EFFECTS OF HYPOXIA ON LOCOMOTOR-RESPIRATORY COUPLING DURING EXERCISE

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Submitted to the faculty of the University Graduate School

in partial fulfillment of the requirements for the degree

Master of Science

in the School of Public Health

Indiana University

April 2017

Accepted by the Graduate Faculty, Indiana University,

in partial fulfillment of the requirements for the degree of Master of Science

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Abstract

To determine if acute exposure to normobaric hypoxia alters locomotor-respiratory coupling (LRC) patterns typically observed in trained runners, 13 trained male distance runners performed a running economy (RE) and maximal oxygen uptake ($\dot{V}O_{2max}$) test in normoxia (NORM) and hypoxia (HYP) (FIO_2 = 15.8%; ~ 2500m / 8000ft) on separate days. RE and LRC measures were taken during the fourth minute of each submaximal speed (12.9, 14.3, and 16.1 km hr^{-1}), while ratings of perceived exertion (RPE) and dyspnea (DYS) were taken during the first 10 seconds of the final minute at each speed, and again at the conclusion of the maximal test. Stride frequency-to-breathing frequency quotients were significantly lower at each submaximal speed in HYP (*12.9 km hr^{-1}*: 2.91 ± 0.20 vs. 2.45 ± 0.17, *14.3 km hr^{-1}*: 2.53 ± 0.17 vs. 2.21 ± 0.14, *16.1 km hr^{-1}*: 2.22 ± 0.14 vs. 1.95 ± 0.09; $p < 0.05$) due to increases in breathing frequency while maintaining stride frequency. Compared with NORM, the degree of LRC (range: 36 - 99%) was not significantly different at any of the three common submaximal speeds with exposure to HYP. However, the degree of LRC was increased at $\dot{V}O_{2max}$ (43.8 ± 3.4% vs. 57.1 ± 3.8%; $p < 0.05$). Breathing frequency (breaths min^{-1}) was significantly increased at each submaximal speed in HYP compared to NORM (*12.9 km hr^{-1}*: 30.3 ± 1.9 vs. 35.9 ± 2.2; *14.3 km hr^{-1}*: 34.8 ± 2.0 vs. 39.8 ± 2.2; *16.1 km hr^{-1}*: 40.4 ± 2.4 vs. 45.2 ± 1.9; all speeds $p < 0.05$), but was not significantly different at $\dot{V}O_{2max}$. RE and RPE were not significantly different at any speed. DYS was only significantly different between NORM and HYP at 16.1 km hr^{-1} ($p < 0.05$). In conclusion, trained distance runners are able to maintain LRC in hypoxia, even when breathing frequency is increased at any submaximal pace. Within this unique population, years of training may enhance and optimize the ability to make

adjustments to maintain LRC in order to minimize metabolic costs. However, there may be individual differences to LRC that could affect performance or the response to training at altitude.

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CHAPTER 1

INTRODUCTION

Endurance athletes commonly use altitude training as a means to improve sea level performance. A large reason altitude training is utilized is due to beneficial hematological adaptations such as increased erythropoietin (EPO) production. Increased EPO production stimulates increases in hemoglobin mass, which results in improved oxygen carrying capacity of the blood, and can ultimately lead to improved endurance performance. While it is ideal to have a large initial EPO response, the ability to continue regular, uninterrupted endurance training during the recommended 3-4 week sojourn to altitude is also essential. Over this timespan, many training adaptations such as increased mitochondrial volume, increased free fatty acid substrate utilization, and increased oxidative enzyme activity can occur, sometimes to greater extent than similar training periods at sea level. However, even when following altitude training best practice guidelines, considerable variation in physiological responses to altitude exposure and subsequent sea level performance exist (Chapman, Stray-Gundersen, & Levine, 1998).

The response to altitude training depends on both physiological acclimatization and training adaptations, so each also represent possible areas of explanation for variation. Although a number of factors can affect the ability to complete endurance exercise training at altitude, one of the most immediate responses to acute altitude exposure is an increase in ventilation at any submaximal exercising workload. The ventilatory response to exercise is unique in having both physiological outcomes (e.g. defending arterial oxyhemoglobin saturation, but with a metabolic cost of increased work

of breathing) and psychological outcomes (e.g. dyspnea). In endurance-trained runners exercising at sea level, a link between the speed of movement across the ground and ventilatory effort exists. However, due to the increases in ventilation with exposure to altitude, this link may become disrupted. As a result, ventilatory control during exercise at altitude can have a strong influence on workload selection, perception of effort, and ultimately the training response at altitude. One factor involved in ventilatory control is locomotor-respiratory coupling (LRC).

LRC is a consistent frequency and phase locking between pulmonary respiration and locomotion, and is believed to aid in decreasing the energetic cost of locomotion. For example, multiple studies have found that higher degrees of LRC during cycling lead to decreases in oxygen consumption during submaximal exercise (Garlando, Kohl, Koller, & Pietsch, 1985; Hoffmann, Torregrosa, & Bardy, 2012; Villard, Casties, & Mottet, 2005). Additionally, Bernasconi et al. (1993) found that a higher degree of LRC while running significantly lowered oxygen uptake (i.e. improved running economy (RE)) when compared to a lower degree of LRC.

Higher degrees of LRC may also be involved in decreasing the amount of discomfort associated with increases in ventilation during exercise tolerance. Dyspnea, which is a subjective sensation of breathing discomfort, is known to be a factor limiting exercise performance (Sheel, 2002). Takano et al. (1997) demonstrated that reduced dyspnea was associated with higher degrees of LRC. Thus, there may be perceptual benefits as well as physiological benefits to increasing the degree of LRC. These perceptual benefits may be especially true for highly trained athletes, who "associate" during exercise and are very cognizant of changes in their own physiological variables

such as breathing frequency or tidal volume (Morgan & Pollock, 1977). While these energetic and perceptual benefits are advantageous for endurance performance, any perturbation to the components of LRC could negate these advantages.

One possible perturbation that may affect endurance runners utilizing altitude training is hypoxia-induced increases in breathing frequency. Currently, evidence of changes to LRC in hypoxia is inconclusive. Patterson et al. (Paterson, Wood, Marshall, Morton, & Harrison, 1987) found decreases in the degree of LRC during hypoxic running when compared to normoxia, while Fabre et al. (2007) and Seebauer et al. (2003) showed no change to LRC in rowers and cyclists, respectively. Moreover, the consequences of altering LRC in hypoxia, such as changes to oxygen uptake and perceptions of ventilatory effort, remain to be elucidated.

Statement of the Problem

The effect of hypoxia on LRC in trained runners is unsubstantiated, and the consequences that alterations to LRC have on running economy and perceptions of ventilatory effort in hypoxia are unknown.

Purpose of the Study

The purpose of the study was to determine if hypoxia alters LRC patterns typically observed in trained runners, and investigate the effects these possible LRC alterations have on RE and perceptions of ventilatory effort.

Significance of the Study

To improve sea level performance, many endurance runners use altitude training to take advantage of beneficial hematological and/or training adaptations that occur above and beyond sea-level training. While there are many physiological responses to altitude exposure, one of the most immediate responses is an increase in ventilation at any submaximal exercising workload. This increase in ventilation may perturb an established harmonization of breathing and locomotor rhythms, known as LRC, which could be detrimental to exercise performance. Specifically, running economy may become worse and/or perceptions of ventilatory effort may be increased. However, the effects altitude exposure has on LRC have not been extensively investigated, especially in trained endurance runners. Therefore, insights into possible consequences are necessary to aid in training and performance strategies of athletes, and may explain some

portion of the variance behind the individual response to altitude training and subsequent sea level performance.

Delimitations

1. Subjects were trained distance runners.
2. A research-grade treadmill, indirect calorimetry system, and data acquisition software were used to measure outcome variables.
3. A single blinded, randomized crossover (normoxia and hypoxia) study design was used.

Limitations

1. Subjects were not a random sample of the entire running population.
2. The sample size of the study was small.

Assumptions

1. Subjects in this study were representative of trained distance runners.
2. Decreased oxygen concentration of inspired gas had effects similar to that of decreased barometric pressure.
3. The method used to measure exercise ventilation did not significantly alter the subjects' normal ventilatory patterns.
4. The method used to measure foot ground contact did not significantly alter the subjects' normal locomotor patterns.

Specific Aims and Hypotheses

Specific Aim 1:

To test if hypoxia alters LRC patterns typically observed in trained runners.

Research Hypotheses:

The degree of LRC will be reduced in hypoxia compared to normoxia due to increases in breathing frequency without concomitant increases in stride frequency.

Specific Aim 2:

To identify the relationships between LRC alterations and RE and perceptions of ventilatory effort.

Research Hypotheses:

1. Running economy will be worse with a decreased degree of LRC.

2. Perceptions of ventilatory effort will increase with a decreased degree of LRC.

Definitions of Terms

Breathing frequency: Number of breaths taken per minute.

Degree of LRC: Percent of breaths that occur within in distinct decile divided by the total number of breaths.

Entrainment: Frequency and phase locking between two periodic systems.

Locomotor-respiratory coupling (LRC): A stable, consistent frequency and phase locking between pulmonary respiration and locomotion

Running economy: The energy demand, or oxygen uptake, for a given velocity of submaximal running.

Step: Ground contact of one foot to ground contact of the opposite foot (ipsilateral foot ground contact to contralateral foot ground contact).

Stride: Ground contact of one foot to the next ground contact of the same foot (ipsilateral foot ground contact to ipsilateral foot ground contact).

Stride frequency: The number of strides taken over a given period of time (per minute in this study).

Minute Ventilation ($\dot{V}_E$): The volume of air leaving the lung each minute; Mathematically, the product of the volume of each breath (tidal volume; V_T) and the frequency of breaths per minute (f_B).

CHAPTER 2

REVIEW OF LITERATURE

The ability to perform, and sustain, endurance exercise relies in part on the successful coordination of the ventilatory and locomotor systems. This synchronization is known as locomotor-respiratory coupling (LRC), and is believed to affect the energetic cost of locomotion and the amount of breathing discomfort (dyspnea) during exercise. Higher degrees of LRC may result in decreased energetic cost of locomotion and decreased dyspnea, thus possibly enhancing endurance exercise tolerance and performance. Consequently, any perturbation to the components of LRC, such as increased ventilation due to hypoxia, may negatively impact performance. Endurance athletes who utilize altitude training in order to improve sea level performance may be affected by these hypoxia-induced increases in ventilation, resulting in a lower degree of LRC. The alteration to LRC may cause deviations in the energetic cost of running and/or dyspnea, either of which could negate advantageous training adaptations that occur during a runners stay at altitude. However, there is limited evidence regarding the effects of hypoxia on LRC, particularly in trained endurance runners. In order to more adequately understand how hypoxia and LRC relate to each other, as well as possible consequences hypoxia may have on LRC, it is pertinent to examine each individually. Therefore, this review will address the following areas: (1) basics of altitude training, (2) mechanics and control of ventilation, (3) mechanics and energetics of locomotion, (4) mechanisms of LRC, and (5) implications and perturbations to LRC.

Altitude Training

Living and training at altitude is a common strategy utilized by endurance athletes for the enhancement of performance at sea level. While the improvements in performance may be principally due to hematological adaptations that cause increases in red cell mass and oxygen carrying capacity, the ability to continue endurance specific training at altitude is imperative in order to obtain non-hematological adaptations. Such adaptations may include increased oxidative enzyme activity, increased free fatty acid substrate utilization, and increased mitochondrial volume (Sinex & Chapman, 2015). In order to take advantage of and maximize any of these mechanisms, athletes must follow best practice guidelines regarding how high to live, how high to train, how long to stay, and when to return to sea level competition. Still, even when following practical and scientific recommendations there appears to be an individual variation in the response to altitude training, and the possible benefits of this type of training may be outweighed by negative physiological responses associated with altitude exposure (Chapman, 2013).

Best Practices

Early investigations of altitude training suggested a live high-train high (LHTH) model in which athletes stayed at a moderate elevation of 1500-3000m continuously (Wilber, Stray-Gundersen, & Levine, 2007). While this range of elevation may cause positive hematological responses, it limits the ability of an athlete to train at intensities necessary to induce adequate oxygen flux for performance improvement. Therefore, a live high-train low (LHTL) model was developed whereby all daily living activities and low intensity workouts are at completed at the high altitude, but high intensity workouts

(above lactate threshold) are done at a lower altitude. In a pioneering study by Levine and Stray-Gundersen (1997), runners who utilized the LHTL model saw improved performance in in a 5,000 meter time trial post altitude training, while runners in the LHTH model did not. A subsequent study by the same laboratory revealed that in order to maximize the hematological response as well as gain performance benefits post altitude training, the optimal elevation to live is between 2,000 and 2,500 meters (Chapman, Karlsen, et al., 2014). Additionally, utilizing an elevation of 1250 meters during the "train low" portion of the model for high intensity workouts appears to be low enough to elicit sufficient oxygen flux necessary for beneficial neuromuscular and metabolic adaptations.

The length of time to stay at altitude and when to return to sea level completion are also important factors to consider when attempting to maximize improvements in performance. The main element involved in the determining the length of stay is the time course of erythropoiesis. Regardless of the type of hypoxia (natural or simulated), there are significant increases in red cell mass (4.3%) after three weeks at altitude, with an additional week of stay (a total of 4 weeks) creating even further increases in the amount of red cell mass gain (7.1-7.9%). In fact, the latter increase is comparable to increases in red cell mass with low dose exogenous EPO injection (8.7%). (Wilber et al., 2007) Therefore, it is strongly recommended to stay at altitude for a minimum of four weeks.

The main reason to partake in altitude training is to improve sea level performance. As such, correctly timing the return to sea level competition after a stay at altitude is vital. However, there are few empirical data to show when the best time to compete may be. Rather, much of what is recommended comes from coaches and/or

athletes and is based on anecdotal evidence. These recommendations generally suggest a period of 12-21 days of sea level only training before competition (Chapman et al., 2014). A number of factors, including the time course of the decline in hematological and ventilatory adaptations, are important to consider when determining this 'window of opportunity'. While hypoxic exposure causes increases in EPO levels above baseline, it is possible for EPO levels to fall *below* baseline upon the return to sea level from altitude. This fall in EPO can cause hemolysis of mature red blood cells, lowering the oxygen carrying capacity of the blood (Rice et al., 2001). The exact time course of this neocytolysis is unknown, but is suggested to occur within the first week back at sea level. Thus, it may be beneficial for athletes to compete sooner rather than later, before a drop in RBC mass occurs. Conversely, the increase in $\dot{V}_E$ at submaximal exercising workloads seen in altitude-acclimatized athletes persists during the return to sea level. This increase in $\dot{V}_E$ can cause increases in the oxygen cost and work of breathing, both of which can hinder performance. In this case, it may be beneficial for athletes to wait to compete until $\dot{V}_E$ returns to pre-altitude training levels. Ultimately, the optimal time for return to competition may depend on individual responses to altitude deacclimatization.

Taken together, best practice guidelines for the optimal response to altitude training include utilizing the LHTL model where living altitude is between 2000-2500 meters and training altitude is $\leq$ 1250 meters, staying at altitude for a minimum of four weeks, and timing the return to sea level competition based on hematological and ventilatory deacclimatization responses.

Ventilation

Ventilation, the movement of air between the environment and the pulmonary system via inhalation and exhalation, serves four specific purposes: 1) the exchange of oxygen, 2) the exchange of carbon dioxide, 3) the control of blood pH, and 4) oral communication (Brooks, Fahey, White, & others, 1996). Ventilation is tightly regulated by the pontomedullary region of the central nervous system through the integration of feed forward (output) and feedback (input) influences (Figure 1).

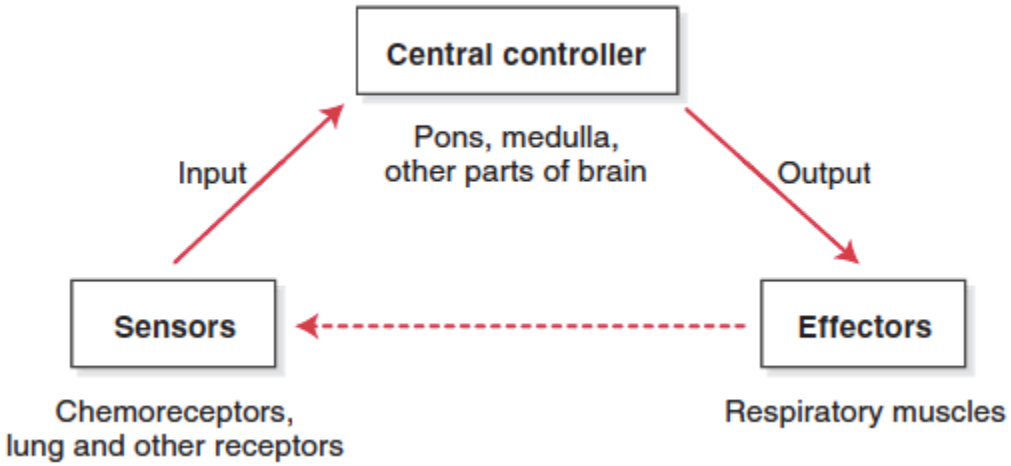

Figure 1. Basic elements of the respiratory control system (West, 2012).

