 3 min CP protocol was not primarily designed as a sensitive measure to detect changes in overall performance but rather establish CP and *W'*. Therefore, the use of fixed intensity exercise tolerance protocol, such as the Cycling Capacity Test 110% (Saunders et al. 2014a), may provide a more appropriate high-intensity protocol to test the difference in efficacy of NaHCO₃ between hypoxic and normoxic environments.

This study provides a unique mechanistic insight into the determinants of *W'*, which is subject to uncertainty within scientific literature (Poole et al. 2016), given the multi-faceted central and peripheral mechanisms of exercise tolerance and fatigue (Amet and Verkerke, 2009). Using ³¹P magnetic resonance spectroscopy (MRS) muscle metabolite responses to exercise above CP have been characterised, with a rapid accumulation of H⁺ and P_i observed (Jones et

al. 2008). Acidosis is associated with exercise above CP and is likely to, at least in part, contribute to exercise intolerance at intensities within the severe intensity domain. Moreover, alleviating acidosis is shown to result in increased muscle glycogen utilisation (Hollidge-Horvat et al. 1999; Percival et al. 2015) and due the association between glycolytic flux and W' (Miura et al. 2000), it is conceivable that increased glycolysis with alkalosis may contribute to an increased W' . Pre-exercise NaHCO_3 supplementation enables an increased H^+ efflux from the intramuscular regions to the extracellular blood compartments (Roth and Brooks, 1990), which corresponds to a reduction in the rate of intramuscular H^+ accumulation during exercise (Stephens et al. 2002) and a concomitant increase in intramuscular glycogen utilisation (Percival et al., 2015). Therefore, the overall improvement in W' and total work done in this study could be attributed to the blood acid-base biochemical changes during exercise. Indeed, a significantly greater reduction in blood $[\text{HCO}^-]$ during exercise with alkalosis is indicative of a superior HCO_3^- buffering activity during exercise. Thereby, attenuating the rate of H^+ accumulation and thus, actively delaying acidosis development. Furthermore, a significant increase in $[\text{bla}]$ was evident following NaHCO_3 treatment in comparison to placebo by 15% under hypoxic conditions and non-significant difference of 10% under normoxia. This enhanced lactate accumulation presents an indirect biomarker of upregulated glycolytic flux during exercise, which has been cited as the mechanism by which NaHCO_3 is ergogenic (Hollidge-Hovart et al. 1999). This significant $[\text{bla}]$ increase under hypoxia may also explain the greater magnitude of effect in hypoxia. Accordingly, it is proposed that a combination of enhanced intramuscular H^+ efflux and increased glycolytic flux offers mechanistic explanations to the enhanced W' and improved TWD with NaHCO_3 .

Nevertheless, this study did not directly quantify anaerobic energy contribution and therefore, the improved W' and TWD cannot be directly attributed to an increased glycolytic flux. Despite lactate cited as an indirect marker of glycolysis, the increase observed could also be explained by a reduction in lactate uptake by inactive tissue (Granier et al., 1996) or an increased lactate efflux working intramuscular regions to extracellular space (Bishop et al., 2004) from the supplementation of NaHCO_3 . Furthermore, a recent investigation has suggested anaerobic exercise is not hindered with acidosis (Morales-Alamo et al. 2015) and therefore without assessment of appropriate glycolytic enzyme activity and muscle glycogen utilisation in this study, the increased anaerobic energy contribution can only be hypothesised. While it may be intuitive to identify W' as an indicator of anaerobic energy supply, more recent definitions have suggested a relationship with $\dot{V}\text{O}_2$ kinetics (Poole et al. 2016). As such,

alterations in O₂ delivery and utilisation may also effect W' . Indeed, Nielson et al. (2002) found an improved maintenance in SpO₂ during a maximal 2000 m rowing with constant infusion of HCO₃⁻ to maintain homeostatic pH during exercise; which the authors cited as a reason for the improved exercise performance. In the current study, end exercise SpO₂ did not differ between conditions, however, this may be due to constant infusion of HCO₃⁻ in the previous study compared to a single pre-exercise bolus in the current investigation. It is conceivable that differences in SpO₂ response during exercise may have occurred in the current study. However, continuous measurement of SpO₂ were not taken and therefore increased O₂ delivery during exercise cannot be ruled out as a potential mechanism for the improved W' and TWD.

An interesting observation in this study was the strong correlation between the effect of alkalosis on TWD and on CP under normoxia and hypoxia. Therefore, highlighting the substantial effect changes in CP can have on TWD, which may be explained as CP represented a larger proportion of intensities up to $\dot{V}O_{2peak}$, in comparison to the severe intensity domain alone (Burnley and Jones, 2016). However, no significant main effect of induced alkalosis on CP was noted, suggesting pre-exercise alkalotic inducement has no clear benefit on exercise performance at intensities at or below CP. This is expected, given a steady state of [H⁺] is maintained within 3 min of exercise at the CP intensity (Jones et al. 2008). Nonetheless, pre-exercise NaHCO₃ supplementation has been demonstrated to improve exercise tolerance at CP by 23.5% (Mueller et al. 2013). Supporting research addressing the ergogenic effect of induced alkalosis on lower intensity exercise performance is scant; however, research does suggest alkalosis can improve performance up to 60 min (McNaughton, Dalton and Palmer 1999). Despite the results of the current investigation, the ergogenic effect of longer duration activities at or below CP intensity cannot be dismissed; although potential ergogenic benefits are likely to more efficacious within W' exercise intensity ranges. Equally, the likelihood of alkalosis to exhibit a negative impact on CP should not be dismissed. Alkalosis increases muscle glycogen utilisation (Percival et al 2015), and due to the association between low muscle glycogen and a lower CP (Muir et al. 2000), it is appropriate to hypothesise NaHCO₃ may diminish CP further during prolonged exercise.

The current study was designed to determine the effect of NaHCO₃ on the W' parameter of the power-duration relationship under normoxia and acute hypoxia. However, the use of a single acute hypoxic magnitude may limit the generisability of the results to alternative hypoxic doses. Indeed, medium term (3 days) severe altitude exposure (5050 m) is suggested to

negatively impair both CP and W' (Valli et al., 2011). Therefore, the response to NaHCO_3 may be different under more severe hypoxic exposures and with a prolonged exposure. Nevertheless, the current study provides an insight into the NaHCO_3 under an acute moderate hypoxic dose, common to environments athletes may train. A further limitation is that respiratory data was not collected during the 3 min CP test and therefore, the cardiopulmonary response to the environmental and supplemental interventions cannot be distinguished. Nevertheless, HR_{peak} and RPE did not differ between conditions suggesting exercise intensity was equivalent between conditions.

5.0. Conclusion

This chapter met the second thesis aim to determine the effect of pre-exercise NaHCO_3 supplementation on CP and W' . This study is the first to demonstrate that pre-exercise alkalosis has a beneficial effect on W' under normoxic and hypoxic conditions. This was accompanied by a greater blood $[\text{HCO}^-]$ reduction and an increased [bla] during exercise with alkalosis, which present indirect markers of HCO_3^- buffering activity and glycolytic flux. Taken together, it suggests W' may be enhanced through improved regulation of acid-base status during exercise, which may mediate an increase in anaerobic energy contribution. Furthermore, this study also demonstrated that individualised NaHCO_3 ingestion improved TWD during the 3 min exercise test, whilst also being the first investigation to report the ergogenic effects of NaHCO_3 under acute hypoxia. Taking a practical perspective, this investigation provides evidence that NaHCO_3 may possess ergogenic characteristics during exercise performed in the severe intensity domain; and accordingly, also taxes the W' parameter. These sporting events can include the 400 m, 800 m and 1500 m running track events, which have previously both demonstrated an ergogenic response from prior NaHCO_3 supplementation (Wilkes, Gledhill and Smyth, 1983; Goldfinch, McNaughton and Davies, 1988; Bird, Wiles and Robbins, 1995). In addition to middle distance cycling events, such as a 4 km TT, which also elicits ergogenic response from NaHCO_3 . The aforementioned performance investigations have however, been conducted at sea level and thus, it currently unknown if the enlargement of W' observed in acute hypoxic conditions is reflected by an improvement of exercise performance in acute hypoxic conditions. Further research should evaluate the effect of NaHCO_3 on exercise performance that is performed in the severe intensity domain. Following from this initial experimental chapter, the subsequent chapter (Chapter five) will evaluate if the enlargement of W' demonstrated in acute hypoxic conditions translates into an enhancement in the volume of

work performed in the severe intensity domain during intermittent exercise with NaHCO_3 in acute hypoxic conditions.

**Chapter Five: Sodium bicarbonate supplementation improves severe-intensity
intermittent exercise under moderate acute hypoxic conditions**

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1.0. Introduction

Acute ambient hypoxic environments are often used as an ergogenic strategy to enhance exercise-induced training adaptations (Lundby et al., 2012). Indeed, methods that involve interspersed acute hypoxic exercise bouts within a training programme, are suggested to augment molecular training adaptations leading to enhanced anaerobic glycolytic activity (Faiss et al., 2013). This benefit is not without cost however, as the lower availability of oxygen (O_2) may elicit an ergolytic effect on exercise intensity and volume during intermittent and continuous exercise (Aldous et al. 2016; Clark et al. 2007). The precise reasons causing these attenuations in exercise performance are ambiguous, however, an integrated central and peripheral fatigue response is likely (Fan and Kayser, 2016). This includes a lower convective O_2 delivery to active skeletal muscle (Amann and Calbet, 2008), an exacerbated disturbance to acid-base balance during exercise (Hogan, Richardson and Haseler, 1999, Romer et al., 2007) and under severe hypoxic conditions (> 3000 m), a further reduction in group III/IV afferent feedback to diminish central motor output is apparent (Amann et al., 2007). The resultant decline in exercise performance presents a challenge to the management of training load during acute hypoxic training regimes to ensure the acute cost to exercise performance does not hamper the potential medium to long term benefits of these strategies.

Acute dietary strategies have previously been used to mitigate for the impaired exercise performance caused by acute hypoxia. This includes dietary nitrate supplementation to enhance convective O_2 delivery (Shannon et al., 2017) and sodium bicarbonate ($NaHCO_3$) supplementation as an alkalotic buffer to dampen the elevated acidic stress (Deb et al., 2017). The latter presents an interesting physiological paradigm, given the relative increase in glycolytic flux with acute hypoxic exposure potentiating hydrogen cation (H^+) production. However, their concurrent removal may be hindered as blood bicarbonate buffering capacity may be diminished under hypoxic conditions, due to a suggested lower bicarbonate anion concentrations ($[HCO_3^-]$) (Cerretelli and Samaja, 2003). It is therefore intuitive to assess ergogenic strategies that may facilitate the removal of excess H^+ during exercise and compensate for the suggested $[HCO_3^-]$ reductions. Indeed, Deb et al., (2017) reported that the efficacy of $NaHCO_3$ supplementation is enhanced under acute hypoxia compared to sea level as the magnitude of improvement was greater during high intensity exercise in acute hypoxic conditions. This should be interpreted with caution however, given that previous studies have either reported no benefit with $NaHCO_3$ under acute hypoxic conditions (Flinn et al., 2014,

Saunders et al., 2014a), or inconsistencies in the overall ergogenic response . Furthermore, there remains considerable contention on the importance of the acid-base balance on fatigue and exercise performance, as exercise performance can be maintained despite perturbations in acid-base balance (Fitts, 2016, Westerblad, 2016). Consequently, further research is required to elucidate the importance of the acid-base balance, particularly under acute hypoxic exposures where pre-exercise alkalotic manipulation may induce beneficial performance outcomes for isolated exercise bouts.

It is evident through viewing blood lactate kinetics during exercise, and corresponding disturbances in acid-base balance, that the ergogenic effects of NaHCO₃ may only arise during exercise intensities at or above the severe intensity domain. This cluster of exercise intensities can be distinguished by physiological markers defined by the second lactate and ventilatory (or otherwise known as the respiratory compensation point) thresholds, or critical power at the lower boundary, whilst the upper boundary is defined as the intensity at the peak rate of oxygen consumption ($\dot{V}O_{2peak}$) (Jones et al., 2010). Within this given intensity range, an inexorable rise in lactate occurs and the acid-base balance becomes substantially perturbed to performance limiting levels (Jones et al., 2007). Indeed, work performed in the severe intensity domain during continuous exercise is enhanced with prior NaHCO₃ supplementation (Egger et al., 2014); however, this is not reflected in exercise tolerance during severe intensity intermittent exercise under hypoxic conditions in acclimatised individuals (Kozak-Collins, Burke and Schoene, 1994). The acclimatised participants used in the latter study may explain the lack of effect, given altitude acclimatisation negates the additional acidic load apparent in acclimatised individuals under acute hypoxia (West, 2007). As the ergogenicity of NaHCO₃ is dependent on the magnitude of acid-base perturbations, it is hypothesised that NaHCO₃ supplementation will improve severe intensity intermittent exercise under acute hypoxic conditions.

2.0. Method

2.1. Participants

Eleven recreationally active male volunteers (mean \pm SD: age 28 ± 6 years; height 179.9 ± 7.2 cm; body mass 81.7 ± 11.8 Kg, $\dot{V}O_{2peak}$ at hypoxia ($FiO_2\% = 14.5\%$) 3.3 ± 0.4 l \cdot min⁻¹; W_{max} : 333 ± 46 W; CP: 222 ± 33 W; and W' : 21.3 ± 4.5), with no sustained altitude exposure in the preceding six months, participated in this investigation. All participants performed regular physical exercise and were also accustomed to repeated high intensity intermittent cycling exercise. This included eight participants that regularly partook in cycling exercise (> 60

km·week⁻¹ and > 7 hrs·week⁻¹), which is in accordance with the training volume that classifies individuals as trained (De Pauw et al., 2013). Whilst the remaining three participants performed cycling activity as part of a regular exercise regime (≥ 4 hrs·week⁻¹), which represents a volume of work that classifies individuals as recreationally active individuals (De Pauw et al., 2013). Prior to obtaining written consent, participants were informed of the purpose, benefits and risks of participation. Ethical approval was attained from the institutional ethics committee and conducted in accordance with the Helsinki Declaration.

2.2. Experimental design

A randomised, double-blind, crossover experimental design was employed with participants attending the laboratory up to six separate occasions at the same time of day (± 1 hr). All exercise trials were a minimum 24 hrs apart and completed within a 3-week period. Pre-experimental procedures were performed as described in chapter two section 2.0. During the first visit, individual time to peak blood alkalosis was established using the methods described in chapter two section 4.0. This formed the timescale for individualised NaHCO₃ ingestion prior to exercise during subsequent experimental trials. **The hypoxic environmental condition was only used during this study, which is described in Chapter two section 5.0.**

Following the first visit to establish the timeframe for attaining peak [HCO₃⁻], baseline $\dot{V}O_{2peak}$ and the VT1 at hypoxic conditions, as described in Chapter two section 6.0. This was followed by familiarisation to the three min all-out test after 30 min recovery from the RAMP test. Subsequently, on separate laboratory visits, participants performed the three min test on a further two occasions under acute hypoxic conditions. However, if a valid test was not completed, participants would repeat the test during additional laboratory visits. The detailed procedure of the three min all-out test is described in Chapter two section 7.0.

The final two visits involved an exhaustive intermittent exercise test performed under two different randomised experimental conditions, with the prior ingestion of either 0.3 g·kg⁻¹ bm of NaHCO₃ or placebo containing 0.21 g·kg⁻¹ bm of sodium chloride (NaCl). The preparation and administration of these supplements described in Chapter two section 1.3, with blood sampling and measurement of other physiological variables taken throughout the experimental trials described in Chapter two section 8.0.

2.3. Intermittent tests

All intermittent tests commenced with 1 min pedalling at 20 W followed by an abrupt start in to repeated intervals of 60 s work and 30 s recovery until exhaustion. The intensity of the work interval was determined by the intensity predicted to attain task failure in four min (P_4), in accordance with the two parameter CP model (equation 1), whilst the recovery was set at 20 W:

$$P_4 = (W'/240) + CP \quad [\text{equation 1}]$$

The use of threshold models to set the work profiles of intermittent exercise is suggested to increase the accuracy of standardising cardiopulmonary and metabolic response to exercise within and between individuals, relative to traditional percentiles of max heart rate, power output or $\dot{V}O_{2\text{peak}}$ (Tschakert and Hofmann, 2013). The work completed in the severe intensity domain could also be calculated by multiplying the time spent above CP by the difference between the work intensity and CP.

