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PULMONARY SYSTEM LIMITATIONS TO ENDURANCE EXERCISE PERFORMANCE IN HUMANS

Markus Amann
University of Utah, Department of Medicine, Salt Lake City, Utah, USA

Abstract

Accumulating evidence over the past 25 years depicts the healthy pulmonary system as a limiting factor of whole body endurance exercise performance. This brief overview emphasizes three respiratory system-related mechanisms which impair O_2 transport to the locomotor musculature [arterial O_2 content (C_aO_2) × leg blood flow (Q_L)], i.e. the key determinant of an individual's aerobic capacity and ability to resist fatigue. First, the respiratory system often fails to prevent arterial desaturation substantially below resting values and thus compromises C_aO_2. Especially susceptible to this threat to convective O_2 transport are well-trained endurance athletes characterized by high metabolic and ventilatory demands and, likely due to anatomical and morphologic gender differences, active females. Second, fatiguing respiratory muscle work (W_{resp}) associated with strenuous exercise elicits sympathetically-mediated vasoconstriction in limb-muscle vasculature which compromises Q_L. This impact on limb O_2 transport is independent of fitness level and affects all individuals, however, only during sustained, high-intensity endurance exercise performed above ~85% VO_2max. And third, excessive fluctuations in intrathoracic pressures accompanying W_{resp} can limit cardiac output and therefore Q_L. Exposure to altitude exacerbates the respiratory system limitations observed at sea level and further reduces C_aO_2 and substantially increases exercise-induced W_{resp}. Taken together, the intact pulmonary system of healthy endurance athletes impairs locomotor muscle O_2 transport during strenuous exercise by failing to ensure optimal arterial oxygenation and compromising Q_L. This respiratory system-related impact exacerbates the exercise-induced development of fatigue and compromises endurance performance.

Keywords

pulmonary ventilation; blood flow distribution; gas exchange; exercise-induced arterial hypoxemia; arterial oxygen saturation; work of breathing

The purpose of this short report is to provide a general overview of endurance exercise limitations primarily pertaining to the pulmonary system. Although an exhaustive discussion of underlying mechanisms cannot be provided given space limitations, the article outlines key characteristics of the human respiratory system which have the potential to impact well-known determinants of endurance performance.

Numerous previous studies substantiate the role of muscle O_2 transport [arterial O_2 content (C_aO_2) × locomotor muscle blood flow (Q_L)] as a major determinant of high-intensity endurance exercise performance in humans. *Reductions* in muscle O_2 transport attenuate VO_2max, exaggerate the rate of fatigue development and deteriorate endurance exercise

Corresponding Author: Markus Amann, Ph.D., VA Medical Center, 500 Foothill Drive, GRECC 182, Salt Lake City, UT 84148, USA, markus.amann@hsc.utah.edu, Phone: 801 582-1565 ext. 4358.

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performance (Amann & Calbet, 2008). In contrast, *increases* in muscle O_2 transport evoke the opposite effects. Consequently, any given factor impeding arterial oxygenation and/or Q_L impairs a human's endurance exercise capacity and performance.

The Respiratory System: Well Designed for the Needs of Most Healthy Young Individuals

In contrast to the heart, the respiratory system of healthy young individuals is usually not considered a major limiting factor for high-intensity endurance exercise. This stems from the fact that the capacity of the healthy pulmonary system in most humans is sufficient to cope with the demands associated with ventilation and gas exchange – even during strenuous endurance exercise. The majority of untrained (VO_2max ≤55 ml/kg/min), but even most well trained, individuals are characterized by only a small 2-3 fold increase in the alveolar to arterial O_2 difference (A-aDO_2; surrogate of gas exchange efficiency) from rest (~5-8 mmHg) to VO_2max (<30 mmHg). This small change indicates a largely uncompromised and adequate rate of O_2 diffusion across the alveolar-capillary membrane (Dempsey & Wagner, 1999).