Mechanics and Control of Ventilation

The pontomedullary region, or "central controller", sends output to the ventilatory musculature through the phrenic and intercostal nerves in order to achieve inspiration and expiration. Inspiration is largely achieved through contraction of the diaphragm, where increases in the volume of the thorax result in a decrease in intrapulmonary pressure that draws atmospheric air into the lung. At rest, expiration is passively achieved as the diaphragm relaxes, and the lung, due to its elastic properties, recoils and returns to

preinspiratory volumes. However, during exercise expiration becomes a more active process as the contractions of the internal intercostals force the ribs down, and the abdominal muscles force the diaphragm upward into the thorax. This transient decrease in thorax volume causes increases in intrapulmonary pressure above atmospheric pressure, driving air out of the lungs.

The increases in muscle involvement during exercise can produce substantial increases in minute ventilation ($\dot{V}_E$). These increases in bulk airflow are caused by increases in tidal volume (V_T), increases in the frequency of breaths per minute (f_B), or by some combination of both (Figure 2). During progressive exercise, the rise in $\dot{V}_E$ at moderate intensities is predominately due to expansions in V_T, with only modest increases in f_B. The increase in V_T is advantageous because it minimizes dead space ventilation and maximizes effective alveolar ventilation. V_T increases also cause reductions in end expiratory lung volume (EELV) below functional residual capacity (FRC), which can help minimize the elastic work of breathing (WOB) and allow for the build up of elastic energy that can be used on the subsequent inspiration. During higher intensity exercise V_T will begin to plateau and further rises in $\dot{V}_E$ are due to continual increases in f_B. The increases in f_B are achieved through reductions in both inspiratory (T_I) and expiratory (T_E) time, with a greater proportional decrease in T_E than T_I relative to total breath time (T_{TOT}).

The increases in $\dot{V}_E$ during exercise are accompanied by increases in inspiratory and expiratory flow rates. If higher flow rates exist, yet airway caliber is unchanged, an increase in airflow resistance, and ultimately WOB can occur. Fortuitously, both the extrathoracic and intrathoracic airways can be altered such that resistance is maintained,

or even lowered during exercise. The main change in the extrathoracic airways, which consist of the upper airways (nasal, pharyngeal, and laryngeal airways), is a shift from the higher resistance nasal pathway to the lower resistance oral pathway. Intrathoracic airway caliber is controlled in part by smooth muscle, and can be increased (bronchodilation) during exercise by a reduction in cholinergic tone and/or an increase in epinephrine binding to B_2 receptors.

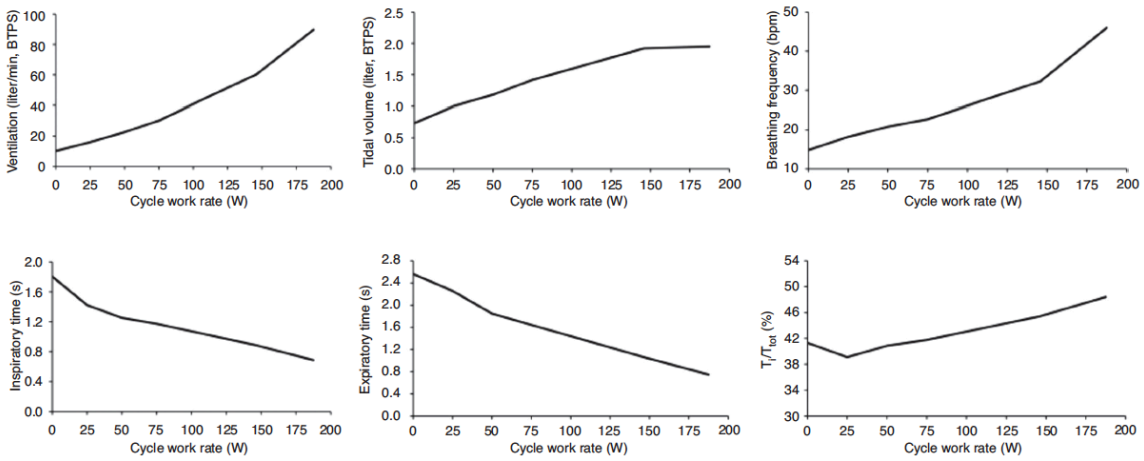

Figure 2. Ventilatory responses to progressive increases in cycling work rate (Scheel & Romer, 2012).

The precise adjustments to ventilation during exercise are of crucial importance, however the current understanding of the *control* of these adjustments is incomplete. Nevertheless, feed forward and feedback influences are two general categories largely agreed upon (Scheel & Romer, 2012). While direct evidence of a feed forward signal in humans is still not available, the idea of a central controller has been around for over a century (Krogh & Lindhard, 1913). This supposition is due to the almost immediate ventilatory responses to exercise that would make an initial non-neural influence

unlikely. Indirect evidence for feed forward influence has been observed using curare to partially blockade the neuromuscular junction in exercising subjects. Both Asmussen et al. (1965) and Galbo et al. (1987) observed higher ventilation at given oxygen uptakes during curarization, suggesting that activity in a "central command" center plays a role in the control of ventilation. Experimental animal studies have shown that ventilatory responses in both brain-intact and decorticate cats begin to develop prior to the onset of spontaneous or stimulated locomotion, suggesting that peripheral feedback mechanisms are not necessarily needed for a response (Eldridge, Millhorn, Killey, & Waldrop, 1985; Eldridge, Millhorn, & Waldrop, 1981). Taken together, the available evidence points toward the presence of a feed forward central controller. Still, it is doubtful that this control exists in complete isolation from any feedback influences.

One likely feedback mechanism adjusting ventilatory responses is linked to locomotor activity. Both group III and group IV muscle afferents are sensitive to changes in mechanical and chemical conditions associated with muscle contraction during exercise, and provide neural input to the central nervous system to mediate ventilatory responses. To assess these nerve fibers contribution to ventilatory control, a sophisticated study by Amann et al. (2010) used lumbar intrathecal fentanyl injections to impair central projection of spinal opioid receptor-sensitive muscle afferents. During cycling exercise, there was a substantial decrease in ventilation compared to placebo, caused by reductions in f_B and in the ventilatory equivalent for CO_2. These findings demonstrate the contribution of muscle afferent feedback to the ventilatory response to rhythmic exercise. Another feedback influence is the arterial partial pressure of oxygen and carbon dioxide. Both central and peripheral chemoreceptors sense deviations in the

chemical composition of the blood and provide input to the central control, which generates the appropriate ventilatory response. Figure 3 provides an overview of the influences to and from the respiratory control center.

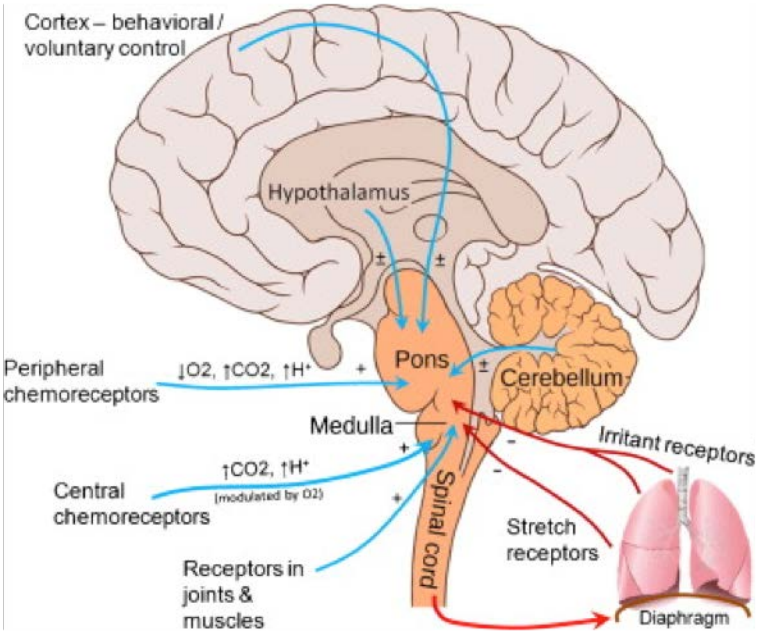

Figure 3. Overview of inputs to, and outputs from, the respiratory control center (Carroll & Agarwal, 2010).

Locomotion

Mechanics of Locomotion

Locomotion is the act of self-powered motion that humans, as well as other organisms, use to change their location. In terrestrial locomotion the speed at which a change in location occurs is dependent on two factors: the distance of each step (or stride) and the number of steps (or strides) taken. The step distance is measured from the ground contact of one foot (footstrike) to the ground contact of the opposite foot

(ipsilateral footstrike to contralateral footstrike). The stride distance is measured from the ground contact of one foot to the next contact of that same foot (ipsilateral footstrike to ipsilateral footstrike). Walking and running are the two most common forms of human locomotion (i.e. gaits), but have dramatically different phases and mechanics (Fig. 4). During walking the body vaults up and over each stiff leg in an arc, similar to an inverted pendulum. During running, however, as the foot strikes the ground, mechanical energy is

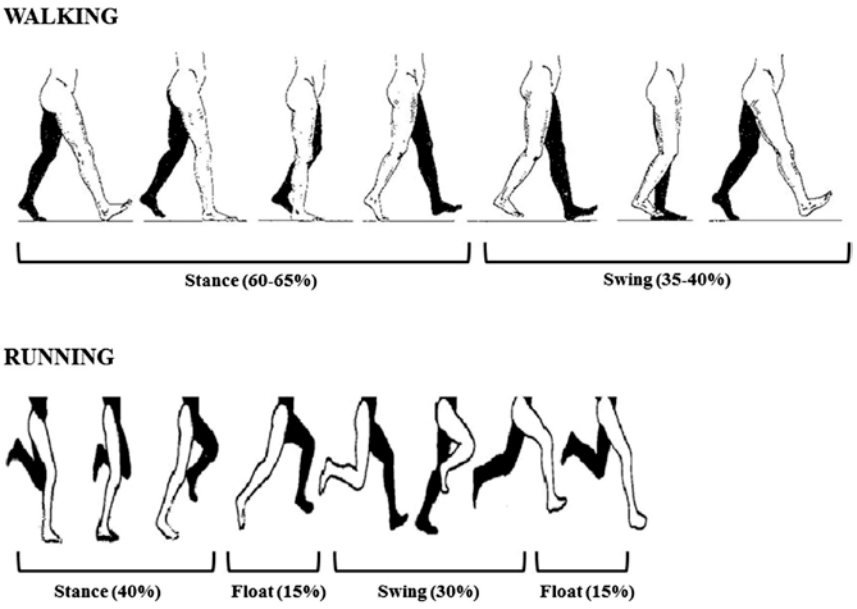

Figure 4. Relative contributions of phases during walking and running gait cycles (Stickford & Stickford, 2014).

momentarily stored in the eccentrically contracting muscles. This energy is subsequently released during the propulsive portion of the stance phase for concentric contraction and forward propulsion. Thus, running is analogous to bouncing on a pogo stick, and can be represented as a spring-mass model (Cappellini, Ivanenko, Poppele, & Lacquaniti, 2006;Dalleau, Belli, Bourdin, & Lacour, 1998) (Fig. 5).

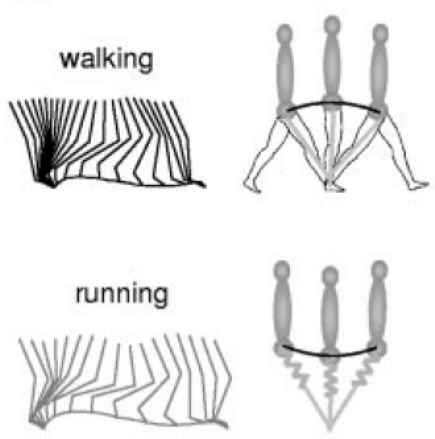

Figure 5. A representation of walking by "vaulting" and running by "bouncing". Adapted from (Cappellini et al., 2006).

Energetic Cost of Locomotion

Humans tend to change gait modes as locomotion speed increase in order to minimize metabolic energy costs. In other words, a transition in gait mode occurs when the metabolic energetic cost for walking at a particular speed becomes greater than the cost of running at that same speed. The metabolic energy demand for any given submaximal velocity is known as the economy of locomotion. Central to this study is running economy (RE), which can be defined as the energy demand for a given velocity of submaximal running, and is determined by measuring steady state oxygen uptake.

A number of physiological and biomechanical factors appear to impact running economy. Thomas et al. (1999) found that among core temperature, heart rate, ventilation, and changes in lactate concentration during a simulated 5k race, only increases in ventilation were significantly correlated with a worse RE ($r=0.64$, $p < 0.05$). Cavanagh and Williams (1981) used multiple regression in an attempt to identify which biomechanical factors influence RE, concluding that lower vertical ground reaction

forces, greater shank, trunk, and plantar flexion angles, and minimal knee velocity all contribute to better RE. Additionally, increased stiffness of the lower extremity seems to allow for greater utilization of the stored elastic energy that occurs during the loading portion of the stance phase, thus lowering oxygen cost and improving RE (Butler, Crowell, & Davis, 2003). Finally, it has been shown that trained runners self select a stride length that minimizes oxygen uptake, with either shorter or longer stride lengths causing increases in oxygen uptake of 2.6 and 3.4 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively (Hunter & Smith, 2007).

Locomotor-Respiratory Coupling

While research examining ventilation or locomotion exclusively has provided insight into the how and why of each, it is critical to recognize that these two systems function in an integrative fashion during dynamic exercise. Indeed, evidence exists to show that breathing and limb patterns are not isolated actions, but rather impact each other in a particular manner. The coordination of these rhythmic actions is known as entrainment, or locomotor-respiratory coupling (LRC), and has been observed across many species, including humans. Early observational research by Bannister et al. (1954) discovered that runners' stride rate was a multiple of their breathing frequency. Further support for LRC was given by Bechbache et al. (1977), who had subjects exercise at two workloads on a cycle ergometer and two speeds on a treadmill (one walking speed and one running speed). Using a cross-correlation approach, subjects were classified as having either strong, weak, or no LRC. The percent of subjects that displayed at least some LRC (i.e. either strong or weak) varied across the different protocols. Interestingly,

more subjects entrained during treadmill running than cycling (80% and 20%, respectively).

However, not all investigations have shown the existence of LRC. While examining the effects of added dead space on pulmonary ventilation during cycling exercise, Kelman and Watson (1973) recorded breathing frequencies at constant pedaling rates. They found no evidence that breathing frequency was related to submultiples of the pedaling rate, and concluded that the subjects' breathing patterns were determined mainly by their respiratory needs. Additionally, Kay et al. (1975) compared ventilatory factors to limb movements during both cycling and treadmill walking. Neither the stride rate nor the pedal rate was found to have any influence on respiratory rate or breathing pattern. It was concluded that the selection of breathing patterns is unrelated to the type of exercise stimulus, but instead closely geared to meet the body's metabolic needs. Ensuing research has continued to both verify and contest the existence of LRC in humans.

These varied findings are most likely due to differences in a) training status, b) exercise intensity, and c) exercise mode. Highly trained individuals tend to display a greater degree of LRC than those who are less trained or not trained at all, and trained runners also show the ability to couple within the first few strides of a run, whereas less experienced runners require a longer time before breathing and gait begin to couple. Bramble and Carrier (1983) noted that a continuum exists for the time to couple, with time to couple being inversely related to training status. Exercise intensity is also believed to be an element that contributes to LRC in humans, with a positive relationship among the degree of LRC and intensity or workload. Bernasconi et al. (1993) observed

increases in the degree of LRC in both triathletes and untrained individuals when running speed was increased from 50% to 80% of anaerobic threshold. Additionally, increasing cycling rates from 50 rpm to 70 rpm in untrained subjects increased the occurrence of LRC by 10% (Bechbache & Duffin, 1977). However, not all studies have observed this intensity dependent influence, as some show no effect of intensity on LRC during cycling (Jasinskas, Wilson, & Hoare, 1980; Paterson, Wood, Morton, & Henstridge, 1986). Finally, exercise mode is another determinant of LRC. Rowing, which presents prohibitive mechanical constraints due to the continual flexion and extension of the spine, requires a high degree of coupling in order to complete both tasks. Furthermore, these mechanics dictate that there are less coupling ratio options in rowing than in running or swimming. A comparison of LRC characteristics across different exercise modes is shown in Table 1.

Table 1. Locomotor-respiratory coupling characteristics in humans.