A pre-established preferred cadence was held throughout the intermittent test, with task failure defined as the inability to maintain cadence within 60% of the preferred cadence (Aman et al. 2008), despite strong verbal encouragement. Exercise tolerance was determined as the time, in seconds, participants could maintain a cadence < 60% of their preferred cadence at the required power output; whilst the cumulative work performed above CP was defined as the work performed in the severe intensity domain during the intermittent test.

2.4. Statistical Analysis

The Shapiro-Wilk test provided no evidence to reject the hypothesis that all data was normally distributed. A paired t-test was used to compare the exercise durations, work completed in severe intensity domain, mean heart rate and SpO₂. Blood variables, including [HCO₃⁻], [H⁺] and [bla], were analysed through a two-way (treatment [placebo vs. NaHCO₃] x time [pre-and post-exercise]) ANOVA. Where a significant main effect was found, Bonferroni post hoc paired comparisons were determined. Effect sizes and their 95% confidence intervals (CI) were calculated using Hedge's *g* for paired comparisons, with the effects interpreted and discussed against effects of the relevant prior literature (Thompson, 2007). These effect sizes can also be interpreted as trivial (<0.20), small (0.20-0.49), moderate (0.50-0.79) or large (≥0.80) (Cohen 1988). The Hedge's *g* correction was used to mitigate positive bias of the Cohen's *d* effect size

when using sample sizes less than 20 (Lakens, 2013). Frequentist inferences were assessed against mean difference \pm 95% CI between experimental conditions, with variances that do not cross the zero-boundary interpreted as significant. All descriptive data are presented as mean \pm standard deviation, unless otherwise stated. Statistical analysis was performed using open source statistical software, R (R Foundation for Statistical Computing, Vienna, Austria).

3.0. Results

The time taken to reach individual peak blood $[\text{HCO}_3^-]$ ranged from 40 to 90 min with a median of value of 70 min. Mean CP and W' were 226 ± 31 W and 20.3 ± 7.0 kJ, respectively. Exercise tolerance during the intermittent test (Figure 5.1) was significantly greater during the NaHCO_3 treatment condition by $14.6 \pm 12.5\%$ from 734.3 ± 175.7 s during the placebo condition to 845.3 ± 242.4 s under NaHCO_3 experimental conditions (mean difference = 110.9 ± 100.6 s, 95% CI: 43.3 s to 178.5 s). Similarly, the work done in the severe intensity domain was significantly increased by 5.8 ± 6.4 kJ (95% CI: 1.3 to 9.9 kJ), from 41.6 ± 14.7 kJ to 47.2 ± 17.6 kJ in the placebo and NaHCO_3 conditions, respectively. Despite the positive outcome, an increase in work completed in the severe intensity domain was not consistent across all participants, with participant 9 experiencing an ergolytic effect and participant 2 showing no difference between experimental conditions (Figure 5.2).

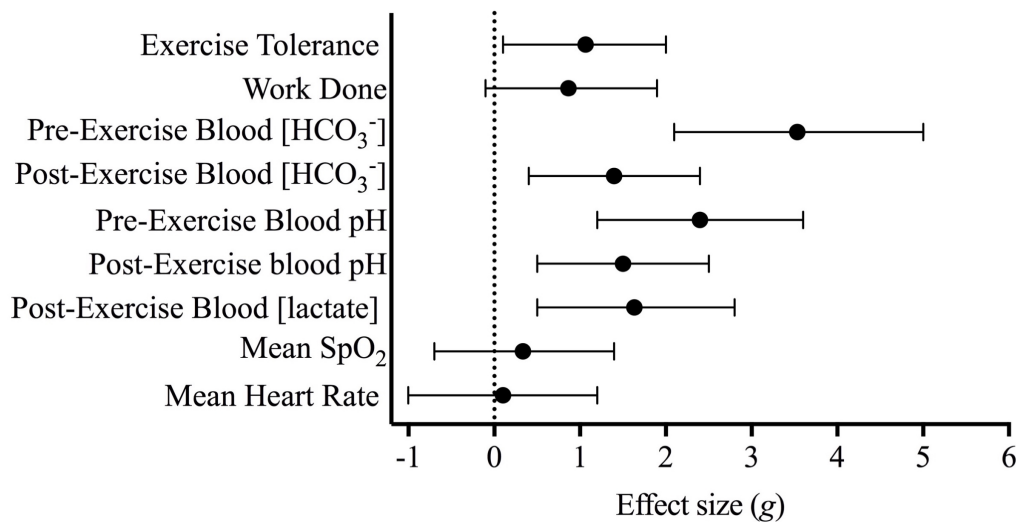


Figure 5.1 Hedge's g effect size and 95% CI of the effect of NaHCO_3 treatment against placebo treatment for all outcome variables.

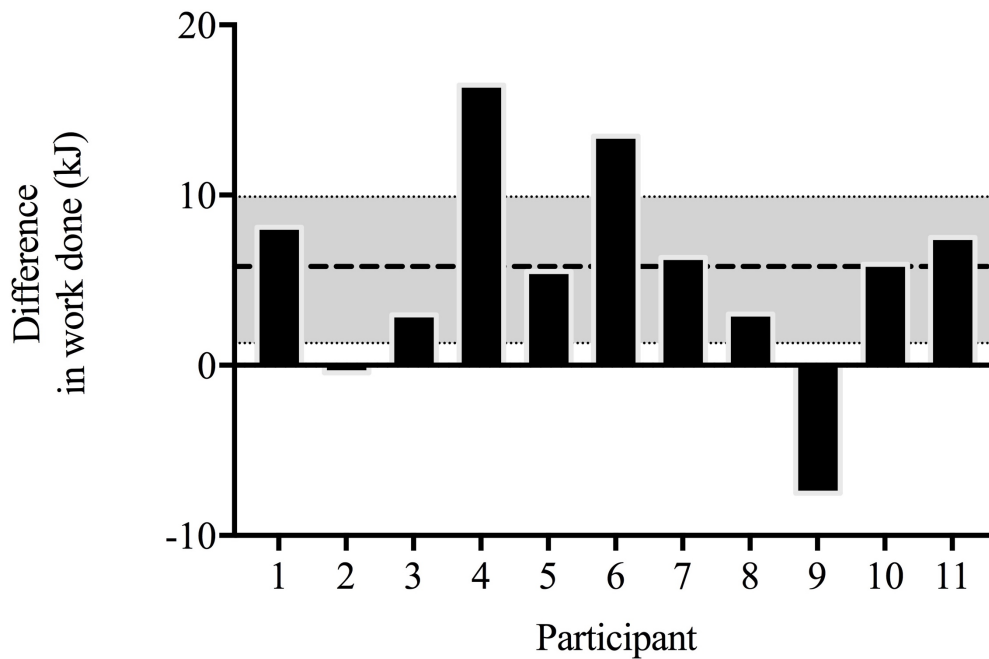


Figure 5.2. Difference in work complete between NaHCO₃ treatment against placebo treatment for all participants. Values greater than zero indicate that a greater volume of work was performed with NaHCO₃ and values lower than zero indicate that less work was performed with NaHCO₃ compared to placebo. Dashed line represents mean difference in work complete and the shaded band shows the $\pm 95\%$ CI of effect between treatments.

An overall main effect for blood [HCO₃⁻] was apparent (Figure 5.3a), with a significantly greater concentration observed with NaHCO₃ compared to placebo prior to exercise (6.9 ± 1.9 mmol·l⁻¹; 95% CI: 5.6 to 8.1 mmol·l⁻¹). Blood [HCO₃⁻] remained elevated in the NaHCO₃ treatment condition post exercise compared to placebo (3.0 ± 2.0 mmol·l⁻¹; 95% CI: 1.6 to 4.3 mmol·l⁻¹), despite the larger reduction in [HCO₃⁻] during exercise in the NaHCO₃ condition (-14.9 ± 2.9 mmol·l⁻¹; 95% CI: -16.9 to -13.0 mmol·l⁻¹) compared to placebo (-11.0 ± 2.6 mmol·l⁻¹; 95% CI: -12.8 to -9.3 mmol·l⁻¹). An equivalent result was found for pH (Figure 5.3b), with a greater pre-exercise values observed in the NaHCO₃ treatment condition compared to placebo (0.08 ± 0.03 ; 90% CI: 0.06 to 0.11); whilst pH also remained elevated following exercise (0.09 ± 0.06 95% CI: 0.05 to 0.15). This difference in pre- and post-exercise pH was apparent given the similar reduction during exercise in the placebo (-0.21 ± 0.08 ; 95% CI: -0.28 to -0.14) and NaHCO₃ conditions (-0.20 ± 0.08 ; 95% CI: -0.24 to -0.15). Post exercise [bla] increased by 4.0 ± 2.4 mmol·l⁻¹ (95% CI: 2.2 to 5.9) from 13.9 ± 4.3 mmol·l⁻¹ during the placebo condition compared to 17.9 ± 5.9 mmol·l⁻¹ with NaHCO₃ treatment. There were no significant differences

in mean heart rate (0.4 ± 4.7 bpm; 95% CI: -3.5 to 4.3 bpm) and SpO₂ ($0.8 \pm 2.3\%$; 95% CI: -1.1 to 2.7%) between conditions.

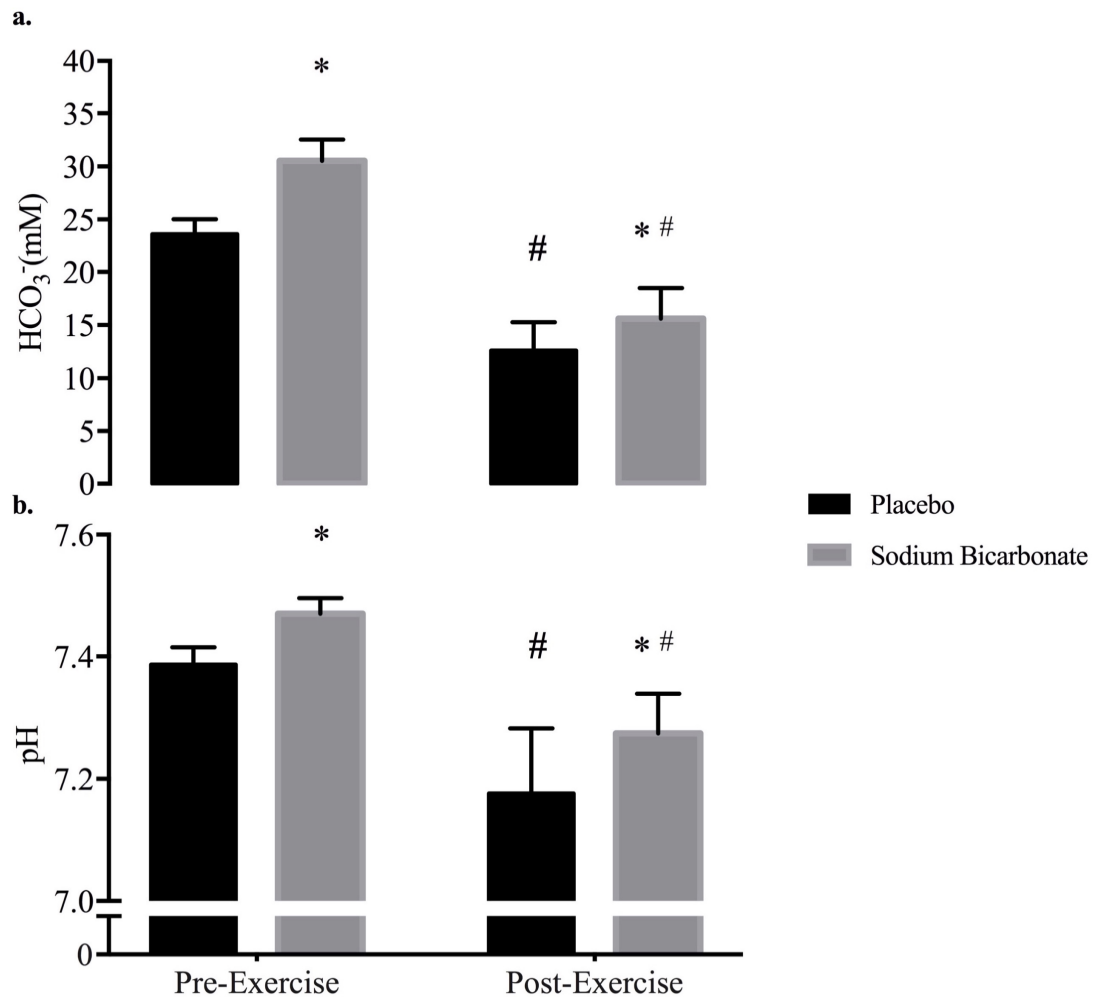


Figure 5.3. Pre- and post-exercise blood [HCO₃⁻] (a) and blood pH (b) during NaHCO₃ and placebo experimental trials. * shows significant (95% CI) difference to corresponding placebo time point. # shows significant (95% CI) difference to corresponding pre- exercise time point within the same experiment condition.

4.0. Discussion

The ergogenicity of NaHCO₃ during intermittent exercise has only been demonstrated with work intervals involving maximal or supra-maximal intensity (Carr et al. 2011). Consequently, this study is the first to report that NaHCO₃ improves exercise tolerance and work performed during intermittent exercise in the severe intensity domain, whilst exposed to acute hypoxic conditions. Furthermore, this study demonstrated NaHCO₃ improves severe intensity intermittent exercise performance under acute hypoxic conditions. The blood acid-base and

[bla] perturbations during exercise observed in the current study are similar to previous investigations (Carr, Hopkins and Gore, 2011), therefore suggesting the ergogenic effects of NaHCO₃ is likely to be mediated through the manipulation of acid-base balance. The current study also adds to the growing body of literature that has utilised a methodology to elicit peak blood [HCO₃⁻] at the onset of exercise by accounting individual variance in blood acid-base kinetics following NaHCO₃ ingestion (Miller et al., 2015, Deb, Gough, et al., 2017). Together, this study demonstrates NaHCO₃ supplementation prescribed to account for the individual variance in time to peak blood [HCO₃⁻], enhances severe intensity intermittent exercise under acute moderate hypoxic conditions. This therefore may offer an ergogenic strategy to improve high intensity intermittent exercise tolerance under acute moderate hypoxic conditions.

This study adds to the paucity of research evaluating the effect of NaHCO₃ supplementation on exercise performed in the severe intensity domain, which have demonstrated equivocal outcomes (George and MacLaren, 1988, Egger et al., 2014). Egger et al. (2014) reported a significant improvement equivalent to 0.41 Hedge's *g* units in 21 well-trained cyclists; whereas George and MacLaren (1988) found no significant effect in seven healthy participants. This disparity between studies and the positive outcome in the current study, could be explained by a dose dependent effect of NaHCO₃. Given that the current study demonstrated positive outcomes with a relative 0.3 g·kg⁻¹ body mass dose compared to the 0.2 g·kg⁻¹ body mass administered by George and MacLaren (1988). Interestingly, the observed effect on exercise tolerance and work done in the severe intensity domain in current study was 2-2.5-fold greater than that previously observed during severe intensity exercise. It is important to highlight the use of intermittent exercise in the current study and continuous exercise in previous research may also account for the larger ergogenic effect observed in exercise performance. A proposition that is supported with meta-analytic evidence, with Carr et al. (2011) reporting greater performance improvements with NaHCO₃ during repeated compared to continuous exercise. Nevertheless, a hypoxic mediated effect cannot be dismissed, as the efficacy of NaHCO₃ may be greater under acute moderate hypoxic conditions (Deb et al. 2017), due to the exacerbated acid-base perturbations (Hogan, Richardson and Haseler, 1999). This hypothesis should, however, be viewed with caution until further research has evaluated the efficacy of NaHCO₃ with normoxic and hypoxic comparators.