Mode of Locomotion	Common LRC Ratios	Reported Prevalence	Proposed Mechanisms
Walk	Variable	0-85%	Primarily neural
Run	3:2, 2:1, 5:2, 3:1, 4:1	43-80%	Primarily neural
Row	1:1, 2:1, 3:1	17-78%	Mechanical and neural
Cycle	2:1, 3:1	20-100%	Primarily neural
Swim	1:1, 2:1, 5:2 3:1, 4:1, 5:1	Nearly 100%	Mechanical, neural, and conscious control

Table adapted from (Stickford & Stickford, 2014).

Mechanisms of Locomotor-Respiratory Coupling

The underlying mechanisms of LRC are both complex and poorly understood, yet two broad areas of explanation exist: 1) biomechanical interactions between locomotion and ventilation, and 2) neural interactions between the control of locomotion and ventilation. Biomechanically, the movement of internal organs during locomotion may physically affect the movement of the diaphragm. Furthermore, the pressure and/or volume changes within the thoracic cavity as a result of ground contact, and possibly also from lumbosacral flexion and extension, may affect the time that inspiration and expiration occur. The mechanical restrictions to ventilation due to locomotion are likely a combination of both factors. However, research quantifying airflow changes during running found no appreciable mechanical effect on ventilation (Banzett, Mead, Reid, & Topulos, 1992). Thus, these factors are believed to have a negligible impact on ventilation, suggesting that LRC is predominately driven by neural factors.

There is an abrupt increase in ventilation at the onset of exercise, with the amount of the increase corresponding to the rate of movement. This relationship, as well as the immediacy with which coupling can occur, imply that central feed forward signals are responsible for LRC. Indeed, evidence exists for this mechanism, as Eldridge et al (1985) demonstrated that stimulating the subthalamic locomotor regions in paralyzed animals still results in increases in ventilation. In addition to the feed forward signal, peripheral afferent feedback signals from the exercising limbs, chest wall, and chemoreceptors all contribute to fluctuations in ventilation (Stickford & Stickford, 2014). In certain animal models when neural feedback from the periphery is blocked, but afferent feedback from the chest wall is allowed, LRC still occurs (Funk, Steeves, &

Milsom, 1992). Taken together, this evidence indicates an integrative response that incorporates an initial feed forward control of ventilation, with later afferent feedback providing a fine-tuning response.

Implications and Perturbations to Locomotor-Respiratory Coupling

The possibility exists that LRC is not only beneficial, but also required, for sustained aerobic activity among endothermic vertebrates (Bramble & Carrier, 1983). Yet, what exactly that benefit is, and why it might be a requirement, remains inconclusive. However, evidence suggests that an energetic and/or perceptual advantage to LRC exists. As demonstrated by numerous studies, LRC during cycling seems to lower metabolic energy expenditure. Villard et al. (2005) discovered that LRC became more stable as cycling exercise progressed, and was accompanied by reductions in $\dot{V}O_2$. Similarly, Garlando et al. (1985) found that greater coupling during cycling was associated with significantly lower oxygen uptake at a submaximal, 50% workload. One explanation for these decreases may be due to a more economical respiratory muscle component of oxygen uptake. Takano et al. found that within certain subjects, LRC caused decreases in respiratory muscle oxygen uptake ($\dot{V}O_{2RM}$). Consequently, at intensities associated with high ventilatory workloads, LRC may aid in decreasing the oxygen cost of performing such work.

The relationship concerning LRC and energetics among other modes of exercise is less clear. A study including untrained male rowers did not find any differences in oxygen uptake using three distinct breathing patterns, however the authors noted that any physiologic benefits of LRC might require months of training before they appear

(Maclennan, Silvestri, Ward, & Mahler, 1994). Likewise, LRC during walking does not appear to have an impact on oxygen uptake (Alphen & Duffin, 1994; Rabler & Kohl, 1996). Conversely, Bernasconi et al. (1993) observed that better running economies (i.e. lower oxygen uptake for a given pace) occurred during the highest degrees of LRC.

A further advantage of LRC could be more perceptual than physiological, such as decreases in breathing discomfort during exercise while coupling. In addition to decreases in $\dot{V}O_{2RM}$ during increased LRC, these increases also correspond to reductions in dyspnea (Takano & Deguchi, 1997). These perceptual benefits may be especially important for highly trained athletes, who "associate" during exercise and are very cognizant of changes in their own physiological variables such as breathing frequency or tidal volume (Morgan & Pollock, 1977).

Although there seem to be specific advantages of LRC, it is possible that any type of perturbation to LRC itself could negate these advantages. One possible disruption to LRC could be hypoxic induced increases in ventilation, resulting in changes to breathing frequency. Paterson et al. (1997) tested this hypothesis in both field and laboratory conditions at varying levels of elevation using a small cohort of five Nepalese porters and two Caucasian mountaineers. In both conditions, the incidence of LRC decreased linearly with increasing levels of hypoxia. The authors concluded that at a constant metabolic rate and stride frequency, the lower degree of LRC resulted primarily from increases in breathing frequency. However, it was noted that the occurrence of LRC varied considerably within and between subjects, possibly stemming from Nepalese porters being unaccustomed to running. Alternatively, Fabre et al. (2007) found no effects of hypoxia on LRC in rowers. While $\dot{V}_E$ and f_B increased as expected with

exposure to hypoxia, the rowers significantly increased their stroke rate, resulting in no change in the LRC ratio or degree of coupling. This result is most likely due to the mechanical constraints of rowing that make the maintenance of LRC a paramount task.

Conclusion

Although ventilation and locomotion are two independent, complex processes, there is strong evidence to suggest that there is a coordinated, and possibly required, link between the two systems. The underlying mechanisms that cause this coordination are still relatively unknown, though evidence points to an integrated neural response from afferent feedback and central command output. Probable benefits of LRC are minimized energetic cost of locomotion and respiratory muscle work, mechanical assistance to locomotion and ventilation, and decreased perception of ventilatory effort. However, continued research is needed to elucidate any effect disruptions such as hypoxia have on these benefits. If disruptions to LRC are caused by hypoxia, they may have a significant effect on distance runners who sojourn to altitude in an attempt to take advantage of both hematological and training adaptations.

CHAPTER 3

EXPERIMENTAL PROCEDURES

Subjects. Subjects included trained male runners who were recruited through the IU-Bloomington campus, the IU cross country/track teams, and the local running community. Inclusion criteria were a) 18-35 years of age, b) non-smoking, c) $\dot{V}O_{2max} \geq$ 60 $ml \cdot kg^{-1} \cdot min^{-1}$ {normoxia}, d) normal pulmonary function as defined by the American Thoracic Society, and e) no injury or illness within three weeks prior to participation in the study. Subjects were tested at the same time of day for each of the visits, and were instructed to arrive at the laboratory having fasted for the previous 5 hours, having abstained from caffeine for the previous 8 hours, and having abstained from alcohol consumption or strenuous exercise in the previous 24 hours. Subjects provided written informed consent before testing, and the Institutional Review Board of Indiana University approved all protocols and procedures used in testing.

Study Design. Qualifying subjects completed a two visit testing protocol, with visits separated by at least 48 hours and a maximum of 14 days. Each visit consisted of pulmonary function tests followed by a RE/LRC treadmill test in normoxia or hypoxia (FIO_2 = 15.8%; equivalent to 2500m / 8000ft) followed immediately by a ramp to volitional exhaustion to obtain maximal oxygen uptake ($\dot{V}O_{2max}$). The order of the inspired gas conditions was randomized and counterbalanced, and subjects were blinded to the inspirate. During RE/LRC tests, ventilation, pulmonary gas exchange, and heart

rate were continuously monitored. Ratings of perceived exertion (RPE) and dyspnea were also collected throughout the treadmill tests.

Pulmonary Function. Resting pulmonary function was assessed using inspired and expired pneumotachographs (Series 3813/4813, Hans Rudolph, Shawnee, KS) and done in accordance with standard ATS procedures (American Thoracic Society, 1995). These tests included the measurement of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF). Subjects were familiarized with the performance of FVC maneuvers, and were provided with verbal and visual feedback. Subjects performed three to five maximal maneuvers consisting of a maximal inspiration to total lung capacity (TLC) followed by a maximal expiration to residual lung volume (RV). Subjects were given verbal encouragement during each maneuver to ensure they reached residual volume, and were provided feedback afterward in order to help them grasp the concept of the varying efforts. The same procedure was performed post-exercise, with the largest FVC and FEV_1 chosen as a representation of the subject's pulmonary function.

Treadmill Tests. Prior to the start of the treadmill test subjects were fitted to an oro-nasal rubber facemask (7540, Hans Rudolph, Shawnee, Kansas), and a heart rate monitor (FT1, Polar Electro Inc., Lake Success, NY) to be worn during exercise. Additionally, flexible and lightweight plastic event switches were adhered to the heel of each foot inside the shoe to determine the timing of foot strikes while running. Once fitted with the necessary equipment, each test will began with five minutes of standing in

order to collect resting measures. Subjects then ran for five minutes at each of three constant submaximal speeds of 12.9, 14.3, and 16.1 km/hr (7:30, 6:45, and 6:00 min/mile) at 0% grade, with four minutes standing rest between speeds. After the fifth minute of the 16.1 km/hr speed, the incline was raised to 2% for the next two minutes, and continued to increase 2% every two minutes thereafter until volitional fatigue. Measurements of RE and LRC were taken during the fourth minute of each speed (3:00-4:00), while RPE and DYS measures were taken during the first 30 seconds of the final minute at each speed (4:00-4:30) such that any disruption in stride or breathing patterns due to the rating task were not included in the LRC analysis. Dyspnea and RPE were assessed again at the conclusion of the test, followed by completion of an associate/dissociation questionnaire.

Metabolic/Ventilatory Measures. Metabolic and ventilatory variables were continuously measured during rest and exercise via open circuit, indirect calorimetry. Subjects wore a facemask (7450, Hans Rudolph, Shawnee, KS) and breathed through a low resistance, two-way non-breathing valve (2700, Hans Rudolph, Shawnee, KS) from which expired gases were collected in a 5-liter mixing chamber. Dried samples from this mixing chamber, sampled at 300 ml min^{-1}, were used to determine fractional concentrations of O_2 and CO_2 by separate O_2 and CO_2 gas analyzers (S-3A /CD-3A, Ametek Thermox Instruments, Pittsburgh, PA). Analyzers were calibrated pre-test with known gas concentrations within the physiological range, and were checked both midway and post-test to correct for any drift. The inspired pneuomotachograph was used to measure minute ventilation, and was calibrated pre-test using a 3-liter syringe. Heart rate

was measured using a telemetry transmitter (FT7, Polar Electro Inc., Lake Success, NY) placed across the subject's chest. Oxyhemoglobin saturation was measured via pulse oximetry (OxiMax N-600x, Nellcor, Minneapolis, MN). All variables were sampled at 50 Hz using a data acquisition system (DASYLab, National Instruments, Norton, MA), with values being averaged over each minute of exercise. $\dot{V}O_{2max}$ was determined as the highest recorded $\dot{V}O_2$ over 60s when the subject met two of the three following criteria: 1) a heart rate ≥ 90% of age predicted maximum (220-age), 2) a respiratory exchange ratio of ≥ 1.10, and 3) a plateau (≤150 ml increase) in $\dot{V}O_2$ with an increase in workload.

Running Economy. Running economy was determined by measuring oxygen consumption at three constant submaximal speeds at 0% grade on a motorized treadmill (Model 18-72, Quinton, Bothell, WA). Treadmill speeds of 12.9, 14.3, and 16.1 km/hr (7:30, 6:45, and 6:00 min/mile) were verified through the use of a laser tachometer (Model: DT-2234C, Mastech, San Jose, CA) and compared to RPM vs. speed charts calculated specifically for the length of the treadmill belt. Running economy was calculated as a) the steady state $\dot{V}O_2$ (ml kg^{-1} min^{-1}) during the fourth minute of each submaximal stage, and b) the slope of the regression line relating steady state $\dot{V}O_2$ (ml kg^{-1} min^{-1}) to running speed (m min^{-1}). Steady state was defined as a plateau (≤150 ml increase) in $\dot{V}O_2$ from the previous minute.

Locomotor-Respiratory Coupling. To determine the timing of foot strikes throughout the treadmill tests, flexible and lightweight plastic event switches (MA-153, Motion Lab Systems, Inc., Baton Rouge, LA) were taped inside the shoe to the heel of

each foot (approximately 4 cm distally from the proximal end of the calcaneus) or the forefoot of each foot (approximately at the distal end of the fifth metatarsal), and connected by a BNC cable to the data acquisition system. The switch was positioned so that it was located at the point of initial ground contact. The timing of inspirations and expirations was determined via pneumotachographs that continuously measured flow rates. The data acquisition system was triggered to start kinematic and ventilatory data collection simultaneously to allow post-hoc analysis, using only the fourth minute of each stage (the same minute as RE), and the minute during which $\dot{V}O_{2max}$ was achieved, for LRC analysis. LRC was determined through two measures, the *degree of LRC* (i.e. the percent of breaths that occur at a distinct step-to-breath ratio), *and phase coupling* (i.e. the relative coordination of the two rhythms, or at which point one rhythm occurs within the other).

Methods to determine the above measures followed previously used procedures (Bernasconi & Kohl, 1993; Berry, Dunn, Pittman, Kerr, & Adair, 1996; Paterson et al., 1987). An in-house, custom software program was used to determine stride and breathing frequency over the measurement periods. To determine the LRC ratio (integer step-to-breath ratio), stride frequency was divided by breathing frequency for each subject and speed. Limits of ± 0.05 of the stride frequency/breathing frequency quotient were used as boundaries for determination of the ratio (e.g. a quotient between 1.95 and 2.05 would produce a ratio of 2:1), with additional limitation of neither integer being greater than 5.

Degree of LRC was determined by first ascertaining the time points of inspiration, expiration, and foot strike. Each step and stride cycle was divided into ten equal parts,

and the decile in which each inspiration or expiration occurs was be recorded. Subsequently, the number of inspirations or expirations beginning in the same decile of the step (or stride) cycle was divided by the total number of breaths to allow for expression of the degree of LRC as a percentage. The highest percentage out of inspirations, expirations, strides, and steps was used as the degree of LRC for that time period. When coupling appeared to switch between two distinct deciles (determined as two, and *only* two, deciles encompassing more breaths than expected to occur by chance; binomial probability < 0.05), the percentages were summed.

Hypoxic delivery. Three 1000-liter weather balloons were placed in-line on the inspired breathing line, distal to the inspired pneomotachograph. The balloons were filled to capacity prior to subject arrival with a gas composition of 15.8% O_2 and balance N_2 using a nitrogen generator (CAT 12, Colorado Altitude Training, Boulder, CO). The balloons were filled during both test days (NORM and HYP) in order to blind subjects to the inspirate, with the balloon valves staying closed during NORM tests such that the subjects breathed only room air, albeit through the same length of tubing. A secondary O_2 gas analyzer was used to determine the fractional O_2 concentrations of inspired air in real time, and this value was used continuously for calculation of oxygen uptake.

Data Analysis. Findings were analyzed using SPSS statistical software (Version 24, IBM, Armonk, NY). Descriptive statistics were used to describe group characteristics, with values presented as mean ± SE. *A priori* power analysis (G*Power 3.1, Franz Faul, Germany) showed that a sample size of 16 would show detection of

meaningful statistical differences. The data were assessed for normality using the Shapiro-Wilk test and for sphericity using the Mauchly's test. A 2 x 4 condition (inspirate) by speed repeated measures ANOVA, with *a priori t* tests and a *post hoc* Tukey's HSD for simple main effects, was used to test for differences in ventilatory, metabolic, footstrike, LRC, RPE, dyspnea, and association/dissociation measures across speeds and between conditions. The alpha for statistical significance for all comparisons was set at $p < 0.05$, with a Bonferroni adjustment made for multiple comparisons.

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CHAPTERS 4 & 5

MANUSCRIPT

Locomotor-respiratory coupling is maintained in hypoxia in trained distance runners

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Abstract

To determine if acute exposure to normobaric hypoxia alters locomotor-respiratory coupling (LRC) patterns typically observed in trained runners, 13 trained male distance runners performed a running economy (RE) and maximal oxygen uptake ($\dot{V}O_{2max}$) test in normoxia (NORM) and in hypoxia (HYP) (FIO_2 = 15.8%; ~ 2500m / 8000ft) on separate days. RE and LRC measures were taken during the fourth minute of each submaximal speed (12.9, 14.3, and 16.1 km hr^{-1}), while ratings of perceived exertion (RPE) and dyspnea (DYS) were taken during the first 15 seconds of the final minute at each speed, and again at the conclusion of the maximal test. Stride frequency-to-breathing frequency quotients were significantly lower at each submaximal speed in HYP (*12.9 km* hr^{-1}: 2.91 ± 0.20 vs. 2.45 ± 0.17, *14.3 km* hr^{-1}: 2.53 ± 0.17 vs. 2.21 ± 0.14, *16.1 km* hr^{-1}: 2.22 ± 0.14 vs. 1.95 ± 0.09; $p < 0.05$) due to increases in breathing frequency while maintaining stride frequency. Compared with NORM, the degree of LRC (range: 36 - 99%) was not significantly different at any of the three common submaximal speeds with exposure to HYP. However, the degree of LRC was increased at $\dot{V}O_{2max}$ (43.8 ± 3.4% vs. 57.1 ± 3.8%; $p < 0.05$). Breathing frequency (breaths min^{-1}) was significantly increased at each submaximal speed in HYP compared to NORM (*12.9 km* hr^{-1}: 30.3 ± 1.9 vs. 35.9 ± 2.2; *14.3 km* hr^{-1}: 34.8 ± 2.0 vs. 39.8 ± 2.2; *16.1 km* hr^{-1}: 40.4 ± 2.4 vs. 45.2 ± 1.9; all speeds $p < 0.05$), but was not significantly different at $\dot{V}O_{2max}$. RE and RPE were not significantly different at any speed. DYS was only significantly different between NORM and HYP at 16.1 km hr^{-1} ($p < 0.05$). In conclusion, trained distance runners are able to maintain LRC in hypoxia, even when breathing frequency is increased at any submaximal pace. Within this unique population, years of training may enhance and optimize the ability to make

adjustments to maintain LRC in order to minimize metabolic costs. However, there may be individual differences to LRC that could affect performance or the response to training at altitude.

Introduction

Endurance athletes commonly use altitude training as a means to improve sea level performance. However, even when following best practice guidelines, considerable variation in physiological responses to altitude and subsequent performance exists (Chapman et al., 1998). Because the response to altitude training depends on both physiological acclimatization and training adaptations, each represent possible areas of explanation for the variation. Of the number of factors that can affect the ability to complete endurance exercise training at altitude, one of the most immediate responses to acute altitude exposure is an increase in ventilation at any submaximal exercising workload. The ventilatory response to exercise is unique in having both physiological outcomes (e.g. defending arterial oxyhemoglobin saturation, but with a metabolic cost of increased work of breathing) and psychological outcomes (e.g. dyspnea). As a result, ventilatory control during exercise at altitude can have a strong influence on workload selection, perception of effort, and ultimately the training response at altitude. Interestingly, one factor involved in ventilatory control is locomotor-respiratory coupling (LRC). Defined as a stable frequency and phase locking between pulmonary respiration and locomotion, any deviation to these LRC components could disrupt the athlete's training response, and therefore ultimately attenuate performance gains.

Although the reasons for the existence of LRC are not fully understood, it is believed to aid in decreasing the energetic cost of locomotion. Higher and more stable degrees of LRC during cycling and running are linked to decreases in oxygen consumption (Bernasconi & Kohl, 1993; Garlando et al., 1985; Hoffmann et al., 2012; Villard et al., 2005). Therefore, any perturbation to the components of LRC such as

hypoxia-induced increases in breathing frequency could have negative energetic consequences. Higher degrees of LRC also decrease the perception of ventilatory effort during exercise (Takano & Deguchi, 1997). Thus, there may be perceptual as well as physiological benefits to increasing the degree of LRC. This may be especially true for trained athletes, who "associate" during exercise, and are very cognizant of changes in their own physiological variables such as breathing frequency or tidal volume (Morgan & Pollock, 1977).

Environments that alter breathing patterns, such as hypoxia, may influence LRC. However, evidence of changes to LRC in hypoxia is inconclusive. Patterson et al. (1987) found decreases in the degree of LRC in runners exercising in hypoxia when compared to normoxia, while Fabre et al. (Fabre et al., 2007) and Seebauer et al. (Seebauer et al., 2003) showed no change to LRC in rowers and cyclists, respectively. Moreover, the consequences of altering LRC in hypoxia, such as changes to running economy (RE) and perceptions of ventilatory effort, remain to be elucidated. Although some studies have shown no alterations in RE during acute hypoxic exposure, none have quantified RE and LRC simultaneously in hypoxia (Dill, Myhre, Phillips, & Brown, 1966; Hogan, Cox, & Welch, 1983; Hughes, Clode, Edwards, Goodwin, & Jones, 1968).

Therefore, the purpose of this study was to determine if acute exposure to hypoxia alters LRC patterns typically observed in trained runners, and investigate the effects these possible LRC alterations have on RE and perceptions of ventilatory effort. Our primary hypothesis was that when compared to normoxia, hypoxic exercise at common submaximal speeds would reduce the degree of LRC due to increased breathing frequency at a stable stride frequency. We also hypothesized that due to reductions in the

degree of LRC, subjects would have worse running economy (i.e. increased oxygen uptake), and increased dyspnea.

Methods

Subjects

Trained male distance runners were recruited for this study. Inclusion criteria were a) 18-35 years of age, b) non-smoking, c) $\dot{V}O_{2max} \geq 60$ ml kg^{-1} min^{-1} in normoxia, and d) normal pulmonary function as defined by the American Thoracic Society (American Thoracic Society, 1995). Subjects were tested at the same time of day for each of the visits, and were instructed to arrive at the laboratory having fasted for the previous 5 hours, having abstained from caffeine for the previous 8 hours, and having abstained from alcohol consumption or strenuous exercise in the previous 24 hours. All subjects provided written informed consent to protocols that were approved by the Institutional Review Board of Indiana University.

Study Design

Qualified subjects completed two visits to the laboratory, with visits separated by at least 48 hours. Each visit consisted of pulmonary function tests followed by a treadmill test to determine RE and LRC. The treadmill test occurred in normoxia (NORM) or hypoxia (HYP; FIO_2 = 15.8%; equivalent to ~2400m / 8000ft) and was followed immediately by a ramp to volitional exhaustion to obtain maximal oxygen uptake ($\dot{V}O_{2max}$). The order of the inspired gas conditions was randomized and counterbalanced, and subjects were blinded to the inspirate.

Protocol

Upon arrival subjects completed physical activity readiness and running history questionnaires followed by anthropometric measurements. Subjects were then instrumented with event switches that were taped to each foot and connected to flexible, lightweight extension cables adhered to the lateral side of each leg and hip. Subjects were subsequently shown and explained the Borg rating of perceived exertion (RPE) and dyspnea (DYS) scales, and performed pulmonary function tests (PFT). The RE/LRC treadmill test began with three to five minutes of quiet standing to collect resting ventilatory and metabolic data. Following rest, subjects ran for five minutes at each of three constant submaximal speeds of 12.9, 14.3, and 16.1 km hr^{-1} (7:30, 6:45, and 6:00 min min^{-1}) at 0% grade on a motorized treadmill (Model 18-72, Quinton, Bothell, WA) with four minutes standing rest between speeds. Treadmill speed was verified through the use of a laser tachometer (Model: DT-2234C, Mastech, San Jose, CA). After the fifth minute of running at the 16.1 km hr^{-1} speed, the incline of the treadmill was raised to 2% for the next two minutes, and continued to increase 2% every two minutes thereafter until volitional fatigue. Measurements of RE and LRC were taken during the fourth minute of each speed (3:00-4:00), while RPE and DYS measures were taken during the first 30 seconds of the final minute at each speed (4:00-4:30) such that any disruption in stride or breathing patterns due to the rating task were not included in the LRC analysis. DYS and RPE were assessed again at the conclusion of the test, followed by completion of an attentional focus questionnaire to determine association (ASSOC) and dissociation

(DISSOC) scores (Brewer, Van Raalte, & Linder, 1996). RPE and DYS were assessed using the original and modified Borg scales, respectively (Borg, 1982).

Pulmonary function

Resting pulmonary function was assessed using inspired and expired pneumotachographs (Series 3813/4813, Hans Rudolph, Shawnee, KS) and done in accordance with standard ATS procedures (American Thoracic Society, 1995). Subjects were familiarized with the performance of forced vital capacity (FVC) maneuvers, and were provided with verbal and visual feedback. Subjects performed three to five maximal maneuvers consisting of a maximal inspiration to total lung capacity (TLC) followed by a maximal expiration to residual lung volume (RV). Subjects were given verbal encouragement during each maneuver to ensure they reached residual volume. The same procedure was performed post-exercise, with the largest FVC and FEV_1 chosen as a representation of the subject's pulmonary function.

Metabolic parameters

Metabolic and ventilatory variables were continuously measured during rest and exercise via open circuit, indirect calorimetry. Subjects wore a facemask (7450, Hans Rudolph, Shawnee, KS) and breathed through a low resistance, two-way non-breathing valve (2700, Hans Rudolph, Shawnee, KS) from which expired gases were collected in a 5-liter mixing chamber. Dried samples from this mixing chamber, sampled at 300 ml min^{-1}, were used to determine fractional concentrations of O_2 and CO_2 by separate O_2 and CO_2 gas analyzers (S-3A /CD-3A, Ametek Thermox Instruments, Pittsburgh, PA).

Analyzers were calibrated pre-test with known gas concentrations within the physiological range, and were checked both midway and post-test to correct for any drift. The previously mentioned inspired pneuomotachograph was used to measure minute ventilation, and was calibrated pre-test using a 3-liter syringe. Heart rate was measured using a telemetry transmitter (FT7, Polar Electro Inc., Lake Success, NY) placed across the subject's chest. Oxyhemoglobin saturation was measured via pulse oximetry (OxiMax N-600x, Nellcor, Minneapolis, MN). All dependent variables were sampled at 50 Hz using a data acquisition system (DASYLab, National Instruments, Norton, MA), with values being averaged over each minute of exercise. RE was calculated as a) the steady state $\dot{V}O_2$ (ml kg^{-1} min^{-1}) during the fourth minute of each submaximal stage, and b) the slope of the regression line relating steady state $\dot{V}O_2$ (ml kg^{-1} min^{-1}) to running speed (km hr^{-1}). Steady state was defined as a plateau (≤150 ml increase) in $\dot{V}O_2$ from the previous minute. $\dot{V}O_{2max}$ was determined as the highest recorded $\dot{V}O_2$ over 60s when the subject met two of the three following criteria: 1) a heart rate ≥ 90% of age predicted maximum (220-age), 2) a respiratory exchange ratio of ≥ 1.10, and 3) a plateau (≤150 ml increase) in $\dot{V}O_2$ with an increase in workload.

Locomotor-respiratory coupling

Locomotor-respiratory coupling was determined as described previously in our laboratory (Stickford et al., 2015). Briefly, to determine the timing of foot strikes during the treadmill tests, flexible and lightweight plastic event switches (MA-153, Motion Lab Systems, Inc., Baton Rouge, LA) were taped inside the shoe to either the heel or fifth metatarsal of each foot depending on the subject's habitual foot strike pattern (heel:

approximately 4 cm distally from the proximal end of the calcaneus; forefoot: approximately at the distal end of the fifth metatarsal). The switch was positioned so that it was located at the point of initial ground contact, and was connected to the data acquisition system by a BNC cable. The timing of inspirations and expirations was determined via pneumotachographs that continuously measured flow rates. The data acquisition system was triggered to start kinematic and ventilatory data collection simultaneously to allow post-hoc analysis, using only the fourth minute of each stage (the same minute as RE), and the minute during which $\dot{V}O_{2max}$ was achieved for LRC analysis.

An in-house software program allowed for calculation of the stride (i.e. left-to-left and right-to-right footstrike), step (i.e. left-to-right and right-to-left footstrike), and breathing frequencies, as well as time points of footstrike, inspiration, and expiration. Following an originally described protocol (Bernasconi & Kohl, 1993) that has previously been utilized in our laboratory (Stickford et al., 2015), each stride and step cycle was divided into ten equal parts, and the decile in which each inspiration or expiration occurred was determined. Subsequently, the highest number of inspirations or expirations beginning in the same decile of the step cycle was divided by the total number of breaths to allow for expression of the degree of LRC as a percentage. The highest percentage out of inspirations, expirations, strides, and steps was used as the degree of LRC for that time period. The percentages were summed when coupling appeared to switch between two distinct deciles (determined as two, and *only* two, deciles encompassing more breaths than expected to occur by chance; binomial probability < 0.05).

Hypoxic delivery

Three 1000-liter weather balloons were placed in-line on the inspired breathing line, distal to the inspired pneomotachograph. The balloons were filled to capacity prior to subject arrival with a gas composition of 15.8% O_2 and balance N_2 using a nitrogen generator (CAT 12, Colorado Altitude Training, Boulder, CO). The balloons were filled during both test days (NORM and HYP) in order to blind subjects to the inspirate, with the balloon valves staying closed during NORM tests such that the subjects breathed only room air, albeit through the same length of tubing. A secondary O_2 gas analyzer was used to determine the fractional O_2 concentrations of inspired air in real time, and this value was used continuously for calculation of oxygen uptake.

Statistical analysis

Findings were analyzed using SPSS statistical software (Version 24, IBM, Armonk, NY). Descriptive statistics were used to describe group characteristics, with values presented as mean ± SE. *A priori* power analysis (G*Power 3.1, Franz Faul, Germany) showed that a sample size of 16 would show detection of meaningful statistical differences. The data were assessed for normality using the Shapiro-Wilk test and for sphericity using Mauchly's test. A 2 x 4 condition (inspirate) by speed repeated measures ANOVA with a *post hoc* Tukey's HSD for simple main effects was used to test for differences in ventilatory, metabolic, footstrike, LRC, RPE, and DYS across speeds and between conditions. Paired t-tests were used to evaluate ASSOC and DISSOC. The alpha for statistical significance for all comparisons was set at $p < 0.05$.

Results

Subjects

Subject characteristics are displayed in Table 1. Sixteen men volunteered to participate in the study, however three were unable to meet the $\dot{V}O_{2max}$ criteria or voluntarily withdrew from the study. Therefore, thirteen trained male distance runners successfully completed the entire study. All subjects displayed normal pulmonary function, similar to those predicted by sex, age, race, and height (87% of predicted FVC; 93% of predicted FEV_1) (Hankinson, Odencrantz, & Fedan, 1999).

Table 1 Subject characteristics and pulmonary function

Age (year)	23.4 ± 0.9
Mass (kg)	68.7 ± 1.8
Height (cm)	170 ± 0.01
$\dot{V}O_{2max}$ (ml kg^{-1} min^{-1}) (NORM)	66.8 ± 1.1
$\dot{V}O_{2max}$ (ml kg^{-1} min^{-1}) (HYP)	59.7 ± 0.8
FVC (L)	4.92 ± 0.07 (87)
FEV_1 (L)	4.32 ± 0.07 (93)
FEV_1 (% FVC)	88 ± 2
PEF (L s^{-1})	8.93 ± 0.1 (105)

Displayed are mean ± SE (Percent Predicted; based on Hankinson et al. 1999)
$\dot{V}O_{2max}$ maximal oxygen uptake, *FVC* forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *PEF* peak expiratory flow

Locomotor Respiratory Coupling

Breathing frequency (breaths min^{-1}) was significantly increased at each submaximal speed in HYP compared to NORM (*12.9 km hr^{-1}*: 30.3 ± 1.9 vs. 35.9 ± 2.2; *14.3 km hr^{-1}*: 34.8 ± 2.0 vs. 39.8 ± 2.2; *16.1 km hr^{-1}*: 40.4 ± 2.4 vs. 45.2 ± 1.9; all speeds $p < 0.05$). At $\dot{V}O_{2max}$ the difference in breathing frequency between NORM and HYP was approaching significance (51.8 ± 1.8 vs. 56.2 ± 1.7; $p = 0.07$). Stride frequency (strides min^{-1}) did not differ between NORM and HYP at any speed (*12.9 km hr^{-1}*: 83.8 ± 1.4 vs.

83.9 ± 1.1; *14.3 km hr^{-1}*: 84.3 ± 1.4 vs. 84.2 ± 1.1; *16.1 km hr^{-1}*: 86.0 ± 1.3 vs. 86.1 ± 1.3; $\dot{V}O_{2max}$: 87.2 ± 1.5 vs. 86.6 ± 1.4; p = 0.50 - 0.93). The combination of consistent stride frequency with elevated breathing frequencies resulted in significantly lower stride frequency-to-breathing frequency quotients (SF/f_b) at the submaximal speeds during HYP compared to NORM (Table 2). The most common coupling quotient was 2:1 (29%), followed by 5:3 (19%) and 5:2 (19%).