Despite this assertion and the ergogenic outcomes found in the current study, a number of previous investigations have not reported similar performance enhancing properties of

NaHCO₃ under acute moderate hypoxic conditions (Flinn et al., 2014, Saunders et al., 2014a). Flinn et al. (2014) performed a similar exhaustive intermittent exercise protocol to the present study that included 60 s work and 30 s recovery intervals to exhaustion, but utilised a supra-maximal exercise intensity under acute hypoxic conditions; while Saunders et al. (2014a) used a repeated sprint protocol prolonged across 90 min to simulate soccer performance, and found no positive performance effect. This discrepancy between the current study and prior research could be attributed to the timing of administering NaHCO₃, since both Saunders et al. (2014a) and Flinn et al. (2014) used a gelatine capsule delivery method over a 4-hr and 90 min period prior to exercise, respectively. In contrast, the current study accounted for the individual temporal characteristics of acid-base kinetics following NaHCO₃ supplementation, by ensuring participants commenced exercise tests at the peak blood [HCO₃⁻], to maximise buffering potential (Jones et al. 2016; Gough et al. 2017). Indeed, the time course to peak blood [HCO₃⁻] using a gelatine capsule has previously been shown to range from 75 to 180 min and a median of 120 min in a similar participant cohort; while the range from liquid supplementation was between 40-90 min in the present study. However, when comparing pre-exercise blood [HCO₃⁻] between current and previous studies it is not clear that utilising an individualised strategy is superior at maximising the ergogenic effect of NaHCO₃. The current study reported a mean 6.9 mmol·l⁻¹ ($g = 3.5$, 95% CI: 2.1 to 5.0) increase in blood [HCO₃⁻] compared to placebo, which is greater than the 5.7 mmol·l⁻¹ ($g = 3.4$, 95% CI: 2.9 to 3.8) increase reported by Saunders et al. (2014a) but Flinn et al. (2014) reported a greater 7.6 mmol·l⁻¹ ($g = 4.4$, 95% CI: 3.7 to 5.0) increase; despite showing no positive performance effect. Interestingly, the standardised effect sizes and corresponding 95% confidence intervals suggest the effect on pre-exercise [HCO₃⁻] was similar between investigations as the confidence intervals overlap. Therefore, while an individualised supplementation strategy may be appropriate to maximised blood [HCO₃⁻] prior to exercise within individuals (Jones et al. 2016; Gough et al. 2017); timing may not be the only residing factor that determines the ergogenicity of NaHCO₃ supplementation. Further research is therefore required to determine the efficacy of individualised timing against a standardised timing strategy.

Despite the contemporary development of personalised NaHCO₃ supplementation ingestion time, the adverse gastrointestinal (GI) side effects remain apparent. As evident in participant 9 (Figure 5.2), who experienced substantial GI complaints, the side effects of supplementation may produce an ergolytic performance effect. Previous research suggests that the variability in NaHCO₃ ergogenic properties may be dependent on presence and severity of GI symptoms

(Saunders et al., 2014b). However, GI complaints and a negative or no performance effect are not always apparent, as the ergogenic and adverse effects of NaHCO₃ have been shown to coexist (McNaughton et al. 2016), with Cameron et al. (2010) reporting a weak association between the two parameters ($r = 0.35$; $p = 0.09$). Given this lack of clarity in this relationship and the failure of the current study to empirically quantify GI complaints, the negative influence of NaHCO₃ can only be inferred in this study as it provides little direct evidence to support the notion that GI complaints from NaHCO₃ supplementation can impair exercise performance or lessen the ergogenic effects.

Independent of individual exercise performance effects, the temporal blood acid-base behaviour following NaHCO₃ supplementation and exhaustive exercise, were comparable to the wider literature base (Carr et al. 2011, Flin et al. 2014 Saunders et al. 2014a, Deb et al. 2017). Oral NaHCO₃ supplementation induced peak blood [HCO₃⁻] concentrations that are greater than 6 mmol·l⁻¹ compared to placebo, which is above the suggested level required for NaHCO₃ to exhibit an ergogenic effect (Carr et al. 2011). The change in blood pH and [HCO₃⁻] was greater during exercise with NaHCO₃ compared to placebo, with an equivalent larger rise in [bla] during the NaHCO₃ experimental trial. Indeed, there is evidence to suggest NaHCO₃ promotes non-oxidative energy metabolism, as observed through greater muscle lactate production, and muscle glycogen utilisation during intermittent exercise performed in the severe intensity domain (Percival et al., 2015). Despite not measuring muscle glycogen utilisation or muscle lactate production in the current study, based on previous research it is appropriate to speculate that the observed ergogenic effects of NaHCO₃ may be mediated through augmenting glycolytic bioenergetic contribution, and an enhanced muscle glycogen utilisation. While this is a plausible theory, it is important to highlight that the rise in blood [bla] during the treatment condition may be explained by a reduction lactate uptake into inactive muscle tissue (Granier et al., 1996) and/or an increase in lactate efflux from intramuscular to extracellular regions (Bishop et al., 2004) following NaHCO₃ supplementation. As such, an increase in glycolytic activity can only be speculated in the current investigation. In addition, it is also prudent to highlight that pH at the end of exercise did not reach comparable values in the experimental and placebo trials, which conforms with previous research (Carr et al. 2011). This suggests that pH may not be the solitary reason for exercise termination in the experimental condition. Given the multi-faceted nature of fatigue alternative explanations may exist; such as the strong ion difference, which refers to the intra- and extracellular ions (e.g. potassium, sodium, chloride) that are involved in skeletal muscle

contraction. Evidence suggests NaHCO_3 can alter the ionic charge of these compartments by attenuating the efflux of potassium ions from the musculature and therefore, maintaining muscle contractile properties during exercise (Siegler et al., 2016). Muscle potassium concentrations were however, not measured in the current study and consequently its role in this context can only be speculated. The SID also has an independent effect on pH (Stewart, 1978), and thus it may exert skeletal muscle performance impairing effects through altering intra- or extra-cellular pH. Further research is required to understand the alternative reasons for exercise termination in the experimental condition despite pH remaining elevated; this may include assessing the function of the strong ion difference.

It is prudent to highlight the diversity in training status of the participant cohort as both trained and recreationally active individuals volunteered for this study. This does not however, limit the applicability of our findings given the wide-ranging applications of acute hypoxic training methods, from trained athletes (Faiss et al. 2013), healthy individuals (Shatilo et al., 2008) to patient cohorts (Millet et al., 2016). Consequently, further research investigating the effects of NaHCO_3 as a training aid during acute hypoxic training programs in a range of population may be beneficial. In addition, a limitation to the application of this study may be in the environment at which NaHCO_3 was ingested; in that, ingesting NaHCO_3 whilst remaining under acute hypoxic conditions prior to exercise may have altered the outcomes of the study as opposed to the ingestion under normoxic conditions in this study. Indeed, exposure to hypoxic conditions is suggested to diminish blood $[\text{HCO}_3^-]$ (Cerretelli and Samaja, 2003) and therefore, prolonged prior hypoxic exposure may have perturbed the manipulation of the acid-base balance following NaHCO_3 ingestion. This however, can only be hypothesised until further experimental work investigates the temporal acid-base response following NaHCO_3 under acute hypoxic conditions and the subsequent impact on exercise performance. Nevertheless, this study is the first to demonstrate NaHCO_3 supplementation in normoxic conditions can improve severe intensity intermittent exercise performance under acute moderate hypoxic conditions. **Therefore, providing a potential ergogenic strategy for individuals undertaking acute hypoxic exercise bouts as part of training programme.** Furthermore, this study demonstrates that ingesting NaHCO_3 at a pre-determined peak blood $[\text{HCO}_3^-]$ prior to commencing exercise is an efficacious method to enhance blood HCO_3^- buffering potential. However, caution should be taken as the adverse GI complaints associated with NaHCO_3 may produce ergolytic effects. **To build on the current investigation and enhance the practical application of this strategy, further empirical research should consider the use of NaHCO_3 as a**

training aid during hypoxic training strategies, to determine if repeated acute supplementation prior to exercise alters the molecular training adaptations associated with intermittent acute hypoxic training.

The current chapter addresses the third aim of this thesis, in identifying if NaHCO_3 supplementation improves severe intensity intermittent exercise under acute hypoxic conditions. This builds on the previous chapter (Chapter four) which demonstrated NaHCO_3 enlarges the W' parameter of the power-duration relationship in acute hypoxia by demonstrating the volume of work performed that can be performed in the severe intensity domain is also increased during intermittent exercise with NaHCO_3 . While this is representative of an increase energy expended in the W' exercise intensity ranges, it is not clear however, if this enlargement is associated with NaHCO_3 altering the recovery kinetics of W' during intermittent, which is in accordance of W'_{bal} model theory. As such the subsequent chapter (Chapter six), will evaluate if NaHCO_3 alters the time constant of W' kinetics during intermittent exercise.

Chapter Six: The ergogenic effect of sodium bicarbonate is similar during severe intensity intermittent exercise under acute hypoxia irrespective of recovery intensity

1.0. Introduction

Exercise within an acute hypoxic environment elicits an adverse effect on exercise performance in a magnitude dependent manner (Deb et al., 2017). While this performance impairment derives from a diminished oxygen availability, this does not contribute to fatigue alone (Amann et al., 2007). The mechanisms of fatigue are binary; in that, an independent and/ or interplay of central and peripheral mechanisms are likely to operate (Fan and Kayser, 2016). Central fatigue refers to the progressive decline in voluntary activation while peripheral fatigue is defined by metabolic and biochemical disturbances, such as a rise in muscle H^+ and phosphate cation concentrations, along with a greater breakdown in PCr (Jones et al., 2007). It is suggested that the prominence of the central and peripheral mechanisms are dependent on the magnitude of hypoxia (Amann et al., 2007) and the intensity of exercise (Black et al., 2017). Fatigue under moderate acute hypoxic exposure (Fractional inspired oxygen (FiO_2) < 13%) is associated with the exacerbated accumulation in metabolites, such as an increase in H^+ accumulation (Hogan, Richardson and Haseler, 1999, Romer et al., 2007), whereas greater hypoxic severity is linked with centrally derived fatigue mechanisms (Amann et al., 2007). The intensity domain that exercise is performed in, is also suggested to dictate the mechanism of fatigue, due to the distinct physiological response evident within each domain (Burnley and Jones, 2007). The moderate intensity domain is associated with centrally driven fatigue mechanisms; while the severe intensity domain is linked to the development of the $\dot{V}O_2$ slow component and biochemical disturbances, including an inexorable rise in H^+ , which perturbs acid-base homeostatic regulation (Burnley and Jones, 2007, Black et al., 2017). On this theoretical premise, if exercise-induced acidosis acts as a causal factor of fatigue, its action would onset within the severe intensity domain and, when exercising under acute hypoxic stress, be most prominent under moderate hypoxic conditions. Therefore, interventions to alleviate acidic stress may be most appropriate during severe intensity exercise under moderate acute hypoxic stress.

The function of exercise-induced acidosis on fatigue is, however a contentious issue (Fitts, 2016, Westerblad, 2016). Repeated sprint performance has for example, been shown to be independent of muscular acidosis following exhaustive exercise (Morales-Alamo et al., 2015), suggesting that a close temporal relationship between exercise performance and acidosis may not exist. Nevertheless, when considering the breadth of research on the ergogenicity of exogenous alkalotic buffering agents, the implications of acidosis on fatigue cannot be dismissed (Carr, Hopkins and Gore, 2011, McNaughton et al., 2016). Sodium bicarbonate is

an example of a buffering agent which acts to support blood bicarbonate (HCO_3^-), through facilitating the efflux of H^+ produced during exercise from intramuscular regions and their subsequent removal (Roth and Brooks, 1990). The meta-analytic effect of NaHCO_3 is determined as 2% (90% confidence interval $\pm 1.7\%$) improvement in power output within trained individuals (Carr, Hopkins and Gore, 2011); however, this ergogenicity is not consistent in the literature given the large inter and intra-individual variability in exercise tolerance (Dias et al., 2015). This variability remains evident in assessing the effect on exercise tolerance within in the severe intensity domain as research has demonstrated both positive (George and MacLaren, 1988, Mueller et al., 2013, Egger et al., 2014, Deb et al., 2017, Deb et al., 2018) and no effect (Vanhatalo, McNaughton, et al., 2010).

Recent methodological developments in the timing of NaHCO_3 administration, to account for individual variations in acid-base kinetics, have however demonstrated more reliable ergogenic outcomes in performance (Gough et al., 2017a). Consistent with this, commencing exercise at an individual's peak blood HCO_3^- concentrations following NaHCO_3 supplementation, has been shown to improve intermittent exercise in the severe intensity domain with light intensity recovery (20 W) under acute hypoxic conditions (Deb et al., 2018). Given acid-base kinetics is dependent on exercise intensity domains, the severe intensity exercise should have elicited sufficient acidic stress to benefit from prior alkalosis. However, there has been little focus on the recovery intensity, despite recovery periods during intermittent exercise bouts performed across the spectrum of exercise intensity domains in training and athletic performance. Indeed, intermittent exercise tolerance is shown to be dependent on intensity domain that recovery resides in (Chidnok et al., 2012); whilst recovery intensity also effects lactate (Menzies et al., 2010) and $\dot{V}\text{O}_2$ kinetics in response to exercise (Chidnok et al., 2012).

The purpose of this investigation was therefore, to build on earlier research (Deb et al., 2018) by investigating the impact of pre-exercise alkalosis on severe intensity intermittent exercise, under acute hypoxic conditions, with recovery performed in the light, moderate and heavy exercise intensity domains. Comparisons in exercise tolerance and work performed in the severe intensity domain during the experimental trials were used to determine the effect of alkalosis at differing recovery intensities. Further analysis was performed through the application of the critical power (CP) concept to intermittent exercise using the work balance (W'_{bal}) model (Skiba et al., 2012). The two parameter CP concept include the parameters of CP and W' ; with CP suggested to represent the boundary that demarcates the onset of the severe

intensity domain (Burnley and Jones, 2007). While according to the CP concept, W' signifies the fixed amount of work that can be expended during exercise in the severe intensity domain prior to exhaustion. Therefore, during intermittent exercise, W' is spent when exercising above CP and, according to the W'_{bal} model, W' recovers exponentially based on recovery intensity during exercise below CP. The rate of recovery is therefore dependant on an individual's W' kinetics (Skiba et al., 2012). The acceleration of the W' time constant, theoretically implies a faster W' recovery when exercise is performed below CP threshold and thus, increasing the volume of work that may be performed in the severe intensity domain during a single exercise bout. Exercise-induced acidosis is suggested to be a, but not the only, physiological determinant of W' (Deb et al., 2017). Consequently, this study also assessed the influence of pre-exercise alkalosis on the recovery kinetics of W' . This will support the principal aim of determining if the effect of alkalosis during intermittent exercise, under acute hypoxic conditions, is influenced by the exercise recovery intensity interval.

2.0. Method

2.1. Participants

Nine trained males (mean \pm SD: age 28.6 ± 6.9 years; height 179.4 ± 7.2 cm; body mass 80.0 ± 11.3 Kg, $\dot{V}O_{2peak}$ at hypoxia ($FiO_2\% = 14.5\%$) 48.4 ± 3.3 ml \cdot kg $^{-1}\cdot$ min $^{-1}$) provided their informed written consent to volunteer for the current investigation. However, due to the presence of substantial gastrointestinal distress, one participant was excluded from the study, therefore data in eight participants who completed the study were analysed and presented here. All participants were sea level natives, with no sustained altitude exposure in the preceding six months. Ethical approval was attained from the institutional ethics committee and conducted in accordance with the Helsinki Declaration.

2.2. Experimental overview

A randomised, double-blind, crossover experimental design was employed, with participants attending the laboratory on nine separate occasion at the same time of day (± 2 hrs). All visits were a minimum 24 hrs apart and completed within a 5-week period. Pre-experimental procedures were performed as described in Chapter two section 2.0 During the first visit, individual time to peak blood alkalosis was established using the methods described in Chapter two section 4.0. This formed the timescale for individualised NaHCO₃ ingestion prior to exercise during subsequent experimental trials. Only the hypoxic environmental condition was used during this study, which are described in Chapter two section 5.0.

The initial exercise trial required participants to perform an incremental RAMP test to ascertain hypoxic $\dot{V}O_{2peak}$ and VT1 by detection of inflection points on gas exchange graphs as outlined in Chapter two section 6.0. This was followed by familiarisation to the three min all-out test after 30 min recovery from the RAMP test. Subsequently, on separate laboratory visits, participants performed the three min test on a further two occasions under acute hypoxic conditions. However, if a valid test was not completed, participants would repeat the test during additional laboratory visits. The detailed procedure of the three min all-out test is described in Chapter two section 7.0. The resultant CP and W' values from the three min test, along with VT1 attained from the RAMP test, were subsequently used to determine the work and recovery intensities during intermittent exercise TTE tests in the experimental trials. This included three different intermittent tests that differed by the recovery intensity but the work intensity and duration of intervals (60 sec work: 30 sec recovery) remained constant.

2.3. Intermittent Experimental trials

Two different treatment conditions were used for each intermittent test, which involved either the supplementation of 0.3 g·kg⁻¹ body mass of NaHCO₃ or a placebo of NaCl, which was matched to ensure an equimolar sodium concentration (0.21 g·kg⁻¹ body mass). The preparation and administration of these supplements described in Chapter two section 3.0, with blood sampling and measurement of other physiological variables taken throughout the experimental trials described in Chapter two section 8.0.