Table 2 Locomotor-Respiratory Coupling measures during treadmill running

	12.9 km hr^{-1}		14.3 km hr^{-1}		16.1 km hr^{-1}		$\dot{V}O_2$max	
	NORM	HYP	NORM	HYP	NORM	HYP	NORM	HYP
SF/f_b	2.91 ± 0.20	2.45 ± 0.17*	2.53 ± 0.17	2.21 ± 0.14*	2.22 ± 0.14	1.95 ± 0.09*	1.70 ± 0.06	1.56 ± 0.06
Degree of LRC (%)	63.6 ± 4.6	61.4 ± 4.8	60.2 ± 3.7	55.1 ± 5.3	56.8 ± 3.9	53.9 ± 3.0	43.8 ± 3.4	57.1 ± 3.8*

Displayed are mean ± SE

SF stride frequency (strides min^{-1}), f_b frequency of breathing (breath min^{-1}), SF/f_b stride frequency-to-breathing frequency quotient, *Degree of LRC* percentage of breaths beginning in the same decile of the step or stride cycle

* Significantly different than NORM at the same speed or at volitional exhaustion ($p < 0.05$)

Across speeds and conditions the average degree of LRC (calculated as the percentage of inspirations or expirations beginning in the same decile of the step or stride cycle) was 56.6 ± 15.5 %. All subjects displayed an average degree of LRC greater than that expected by chance. Compared with NORM, the degree of LRC was not significantly different at any of the three common submaximal speeds with exposure to HYP (p = 0.18 - 0.61), however it was significantly increased at $\dot{V}O_{2max}$. Group data are presented in Table 2, and individual data in Table 3. The degree of LRC and breathing frequency were significantly inversely correlated when running at 16.1 km hr^{-1} in NORM (r = -0.62), and were approaching significance (p = 0.096) at 16.1 km hr^{-1} in HYP (r= -0.48).

Table 3 Individual subject stride frequency-to-breathing frequency quotient and degree of locomotor-respiratory coupling

	12.9 km hr^{-1}		14.3 km hr^{-1}		16.1 km hr^{-1}		$\dot{V}O_2$max	
Subject	NORM	HYP	NORM	HYP	NORM	HYP	NORM	HYP
1	2.47 (99)	2.07 (74)	2.28 (76)	1.85 (72)	1.86 (73)	1.85 (70)	1.73 (44)	1.70 (50)
2	2.93 (54)	2.81 (28)	2.69 (50)	2.80 (28)	2.57 (51)	2.47 (39)	1.70 (43)	1.81 (33)
3	3.03 (54)	2.16 (63)	2.73 (51)	2.08 (80)	2.29 (58)	1.85 (48)	1.65 (27)	1.53 (61)
4	2.82 (74)	2.15 (80)	2.30 (73)	1.86 (54)	2.01 (60)	1.78 (62)	1.79 (48)	1.63 (82)
5	3.02 (63)	2.33 (56)	2.54 (56)	2.08 (47)	2.15 (45)	1.94 (54)	1.91 (52)	1.89 (67)
6	3.95 (60)	3.82 (60)	3.04 (59)	3.05 (65)	3.03 (75)	2.59 (58)	1.98 (58)	1.82 (70)
7	2.58 (51)	2.50 (52)	2.02 (50)	2.08 (41)	1.76 (44)	1.92 (52)	1.61 (18)	1.53 (52)
8	3.95 (50)	3.04 (62)	3.95 (66)	2.61 (53)	3.11 (72)	2.13 (60)	n/a (n/a)	1.23 (45)
9	3.90 (94)	3.12 (96)	3.09 (92)	3.07 (95)	2.64 (80)	2.22 (74)	1.84 (51)	1.43 (56)
10	2.44 (71)	2.46 (47)	2.29 (56)	1.93 (53)	2.25 (40)	1.73 (46)	1.73 (51)	1.56 (67)
11	1.77 (50)	1.56 (76)	1.55(59)	1.47 (55)	1.40 (42)	1.41 (47)	1.18 (34)	1.29 (42)
12	1.94 (47)	1.75 (45)	2.11 (45)	1.92 (28)	2.04 (49)	1.79 (56)	1.63 (44)	1.33 (48)
13	3.00 (60)	2.14 (59)	2.30 (50)	1.88 (45)	1.81 (49)	1.62 (36)	1.70 (55)	1.53 (69)

Displayed are mean ± SE

Presented as SF/f_b (*Degree of LRC as a percent*)

Metabolic Variables

All subjects were able to reach a steady state of oxygen uptake (≤150 ml increase in $\dot{V}O_2$ from the previous minute) within three minutes at each submaximal speed. Running economy, expressed as steady state oxygen uptake (ml kg^{-1} min^{-1}) was not statistically significant between NORM and HYP (Table 4), nor was running economy expressed as the slope of the regression line relating steady state oxygen uptake (ml kg^{-1} min^{-1}) to running speed (km min^{-1}). The submaximal running speeds corresponded to $\dot{V}O_2$ values that were 64, 70, and 79% of $\dot{V}O_{2max}$ in NORM, and 72, 79, and 88% of $\dot{V}O_{2max}$ in HYP. The degree of LRC and oxygen uptake were not significantly correlated at any submaximal speed or at $\dot{V}O_{2max}$ in either NORM or HYP, nor were any percent changes in degree of LRC and oxygen consumption from NORM to HYP.

Ventilatory measures are summarized in Table 4. Minute ventilation was significantly higher at each common submaximal speed in HYP compared to NORM, but did not differ at $\dot{V}O_{2max}$. As tidal volume did not differ between NORM and HYP at any

speed, or at $\dot{V}O_{2max}$, the achievement of increased ventilation was due to increases in breathing frequency. The ventilatory equivalent for oxygen was significantly greater at each common speed, and at $\dot{V}O_{2max}$, in HYP compared to NORM. Oxyhemoglobin saturation was significantly lower prior to exercise in HYP compared to NORM (92 ± 0.6% vs. 98 ± 0.3%) and significantly lower at $\dot{V}O_{2max}$ in HYP compared to NORM (80 ± 1.2% vs. 91 ± 0.9%)

Table 4 Physiological measures during treadmill running

	12.9 km hr^{-1}		14.3 km hr^{-1}		16.1 km hr^{-1}		$\dot{V}O_2$max	
	NORM	HYP	NORM	HYP	NORM	HYP	NORM	HYP
$\dot{V}O_2$ (ml kg^{-1} min^{-1})	42.9 ± 1.0	43.0 ± 0.8	46.4 ± 1.0	47.0 ± 0.9	52.5 ± 1.0	52.6 ± 0.9	66.8 ± 1.1	59.7 ± 0.8*
$\dot{V}E$ (L min^{-1})	71.3 ± 2.3	85.3 ± 3.1*	82.8 ± 2.5	97.3 ± 3.5*	100.6 ± 3.3	119.1 ± 4.4*	157.4 ± 3.7	159.9 ± 4.7
f_b (breath min^{-1})	30.3 ± 1.9	35.9 ± 2.2*	34.8 ± 2.0	39.8 ± 2.2*	40.4 ± 2.4	45.2 ± 1.9*	51.8 ± 1.8	56.2 ± 1.7
TV (L breath^{-1})	2.44 ± 0.15	2.47± 0.16	2.45 ± 0.13	2.52 ± 0.14	2.56 ± 0.13	2.67 ± 0.12	3.06 ± 0.13	2.88 ± 0.12
HR (beats min^{-1})	142 ± 4	149 ± 3	155 ± 4	163 ± 3	170 ± 3	176 ± 3	194 ± 2	189 ± 2*
$\dot{V}E/\ \dot{V}O_2$	24.2 ± 0.7	29.0 ± 0.8*	26.0 ± 0.7	30.0 ± 0.8*	27.9 ± 0.9	33.0 ± 1.0*	34.3 ± 0.9	39.1 ± 0.9*

Displayed are mean ± SE

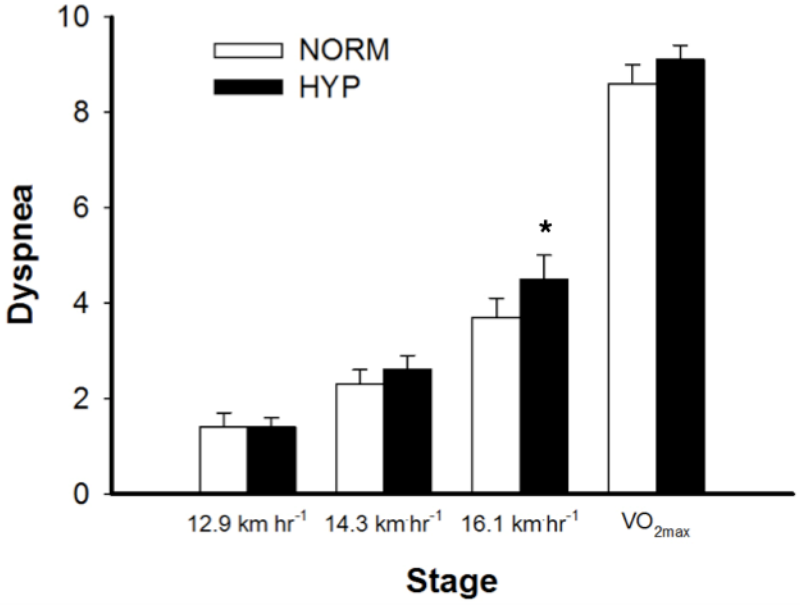
$\dot{V}O_2$ volume of oxygen uptake, $\dot{V}E$ minute ventilation, f_b frequency of breathing, *TV* tidal volume, *HR* heart rate, $\dot{V}E/\ \dot{V}O_2$ ventilatory equivalent for oxygen. NORM, normoxia; HYP, hypoxia (15.8%).

* Significantly different than NORM at the same speed or at volitional exhaustion ($p < 0.05$)

Perceptual Variables

DYS was significantly higher in HYP than in NORM, but only when running at 16.1 km hr^{-1} (Figure 1A). No significant differences were found for RPE between conditions (Figure 1B). DYS was significantly correlated to minute ventilation at $\dot{V}O_{2max}$ in NORM (r = 0.82), and also to the degree of LRC at 12.9 km hr^{-1} in HYP (r = 0.56). Subjects' ASSOC scores (56 ± 2 in NORM and 52 ± 3 in HYP) were significantly higher than their DISSOC scores (27 ± 1 in NORM and 26 ± 2 in HYP).

A.


10
8
6
4
2
0
Dyspnea
NORM
HYP
*
12.9 km hr-1
14.3 km·hr-1
16.1 km·hr-1
VO2max
Stage

B.

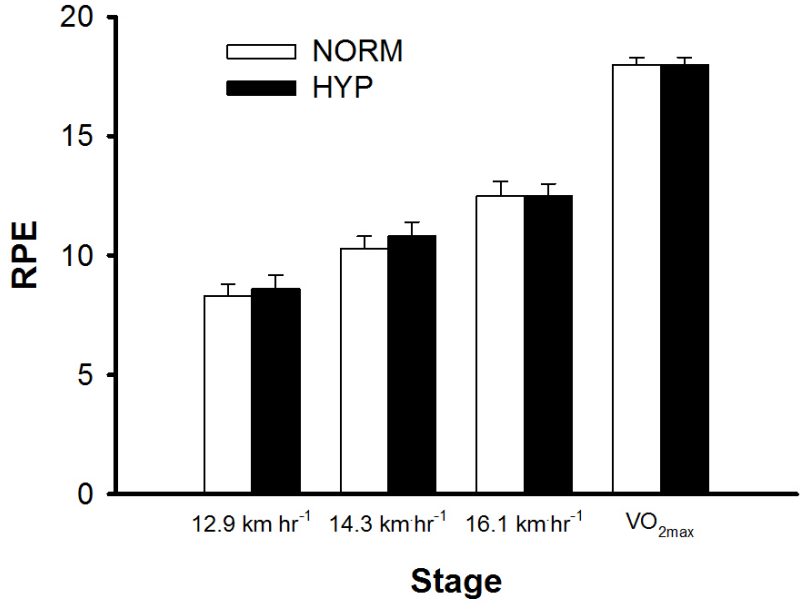

20
15
10
5
0
RPE
NORM
HYP
12.9 km hr-1
14.3 km·hr-1
16.1 km·hr-1
VO2max
Stage

Figure 1.
A. Ratings of dyspnea and B. perceived exertion during NORM (*white bars*) and HYP *(black bars*) across all four stages. Values are means ± SE * Significantly different than NORM at the same speed ($p < 0.05$*)*

Discussion

The primary finding of this investigation is that stride-to-breathing frequency ratios during running at constant submaximal speeds in hypoxia are altered compared to normoxia. However, contrary to our hypothesis, there were no changes to the degree of LRC at submaximal oxygen uptake levels. Additionally, running economy and most measures of perception of effort were not altered during submaximal exercise in hypoxia compared to normoxia. The ability of trained distance runners to maintain LRC in a hypoxic environment may be especially advantageous when training or competing with acute exposure to altitude.

Due to increased breathing frequencies, the stride-to-breathing frequency ratios were lower during HYP compared to NORM, but in both conditions the most common whole integer ratio was two strides to one breath (2:1). This ratio is consistent with previous work in our laboratory (Stickford et al., 2015), as well as several other investigations on LRC during running (Bernasconi & Kohl, 1993; Bramble & Carrier, 1983; McDermott, Van Emmerik, & Hamill, 2003; Paterson et al., 1987; Takano & Deguchi, 1997). An elegant study by Daley et al. (2013) suggests that this ratio is used by humans to minimize antagonistic loading of the respiratory muscles by coordinating step driven flows and breathing such that footstrikes are able to aid in ventilatory transitions.

Although running in hypoxia did increase breathing frequency in the face of a stable stride frequency, it did not reduce the degree of LRC, contrary to our initial hypothesis. Previously, Patterson et al. (1987) did observe decreases in the degree of LRC during hypoxic running (~65% at 915m, ~62% at 2135m, ~50% at 3200m, ~33% at 4420m, and ~23% at 5030 m), suggesting that hypoxia increases breathing frequency to such an extent that it causes uncoupling. Perhaps the reason we did not observe a similar outcome was that our hypoxic stimulus was not strong enough to elicit this response. We chose to utilize an inspired gas of 15.8% oxygen (equivalent to ~2400m / 8000ft) as this is most similar to the elevation endurance athletes sojourn to during altitude training camps. Paterson et al. (1987) tested subjects across a range of elevations, with the most drastic decreases in the degree of LRC occurring at elevations from 3000-5000+ meters.

The maintenance of the degree of LRC in our study is consistent with the findings of Fabre et al. (2007) and Seebauer et al. (2003). Fabre et al. (2007) did not observe any changes in the degree of LRC in rowers while exercising in hypoxia compared to normoxia. While $\dot{V}_E$ and f_B increased as expected with exposure to hypoxia, the rowers concomitantly increased their stroke rate, which also resulted in a consistent LRC ratio (stroke rate-to-breathing frequency). It was suggested that the neuro-mechanical stimuli linking the specific locomotor aspects of rowing and respiration was "stronger" than the peripheral chemoreceptor stimuli induced by hypoxia. We believe our results mirror this conclusion, as the rowers completed the hypoxic tests at an elevation of 2877 meters, only slightly higher than our inspired gas equivalent. Seebauer et al. found comparable effects of hypoxia during cycling exercise, where no decrements in the degree of LRC were observed at any of three separate workloads. In fact, the degree of LRC was

increased at a workload of 95% peak oxygen consumption. This finding is parallel to our results, as we observed a significantly higher degree of LRC at $\dot{V}O_{2max}$ in hypoxia compared to normoxia. This increase in the degree of LRC, as well as maintenance at submaximal workloads in hypoxia, may be an additional illustration of the established ability of trained endurance runners to self-optimize kinematic and physiological variables (Cavanagh & Kram, 1989; Hunter & Smith, 2007; Stickford et al., 2015).

Subjects in our study exhibited a much higher associative than dissociative focus during exercise in both normoxia and hypoxia. These results are consistent with the hypothesis that trained distance runners tend to use associative attentional strategies during exercise instead of dissociative strategies employed by novice individuals in order to maximize exercise performance (Brewer et al., 1996; Clingman & Hilliard, 1990; Morgan & Pollock, 1977). It is plausible that subjects in our study utilized an attentional strategy to monitor changes in physiological variables such as breathing frequency and stride frequency in order to maintain the degree of LRC in hypoxia, and therefore maintain RE. This maintenance of LRC and RE are in agreement with previous work examining the degree of LRC and oxygen uptake (Alphen & Duffin, 1994; Maclennan et al., 1994). Although the worsening of RE (increase in oxygen uptake) in parallel with a decrease in the degree of LRC has been observed by Bernasconi and Kohl (1993), as well as Garlando et al. (1985), as we did not detect changes to the degree of LRC, we would not expect economy to differ. The associative strategy used to maintain the degree of LRC seemed to allow RPE and DYS to remain relatively unchanged as well.

Despite the lack of mean differences, the ability to maintain LRC in hypoxia was not universally seen across our cohort of well-trained runners. For example, select

subjects (e.g. subject 2 in Figure 2A) displayed large decreases in the degree of LRC from NORM to HYP across stages, while others (e.g. subject 3 in Figure 2A) had a similar, or even elevated, degree of LRC between conditions. Concurrent with the decreases in the degree of LRC, subject 2 also had increased oxygen uptake from NORM to HYP at the first two stages, while subject 3 was able to maintain oxygen uptake (Figure 2B). While both subjects saw decreases in $\dot{V}O_{2max}$ from NORM to HYP, subject 3, who had a substantial increase in the degree of LRC in hypoxia, had less of a decrement in $\dot{V}O_{2max}$ than subject 2. The responses of subject 2 suggest that if there are substantial reductions in the degree of LRC in hypoxia it may (as others have shown) lead to increases in oxygen uptake, while the responses of subject 3 may be evidence that the maintenance of the degree of LRC in hypoxia is beneficial for mitigating the decline in VO2max at altitude. Due to the well-established presence of individual variation in the response to hypoxia (Chapman et al., 1998), future inquiries into factors limiting exercise performance at altitude should consider including LRC as a variable of interest.