All intermittent tests began with three min pedalling at 20 W, followed by a repeated 60 sec work and 30 sec rest intervals to exhaustion. The intensity of the work interval was determined by the intensity predicted to attain task failure in four min (P_4) in accordance with the two parameter CP model:

$$P_4 = (W'/240) + CP \quad \text{[Equation 1]}$$

The recovery intensities used were equivalent to light, moderate and heavy intensity domains (Burnley and Jones, 2007). The light intensity involved recovery at 20 W, a moderate intensity with a power output equivalent to 90% of VT1 and a heavy intensity corresponding to the power output at VT1 plus 50% of the difference between VT1 and CP. These work and recovery profiles were chosen to replicate the original protocol used to establish the W'_{bal} model (Skiba et al., 2012). The application of threshold models to prescribe exercise intensity during intermittent exercise also enhances the accuracy of standardising the cardiopulmonary

and metabolic responses of intermittent exercise, as opposed to using traditional percentiles of HR, power output or $\dot{V}O_{2peak}$ (Tschakert and Hofmann, 2013). Exercise tolerance was determined as the time in seconds that participants could maintain exercise required power output. This was defined as the inability to maintain cycling cadence within 60% of the participants preferred cadence (Amann, Hopkins and Marcora, 2008). Strong verbal encouragement was provided by the same researcher throughout the experimental trials. The total time of exercise tolerance and the volume of work performed in the severe intensity domain were analysed for each test to determine if the ergogenicity of $NaHCO_3$ was apparent.

2.4. Application of the W'_{bal} model

Intermittent exercise tests were fitted individually to the W'_{bal} equation (equation 2) with power output at a sampling frequency of one hertz.

$$W'_{bal} = W' - \int_0^t W'_{exp} \cdot e^{-(t-u)/\tau_{W'}} \quad [\text{Equation 2}]$$

Whereby, W' represents the *priori* determination of W' from two-parameter CP test, W'_{exp} represents the expended W' during work above CP ($(PO - CP) \cdot \text{duration of work}$), $(t - u)$ represents the time in seconds between exercise intervals which deplete W' , and $\tau_{W'}$ represents the time constant of W' recovery (in seconds). Therefore, this equation illustrates that the amount of W' remaining at any time (W'_{bal}) is a function of the difference between the known W' and the sum W' expended (in joules) while exercising above CP and subsequent recovery during work below CP; which recovers exponentially. The $\tau_{W'}$ was then altered through a process of iteration until W'_{bal} was equal to zero at the time of exhaustion. This calculation was performed using a customised script developed in R (R Foundation for Statistical Computing, Vienna, Austria). The three-time constants for each intermittent exercise were then plotted against the difference between CP and the respective recovery intensity (which is herein referred to as D_{CP}). A subsequent non-linear regression was applied using Graphpad Prism 7 (Graphpad Software, San Diego, California, USA) to allow for group comparisons of the time constant in the W'_{bal} model between placebo and treatment conditions. This analysis to determine the time constant replicates the seminal work conducted by Skiba et al. (2012).

2.5. Statistical Analysis

The Shapiro-Wilk test provided no evidence to reject the hypothesis that all data was normally distributed. A repeated measures ANOVA was used to compare the exercise durations, volume of work performed in the severe intensity domain, [bla], mean heart rate and mean %SpO₂ from the light, moderate and heavy intermittent tests between experimental conditions. Blood acid-

base variables, $[\text{HCO}_3^-]$ and pH, taken during experimental trials were analysed through a two-way (treatment [placebo vs. alkalosis] x time [pre vs post exercise]) ANOVA. Where a significant main effect was found, Bonferroni post hoc paired comparisons were determined. Furthermore, the difference in the volume of work in severe intensity domain performed between placebo and NaHCO_3 groups were compared for each of the exercise tests using a repeated measures ANOVA (difference in work x exercise test). Effect size and their 95% confidence intervals (CI) were calculated using Hedges g for paired comparisons as it mitigates for the positive bias present for Cohens d effect size when sample sizes are less than 20 (Lakens, 2013). These effect sizes were interpreted and discussed against the effects of relevant prior literature (Thompson, 2007). Frequentist inferences were reported as the mean difference \pm 95% CI between treatments. Instances where the 95% CI overlapped zero, the statistical inference of effect was deemed to be non-significant. All descriptive data is presented as mean \pm standard deviation (SD). All statistical tests were performed using SPSS v22 for MAC (SPSS Inc., Chicago, IL, USA).

3.0. Results

The median time taken to achieve peak blood $[\text{HCO}_3^-]$ was 70 min (range 40-90 min) within this participant cohort. Critical power and W' determined through the 3 min CP test under acute hypoxic conditions were 228 ± 29 W and 21.8 ± 5.0 kJ, respectively. The moderate and heavy intermittent test recovery intensities were 144 ± 24 W and 198 ± 29 W, respectively. Exercise tolerance was significantly greater during the light ($+149.3 \pm 79.2$ sec; 95% CI: 83.0 to 215.5 sec; $g = 0.91$, 95% CI: -0.1 to 2.0), moderate ($+118.0 \pm 117.7$ sec; 95% CI: 19.7 to 216.3 sec; $g = 1.3$, 95% CI: 0.2 to 2.4) and heavy ($+36.1 \pm 39.9$ sec; 95% CI: 2.6 to 69.7 sec; $g = 0.8$, 95% CI: -0.2 to 2.4) intermittent exercise tests with NaHCO_3 compared to the placebo condition. As such, NaHCO_3 also enhanced the volume of work performed in the severe intensity domain during light ($+7.7 \pm 5.4$ kJ; 95% CI: 3.2 to 12.2 kJ), moderate ($+5.6 \pm 4.8$ kJ; 95% CI: 1.6 to 9.7 kJ) and heavy ($+2.1 \pm 0.9$ kJ; 95% CI: 0.1 to 4.2 kJ) intermittent exercise tests. Similar effect sizes were calculated during the light ($g = 0.38$; 95% CI: -0.7 to 1.5) and moderate ($g = 0.36$; 95% CI: -0.7 to 1.5) intensity tests, which were two-fold greater than the effect size during the heavy intensity intermittent test ($g = 0.17$; 95% CI: -0.9 to 1.2) (Figure 6.1). There was an overall significant main effect ($p = 0.024$) calculated between light, moderate and heavy exercise tests for the difference in work completed in the severe intensity domain between the placebo and NaHCO_3 conditions. However, no significant pairwise interactions were reported between light vs. moderate (2.0 ± 4.5 kJ; 95% CI: -3.1 to 7.2 kJ), moderate vs. heavy ($3.5 \pm$

5.7 kJ; 95% CI: -2.5 to 9.5 kJ) or light vs. heavy (5.5 ± 5.4 kJ; 95% CI: -0.1 to 11.1 kJ) exercise tests.

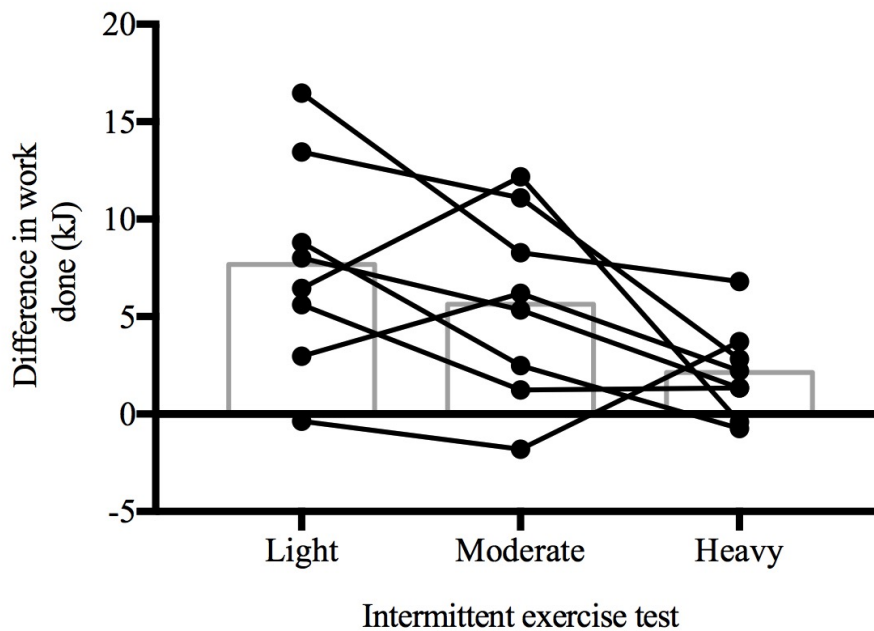


Figure 6.1. Difference in work done between placebo and NaHCO₃ conditions during the three difference exercise tests. Scatter dots connected by lines show the data from individual participants. Positive value bars and scatter dots indicates an ergogenic effect following NaHCO₃ supplementation, while negative value scatter dots indicate and ergolytic effect.

The time constants determined from the iterative process for all experimental trials were subsequently plotted to determined two equations; the placebo (equation 3; $r^2 = 0.89$) and NaHCO₃ (equation 4; $r^2 = 0.76$) experimental groups (Figure 6.2). Derived from the below equations and mean D_{CP} for each test, a 16.2%, 19.3% and 14.2% reduction in $\tau_{W'}$ was determined during light, moderate and heavy intermittent exercise tests with NaHCO₃ supplementation.

$$\tau_{W'} = 535 \cdot e^{(-0.003D_{CP})} + 211 \quad \text{[Equation 3]}$$

$$\tau_{W'} = 317.6 \cdot e^{(-0.01D_{CP})} + 372 \quad \text{[Equation 4]}$$

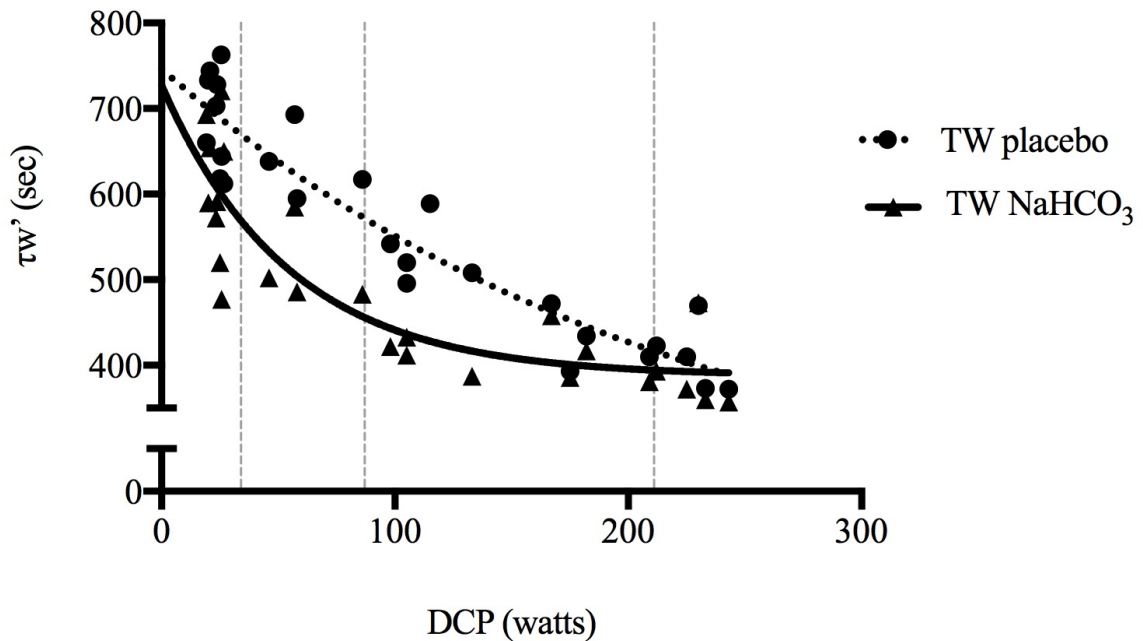


Figure 6.2. A plot of $\tau_{W'}$ against D_{CP} for the three exercise tests under both placebo and NaHCO_3 experimental conditions. The best fit lines represent the $\tau_{W'}$ equations for placebo ($\tau_{W'} = 535 \cdot e^{(-0.003D_{CP})} + 211$) and NaHCO_3 ($\tau_{W'} = 317.6 \cdot e^{(-0.01D_{CP})} + 372$), respectively. The three dashed vertical lines represent the mean D_{CP} during the light, moderate and heavy intermittent exercise tests, shown from left to right.

A significant main effect for supplement treatment was reported for the measured blood parameters of [bla] ($p = 0.003$), pH ($p < 0.001$) and $[\text{HCO}_3^-]$ ($p < 0.001$). A similar effect of NaHCO_3 was reported in all three intermittent exercise conditions in [bla]; with a $2.6 \pm 2.8 \text{ mmol} \cdot \text{l}^{-1}$ (95% CI: 0.2 to 5.0 $\text{mmol} \cdot \text{l}^{-1}$) increase during the light exercise test, an increase of $3.1 \pm 3.4 \text{ mmol} \cdot \text{l}^{-1}$ (95% CI: 0.2 to 5.9 $\text{mmol} \cdot \text{l}^{-1}$) during the moderate exercise test and a similar $3.1 \pm 2.8 \text{ mmol} \cdot \text{l}^{-1}$ (95% CI: 0.6 to 5.5 $\text{mmol} \cdot \text{l}^{-1}$) increase during the heavy exercise test. In addition to a supplement effect, there was also a significant time effect noted for blood pH ($p < 0.01$) and $[\text{HCO}_3^-]$ ($p < 0.01$), with all exercise tests lowering both blood variables (Figure 6.3). However, recovery intensity had no effect on blood pH ($p = 0.569$) or $[\text{HCO}_3^-]$ ($p = 0.468$). Similarly, no effect was observed for either $\% \text{SpO}_2$ ($p = 0.896$) or heart rate ($p = 0.379$) across conditions.

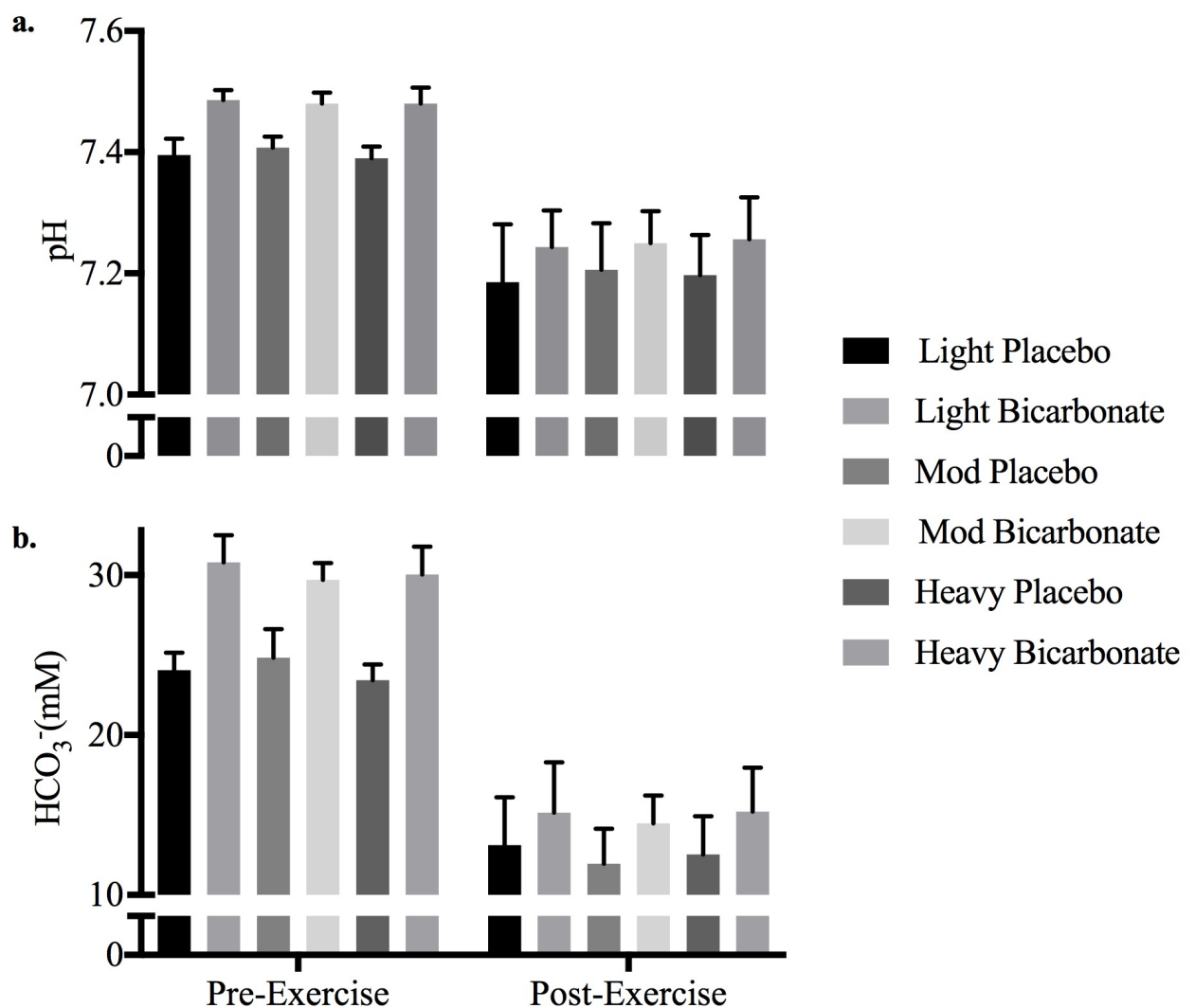


Figure 6.3. Mean \pm SD pre- and post-exercise blood pH (a) and blood $[\text{HCO}_3^-]$ (b) during NaHCO_3 and placebo experimental trials.

4.0. Discussion

This study demonstrates that NaHCO_3 elicits an ergogenic effect on severe intensity intermittent exercise in acute moderate hypoxia, independent of the exercise intensity domain recovery intervals were performed. The largest supplement effects were observed during light and moderate exercise tests, although there was no significant difference in the magnitude of effect between the three intermittent exercise tests. This study is also the first to assess and demonstrate that the time constant of W' recovery during intermittent exercise, as applied in the W'_{bal} model, is a mutable factor; with the manipulation of the acid-base balance found to be a contributing variable. This study therefore demonstrates that NaHCO_3 can be used as an

effective ergogenic aid under moderate acute hypoxic conditions, with NaHCO₃ ergogenicity evident irrespective of recovery intensity used.

The current study reaffirms and adds to previous research (Deb et al., 2018), that suggests NaHCO₃ elicits an ergogenic effect during severe intensity intermittent exercise under acute hypoxic conditions. Utilising the same intermittent exercise test with light recovery intervals (20 W), Deb et al. (2018) reported a larger effect size ($g = 0.8$; 95% CI: -0.1 to 1.9) than the current investigation ($g = 0.38$; 95% CI: -0.7 to 1.5). However, it remains within the 95% CI originally reported, which indicates the effect of NaHCO₃ during severe intensity intermittent exercise is variable. Both moderate and heavy intermittent tests also had effect sizes that crossed the negative boundary. As such, while significant increases were observed in the current study, it does not conclude that the ergogenicity of NaHCO₃ under moderate acute hypoxia is omnipresent. Indeed, a number of previous investigations have concluded a null effect of NaHCO₃ during intermittent exercise under acute hypoxic conditions (Flinn et al., 2014, Saunders et al., 2014a). While the effect of NaHCO₃ during exercise tolerance tests (i.e. those performed to the point of exhaustion) has been demonstrated to be inconsistent when taken prior to repeated but separate exercise tests (Dias et al., 2015). There are, however, two differentiating factors between the current investigation, that of Deb et al. (2018), and investigations that reported null or inconsistent findings under acute hypoxia (Flinn et al., 2014, Saunders et al., 2014a, Dias et al., 2015). This included the timing prior to exercise that the bolus of NaHCO₃ was administered, as the present study accounted for the individual variations in blood acid-base kinetics following NaHCO₃ ingestion (Jones et al., 2016, Gough et al., 2017a), by pre-determining the time taken for peak blood [HCO₃⁻] to transpire for each participant. Conversely, studies reporting a null effect have used a blanket ingestion period for all participants. Despite maximising blood buffering capacity, it is not yet clear if individualising NaHCO₃ to attain peak availability of blood [HCO₃⁻] is a superior ergogenic strategy to standard ingestion times, as this is yet to be investigated. However, early research has shown promising signs with a more consistent ergogenic response reported during 4 km cycling TT performance with trained cyclists when individualising the time of ingestion prior to exercise (Gough et al., 2017a). In addition, the current study and Deb et al. (2018), used trained participants as opposed to recreationally active participants (Flinn et al., 2014, Saunders et al., 2014a, Dias et al., 2015), which may also account for the discrepancy. Meta-analytic data suggests that trained individuals elicit a greater ergogenic effect from NaHCO₃ (Carr,

Hopkins and Gore, 2011); however, this is yet to be empirically tested and therefore, can only be speculated as a reason for the conflicting data.

Despite the overall variability in the effect of NaHCO_3 , this study demonstrated the ergogenic effect is apparent irrespective of the exercise intensity domain the recovery interval is performed. The magnitude of ergogenicity was also found to be similar across the three exercise tests, however, the light and moderate intensities calculated an effect size twice that of the heavy intensity recovery intervals. Performing recovery intensity intervals in the heavy exercise intensity domain has previously been shown to accelerate rate of lactate removal, relative to recovery intervals performed at lower intensities (Menziés et al., 2010). More specifically, these authors demonstrated recovery performed equivalent to 80-100% of lactate threshold (LT), a marker that is thought to coincide with the CP threshold used in the current study (Keir et al., 2015), yielded the quickest rate of lactate clearance from the blood compared to 60% and 40% of LT. Furthermore, the rate of lactate efflux from active skeletal muscle is greater with increasing exercise intensities, as demonstrated by Hollidge-Horvat et al. (2000) from exercise intensities equivalent to 30%, 60% and 75% of $\dot{V}\text{O}_{2\text{max}}$. Indeed, exercising rat models have suggested that monocarboxylic transporters (MCT) expression, which are responsible for the main efflux of lactate and H^+ to extracellular fluid (Ferguson et al., 2018), are augmented with increasing exercise intensity (Hamada and Takimoto, 2013). If reflective of human MCT physiology, the heavy intensity exercise tests may have activated a greater proportion of MCT transporters compared to the lower intensity exercises, which may lower the number of MCT transporters available for further stimulation by NaHCO_3 . As such, highlighting a potential physiological hypothesis for the diminished effect noted during heavy compared to light and moderate exercise tests.

The current study is the first to assess and demonstrate that the time constant of W' recovery, as applied to the W'_{bal} model, is a mutable variable and is sensitive to the inducement of alkalosis during severe intensity intermittent exercise. These data contradicts evidence reported during single leg intermittent knee extension exercise above CP, whilst monitoring muscle metabolites using magnetic spectroscopy (Skiba et al., 2015). Skiba et al. (2015) also reported a disconnect between the rate of W' recovery following an exhaustion work interval and the rate at which pH recovers; thereby questioning the notion of pH as a metabolic determinant of W' . Interestingly, Skiba and colleagues (2015) also found a negative correlation between W' recovery kinetics and muscle carnosine content, suggesting the physiological actions of

carnosine may be implicated in the rate of W' recovery during intermittent exercise. Although carnosine possesses multiple roles in sustaining skeletal muscle contractions during exercise (Begum, Cunliffe and Leveritt, 2005), it is pertinent to highlight carnosine's role as an extracellular buffer. The current investigation increased the availability of blood $[\text{HCO}_3^-]$ to potentiate extracellular buffering capacity, which subsequently led to an improvement in exercise tolerance and W' recovery kinetics. Together, this indicates buffering capacity may be a determinant of W' recovery kinetics during intermittent exercise. A recent investigation, attempted to test this hypothesis by evaluating the effect of beta-alanine (BA) loading on CP and W' ; however, the BA loading period was ineffectual as muscle carnosine content did not change and in turn, no change in the power-duration parameters were observed (Black et al., 2018). As such, further research is needed to ascertain if this proposed relationship between buffering capacity, pH and W' recovery kinetics is apparent.

The blood acid-base response across all three exercise tests, during the respective placebo and treatment conditions, displayed similar responses. Interestingly, post exercise [bla] was significantly greater following NaHCO_3 supplementation in all three exercise tests, compared to placebo. This observation may offer an interesting physiological insight, given a greater [bla] may be indicative of an enhanced anaerobic glycolytic contribution. Indeed, exercise-induced acidosis is shown to impair glycolytic enzyme activity and therefore, the maintenance of a higher blood pH throughout the treatment trials may have facilitated an enhanced glycolytic contribution (Hollidge-Horvat et al., 2000). This interpretation should however, be viewed with a caveat that [bla] does not directly represent muscle physiology, as this increase may be a result of reduced uptake of blood lactate into inactive tissue (Granier et al., 1996) or the enhanced efflux of lactate to extracellular space (Roth and Brooks, 1990). Alternatively, this enhanced activity could be explained by the alterations in the balance of intra- and extracellular strong ions that is concomitant with alkalosis (Raymer et al., 2004). Supplementation of NaHCO_3 can attenuate the efflux of potassium cations from active skeletal muscle (Siegler et al., 2016), which can consequently support the maintenance of resting membrane potential and thus sarcolemma excitability to prolong the sustainability of muscular contractions (Cairns and Lindinger, 2008). Nevertheless, these mechanisms may only be postulated in the current study, with further work required to elucidate the mechanistic contributions to enhanced exercise performance.

In conclusion, this study addresses the fourth thesis aim and reports that severe intensity intermittent exercise performed under moderate acute hypoxic conditions is improved with the supplementation of NaHCO₃, irrespective of the intensity of recovery intervals. However, a smaller effect size was found when recovery was performed in the heavy intensity domain, as opposed to moderate and light recovery intervals. Therefore, the ergogenic efficacy of NaHCO₃ may be dependent by exercise intensity; although, further research is required to qualify this hypothesis. This study also suggested that enhancing extracellular blood [HCO₃⁻] buffering capacity, may mediate the *W'* parameter of the power-duration relationship, particularly *W'* recovery kinetics during intermittent exercise performed under acute hypoxic conditions. Given the lower recovery intensity exercise tests demonstrated a larger effect size, this outcome provides the basis for the fifth thesis aim; which looks to understand the effect of NaHCO₃ on constant load exercise performance across different exercise intensities.

Chapter Seven: Pre-exercise alkalosis enhances W' but reduces CP of the power-duration relationship during constant load exercise at acute moderate hypoxia

1.0. Introduction

The ergogenic effect of NaHCO_3 , when administered through an individualised timing strategy, was demonstrated during a three min all-out CP test in study one (Chapter four); with the improvement in performance mediated via an increase in W' . This therefore, indicated the role of the acid-base balance as a physiological determinant of W' ; in that, the attenuation in blood H^+ accumulation during exercise through enhancing pre-exercise blood HCO_3^- buffering capacity increased the volume of work that could be performed above CP (i.e. W'). These results did however, contradict previous research that demonstrated NaHCO_3 had no effect on the performance parameter of the three min all-out CP test (Vanhatalo et al., 2010). The difference in outcomes were attributed to the individually timed method of administering NaHCO_3 and the use of trained participants in study one. Nevertheless, these positive outcomes could be questioned, as the three min all-out CP test is suggested to overestimate the volume of work that can be performed in the severe intensity domain (Nicolò, Bazzucchi and Sacchetti, 2017). Indeed, the validity of the three min test has been questioned, as measurements of CP and W' are found to be significantly different against the suggested 'gold standard' multi-test method of establishing CP and W' (Wright, Bruce-Low and Jobson, 2017). Similarly, the reliability of the three min all-out test in determining W' was found to be greater than the multi-trial method, with coefficient of variations of 8.44% and 5.9%, respectively (Wright, Bruce-Low and Jobson, 2017). Together, the contrasting outcomes of previous research and the debate regarding the validity of the three min all-out CP test, presents a degree of uncertainty regarding the effect of NaHCO_3 on the W' parameter of the power-duration relationship.

A number of different methods have been used to measure CP and W' , which have involved differing exercise types, durations and intensities; along with the use of different mathematical approaches to determine CP and W' from multiple exercise tests (Mattioni Maturana et al., 2017). The estimates of CP and W' are however, influenced by the test protocol used. Indeed, for an accurate estimation of CP and W' , Morton (2006) suggested that multiple exercise tests were required that ranged from 1 to 20 min, while Derkele et al. (Dekerle, Vanhatalo and Burnley, 2008) suggested a range of exercise durations between 2 to 15 min is required. Given the conflicting theories, Mattioni Maturana et al., (2017) compared estimates of CP and W' using a different number of exercise bouts (2 to 5 bouts), a range durations (1 to 20 min) and a number of different mathematical approaches. The authors concluded that using exercise bouts of less than 10 min only, resulted in the overestimation of CP and underestimation of W' ; while the inclusion of two exercise bouts between 12 to 20 min elicited the most accurate

representation of CP and W' against the criterion method. As such, to investigate the effect of experimental interventions on CP and W' , protocols should use TTE tests that include two trials that last between 12-20 min to provide the most accurate representation of CP and W' . The ergogenic effect of NaHCO_3 has previously been assessed across a range of maximal and supra-maximal intensity TTE tests, and reported a significant improvement during 100% W_{max} test but not during 110% and 120% W_{max} tests to exhaustion (Higgins, James and Price, 2013). These differential outcomes could be attributed to the within subject variability of NaHCO_3 ergogenic effect evident during constant load TTE tests in recreationally trained participants (Dias et al. 2015). Nonetheless, an intensity dependant effect cannot be dismissed, when considered in conjunction with the outcomes of study 4 (Chapter 6) of the current thesis. This study observed that intermittent exercise tests with recovery intervals at a higher intensity, and thus higher overall mean intensity, elicited a smaller benefit from NaHCO_3 supplementation. On this evidence, it is prudent to hypothesise that the efficacy of NaHCO_3 supplementation may be dependent on the intensity of exercise, but only limited to exercise that is above CP, which demarcates the severe intensity domain (Jones et al., 2010). The aims of this study are therefore, twofold: 1) to investigate the effect of NaHCO_3 during constant load TTE tests across a range from sub- to supra-maximal exercise intensities; and 2) subsequently apply the two-parameter CP model to these exercise tests in order to determine the effect of NaHCO_3 on CP and W' .

2.0. Method

2.1. Participants

Ten trained males (mean \pm SD: age 25 ± 8 years; body mass 76.5 ± 5.8 Kg, $\dot{V}\text{O}_{2\text{peak}}$ at hypoxia ($\text{FiO}_2\% = 14.5\%$) 48.3 ± 3.7 ml \cdot kg $^{-1}\cdot$ min $^{-1}$) provided their informed written consent to volunteer for the current investigation. All participants were sea level natives, with no sustained altitude exposure in the preceding six months. Ethical approval was attained from the institutional ethics committee and conducted in accordance with the Helsinki Declaration.

2.2. Experimental overview

A randomised, double-blind, crossover experimental design was employed, with participants attending the laboratory on nine separate occasion at the same time of day (± 2 hrs). All visits were a minimum 24 hrs apart and completed within a 5-week period. Pre-experimental procedures were performed as described in chapter two section 2.0. During the first visit, individual time to peak blood alkalosis was established using the methods described in chapter two section 4.0. This formed the timescale for individualised NaHCO_3 ingestion prior to

exercise during subsequent experimental trials. Only the hypoxic environmental condition was used during this study, which are described in chapter two section 5.0.

The initial exercise trial required participants to perform an incremental RAMP test to ascertain hypoxic $\dot{V}O_{2\text{peak}}$ and W_{max} as outlined in chapter two section 6.0. This was followed by familiarisation to the four TTE tests (described below) used in the experimental trials in single session with 30 min recovery between each test. The experimental trials involved four TTE tests to exhaustion performed at 75%, 80%, 100% and 105% of W_{max} ; with either NaHCO_3 or a placebo supplement prescribed prior to exercise (as described in chapter two section 1.3). The eight experimental trials were: Placebo at 75% W_{max} (P75), NaHCO_3 at 75% W_{max} (S75), Placebo at 80% W_{max} (P80), NaHCO_3 at 80% W_{max} (S80), Placebo at 100% W_{max} (P100), NaHCO_3 at 100% W_{max} (S100), and Placebo at 105% W_{max} (P105), NaHCO_3 at 105% W_{max} (S105). Capillary blood sample taken and analysed for blood acid-base variables, HR and $\text{SPO}_2\%$ taken during each experimental trial as described in chapter two section 8.0.