Conclusion

Trained distance runners are able to maintain LRC in hypoxia, even when breathing frequency is increased at any submaximal pace. It is possible that within this unique population, years of training enhance and optimize the ability to make adjustments to LRC in order to minimize metabolic costs. However, there may be individual differences to LRC that could affect performance or the response to training at altitude.

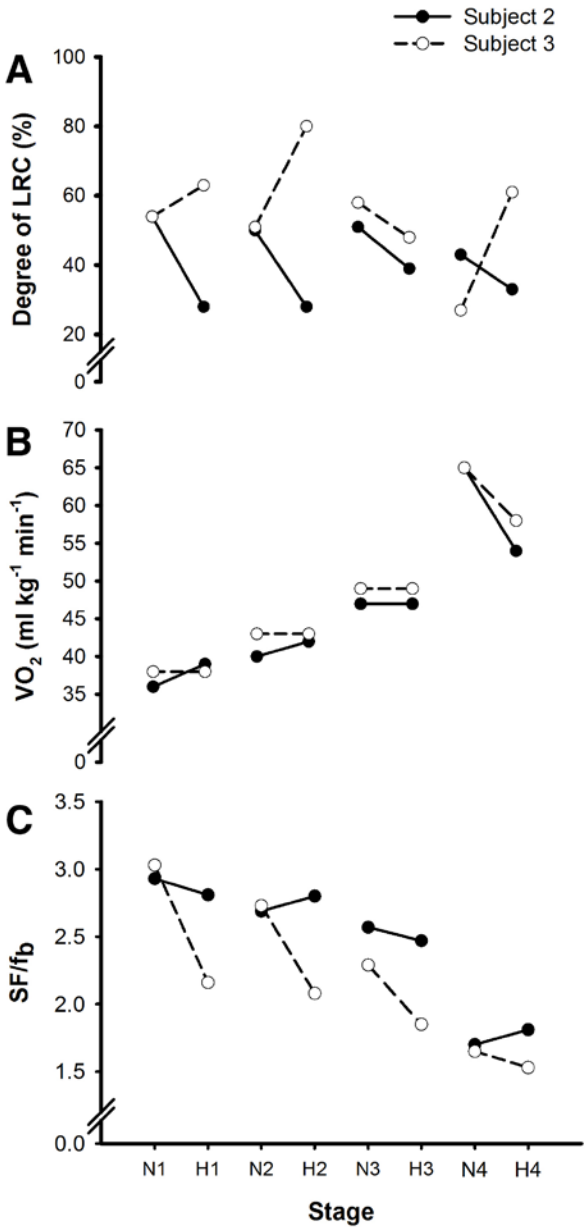


Figure 2
A. Degree of LRC, B. $\dot{V}O_2$, and C. SF/f_b for individual subject #2 (line and filled circle) and subject #3 (dashed line and open circle) across all four stages (N = NORM, H = HYP; 1 = 12.9 km hr^{-1}, 2 = 14.3 km hr^{-1}, 3 = 16.1 km hr^{-1}, 4 = $\dot{V}O_{2max}$).

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APPENDIX A

Variable Names & Raw Data

Variable Name	Description
Subject	Subject ID number
VO2_N1	VO_2 in normoxia at speed 1
VO2_N2	VO_2 in normoxia at speed 2
VO2_N3	VO_2 in normoxia at speed 3
VO2_NM	VO_2 max in normoxia
VO2_H1	VO_2 in hypoxia at speed 1
VO2_H2	VO_2 in hypoxia at speed 2
VO2_H3	VO_2 in hypoxia at speed 3
VO2_HM	VO_2 max hypoxia
RTO_N1	Stride frequency-to-breathing frequency quotient in normoxia at speed 1
RTO_N2	Stride frequency-to-breathing frequency quotient in normoxia at speed 2
RTO_N3	Stride frequency-to-breathing frequency quotient in normoxia at speed 3
RTO_NM	Stride frequency-to-breathing frequency quotient in normoxia at VO_2 max
RTO_H1	Stride frequency-to-breathing frequency quotient in hypoxia at speed 1
RTO_H2	Stride frequency-to-breathing frequency quotient in hypoxia at speed 2
RTO_H3	Stride frequency-to-breathing frequency quotient in hypoxia at speed 3
RTO_HM	Stride frequency-to-breathing frequency quotient in normoxia at VO_2 max
LRC_N1	Degree of LRC in normoxia at speed 1
LRC_N2	Degree of LRC in normoxia at speed 2
LRC_N3	Degree of LRC in normoxia at speed 3
LRC_NM	Degree of LRC in normoxia at VO_2 max
LRC_H1	Degree of LRC in hypoxia at speed 1
LRC_H2	Degree of LRC in hypoxia at speed 2
LRC_H3	Degree of LRC in hypoxia at speed 3
LRC_HM	Degree of LRC in hypoxia at VO_2 max
VE_N1	Minute ventilation in normoxia at speed 1
VE_N2	Minute ventilation in normoxia at speed 2
VE_N3	Minute ventilation in normoxia at speed 3
VE_NM	Minute ventilation in normoxia at VO_2 max
VE_H1	Minute ventilation in hypoxia at speed 1
VE_H2	Minute ventilation in hypoxia at speed 2
VE_H3	Minute ventilation in hypoxia at speed 3
VE_HM	Minute ventilation in hypoxia at VO_2 max
BF_N1	Breathing frequency in normoxia at speed 1
BF_N2	Breathing frequency in normoxia at speed 2
BF_N3	Breathing frequency in normoxia at speed 3
BF_NM	Breathing frequency in normoxia at VO_2 max
BF_H1	Breathing frequency in hypoxia at speed 1
BF_H2	Breathing frequency in hypoxia at speed 2
BF_H3	Breathing frequency in hypoxia at speed 3
BF_HM	Breathing frequency in hypoxia at VO_2 max

Variable Name	Description
TV_N1	Tidal Volume in normoxia at speed 1
TV_N2	Tidal Volume in normoxia at speed 2
TV_N3	Tidal Volume in normoxia at speed 3
TV_NM	Tidal Volume in normoxia at VO_2 max
TV_H1	Tidal Volume in hypoxia at speed 1
TV_H2	Tidal Volume in hypoxia at speed 2
TV_H3	Tidal Volume in hypoxia at speed 3
TV_HM	Tidal Volume in hypoxia at VO_2 max
HR_N1	Heart Rate in normoxia at speed 1
HR_N2	Heart Rate in normoxia at speed 2
HR_N3	Heart Rate in normoxia at speed 3
HR_NM	Heart Rate in normoxia at VO_2 max
HR_H1	Heart Rate in hypoxia at speed 1
HR_H2	Heart Rate in hypoxia at speed 2
HR_H3	Heart Rate in hypoxia at speed 3
HR_HM	Heart Rate in hypoxia at VO_2 max
S_NR	Arterial Oxygen Saturation in normoxia at rest
S_N1	Arterial Oxygen Saturation in normoxia at speed 1
S_N2	Arterial Oxygen Saturation in normoxia at speed 2
S_N3	Arterial Oxygen Saturation in normoxia at speed 3
S_NM	Arterial Oxygen Saturation in normoxia at VO_2 max
S_HR	Arterial Oxygen Saturation in hypoxia at rest
S_H1	Arterial Oxygen Saturation in hypoxia at speed 1
S_H2	Arterial Oxygen Saturation in hypoxia at speed 2
S_H3	Arterial Oxygen Saturation in hypoxia at speed 3
S_HM	Arterial Oxygen Saturation in hypoxia at VO_2 max
RPE_N1	Rating of Perceived Exertion in normoxia at speed 1
RPE_N2	Rating of Perceived Exertion in normoxia at speed 2
RPE_N3	Rating of Perceived Exertion in normoxia at speed 3
RPE_NM	Rating of Perceived Exertion in normoxia at VO_2 max
RPE_H1	Rating of Perceived Exertion in hypoxia at speed 1
RPE_H2	Rating of Perceived Exertion in hypoxia at speed 2
RPE_H3	Rating of Perceived Exertion in hypoxia at speed 3
RPE_HM	Rating of Perceived Exertion in hypoxia at VO_2 max
DYS_N1	Dyspnea in normoxia at speed 1
DYS_N2	Dyspnea in normoxia at speed 2
DYS_N3	Dyspnea in normoxia at speed 3
DYS_NM	Dyspnea in normoxia at VO_2 max
DYS_H1	Dyspnea in hypoxia at speed 1
DYS_H2	Dyspnea in hypoxia at speed 2
DYS_H3	Dyspnea in hypoxia at speed 3
DYS_HM	Dyspnea in hypoxia at VO_2 max

Variable Name	Description
ST_N1	Stride frequency in normoxia at speed 1
ST_N2	Stride frequency in normoxia at speed 2
ST_N3	Stride frequency in normoxia at speed 3
ST_NM	Stride frequency in normoxia at VO_2 max
ST_H1	Stride frequency in hypoxia at speed 1
ST_H2	Stride frequency in hypoxia at speed 2
ST_H3	Stride frequency in hypoxia at speed 3
ST_HM	Stride frequency in hypoxia at VO_2 max
SLOPE_N	Slope of the running economy regression line in normoxia
SLOPE_H	Slope of the running economy regression line in normoxia
VEO2_N1	Ventilatory equivalent for oxygen in normoxia at speed 1
VEO2_N2	Ventilatory equivalent for oxygen in normoxia at speed 2
VEO2_N3	Ventilatory equivalent for oxygen in normoxia at speed 3
VEO2_NM	Ventilatory equivalent for oxygen in normoxia at VO_2 max
VEO2_H1	Ventilatory equivalent for oxygen in hypoxia at speed 1
VEO2_H2	Ventilatory equivalent for oxygen in hypoxia at speed 2
VEO2_H3	Ventilatory equivalent for oxygen in hypoxia at speed 3
VEO2_HM	Ventilatory equivalent for oxygen in hypoxia at VO_2 max
CH_LRC_N_12	Percent change in the degree of LRC between speed 1 and speed 2 in normoxia
CH_LRC_N_23	Percent change in the degree of LRC between speed 2 and speed 3 in normoxia
CH_LRC_N_34	Percent change in the degree of LRC between speed 3 and VO_2 max in normoxia
CH_LRC_H_12	Percent change in the degree of LRC between speed 1 and speed 2 in hypoxia
CH_LRC_H_23	Percent change in the degree of LRC between speed 2 and speed 3 in hypoxia
CH_LRC_H_34	Percent change in the degree of LRC between speed 3 and VO_2 max in normoxia
CH_V02_N_12	Percent change in oxygen uptake between speed 1 and speed 2 in normoxia
CH_V02_N_23	Percent change in oxygen uptake between speed 2 and speed 3 in normoxia
CH_V02_N_34	Percent change in oxygen uptake between speed 3 and VO_2 max in normoxia
CH_VO2_H_12	Percent change in oxygen uptake between speed 1 and speed 2 in hypoxia
CH_VO2_H_23	Percent change in oxygen uptake between speed 2 and speed 3 in hypoxia
CH_VO2_H_34	Percent change in oxygen uptake between speed 3 and VO_2 max in hypoxia
CH_BF_N_12	Percent change in breathing frequency between speed 1 and speed 2 in normoxia
CH_BF_N_23	Percent change in breathing frequency between speed 2 and speed 3 in normoxia
CH_BF_N_34	Percent change in breathing frequency between speed 3 and VO_2 max in normoxia
CH_BF_H_12	Percent change in breathing frequency between speed 1 and speed 2 in hypoxia
CH_BF_H_23	Percent change in breathing frequency between speed 2 and speed 3 in hypoxia
CH_BF_H_34	Percent change in breathing frequency between speed 3 and VO_2 max in hypoxia
CH_V02_NH_1	Percent change in oxygen uptake between normoxia and hypoxia at speed 1
CH_V02_NH_2	Percent change in oxygen uptake between normoxia and hypoxia at speed 2
CH_V02_NH_3	Percent change in oxygen uptake between normoxia and hypoxia at speed 3
CH_V02_NH_4	Percent change in oxygen uptake between normoxia and hypoxia at VO_2 max

Variable Name	Description
CH_LRC_NH_1	Percent change in the degree of LRC between normoxia and hypoxia at speed 1
CH_LRC_NH_2	Percent change in the degree of LRC between normoxia and hypoxia at speed 2
CH_LRC_NH_3	Percent change in the degree of LRC between normoxia and hypoxia at speed 3
CH_LRC_NH_4	Percent change in the degree of LRC between normoxia and hypoxia at VO_2 max
CH_DYS_NH_1	Percent change in Dyspnea between normoxia and hypoxia at speed 1
CH_DYS_NH_2	Percent change in Dyspnea between normoxia and hypoxia at speed 2
CH_DYS_NH_3	Percent change in Dyspnea between normoxia and hypoxia at speed 3
CH_DYS_NH_4	Percent change in Dyspnea between normoxia and hypoxia at VO_2 max
CH_VE_NH_1	Percent change in minute ventilation between normoxia and hypoxia at speed 1
CH_VE_NH_2	Percent change in minute ventilation between normoxia and hypoxia at speed 2
CH_VE_NH_3	Percent change in minute ventilation between normoxia and hypoxia at speed 3
CH_VE_NH_4	Percent change in minute ventilation between normoxia and hypoxia at VO_2 max
CH_BF_NH_1	Percent change in breathing frequency between normoxia and hypoxia at speed 1
CH_BF_NH_2	Percent change in breathing frequency between normoxia and hypoxia at speed 2
CH_BF_NH_3	Percent change in breathing frequency between normoxia and hypoxia at speed 3
CH_BF_NH_4	Percent change in breathing frequency between normoxia and hypoxia at VO_2 max
RER_N	Respiratory exchange ratio in normoxia at VO_2 max
RER_H	Respiratory exchange ratio in hypoxia at VO_2 max
AGE	Age of subject
HEIGHT	Height of subject
MASS	Body mass of subject
A_N	Association score in normoxia
D_N	Dissociation score in normoxia
A_H	Association score in normoxia
D_H	Dissociation score in hypoxia

Subject	VO2_N1	VO2_N2	VO2_N3	VO2_NM	VO2_H1	VO2_H2	VO2_H3	VO2_HM
01	42.10	45.89	52.08	71.92	43.81	49.04	50.95	58.84
02	36.94	40.32	46.99	65.28	39.01	42.15	47.01	53.88
03	38.2	43.85	48.97	64.81	38.74	43.36	49.34	58.03
04	42.94	47.14	53.39	61.13	43.83	49.1	55.24	60.21
05	40.06	42.83	47.35	68.27	41.9	47.45	53.89	64.9
06	43.68	45.75	52.87	68.01	44.7	47.96	53.45	61.09
07	47.09	52.52	58.73	70.8	47.03	48.43	54.99	60.14
08	49.49	51.13	56.59	70.05	49.5	53.35	58.39	59.04
09	42.18	46.21	51.55	71.2	41.57	45.67	51.38	62.56
10	41.36	44.86	52.72	69.14	41.07	45.03	49.88	56.42
11	45.37	48.11	53.45	62.04	43.93	49.25	56.18	63.28
12	40.54	43.58	50.94	61.97	40.41	42.77	50.26	59.72
13	47.65	50.65	56.6	63.54	43.28	47.24	53.47	57.66

Subject	RTO_N1	RTO_N2	RTO_N3	RTO_NM	RTO_H1	RTO_H2	RTO_H3	RTO_HM
01	2.47	2.28	1.86	1.73	2.07	1.85	1.85	1.7
02	2.93	2.69	2.57	1.7	2.81	2.8	2.47	1.81
03	3.03	2.73	2.29	1.65	2.16	2.08	1.85	1.53
04	2.82	2.3	2.01	1.79	2.15	1.86	1.78	1.63
05	3.02	2.54	2.15	1.91	2.33	2.08	1.94	1.89
06	3.95	3.04	3.03	1.98	3.82	3.05	2.59	1.82
07	2.58	2.02	1.76	1.61	2.5	2.08	1.92	1.53
08	3.95	3.95	3.11	n/a	3.04	2.61	2.13	1.23
09	3.9	3.09	2.64	1.84	3.12	3.07	2.22	1.43
10	2.44	2.29	2.25	1.73	2.46	1.93	1.73	1.56
11	1.77	1.55	1.4	1.18	1.56	1.47	1.41	1.29
12	1.94	2.11	2.04	1.63	1.75	1.92	1.79	1.33
13	3	2.3	1.81	1.7	2.14	1.88	1.62	1.53

Subject	LRC_N1	LRC_N2	LRC_N3	LRC_NM	LRC_H1	LRC_H2	LRC_H3	LRC_HM
01	99	76	73	44	74	72	70	50
02	54	50	51	43	28	28	39	33
03	54	51	58	27	63	80	48	61
04	74	73	60	48	80	54	62	82
05	63	56	45	52	56	47	54	67
06	60	59	75	58	60	65	58	70
07	51	50	44	18	52	41	52	52
08	50	66	72	n/a	62	53	60	45
09	94	92	80	51	96	95	73	56
10	71	56	40	51	47	53	46	67
11	50	59	42	34	76	55	47	42
12	47	45	49	44	45	28	56	48
13	60	50	49	55	59	45	36	69

Subject	VE_N1	VE_N2	VE_N3	VE_NM	VE_H1	VE_H2	VE_H3	VE_HM
01	77.56	87.9	105.28	163.35	94.78	109.26	128.65	164.59
02	56.56	68.09	84.11	157.59	75.27	81.33	97.12	141.87
03	71.15	80.54	95.54	158.18	77.89	89.85	112.8	153.97
04	82.82	97.78	118.89	158.97	109.39	126.16	153.71	183.77
05	66.64	77.35	88.48	158.46	84.62	100.67	123.53	162.34
06	66.15	76.14	92.91	150.41	75.87	93.51	106.18	158.86
07	76.22	91.72	113.15	156.26	80.71	91.04	112.39	143.69
08	69.79	74.95	93.3	171.83	89.17	97.34	115.84	180.73
09	68.01	82.13	100.6	180.06	86.11	93.24	124.11	182.01
10	63.67	73.54	90.75	141.77	70.47	84.95	103.08	137.28
11	87.8	94.85	122.75	169.55	100.61	115.91	142.85	174.1
12	74.27	83.17	97.73	153.75	86.92	90.73	112.07	160.11
13	65.68	87.63	104.29	126.26	76.86	91.04	115.6	135.39

Subject	BF_N1	BF_N2	BF_N3	BF_NM	BF_H1	BF_H2	BF_H3	BF_HM
01	34	37	46	49	41	46	46	50
02	30	32	35	54	32	32	38	52
03	29	33	39	55	40	42	49	59
04	28	35	41	46	37	43	46	51
05	29	35	40	47	35	40	44	46
06	21	28	29	46	22	28	34	50
07	33	42	50	56	33	40	44	55
08	21	21	27	n/a	28	32	40	69
09	21	27	32	46	26	27	38	59
10	35	38	40	52	36	45	52	57
11	43	49	55	67	49	52	55	60
12	39	35	39	48	46	42	46	60
13	31	40	52	55	42	48	56	62

Subject	TV_N1	TV_N2	TV_N3	TV_NM	TV_H1	TV_H2	TV_H3	TV_HM
01	2.28	2.38	2.29	3.33	2.31	2.38	2.8	3.29
02	1.89	2.13	2.4	2.92	2.35	2.54	2.56	2.73
03	2.45	2.44	2.45	2.88	1.95	2.14	2.3	2.61
04	2.96	2.79	2.9	3.46	2.96	2.93	3.343	3.6
05	2.3	2.21	2.21	3.37	2.42	2.52	2.81	3.53
06	3.15	2.72	3.2	3.27	3.45	3.34	3.12	3.18
07	2.31	2.18	2.26	2.79	2.45	2.28	2.55	2.61
08	3.32	3.57	3.46		3.18	3.04	2.9	2.62
09	3.24	3.04	3.14	3.91	3.31	3.45	3.27	3.08
10	1.82	1.94	2.27	2.73	1.96	1.89	1.98	2.41
11	2.04	1.94	2.23	2.53	2.05	2.23	2.6	2.9
12	1.9	2.38	2.51	3.2	1.89	2.16	2.44	2.67
13	2.12	2.19	2.01	2.3	1.83	1.9	2.06	2.18

Subject	HR_N1	HR_N2	HR_N3	HR_NM	HR_H1	HR_H2	HR_H3	HR_HM
01	122	140	155	186	140	153	166	177
02	127	138	165	196	155	166	174	193
03	145	157	168	192	150	156	174	187
04	132	158	173	187	145	159	174	181
05	141	148	158	187	147	158	170	183
06	142	155	167	197	130	153	181	200
07	145	157	171	188	153	164	173	181
08	145	154	172	193	153	165	172	182
09	126	137	155	187	142	148	165	180
10	142	150	177	199	152	173	189	198
11	164	176	189	202	167	181	189	198
12	144	156	168	192	152	163	174	193
13	169	188	196	211	159	176	185	201

Subject	S_NR	S_N1	S_N2	S_N3	S_NM	S_HR	S_H1	S_H2	S_H3	S_HM
01	99.67	98.33	97.7	95.66	88.57	93.01	84.71	81.23	79.44	72.53
02	98.46	97.94	94.11	91.48	92.37	91.06	85.95	83.46	83.65	84.41
03	96.91	n/a	n/a	93.81	91.95	88.74	88.49	88.21	87.07	84.59
04	99.77	100	99.58	96.73	99.77	96.69	92.25	74.4	69.16	75.81
05	97.69	n/a	n/a	93.21	89.84	90.96	81.65	84.48	84.71	84.32
06	n/a	n/a	n/a	n/a	n/a	94.71	84.89	83.36	81.8	80.08
07	98.08	97.29	98.07	97.03	93.4	92.93	72.91	75.3	80.97	80.01
08	n/a	n/a	n/a	n/a	n/a	91	85.99	n/a	74.01	81.19
09	99.9	97.51	97.55	97.37	90.36	94.06	88.34	84.21	81.96	75.5
10	98.63	76.99	95.59	91.96	90.31	91.07	86.72	80.1	78.15	74.61
11	99.12	n/a	92.02	92.84	88.12	93.12	82.11	85.18	84.66	85.74
12	96.54	94.92	95.31	93.72	93.01	89.77	85.81	81.93	81.52	81.79
13	98.56	n/a	n/a	89.29	88.78	93.01	87.25	87.73	85.21	80.49

Subject	RPE_N1	RPE_N2	RPE_N3	RPE_NM	RPE_H1	RPE_H2	RPE_H3	RPE_HM
01	11	13	14	19	9	13	15	19
02	7	10	13	17	6	9	12	18
03	7	9	13	19	8	9	11	16
04	8	12	15	18	11	13	16	20
05	6	8	10	19	6	7	11	17
06	9	10	12	19	9	10	12	18
07	9	12	13	17	7	10	13	18
08	11	13	15	18	11	13	14	18
09	8	10	11	20	9	11	13	20
10	8	10	13	17	9	12	14	19
11	8	10	12	18	7	11	14	20
12	10	11	14	16	13	14	16	18
13	6	6	7	17	7	8	10	17

Subject	DYS_N1	DYS_N2	DYS_N3	DYS_NM	DYS_H1	DYS_H2	DYS_H3	DYS_HM
01	3	4	4	9	2	4	5	10
02	1	2	4	7	1	3	4	8
03	0.5	2	4	9	1	2	5	9
04	3	4	6	9	3	4	8	9
05	0.5	0.5	2	10	0.5	1	2	10
06	2	2	3	8	1	2	3	8
07	0.5	2	4	10	0.5	3	5	10
08	3	4	5	8	2	3	5	9
09	1	2	3	10	2	2	4	10
10	1	2	4	9	1	2	4	9
11	1	2	3	9	2	3	5	9
12	1	3	5	9	2	4	6	10
13	0.5	0.5	1	5	0.5	1	2	7

Subject	RER_N	RER_H
01	1.19	1.24
02	1.18	1.15
03	1.19	1.06
04	1.06	1.08
05	1.11	1.04
06	1.15	1.15
07	1.13	1.14
08	1.22	1.23
09	1.18	1.12
10	1.14	1.08
11	1.11	1.03
12	1.11	1.03
13	1.13	1.11

Subject	ST_N1	ST_N2	ST_N3	ST_NM	ST_H1	ST_H2	ST_H3	ST_HM
01	84	84.5	85.5	85	85	85	85	85
02	88.0	86.0	90.0	92.0	90.0	89.5	94.0	94.0
03	88.0	90.0	89.5	90.5	86.5	87.5	90.5	90.5
04	79.0	80.5	82.5	82.5	79.5	80.0	82.0	83.0
05	87.5	89.0	86.0	90.0	81.5	83.0	85.5	87.0
06	83.0	85.0	88.0	91.0	84.0	85.5	88.0	91.0
07	85.0	85.0	88.0	90.0	82.5	83.0	84.5	84.0
08	83.0	83.0	84.0	n/a	85.0	83.5	85.0	85.0
09	82.0	83.5	84.5	84.5	81.0	83.0	84.5	84.5
10	85.5	87.0	90.0	90.0	88.5	87.0	90.0	89.0
11	76.0	76.0	77.0	79.0	76.5	76.5	77.5	77.5
12	75.5	74.0	79.5	78.0	80.5	80.5	82.5	80.0
13	93.0	92.0	94.0	93.5	90.0	90.0	90.5	95.0

Subject	SLOPE_N	SLOPE_H
01	3.134	2.177
02	3.167	2.509
03	3.341	3.313
04	3.34	3.558
05	2.289	3.739
06	3.956	3.05
07	3.629	2.541
08	2.257	2.779
09	2.93	3.071
10	3.588	2.75
11	2.546	3.829
12	3.289	3.129
13	2.784	3.197

Subject	VEO2_N1	VEO2_N2	VEO2_N3	VEO2_NM	VEO2_H1	VEO2_H2	VEO2_H3	VEO2_HM
01	24.07	25.03	26.41	29.68	28.62	29.47	33.40	37.00
02	22.31	24.60	26.08	35.17	28.35	28.35	30.35	38.68
03	26.95	26.57	28.23	35.31	28.83	29.71	32.78	38.04
04	23.53	25.30	27.16	31.72	29.73	30.60	33.14	36.35
05	22.69	24.63	25.49	31.66	28.16	29.58	31.96	34.87
06	21.30	23.41	24.72	31.11	24.19	27.79	28.31	37.06
07	25.41	27.41	30.24	34.64	27.93	30.59	33.26	38.88
08	20.92	21.75	24.46	36.39	26.67	27.01	29.37	45.32
09	22.52	24.82	27.26	35.32	28.93	28.52	33.74	40.64
10	23.92	25.48	26.75	31.86	26.50	29.14	31.92	37.58
11	30.63	31.21	36.35	43.26	37.17	38.20	41.27	44.66
12	25.63	26.70	26.84	34.71	30.04	29.63	31.14	37.44
13	24.57	30.85	32.85	35.43	31.50	34.19	38.35	41.65

Subject	CH_LRC_N_12	CH_LRC_N_23	CH_LRC_N_34
01	-23.23	-3.95	-39.73
02	-7.41	2.00	-15.69
03	-5.56	13.73	-53.45
04	-1.35	-17.81	-20.00
05	-11.11	-19.64	15.56
06	-1.67	27.12	-22.67
07	-1.96	-12.00	-59.09
08	32.00	9.09	
09	-2.13	-13.04	-36.25
10	-21.13	-28.57	27.50
11	18.00	-28.81	-19.05
12	-4.26	8.89	-10.20
13	-16.67	-2.00	12.24

Subject	CH_LRC_H_12	CH_LRC_H_23	CH_LRC_H_34
01	-2.70	-2.78	-28.57
02	0.00	39.29	-15.38
03	26.98	-40.00	27.08
04	-32.50	14.81	32.26
05	-16.07	14.89	24.07
06	8.33	-10.77	20.69
07	-21.15	26.83	0.00
08	-14.52	13.21	-25.00
09	-1.04	-23.16	-23.29
10	12.77	-13.21	45.65
11	-27.63	-14.55	-10.64
12	-37.78	100.00	-14.29
13	-23.73	-20.00	91.67

Subject	CH_V02_N_12	CH_V02_N_23	CH_V02_N_34
01	9.00	13.49	38.10
02	9.15	16.54	38.92
03	14.79	11.68	32.35
04	9.78	13.26	14.50
05	6.91	10.55	44.18
06	4.74	15.56	28.64
07	11.53	11.82	20.55
08	3.31	10.68	23.79
09	9.55	11.56	38.12
10	8.46	17.52	31.15
11	6.04	11.10	16.07
12	7.50	16.89	21.65
13	6.30	11.75	12.26

Subject	CH_VO2_H_12	CH_VO2_H_23	CH_VO2_H_34
01	11.94	3.89	15.49
02	8.05	11.53	14.61
03	11.93	13.79	17.61
04	12.02	12.51	9.00
05	13.25	13.57	20.43
06	7.29	11.45	14.29
07	2.98	13.55	9.37
08	7.78	9.45	1.11
09	9.86	12.50	21.76
10	9.64	10.77	13.11
11	12.11	14.07	12.64
12	5.84	17.51	18.82
13	9.15	13.19	7.84

Subject	CH_BF_N_12	CH_BF_N_23	CH_BF_N_34
01	8.82	24.32	6.52
02	6.67	9.38	54.29
03	13.79	18.18	41.03
04	25.00	17.14	12.20
05	20.69	14.29	17.50
06	33.33	3.57	58.62
07	27.27	19.05	12.00
08	0.00	28.57	-100.00
09	28.57	18.52	43.75
10	8.57	5.26	30.00
11	13.95	12.24	21.82
12	-10.26	11.43	23.08
13	29.03	30.00	5.77

Subject	CH_BF_H_12	CH_BF_H_23	CH_BF_H_34
01	12.20	0.00	8.70
02	0.00	18.75	36.84
03	5.00	16.67	20.41
04	16.22	6.98	10.87
05	14.29	10.00	4.55
06	27.27	21.43	47.06
07	21.21	10.00	25.00
08	14.29	25.00	72.50
09	3.85	40.74	55.26
10	25.00	15.56	9.62
11	6.12	5.77	9.09
12	-8.70	9.52	30.43
13	14.29	16.67	10.71

Subject	CH_LRC_NH_1	CH_LRC_NH_2	CH_LRC_NH_3	CH_LRC_NH_4
01	-25.25	5.26	4.11	-13.64
02	-48.15	44.00	23.53	23.26
03	16.67	-56.86	17.24	-125.93
04	8.11	26.03	-3.33	-70.83
05	-11.11	16.07	-20.00	-28.85
06	0.00	-10.17	22.67	-20.69
07	1.96	18.00	-18.18	-188.89
08	24.00	19.70	16.67	
09	2.13	-3.26	8.75	-9.80
10	-33.80	5.36	-15.00	-31.37
11	52.00	6.78	-11.90	-23.53
12	-4.26	37.78	-14.29	-9.09
13	-1.67	10.00	26.53	-25.45

Subject	CH_V02_NH_1	CH_V02_NH_2	CH_V02_NH_3	CH_V02_NH_4
01	4.06	6.86	-2.17	-18.19
02	5.60	4.54	0.04	-17.46
03	1.41	-1.12	0.76	-10.46
04	2.07	4.16	3.47	-1.50
05	4.59	10.79	13.81	-4.94
06	2.34	4.83	1.10	-10.17
07	-0.13	-7.79	-6.37	-15.06
08	0.02	4.34	3.18	-15.72
09	-1.45	-1.17	-0.33	-12.13
10	-0.70	0.38	-5.39	-18.40
11	-3.17	2.37	5.11	2.00
12	-0.32	-1.86	-1.33	-3.63
13	-9.17	-6.73	-5.53	-9.25

Subject	CH_DYS_NH_1	CH_DYS_NH_2	CH_DYS_NH_3	CH_DYS_NH_4
01	-33.33	0.00	25.00	11.11
02	0.00	50.00	0.00	14.29
03	100.00	0.00	25.00	0.00
04	0.00	0.00	33.33	0.00
05	0.00	100.00	0.00	0.00
06	-50.00	0.00	0.00	0.00
07	0.00	50.00	25.00	0.00
08	-33.33	-25.00	0.00	12.50
09	100.00	0.00	33.33	0.00
10	0.00	0.00	0.00	0.00
11	100.00	50.00	66.67	0.00
12	100.00	33.33	20.00	11.11
13	0.00	100.00	100.00	40.00

Subject	CH_VE_NH_1	CH_VE_NH_2	CH_VE_NH_3	CH_VE_NH_4
01	22.20	24.30	22.20	0.76
02	33.08	19.44	15.47	-9.98
03	9.47	11.56	18.07	-2.66
04	32.08	29.02	29.29	15.60
05	26.98	30.15	39.61	2.45
06	14.69	22.81	14.28	5.62
07	5.89	-0.74	-0.67	-8.04
08	27.77	29.87	24.16	5.18
09	26.61	13.53	23.37	1.08
10	10.68	15.52	13.59	-3.17
11	14.59	22.20	16.37	2.68
12	17.03	9.09	14.67	4.14
13	17.02	3.89	10.84	7.23

Subject	CH_BF_NH_1	CH_BF_NH_2	CH_BF_NH_3	CH_BF_NH_4
01	20.6	24.3	0.0	2.0
02	6.7	0.0	8.6	-3.7
03	37.9	27.3	25.6	7.3
04	32.1	22.9	12.2	10.9
05	20.7	14.3	10.0	-2.1
06	4.8	0.0	17.2	8.7
07	0.0	-4.8	-12.0	-1.8
08	33.3	52.4	48.1	
09	23.8	0.0	18.8	28.3
10	2.9	18.4	30.0	9.6
11	14.0	6.1	0.0	-10.4
12	17.9	20.0	17.9	25.0
13	35.5	20.0	7.7	12.7

Subject	AGE	HEIGHT	MASS
01	21	1.76	75.6
02	21	1.82	68.07
03	22	1.8	69.12
04	28	1.81	81.98
05	22	1.79	71.73
06	23	1.79	70.16
07	20	1.79	61.45
08	26	1.84	67.41
09	30	1.86	71.59
10	22	1.81	64.35
11	28	1.76	63.17
12	20	1.77	71.6
13	21	1.67	56.37

Subject	A_N	D_N	A_H	D_H
01	50	21	42	24
02	63	30	55	25
03	66	28	60	25
04	52	31	62	31
05	61	26	60	19
06	39	29	47	22
07	55	32	45	29
08	58	27	45	24
09	67	23	51	26
10	45	23	38	19
11	63	28	71	45
12	47	25	47	20
13	59	31	49	32

APPENDIX B

Indiana University Institutional Review Board Approval

INDIANA UNIVERSITY

OFFICE OF THE VICE PRESIDENT FOR RESEARCH

Office of Research Compliance

To: Robert Chapman
KINESIOLOGY

Timothy Fulton
KINESIOLOGY

From:

Chair - IRB-05
Human Subjects Office
Office of Research Compliance – Indiana University

Date: February 01, 2016

RE: **NOTICE OF APPROVAL - NEW STUDY**

Protocol Title: Effects of hypoxia on locomotor respiratory coupling during exercise

Study #: 1510451822

Funding Agency/Sponsor: None

Status: Approved | Active - Open to Enrollment

Study Approval Date: February 01, 2016

Study Expiration Date: January 26, 2017

The Indiana University Institutional Review Board (IRB) IRB00004961 | IRB-05 recently took action on the above-referenced protocol. The IRB has subsequently verified that the investigator's response to the review satisfies the conditions for approval. In compliance with (as applicable) 21 C.F.R. § 56.109 (e) and 46 C.F.R. § 46.109 (d), this letter serves as written notification of the IRB's determination.