2.3. Time to Exhaustion Tests and Application of Two parameter CP model

The intensity of the TTE tests (80%, 100% and 105% of W_{max}) were chosen as they have been shown to produce a reliable and valid protocol to determine CP (Karsten et al., 2015). With an additional 75% W_{max} TTE test included to ensure two exercise trials were included that were between 12 to 20 min, in order to maximise the precision of estimating CP and W' (Mattioni Maturana et al., 2017). These test intensities were determined as a percentage of the initial RAMP test performed to determine W_{max} , with the required intensity administered through an electrically braked ergometer (Lode Excalibur Sport, Groningen, The Netherlands) during the exercise test. Prior to the test participants were instructed to reach their preferred cadence that would try to maintain throughout the duration of the test. Exercise tolerance was defined as the time in seconds participants were able produced the desire power output, with exhaustion defined as the inability to maintain cycling cadence within 60% of the participants preferred cadence (Amann, Hopkins and Marcora, 2008). Strong verbal encouragement was provided throughout and visual feedback on current cadence but no feedback on time elapsed was provided. The total time of exercise tolerance was recorded and further analysed to determine any apparent ergogenicity following NaHCO_3 . Furthermore, this data was used to calculate CP and W' using the two-parameter hyperbolic model, which was produced through a non-linear regression between power output and exercise tolerance. As such, CP and W' was modelled by the following equation outlined by Hill (1993):

$$\text{TTE} = W' / (P / \text{CP}) \quad (\text{Equation 1})$$

2.4. Statistical Analysis

The Shapiro-Wilk test provided no evidence to reject the hypothesis that all data was normally distributed. A repeated measures ANOVA (exercise test [75% vs 80% vs 100% vs 105% W_{\max}] x treatment [placebo vs. NaHCO_3]) was used to compare the exercise durations, [bla], mean heart rate and mean %SpO₂ from the four different TTE tests between experimental conditions. Blood acid-base variables, [HCO_3^-] and pH, taken during experimental trials were analysed through a two-way (treatment [placebo vs. NaHCO_3] x time [pre vs post exercise]) ANOVA. Where a significant main effect was found, Bonferroni post hoc paired comparisons were determined. Effect size and their 95% confidence intervals (CI) were calculated using Hedges g for paired comparisons as it mitigates for the positive bias present for Cohens d effect size when sample sizes are less than 20 (Lakens, 2013). These effect sizes were interpreted and discussed against the effects of relevant prior literature (Thompson, 2007). Frequentist inferences were reported as the mean difference \pm 95% CI between treatments. Instances where the 95% CI overlapped zero, the statistical inference of effect was deemed to be non-significant. All descriptive data is presented as mean \pm standard deviation (SD). All statistical tests were performed using SPSS v22 for MAC (SPSS Inc., Chicago, IL, USA).

3.0. Results

The median time taken to achieve peak blood [HCO_3^-] was 65 min (range 40-90 min) within this participant cohort. The mean constant load intensities for the four exercise tests were 249 ± 24 W (75% W_{\max}), 265 ± 26 W (80% W_{\max}), 332 ± 32 (100% W_{\max}) and 348 ± 34 W (105% W_{\max}). Critical power exhibited an ergolytic effect from NaHCO_3 supplementation, with CP significantly lower from 216.6 ± 18.4 W during placebo condition compared 214.4 ± 18.7 W during NaHCO_3 condition (mean difference: -2.2 ± 2.2 W; 95% CI: -4.4 to -1.5 W; $g = -0.1$; 95% CI: -1.0 to 0.8). While W' significantly increased with NaHCO_3 by 3.2 ± 2.2 kJ (95% CI: 1.7 to 5.5 kJ; $g = 0.5$; 95% CI: -0.5 to 1.4) from 27.9 ± 5.9 kJ to 31.3 ± 6.7 kJ during placebo and NaHCO_3 conditions, respectively. Furthermore, a significant negative correlation was observed between the change in CP and the change in W' from placebo to NaHCO_3 trials ($r = -0.84$; $p = 0.002$), which suggests increases in W' with NaHCO_3 were accompanied with a reduction in CP. Exercise tolerance was significantly enhanced with NaHCO_3 during the 75% W_{\max} (mean difference: 48.5 ± 48.3 s; 95% CI: 2.4 to 94.5 s) and 80% W_{\max} exercise test (mean difference: 74.8 ± 48.4 s; 95% CI: 40.0 to 109.5 s); however, there was no supplement effect

during the 100% W_{\max} (mean difference: 8.6 ± 22.1 s; 95% CI: -7.3 to 24.5 s) or 105% W_{\max} (mean difference: 4.8 ± 9.8 s; 95% CI: -2.2 to 11.8 s) trials (Figure 7.1). The supplement effect sizes were equivalent during 75% W_{\max} ($g = 0.3$; 95% CI: -0.6 to 1.2), 100% W_{\max} ($g = 0.2$; 95% CI: -0.7 to 1.2) nor 105% W_{\max} ($g = 0.1$; 95% CI: -0.8 to 1.0) trials but were over two-fold greater during the 80% W_{\max} trials ($g = 0.7$; 95% CI: -0.2 to 1.7). Indeed, a significant negative correlation between exercise intensity and the change in exercise tolerance between supplement trials was observed ($r = -0.6$; $p < 0.001$), which suggests as intensity increases the ergogenic effect of NaHCO_3 diminished.

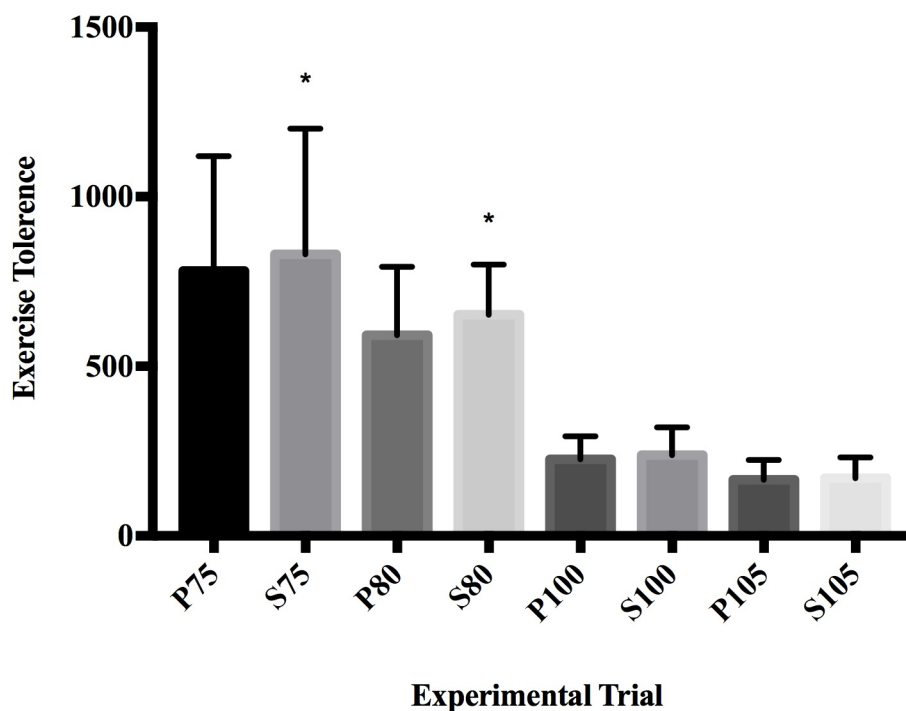


Figure 7.1. Mean \pm SD exercise tolerance (sec) during placebo (p) and NaHCO_3 (s) conditions across each TTE test intensity. * indicate significant difference to corresponding placebo trial ($P < 0.05$).

An overall significant supplement main effect was found for the blood variables of [bla] (mean difference: 2.3 ± 2 $\text{mmol}\cdot\text{L}^{-1}$; 95% CI: 0.79 to 3.71 $\text{mmol}\cdot\text{L}^{-1}$), pH (mean difference: 0.106 ± 0.001 ; 95% CI: 0.096 to 0.116) (Figure 7.2a) and $[\text{HCO}_3^-]$ (mean difference: 4.8 ± 2.7 $\text{mmol}\cdot\text{L}^{-1}$; 95% CI: 4.19 to 5.4 $\text{mmol}\cdot\text{L}^{-1}$) (Figure 7.2b). Further pairwise comparisons on [bla] reported a significant effect of NaHCO_3 during the 75% W_{\max} (mean difference: 2.2 ± 2.3 $\text{mmol}\cdot\text{L}^{-1}$; 95% CI: 0.52 to 3.9 $\text{mmol}\cdot\text{L}^{-1}$), 80% W_{\max} (mean difference: 2.6 ± 2.4 $\text{mmol}\cdot\text{L}^{-1}$; 95% CI: 0.8 to 4.4 $\text{mmol}\cdot\text{L}^{-1}$) and 100% W_{\max} (mean difference: 2.3 ± 2.5 $\text{mmol}\cdot\text{L}^{-1}$; 95% CI: 0.52 to 4.1 $\text{mmol}\cdot\text{L}^{-1}$) trials; however, the 105% W_{\max} trial was non-significant (mean difference: $1.9 \pm$

4.2 mmol·L⁻¹; 95% CI: -1.1 to 4.9 mmol·L⁻¹). Similarly, no effect was observed for either mean %SpO₂ ($p < 0.05$) or mean heart rate ($p < 0.05$) across conditions.

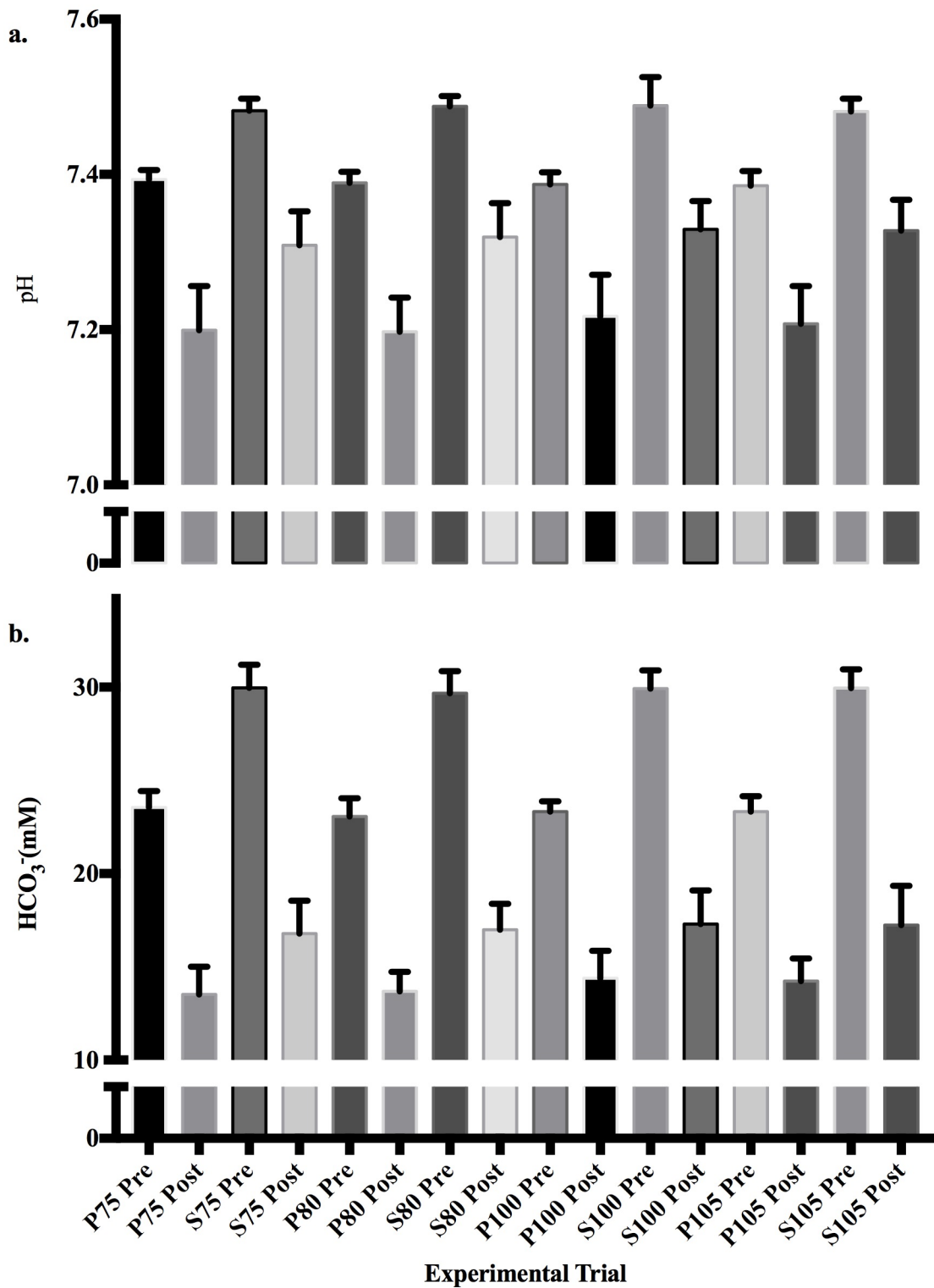


Figure 7.2. Mean ± SD pre- to post-exercise blood pH (a) and blood [HCO₃⁻] (b) during NaHCO₃ and placebo experimental trials.

4.0. Discussion

This study is the first to demonstrate the effect of pre-exercise alkalosis on the power-duration relationship when assessed through constant load exhaustive exercise performed under acute hypoxic conditions. Supplementation of NaHCO_3 elicited an ergogenic effect on W' , which supports the outcomes reported in Chapter four; however, this study also demonstrated a small negative effect on CP. Moreover, this study also identified the ergogenicity of NaHCO_3 may be moderated by exercise intensity, as exercise tolerance was enhanced during constant load exercise performed at 75% and 80% W_{max} but not 100% nor 105% W_{max} . Together, the current study suggests NaHCO_3 may be an effective ergogenic aid during severe intensity exercise performed under acute hypoxic conditions, an effect that may be mediated via the enhancement of W' ; however, NaHCO_3 did not change constant load maximal or supra-maximal intensity exercise.

The significant 11.5% increase in W' following NaHCO_3 supplementation in the current study replicates outcomes reported in Chapter four during the three min all-out CP test under acute hypoxic conditions. Indeed, the effect sizes between placebo and NaHCO_3 conditions of the two investigations are equivalent, with the three min all-out test reporting a hedge's g equal to 0.53 (95% CI: -0.4 to 1.4) and the constant load exercise tests eliciting a hedge's g of 0.5 (95% CI: -0.5 to 1.4). Consequently, this provides an interesting mechanistic insight into the determinants of W' ; in that, maintaining acid-base balance during exercise, by enhancing the HCO_3^- buffering capacity, contributes exercise tolerance and enhances fatigue resistance to exercise performed at intensities within the W' ranges (i.e. the severe intensity domain). Indeed, the assessment of muscle metabolites, through ^{31}P MRS, during exercise performed above CP discovered an inexorable rise in muscle H^+ , which indicates that the accumulation of these cations could be physiologically associated with and may limit W' (Jones et al. 2008). Furthermore, this accumulation of H^+ may be a result of an augmented glycolytic flux during severe intensity exercise (Black et al. 2017); which may also contribute to the magnitude of W' (Miura et al. 2000). This investigation reported a significant increase [bla] accumulation with NaHCO_3 during exercise, which may be indicative of enhanced glycolytic flux during constant load exercise; indeed, supplementation of NaHCO_3 has been shown to enhance the rate of muscle glycogen utilisation during exercise (Hollidge-Horvat et al. 1999; Percival et al. 2015). Equally, this increased blood lactate concentrations could be simply explained by a greater efflux of lactate from intramuscular regions to extracellular blood compartments (Bishop et al.

2004) or a reduction in the uptake of lactate in to inactive skeletal muscle (Grainer et al. 1996). While this investigation can infer increased W' following NaHCO_3 was facilitated by maintaining the acid-base balance and enhanced contribution of glycolysis, this theory should be viewed with caution until further research has investigated muscle metabolic response during severe intensity exercise with NaHCO_3 supplementation. Similarly, previous research from an independent research group identified NaHCO_3 had no effect on neither W' or CP (Vanhatalo et al. 2008); therefore, the outcomes of this study should be viewed in the context of uncertainty within scientific literature.