The study is approved, with the following determinations, as applicable:

- **Minimal Risk**

Approval of this study is based on your agreement to abide by the policies and procedures of the Indiana University Human Research Protection Program and does not replace any other approvals that may be required. Relevant policies and procedures governing Human Subject Research can be found at: http://researchadmin.iu.edu/HumanSubjects/hs_policies.html.

As a reminder, IRB approval is required prior to implementing any changes or amendments in the protocol, regardless of how minor, except to eliminate immediate hazards to subjects. No changes to the informed consent document may be made without prior IRB approval.

If you submitted and/or are required to provide participants with an informed consent document, **a copy of the most recently approved stamped document is enclosed and must be used to enroll participants.**

The study expiration date is noted above. Failure to receive notification from the Human Subjects Office will not relieve you of your responsibility to ensure compliance with Federal Regulations regarding annual review [as applicable, 21 C.F.R. § 56.109(f) and 45 C.F.R. § 46.109(e)].

You should retain a copy of this letter and all associated approved study documents for your records. Please refer to the assigned study number and exact study title in future correspondence with our office. Additional information is available on our website at http://researchadmin.iu.edu/HumanSubjects/.

If your source of funding changes, you must submit an amendment to update your study documents immediately via an amendment.

APPENDIX C

Informed Consent

IRB study #1510451822

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

Effects of hypoxia on locomotor-respiratory coupling during exercise

You are invited to participate in a research study that will help determine the effects that hypoxia (low oxygen content of the air) has on running mechanics and running economy. You were selected as a possible subject because of your status as a highly trained distance runner. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

Disclaimer: It is possible that after completing the study questionnaires that you will not qualify for the study.

The study is being conducted by Robert F. Chapman, Ph.D. (Principal Investigator), and co-investigator Timothy Fulton in the Department of Kinesiology at Indiana University-Bloomington.

STUDY PURPOSE

The purpose of the proposed study is to investigate the relationship of the rhythmic pairing of breathing and foot strikes while running and the energy cost associated with running, both in normal oxygen and low oxygen environments.

NUMBER OF PEOPLE TAKING PART IN THE STUDY:

If you agree to participate, you will be one of approximately 40 subjects who will be participating in this research.

PROCEDURES FOR THE STUDY:

If you agree to be in the study, the following items are included:

An invitation will be extended to visit the Human Performance laboratory on two occasions at a previously agreed-upon time. The visits will last approximately 75 minutes and 45 minutes respectively.

The testing session includes completion of two written questionnaires, measures of your height and weight, measure of your body composition (fat and lean mass), resting pulmonary function (breathing) testing, and a running test on a treadmill.

Each of these tests is described below.

Height and weight measures. Height will be measured by asking you to stand against a wall and a device will be lowered until it touches the top of your head. Weight will be

measured by having you sit on a chair, which is placed on a scale. This test will be completed in both visits to the lab.

Body composition measures. You will be asked to stand on a scale in bare feet and hold two handles connected to the scale. A small, imperceptible electrical current will pass through your body for about two seconds. The scale will calculate an estimate of the percent of your mass that is lean mass and the percent that is fat mass. This test will be completed only on the first visit to the lab.

Resting pulmonary function (breathing tests). You will be asked to sit in a chair and rest comfortably for 10 minutes. You will be asked to put noseclips on your nose and breathe through a plastic mouthpiece. The noseclips are cleaned in detergent and an antibacterial solution after each use, and the plastic mouthpiece is new for each subject. While sitting in the chair, you will be asked to complete various breathing maneuvers which measure the size of your lungs, how fast you can move air in and out of your lungs, and the ability of your lungs to transfer gas to the blood.

Running Test. This exercise test will be completed on a treadmill. You will be allowed to warm up on the treadmill for five minutes at any pace you would like to select. A strap will be placed around your chest which will measure your heart rate. Small sensors will be taped to your skin on both heels, using standard athletic tape. Attached to the sensors will be a thin cable that will be taped to your leg and secured to your waist with a Velcro strap. You will be asked to complete the treadmill running while breathing through a face mask which covers your nose and mouth. Air will flow into and out of your lungs as you breathe through the face mask. The face mask and heart rate monitor are cleansed in a detergent and antibacterial solution following each use. You will be asked to run 3 repetitions of 5 minutes each. The paces will be at progressively faster speeds which correspond approximately to marathon pace, 10k pace, and 5k pace. A rest period of 3 minutes will follow the first two 5 minute running stages. At the end of the third stage, you will be asked to continue running at the same pace. The slope of the treadmill will increase slightly every two minutes until you fatigue and need to stop. The goal is for you to run for as long as you can. In most subjects, this occurs after approximately 5-8 minutes of running. This test will be completed on both visits to the lab. In one visit, the air you breathe while running will be normal room air. In the other visit, the air you breathe while running will have a reduced oxygen content, equivalent to an altitude of approximately 2500m or 8000ft. You will not be told which air you are breathing, and the order will be selected at random.

RISKS OF TAKING PART IN THE STUDY:

While in the study, the risks are:

Submaximal and maximal exercise tests of healthy individuals, as described by the American College of Sports Medicine, present little risk to the subject and do not require medical clearance for subjects under the age of 40. Potential risks and/or discomforts can include episodes of temporary light-headedness, chest discomfort, leg cramps, occasional

irregular heartbeats, and abnormal blood pressure responses. The risk of heart attack, although minor, (approximately 1 to 2 in 10,000) does exist. One death occurs for roughly every 880,000 man hours of submaximal exercise in apparently healthy individuals. During the test you will be closely monitored for any abnormal changes in heart rate or breathing. You are free to indicate any discomfort and discontinue participation at any time. There are potential risks associated with running on a treadmill, such as falling.

All face masks will be cleaned in detergent and antibacterial solution after each use, minimizing the risk of virus transmission between subjects.

There is a potential risk of loss of confidentiality.

BENEFITS OF TAKING PART IN THE STUDY:

The benefits to participation that are reasonable to expect are information regarding your overall level of fitness. Other than this information, you will gain little benefit. All subjects will be provided with feedback concerning their own results and the general findings of the study upon request.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. Data will be stored on password protected computers in locked rooms with limited public access. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published and databases in which results may be stored.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the IU Institutional Review Board or its designees, and (as allowed by law) state or federal agencies, specifically the Office for Human Research Protections (OHRP) who may need to access the collected medical and/or research data.

PAYMENT

Should you qualify for the study, you will be paid a $50 gift card for completing the first session of testing and completing or attempting to complete the second session of testing. Should you withdraw from the study after completing or attempting to complete the first session of testing, you will be paid a $20 gift card. Payment is made via a gift card, which will be given to you at the end of your final testing session.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you at your own expense. Costs not covered by your health care insurer will be your responsibility. Also, it is your

responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, by signing this form you are not giving up any legal rights or benefits to which you are otherwise entitled.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher Robert Chapman, Ph.D. at (812) 856-2452 or rfchapma@indiana.edu. If you cannot reach the researcher during regular business hours (i.e. 8:00AM-5:00PM), please call the IU Human Subjects Office at (812) 856-4242 or (800) 696-2949.

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information, or offer input, contact the IU Human Subjects Office at (812) 856-4242 or (800) 696-2949.

VOLUNTARY NATURE OF STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with the investigators or Indiana University.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances: an abnormal response to exercise testing or an inability to complete the exercise tests.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study.

I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject's Printed Name:_____

Subject's Signature:_____
Date:_____
(must be dated by the subject)

Printed Name of Person Obtaining Consent:_____

Signature of Person Obtaining Consent:_____
Date:_____

APPENDIX D

Modified Physical Activity Readiness Questionnaire

Modified Physical Activity Readiness Questionnaire (PAR-Q)

Name			**Date**
DOB	**Age**	**Home Phone**	**Work Phone**

Regular exercise is associated with many health benefits, yet any change of activity may increase the risk of injury. Please read each question carefully and answer every question honestly:

Yes	**No**	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
Yes	**No**	**2. Do you feel pain in your chest when you do physical activity?**
Yes	**No**	3. **In the past month, have you had chest pain when you were not doing physical activity?**
Yes	**No**	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
Yes	**No**	**5. Do you have a bone or joint problem that could be made worse by a change in your physical activity?**
Yes	**No**	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
Yes	**No**	**7. Do you know of any other reason you should not do physical activity?**
Yes	**No**	**8. Has your doctor ever told you that you have diabetes?**
Yes	**No**	**9. Has your doctor ever told you that you have high blood pressure?**
Yes	**No**	**10. Has your doctor ever told you that you have high cholesterol?**
Yes	**No**	**11. Has your doctor ever told you that you have high blood sugar?**
Yes	**No**	**12. Do you smoke?**
Yes	**No**	**13. Are you currently inactive?**
Yes	**No**	**14. Do you have a father, brother or son with heart disease before the age of 55 years old or a mother, sister or daughter with heart disease before the age of 65 years old?**

15. (Researcher will complete) Measure height and weight to determine BMI:
Height:_____
Weight:_____

Participant Signature	**Date**

APPRENDIX E

Preliminary Survey

General Study Questionnaire

Name	**Date**

Do you consider yourself to be a highly endurance trained individual?	**(Circle one)**	**YES**	**NO**
Have you run on a treadmill before?	**(Circle one)**	**YES**	**NO**
Do you feel that you can run comfortably on a treadmill at three paces between 5k and marathon pace for five minutes?	**(Circle one)**	**YES**	**NO**
Please list your best running event and the best time you have achieved in the past two years:	**Best event:** **Best time in last two years:**		

Participant Signature	**Date**

APPRENDIX F

Curriculum Vitae

TIMOTHY J. FULTON
1320 South Curry Pike
Bloomington, IN 47403
(319) 290-5529
tifulton@indiana.edu

EDUCATION

Ph.D. Expected 2019 Indiana University
School of Public Health
Exercise Physiology
Minor: Medical Physiology

M.S. 2017 Indiana University
School of Public Health
Exercise Physiology

B.A. 2010 University of Northern Iowa
College of Business
Economics and Finance

TEACHING EXPERIENCE

Associate Instructor, Medical Sciences Program, IU School of Medicine — Aug. 2016 - Present
- PHYS P215 - Basic Human Physiology Laboratory

Associate Instructor, Department of Kinesiology, Indiana University — Aug. 2015 - Aug. 2016
- SPH K409 - Basic Exercise Physiology Laboratory
- SPH I133 - Fitness and Jogging

Adjunct Instructor, Department of Kinesiology, Indiana University — Aug. 2014 - Aug. 2015
- SPH I133 - Fitness and Jogging

Undergraduate Research Assistant, Motor Behavior Lab, Northern Iowa — Aug. 2012 - Dec. 2013
- Oversaw five lab assistants and conducted research involving mobile eye tracking and accelerometery/physical activity levels

Academic Tutor, Department of Athletics, Northern Iowa — Jan. 2013 - Dec. 2013
- Tutored student-athletes in exercise physiology, anatomy, biomechanics, and economics courses

Adjunct Faculty, Mathematics, Northeast Iowa Community College — Aug. 2010 - Dec. 2010
- MAT 063 - Elementary Algebra
- MAT 102 - Intermediate Algebra

PUBLICATIONS

Fulton TJ, Paris HL, Stickford AS, Gruber AH, Mickleborough TD, Chapman RF. Locomotor-respiratory coupling is maintained in hypoxia in trained distance runners. In preparation.

Paris HL, **Fulton TJ**, Mickleborough TD. Macronutrient oxidation alters operating lung volumes during cycling exercise. In preparation.

Fulton TJ, Noble, TJ, and Chapman RF. Does prior Olympic or World Championship experience affect performance at future championships? In preparation.

Constantini K, **Fulton TJ**, Hursh DG, Noble TJ, Paris HLR, Wiggins CC, Chapman RF, Levine BD. Commentary on Viewpoint: Time for a new metric for hypoxic dose? *J Appl Physiol.* 121: 356-358, 2016.

Fulton TJ, Ertz J, Rohler A, Mack MG, Fontana F. Effects of a visual distraction on quiet eye duration and putting performance of collegiate golfers. *International Journal of Golf Science.* 3: 26-34, 2014.

PRESENTATIONS

Fulton TJ, Paris HL, Stickford AS, Gruber AH, Mickleborough TD, Chapman RF. "Locomotor-respiratory coupling is maintained in hypoxia in trained distance runners" ACSM Annual Meeting. Denver, May 2017.

Paris HL, Murray KO, **Fulton TJ**, Mickleborough TD. "The repercussion of expectoration: When a carbohydrate rinse becomes detrimental to performance" ACSM Annual Meeting. Denver, May 2017.

Fulton TJ and Chapman RF. "Does Prior Olympic or World Championship Experience Affect Performance at Future Championships?" ACSM Annual Meeting. San Diego, May 2015.

Fulton TJ, Ertz J, Rohler A, Mack MG, Fontana F "Effects of a visual distraction on quiet eye duration and putting performance in collegiate golfers" NASPSPA Annual Conference, Minneapolis, June 2014

Fulton TJ and Fontana F. "Using Receiver Operating Characteristic Curves and Accelerometry to Establish Step-Count Guidelines for Twelve-Year-Old Children" ACSM Annual Meeting, Indianapolis, May 2013.

GRANTS

Indiana University Graduate and Professional Student Government Research Grant, March 2017. Effects of hypoxia on physiology and psychology during exercise in women. Unfunded.

Indiana University Department of Kinesiology Graduate Student Travel Grant, March 2017. $300.

Indiana University School of Public Health Graduate Student Research Grant, November 2015. Effects of hypoxia on locomotor-respiratory coupling during exercise. $1000.

Indiana University School of Public Health Graduate Student Travel Grant, May 2015. $400.

UNI College of Education Dean's Undergraduate Research Grant, April 2013. Effects of a visual distraction on quiet eye duration and putting performance in collegiate golfers. $500.

FELLOWSHIP

Department of Kinesiology Graduate Fellowship, Academic year 2016-2017.

Hal Morris Research Fellowship, Academic year 2016-2017.

SERVICE

School of Public Health Student Ambassador, Indiana University — Sep. 2016 - Dec. 2016

- Serve as a link between the school, alumni, donors, and prospective students
- Represent the student body during Office of Development events by engaging and interacting with guests

Undergraduate Curriculum Development, Indiana University — May 2016 - Dec. 2016

- Assisted in graduate student led development of a new undergraduate physiology course: 'Human Performance & Nutrition'

Jim Holland Summer Enrichment Program, Indiana University — Summer 2016

- Led underrepresented high school students through hands-on laboratory experiences to help broaden their horizons in science

PROFESSIONAL EXPERIENCE

Consultant — 2015 - Present
USA Track & Field, Indianapolis, IN