Interestingly, this study is the first to report a small significant ergolytic effect of NaHCO_3 supplementation on CP. Given CP is associated with highest exercise intensity that is predominantly oxidative and where a steady state in $\dot{V}\text{O}_2$ and [bla] is attained, a direct physiological explanation explaining the effect is not overtly apparent. Previous research has however, identified CP and W' do not operate in isolation and possess a dynamic relationship. Indeed, a number of investigations have found interventions that enhance CP, such as hyperoxic gas exposure or exercise training, have a corresponding diminishing effect on W' (Jenkins and Quigley, 1992, Vanhatalo et al., 2010b). This is the first study to demonstrate an opposite correlation; in that, as W' increased a reduction in CP was observed. In line with the previous discussion of NaHCO_3 facilitating greater glycolytic activity, it could be speculated that NaHCO_3 may result in a small shift in relative energy contribution to exercise; with a larger relative contribution from anaerobic sources and lower the relative contribution of aerobic energy sources. Indeed, maximal oxygen accumulated deficit (MAOD), which is considered the best available method to assess anaerobic contribution to exercise (Noordhof, Skiba and de Koning, 2013), is enhanced with NaHCO_3 supplementation (Brisola et al., 2015). Therefore, the observations of CP and W' in the current study could be explained by alteration in the energetic contribution to exercise.

The current investigation is also the first study to report a significant negative correlation between the ergogenicity of NaHCO_3 and intensity of constant load exercise in the severe intensity domain, with higher intensities corresponding to a lower ergogenic effect of NaHCO_3 . Indeed, both 75% and 80% W_{max} was increased but 100% or 105% W_{max} TTE tests did not change in response to the treatment condition. This intensity dependant effect reflects the outcomes reported in Chapter six during intermittent exercise and that previously indicated by Higgins et al. (2013). This intensity mediated effect is however, counter intuitive to previously

held hypothesis, which postulates the ergogenic effect of NaHCO_3 may be most apparent during supra-maximal exercise which evokes the greatest acidic stress (Sale et al., 2011b). As such, the explanation behind this negative correlation is unclear; however, exercising rat models have alluded to an intensity dependant stimulation of H^+ /lactate MCT transporters, with increasing exercise intensity stimulating a greater proportion of these transporters (Hamada and Takimoto, 2013). Given NaHCO_3 also facilitates the removal of intramuscular H^+ by stimulating these MCT transporters (Roth and Brooks, 1990), it could be speculated lower intensity exercise, but which does not fall below the severe intensity domain, may have a greater proportion of these transporters available to stimulate via NaHCO_3 supplementation. As a consequence, the ergogenic effect of NaHCO_3 may be most efficacious at lower intensity exercise within the severe intensity domain, as opposed to maximal and supra-maximal exercise as previously thought. This however, remains speculative until further research has assessed the interaction between exercise intensity and MCT transporter activity in exercising humans and the subsequent effect of NaHCO_3 .

It could be argued that the correlations between exercise intensity and the ergogenicity of NaHCO_3 may have occurred by chance, as a within participant variability in the effect of NaHCO_3 has previously been demonstrated during constant load supra-maximal TTE exercise (Dias et al. 2015). The authors assessed the effect of NaHCO_3 on 110% W_{\max} TTE test across three different experimental trials, with the resultant outcomes suggesting a variability in performance response to NaHCO_3 supplementation compared to placebo. It is therefore important to interpret the findings of the current study in the context of this evidence, which implies the outcomes of the current study may be altered if participants were asked to perform additional experimental trials. Nonetheless, more recent research that used an equivalent individually timed NaHCO_3 administration protocol within a similarly trained participant cohort demonstrated a consistent response in the ergogenicity of NaHCO_3 during a lower intensity 4 km TT performance (Gough et al., 2017a). Although not conclusive, these factors may contribute to the consistency of NaHCO_3 ergogenic effect and therefore, may strengthen the interpretation of the current investigation. Beyond the consistency of NaHCO_3 response, it should also be highlighted that a larger performance effect was noted during 80% W_{\max} compared to 75% W_{\max} , while these intensities are proximal it does oppose the reported correlation between exercise intensity and the ergogenicity of NaHCO_3 . Furthermore, the use of exercise intensities relative to W_{\max} as opposed to exercise intensities relative to the presence of physiological thresholds of exercise intensity, such as CP, may have resulted in a between

participant difference in the physiological response experienced to exercise (Lansley et al., 2011). As such, the potential differential physiological response to exercise may have confounded the effect of NaHCO₃; although there was no evidence of this in the current study as end exercise acid-base and lactate response displayed similar characteristics between participants in all trials. Taken together, it is important for further research to address this intensity dependant hypothesis in more focussed investigation across a range of exercise intensities from the severe intensity domain to supra-maximal intensities, whilst also addressing the potential confounding within participant variability effect.

In conclusion, this study demonstrated NaHCO₃ enhances the amount of work that can be performed in the severe intensity domain due to the increase in W' , while also causing a reduction in the CP parameter. Therefore, NaHCO₃ supplementation may act as an effective ergogenic aid during exercise that utilises the W' parameter (i.e. within the severe intensity domain); with this action speculated to be a result of an enhance anaerobic energy contribution. Furthermore, this study tested the fifth aim of this thesis and identified a negative correlation between exercise intensity and the performance enhancing effect of NaHCO₃. As such, lower intensity exercise, within the severe intensity domain, may experience a larger ergogenic effect to NaHCO₃ compared to supra-maximal exercise. Further research is however necessary to test this hypothesis.

Chapter Eight: General Discussion and Conclusion

The aim of this thesis was to initially evaluate the effect of acute hypoxic exposure on exercise capacity and performance through a meta-analysis. Followed by a series of investigations evaluating the effect of NaHCO₃ on exercise performed in the severe intensity domain when in acute hypoxic conditions, which were applied to the critical power concept. The outcomes of the meta-analysis and four experimental chapters are as follows:

Study 1: The aim of this study was to quantify the effect of acute hypoxic exposure on exercise performance and capacity. This study is the first to meta-regress the effect of acute hypoxic exposure on exercise performance/capacity and report a curvilinear relationship; with an increasing magnitude of acute hypoxia eliciting a larger ergolytic effect on exercise performance/capacity. Furthermore, this study reported RSE and exercise less than 2 min were largely unaffected under acute hypoxia, although isolated studies have suggested that a decline may be evident under severe hypoxic conditions.

Study 2: The aim of this study was to assess the effect of NaHCO₃ on CP and W' determined via the three min all-out test in normoxic and acute hypoxic conditions. This study is the first to observe that prior NaHCO₃ supplementation can enhance the W' parameter of the power-duration relationship in normoxic and acute hypoxic conditions. Furthermore, this study was also the first to report the ergogenic effect of NaHCO₃ on exercise performed in acute hypoxic conditions; with this effect found to be greater than in hypoxic conditions.

Study 3: The aim of this study was to assess the effect of NaHCO₃ on severe intensity exercise performed in acute hypoxic conditions. Given the focus of previous NaHCO₃ research has been to determine the effect of repeated sprint and supra-maximal exercise, this is the first to report NaHCO₃ can act as an ergogenic aid to severe intensity intermittent exercise in acute hypoxic conditions.

Study 4: The aim of this investigation was two-fold; which were to evaluate if altering recovery intensity across exercise intensity domains effected the ergogenic response of NaHCO₃ during severe intensity intermittent exercise. Subsequently these exercise tests were applied to the W'_{bal} model of intermittent exercise to assess if the time constant of W' recovery kinetics is affected by NaHCO₃. This study was the first to report NaHCO₃ enhances exercise tolerance during severe intensity intermittent exercise irrespective of the intensity of the recovery interval in acute hypoxic

conditions. Furthermore, this study is the first to report the time constant of W' recovery kinetics during intermittent exercise, within the W'_{bal} model, is a mutable mathematical term that is to sensitive physiological interventions that alters acid-base status during exercise.

Study 5: The aim of this study was to assess the effect of NaHCO_3 supplementation on CP and W' in acute hypoxic conditions, when determined via constant load TTE exercise of four different exercise intensities: 75%, 80%, 100% and 105% W_{\max} . This study reported NaHCO_3 enhanced the W' parameter of the power-duration relationship, whilst also the first to demonstrate a negative effect on CP. Furthermore, this study found a significant negative relationship between exercise intensity and the ergogenicity of NaHCO_3 ; in that, as exercise intensity increased from 75% to 105% W_{\max} the ergogenic effect of NaHCO_3 reduced.

This thesis includes the first series of investigations that demonstrated the ergogenic effects of NaHCO_3 on exercise performed in acute hypoxic conditions. This contrasts with previous research that have reported a null effect from NaHCO_3 in acute hypoxia (Flinn et al., 2014, Saunders et al., 2014a). A brief meta-analysis of data was performed, for illustrative purposes, to quantify the experimental effect of NaHCO_3 as a percentage across the investigations of this thesis. This was calculated using the same method outlined in Chapter three, which quantified the overall percentage effect of acute hypoxia on exercise performance/capacity. The corresponding outcome was an overall significant positive $9.0 \pm 5.4\%$ (95% CI: 5.6 to 12.4%) improvement in exercise performance/capacity with NaHCO_3 , with a $9.4 \pm 5.9\%$ (95% CI: 5.7% to 13.0%) improvement when experimental trials that were conducted in acute hypoxia were only considered. Whilst this only represents the effect of 10 experimental interventions where study bias or heterogeneity were not determined, this outcome is larger than the 1.7% (90% CI: -0.3 to 3.7%) effect of NaHCO_3 previously reported in meta-analysis of 38 normoxic studies (Carr et al. 2011). The difference in effect could be attributed to the number of estimates used or the differing statistical methods used to establish the effect size; however, the discrepancies could equally be attributed to several moderating factors that distinguishes the studies in the current thesis, such as the exercise intensity and ambient environment. Furthermore, Figure 8.1 depicts the effect sizes and corresponding 95% confidence intervals across the individual experimental trials throughout this thesis. It is apparent that the ergogenic effect of NaHCO_3 is not consistent in all exercise tests as the overall positive meta-analysis

results may indicate. This variability in NaHCO₃ ergogenicity is common throughout literature (Dias et al. 2015; McNaughton et al. 2016) and in this series of investigations be explained by the type and intensity of exercise tests, the use of an individually timed NaHCO₃ administration protocol or the use of acute hypoxia.

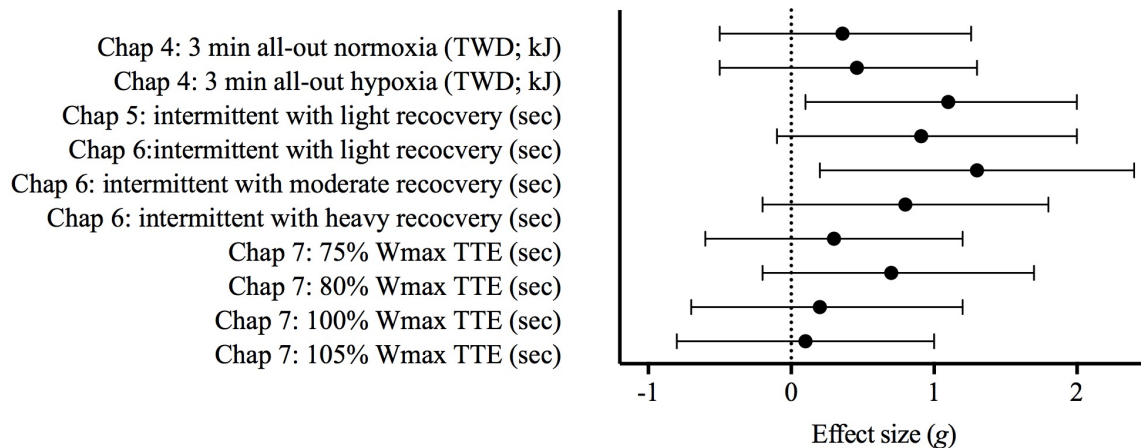


Figure 8.1. Effect sizes (Hedges *g*) and corresponding 95% CI showing the effect of NaHCO₃ compared to placebo in all the exercise tests within this thesis

The effect of NaHCO₃ on exercise in the severe intensity domain

This study added to the limited body of scientific literature that has shown NaHCO₃ can improve exercise performed in the severe intensity domain. It was previously demonstrated that NaHCO₃ enhances exercise tolerance at a constant load intensity equivalent to LT2 (George and McLaren, 1988; Egger et al. 2014) and CP (Mueller et al. 2013) in normoxic conditions; whereas severe intensity intermittent exercise was not enhanced in acclimatised females at altitude (Kozak-Collins et al. 1994). This thesis advanced previous literature regarding the ergogenic effect of NaHCO₃ during severe intensity exercise by demonstrating a positive effect in acute moderate hypoxic conditions during constant load and intermittent exercise. Furthermore, these investigations are the first to assess the ergogenic effect of NaHCO₃ in acute hypoxic conditions by modelling severe intensity exercise through the power-duration relationship. Indeed, it was demonstrated that *W'* is enhanced with prior NaHCO₃ supplementation when assessed through the three min all-out CP test and multiple TTE tests. Furthermore, during intermittent exercise, NaHCO₃ has been shown to accelerate the time constant of *W'* recovery kinetics during intermittent exercise, which allows for a greater volume of work to be performed in the severe intensity domain before exercise exhaustion. While the presence of an ergogenic effect for exercise below CP cannot be

dismissed due to the lack of scientific evidence; it is likely that CP represents the lowest intensity at which NaHCO₃ may possess ergogenic benefit due to its association with a [bla] steady state. Consequently, this suggests the acid-base balance may not be a limiting physiological factor to exercise at these intensities below CP.

The physiological determinants of W' are currently subject to increased science interest, given the traditional definition of W' as finite anaerobic work capacity is thought to be incorrect (Poole et al. 2106). Indeed, W' is associated with the amplitude of the $\dot{V}O_2$ slow component (Murgatroyd et al. 2011), along with ³¹P MRS studies demonstrating perturbations to muscle metabolite characteristics during exercise above CP; with a continuous rise in [Pi], a reduction in muscle PCr content and pH (Jones et al. 2008). These investigations only offer description of physiological characteristics during exercise and therefore, assessing the impact on W' following the manipulation of these correlates may provide evidence of a mechanistic relationship. Indeed, this thesis suggests that the reductions in pH that occurred with NaHCO₃ during severe intensity exercise contribute to the magnitude of W' and that alleviating the acidic stress increases this magnitude. Through observing differences in acid-base balance between placebo and NaHCO₃ conditions, it is apparent that blood pH remains elevated throughout exercise due the consistently higher end-exercise blood pH. Furthermore, a greater reduction in blood [HCO₃⁻] is observed from pre-to-post exercise, with NaHCO₃ compared to placebo. This suggests blood buffering activity may be enhanced with supplementation and therefore, the corresponding enlargement of W' may be a function of an increased buffering capacity. Equally, alleviating acidic stress during exercise may augment glycolytic contribution to exercise and thus, increases the use of muscle glycogen (Hollidge-Horvat et al., 2000). Indeed, the current investigations also reported a greater accumulation of [bla] during exercise, which can allude to a larger bioenergetic contribution from glycolysis. As such, the enlarged W' observed in these investigations may be a function of greater glycolytic activity. This hypothesis is supported further when considering previous research has demonstrated that attenuating glycolytic activity, through prior muscle glycogen depletion, impairs W' (Miura et al. 2000) Nevertheless, a direct mechanistic explanation cannot be inferred from the current series of investigations as no metabolic markers at the site of action (i.e. active skeletal muscle) were taken. Further research should consider monitoring muscle glycogen utilisation and glycolytic energy contribution during exercise above CP; along with, assessing real time muscle metabolite response using ³¹P MRS techniques following the supplementation of

NaHCO₃. This may offer a more detailed insight into the relationship between acid-base balance and W' .

Is the ergogenic effect of NaHCO₃ mediated by exercise intensity?

A novel finding of the current thesis is the identification of a negative correlation between exercise intensity and the ergogenic effect of NaHCO₃; in that, as exercise intensity increases the magnitude of effect from NaHCO₃, compared to placebo, decreases. This hypothesis was initially identified with observations in chapter five, with larger effect observed during severe intensity intermittent exercise with a light intensity recovery interval compared to those with a moderate and heavy recovery intensity. In the succeeding investigation, it was demonstrated that the ergogenic effect of NaHCO₃ diminished with increasing exercise intensity during constant load TTE test in acute hypoxia, from 75% W_{max} to 105% W_{max} . While this hypothesis has not previously been addressed in scientific literature, Higgins et al. (2013) demonstrated NaHCO₃ improved exercise performance in 100% W_{max} TTE test but not 110% or 120% W_{max} TTE tests. The authors subsequently suggested that ergogenic effect of NaHCO₃ is dependent on the rate of change in pH during exercise, with a faster rate of change lessening the effect of NaHCO₃. While this explanation offers a reasonable insight in to a potential mechanism behind the ergogenicity of NaHCO₃, the presence of scientific data or mechanism of action to support this rationale is currently missing. In viewing data from exercising rat models, however, it possible to identify a plausible mechanistic explanation for the results (Hamada and Takimoto, 2013). The activity of MCT transporters is mediated via pH gradient between intramuscular and extracellular blood compartment, with a larger gradient stimulating MCT activity (Roth and Brooks, 1990). As such, exercising rat models have shown that sub-maximal intensity exercise stimulates a lower volume of MCT transporters compared to higher intensity exercise (Hamada and Takimoto, 2013). It could therefore be speculated that with NaHCO₃ supplementation, which acts by increasing blood pH and thus activity of these MCT transporters, there may be a larger proportion of MCT transporters available to stimulate during sub-maximal exercise, whereas these transporters may become saturated with higher intensity exercise. Nevertheless, this theory should also be viewed with caution as it known if an intensity dependant effect of these MCT transporters is present within exercising humans; and furthermore, no study, in rat or human models, has investigated the effect alkalosis on MCT transporter activity in sub-maximal and higher intensity exercise. Given this lack of direct robust physiological evidence in humans to explain the correlation in chapter seven, it is

necessary that further research is required to verify the presence of intensity dependant effect, prior to further assessment of potential mechanisms of action involving MCT transporters.

Personalised NaHCO₃ supplementation

Supplementation with NaHCO₃ has been identified to present a variable ergogenic effect, with investigations demonstrating both a positive and null effect following ingestion (McNaughton et al. 2016). An investigation conducted by Dias et al. (2015) identified the presence of a large within participant variability in response to NaHCO₃ three independent 110% W_{max} TTE tests compared to a placebo experimental condition. The authors reported that participants did not exhibit performance improvements across all treatment conditions, with some participants showing no effect from supplementation in any of the treatment trials (Dias et al. 2015). Consequently, this represented a significant mean improvement in only one experimental trial compared to the placebo conditions and non-significant outcomes in other two experimental trials. This thesis, however, demonstrated a more consistent response to that previously observed, with only two experimental conditions showing no effect. A reason for the consistency in the current investigation could be adoption of a contemporary method of administering NaHCO₃ prior to exercise, which accounts for the individual variation in blood acid-base response to supplementation (Jones et al., 2016, Gough et al., 2017c). Theoretically commencing exercise at an individual's peak blood [HCO₃⁻] may maximise blood HCO₃⁻ buffering capacity during exercise and thus potentially provide enhanced physiological conditions to elicit an improvement in exercise performance. This theory, however, is based upon the assumption that personalised timing of supplementation is superior to the standardised timing method of administration (i.e. 60 min prior to exercise). Siegler et al. (2013) evaluated the effect of NaHCO₃ on repeated sprint performance across three different time frames prior to exercise (60 min, 120 min and 180 min). The authors observed the largest rise in blood [HCO₃⁻] occurred 180 min post supplementation; although, performance did not improve at any time point. This investigation cannot be used, however, to suggest timing of NaHCO₃ supplementation does not matter as performance was unaffected and therefore, does not allow for the comparison of NaHCO₃ ergogenicity. To evaluate if supplement timing governs the ergogenic effect, an exercise test that exhibits consistency in ergogenicity must be used. Indeed, Gough et al. (2017a) demonstrated the use of a personalised dosage strategy enabled consistent replication of NaHCO₃ ergogenic effect ($r = 0.9$; $p > 0.05$) during a 4 km TT performance compared to placebo. Further research should therefore, evaluate the effect of NaHCO₃ across

a range of time frames on either side of a participants pre-determined peak blood $[\text{HCO}_3^-]$; for example, 50% of the time below and above the peak. If peak blood $[\text{HCO}_3^-]$ occurred at 60 min the participants would also perform separate exercise trials at 30 and 90 min post supplementation. An investigation of this nature would begin to elucidate if timing is moderator of NaHCO_3 ergogenicity.

Environment

A novel finding of this thesis was that NaHCO_3 can be used as an ergogenic aid to improve exercise performance and capacity under acute moderate hypoxic conditions. Furthermore, the first experimental study (Chapter four) alluded to larger ergogenic effect from NaHCO_3 in acute hypoxic conditions compared to normoxic during the TWD in the three min all-out test. Indeed, acute hypoxia is known to exacerbate the rate at which H^+ accumulate during exercise compared to normoxia (Hogan, Cox and Welch, 1983). This is thought to be a result of a reduced energetic contribution to of oxidative energy pathways during exercise and a subsequent increase in the relative contribution of glycolytic energy pathways (Scott, Goods and Slattery, 2016). As such, it is hypothesised that exercise in acute hypoxic conditions benefits from additional blood HCO_3^- buffering capacity to mitigate for the elevated rise in H^+ , when compared to matched exercise in normoxia. This investigation is currently the only study however, that has compared the effect of NaHCO_3 in both environmental conditions within the same participant cohort and therefore, further investigations are required to reaffirm or refute this hypothesis. Nonetheless, this series of studies is the first to identify NaHCO_3 can be an ergogenic aid to improve exercise capacity and performance in acute moderate hypoxia.

In interpreting the current findings, it is important to consider the context in which these outcomes may be applicable. In this thesis all hypoxic experimental conditions were maintained consistently at an acute moderate ($\text{FiO}_2\% = 14.5\%$) severity within a normobaric environmental chamber. This does not however reflect the diverse range of environmental conditions individuals may experience in simulated and terrestrial environments. A major difference between the simulated environments used in this thesis and terrestrial altitudes, is the presence of hypobaric conditions in the latter. A hypobaric environment refers to a lower density of atmospheric air that causes a reduction in the partial pressure of O_2 as opposed to lowering the concentration of O_2 in the gaseous environment with a normobaric chamber. This difference in environment is suggested to alter physiological response, such as lower minute

ventilation, reduced nitric oxide bioavailability and elevated plasma pH in hypobaric hypoxia compared to a simulated normobaric hypoxia (Coppel et al., 2015). Furthermore, TT performance is impaired to a greater extent in hypobaric hypoxia ($-33.2 \pm 12.4\%$; $p < 0.05$) than in normobaric hypoxia ($-24.1 \pm 6.6\%$; $p < 0.05$) when compared to normoxia (Saugy et al., 2015). Given the larger decrement in exercise performance and altered physiological response, in particular the higher plasma pH, it is reasonable to suggest the ergogenic effect of NaHCO_3 may differ between normobaric and hypobaric hypoxic conditions. Therefore, when interpreting these findings in the context of using NaHCO_3 in terrestrial conditions, individuals should consider the outcomes of these studies cannot be directly translated and therefore, further research is required in these environmental conditions.

This thesis used a consistent moderate hypoxic magnitude throughout, equivalent to 3500 m ($\text{FiO}_2\% = 14.5\%$). In chapter three, through a meta-analysis of available studies it was identified that a curvilinear effect is present between level of acute hypoxic exposure and magnitude at which exercise performance and capacity was impaired. Furthermore, RSE and high intensity exercise bouts less than 2 min were shown to be largely unaffected, although performance declines during RSE are apparent in severe acute hypoxic conditions equivalent to 4000 m or above (Bowtell et al., 2014, Goods et al., 2016). Furthermore, the W' parameter of the power-duration relationship is also unaffected until severe acute hypoxic conditions, equivalent to 4000 m, where it begins to diminish (Townsend et al. 2017). It has been reported that severe acute hypoxia exacerbates the reduction in cerebral oxygenation compared to lower hypoxic magnitudes and an associated reduction in cortical voluntary activation, which results in a diminished neural drive and voluntary activation during exercise in severe acute hypoxic compared to lower hypoxic magnitudes (Goodall et al., 2012, Willis et al., 2017). As such, it is suggested that central fatigue is exacerbated in severe acute hypoxia and therefore, may explain the curvilinear relationship and the reduction in RSE and W' that occurs at severe hypoxia only. On this premise, it is reasonable to postulate that the ergogenic effect of NaHCO_3 may be altered in severe hypoxic conditions due to the differing physiological characteristics of fatigue.

A principal rationale for the overall aims of the thesis was based on the premise acute hypoxic conditions exacerbates the accumulation of H^+ compared to equivalent exercise at normoxia (Arthur et al., 1992, Hogan, Richardson and Haseler, 1999). Athletes and mountaineers are unlikely, however, to perform or undertake expeditions without appropriate prior altitude

acclimatisation. Prolonged exposure to hypoxic conditions has been shown reduce the accumulation of lactate during exercise, a phenomenon known as the lactate paradox (van Hall, 2010). Indeed, acclimatised individuals have shown a reduction in [bla] at an absolute exercise intensity and a lower maximal blood lactate accumulation after exhaustive exercise, compared to acute hypoxia and normoxia (Kayser, 1996). This behaviour of blood lactate is also reflective of intramuscular pH activity, as five weeks of altitude exposure has been shown to diminish the reductions in pH during exhaustive exercise (Kayser, 1996). Given this apparent attenuation of acidic stress during exercise, it could be suggested that the efficacy of NaHCO_3 may be reduced during exercise following a period of altitude acclimatisation. This however, is not a simple inference of the physiological response to altitude, as there is considerable debate over the existence of a lactate paradox (Bartlett and Lehnhard, 2010). Furthermore, activity of the HCO_3^- buffering system appears to diminish further with prolonged altitude exposure (Cerretelli and Samaja, 2003). Together, this suggests the supplementation of NaHCO_3 may still be beneficial following a period of acclimatisation. However, taking these physiological perspectives in context, it is difficult to ascertain if NaHCO_3 may exert an ergogenic effect in acclimatised individuals. Indeed, Kozak-Collins et al. (1993) reported NaHCO_3 had no significant effect on severe intensity intermittent in seven trained acclimatised female participants; despite a mean 19% increase in exercise tolerance in the supplement group. While this lack of significance could be attributed to insufficient sample power, it does not clarify if there is a difference in NaHCO_3 response in acute hypoxic and chronic hypoxic conditions. Further research should therefore elevate this hypothesis to establish if supplementation may be beneficial in acclimatised athletes and mountaineers at altitude.

Considering the potential moderating factor of hypobaria, magnitudes of hypoxia and acclimatisation, it highlights the importance of interpreting the outcomes of this thesis in the appropriate context. As such, this thesis demonstrate NaHCO_3 may be an efficacious ergogenic aid under acute normobaric moderate hypoxic conditions, with further research required to prior to the application in alternative environmental conditions. In addition, it is important to consider that extreme environmental stressors seldom occur in isolation and individuals may often find themselves in hypoxic and cold ambient environments (Tipton, 2012). Indeed, a combined acute hypoxic-cold stressor impairs exercise tolerance to a greater extent than acute hypoxia alone (Lloyd et al., 2016). Furthermore, acute cold exposure ($-20\text{ }^\circ\text{C}$), compared to temperate conditions, is reported to reduce [bla] and attenuate the reduction of blood [HCO_3^-] that occurs during exhaustive exercise (Quirion et al., 1989). This itself indicates that the blood

HCO₃⁻ buffering activity is reduced with cold exposure, possibly due to a diminished acidic load that accumulates during exercise in the cold. The acid-base physiology during exercise with a cold stressor is in contrast with that expected in acute hypoxic conditions; however, the combined effect of these stressors on acid-base balance is unknown. Further research is therefore required to evaluate acid-base behaviour during exercise in a combined acute hypoxic-cold stressor and the subsequent effect of NaHCO₃ on exercise performance or capacity.

Practical application

The effect of NaHCO₃ on the W' at sea level and acute moderate hypoxia offers interesting insight for sport performance. In particular, sporting events that require individuals to perform exercise within the severe intensity domain (i.e. exercise that taxes W') may benefit from NaHCO₃ supplementation. For example, middle distance running track events, such as 800 m and 1500 m, and intermittent sports, such as football and tennis, are all sports that tax the severe intensity domain. In relation to the former, previous research has demonstrated the ergogenic effect of NaHCO₃ during both 800 m and 1500 m track events at sea level (Wilkes, Gledhill and Smyth, 1983; Goldfinch, McNaughton and Davies, 1988; Bird, Wiles and Robbins, 1995). When interpreted in conjunction with the finding of this thesis, it may be speculated that the improvement in 800 m and 1500 m track performance was mediated via NaHCO₃ ergogenic effect on W' . It is not yet apparent if this effect on middle distance running is evident in hypoxic environments, given research has only been undertaken in ambient sea level conditions. It has been suggested that altitude begins to impede exercise performance from the 800 m distance events and above when measured during world athletics competitions (Chapman et al. 2011); therefore, athletes competing in these events will benefit from ergogenic strategies to mitigate for these hypoxic mediated performance declines. Further research should use the outcomes from this thesis to test if NaHCO₃ enhances 800 m and 1500 m running performance through an effect mediate via the enhancement in W' parameter. Further to this, the positive effect on the severe intensity intermittent exercise provides promising application to intermittent sports in acute hypoxic conditions. Current research however, has suggested NaHCO₃ has no effect on team sport simulated activity (Saunders et al. 2014). The lack of effect could be attributed to the dosing regime used for all participants rather than the personalised timing strategy used within this thesis. Research should consider utilising the personalised timing strategy prior to

intermittent team sport simulation tests to evaluate if NaHCO_3 can be an efficacious ergogenic aid during performance at altitude.

While this thesis demonstrated NaHCO_3 can be an ergogenic aid during acute hypoxic conditions, it is important to consider that acclimatisation to hypoxia alters the acid-base characteristics during exercise. In that, acclimatisation reduces the maximal lactate and reduces intramuscular pH responses to exercise (Kayser, 1996). As such, athletes who spend extended periods of time at altitude prior to competing may exhibit an altered exercise response to NaHCO_3 . Further research is required to address the practical limitations of the findings within this thesis, prior to adopting NaHCO_3 as a recommendation for acclimatised athletes. Sodium bicarbonate could however be considered in the early stage of altitude exposure. Indeed, it has been suggested that a large degree of acclimatisation occurs following the initial 24 hr exposure (Wyatt, 2014), with the greatest performance decrements suggested to remain after the first days of arrival to the altitude environment (Chapman, 2013). It could therefore be speculated that supplementation of NaHCO_3 may be most efficacious during the initial days of arrival and particularly within the first 24 hrs of arrival. This may offer a cheap viable option for athletes who do not possess the resources to arrive at high altitude climates prior to events in sufficient time to appropriately acclimatise. As such, NaHCO_3 and other ergogenic strategies may be beneficial to mitigate for the decrements in exercise performance that occur during this early arrival period.

Conclusion

Through systematic review and meta-regression analysis this thesis initially quantified the ergolytic effect of acute hypoxic exposure on exercise performance and capacity. The consequent outcomes were a curvilinear relationship between the magnitude of acute hypoxic exposure and the decrement in exercise performance and capacity. Subsequently this thesis found that NaHCO_3 is likely to mediate an ergogenic effect on exercise performed in acute moderate hypoxic conditions, thereby mitigating the hypoxic-mediated decline in performance. More specifically, this ergogenic effect was observed in exercise undertaken in the severe intensity domain, which is suggested to be the lowest intensity whereby NaHCO_3 may exhibit the ergogenic effect via the HCO_3^- blood buffering system. Interestingly, this thesis is the first to suggest the efficacy of NaHCO_3 may be dependent on exercise intensity, with increasing exercise intensity, above CP to supra-maximal exercise intensities, may lessen

the ergogenic effect of NaHCO₃. Although, further research is required to test this hypothesis. The ergogenic effect of NaHCO₃ was predominantly observed through discovering the positive effect on the W' parameter of the power-duration relationship. Indeed, the studies in this thesis were the first to demonstrate pre-exercise alkalosis, via NaHCO₃ supplementation, increases the volume of work that can be performed in the severe intensity domain when determined via the three min all-out CP test and modelled through multiple TTE tests. Furthermore, this thesis was also the first to demonstrate that the time constant of W' recovery during intermittent exercise can be accelerated with NaHCO₃. This consequently demonstrates that the $\tau_{W'}$ of the W'_{bal} model is sensitive to physiological interventions and thus, may be manipulated through training or dietary intake. While this thesis provides evidence of linking the acid-base balance as a physiological determinant of W' , it is not clear if this is a direct effect mediated through the acid-base balance or indirect effect through an enhanced glycolytic flux. Nevertheless, taking the evidence presented in this thesis, in acute moderate hypoxic conditions NaHCO₃ may be used as an effective ergogenic aid during exercise performed in the severe intensity domain. Further research is required to evaluate the effect within alternative intensity ranges; while the practical application of these findings is only limited to acute moderate hypoxic conditions and further research should assess the implications of NaHCO₃ in other extreme environmental conditions.

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