Furthermore, in most humans, alveolar ventilation during exercise can rise unrestricted and out of proportion to CO_2 production as arterial PCO_2 (P_aCO_2) is reduced to ≥10 mmHg below resting levels. In other words, alveolar hyperventilation can increase sufficiently and raise alveolar PO_2 (P_AO_2) high enough to enable a compensation for the widened A-aDO_2. The net effect is a nearly unchanged P_aO_2 from rest to VO_2max and only a fairly small reduction in arterial haemoglobin saturation (S_aO_2) which is, however, nearly exclusively caused by the exercise-induced increases in core temperature and metabolic acidosis (see below). Also, airway resistance and lung compliance during exercise are maintained near resting levels and, in untrained subjects, breathing requires only ≤10% of both VO_2max and maximum cardiac output (Aaron *et al*., 1992; Harms *et al*., 1998b), and intrathoracic pressure changes developed by the respiratory muscles approximate only 40-50% of their maximal dynamic capacity (Johnson *et al*., 1992).

Overall, the respiratory system in healthy young individuals might generally be considered as sufficiently "equipped" to handle the pulmonary gas exchange requirements associated with even high intensity endurance exercise.

Weaknesses and Limits of the Healthy Respiratory System

In some, not all, trained endurance athletes, the metabolic requirement associated with high intensity exercise demands extreme ventilation and pulmonary gas exchange which can actually reach and outstrip the functional capacity of their respiratory system and eventually compromise arterial oxygenation and limb O_2 transport (Dempsey *et al*., 1984; Williams *et al*., 1986; Powers *et al*., 1988; Harms *et al*., 1997). I briefly cover three respiratory system related mechanisms which present significant limitations to locomotor muscle O_2 transport during exercise.

1. Exercise-Induced Arterial Oxyhaemoglobin Desaturation

High-intensity endurance exercise in some fit athletes causes a time-dependant decrease in S_aO_2 of greater than 5% from resting levels (~98%) – extreme drops into the mid 80% range have been reported (Dempsey & Wagner, 1999). The oxyhaemoglobin desaturation during exercise is based on both respiratory and non-respiratory influences. Briefly, non-respiratory influences encompass the rightward shift of the oxyhaemoglobin dissociation curve mediated by metabolic acidosis and hyperthermia (Wasserman *et al*., 1967; Rasmussen *et al*., 1991).

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In a minority of athletes, frequently those characterized by the greatest fitness (Williams *et al*., 1986), arterial oxyhaemoglobin desaturation also occurs due to a fall in P_aO_2 (Holmgren & Linderholm, 1958) secondary to an abnormally widened A-aDO_2 (Hopkins & McKenzie, 1989; Dempsey & Wagner, 1999). At maximal exercise in healthy untrained individuals, A-aDO_2 is usually up to 20-30 mmHg, however, in some elite athletes, this difference might be as wide as 35-50 mmHg (Dempsey *et al*., 1984).

Arterial desaturation during exercise can also occur due to an inadequate hyperventilatory response secondary to low chemoresponsiveness [i.e. attenuated response to circulating chemical stimuli like protons, catecholamines, adenosine, or potassium (Lumb & Nunn, 2000) – and maybe also O_2 and CO_2 (Harms & Stager, 1995; Guenette *et al*., 2004)] and/or mechanical constraints presented by the airways (Dempsey *et al*., 1984; Johnson *et al*., 1992; Dempsey & Wagner, 1999). Inadequate ventilatory responses during exercise have been shown to reduce P_AO_2 which negatively affects arterial blood gas status and S_aO_2 (Johnson *et al*., 1992).

Some recent studies indicate a greater prevalence of arterial oxyhaemoglobin desaturation in active females compared to their male counterpart (Harms *et al*., 1998a; Hopkins *et al*., 2000; Hopkins & Harms, 2004). Various pulmonary structural and functional differences have been found between females and age- and height-matched males (Hopkins & Harms, 2004). For example, women are characterized by smaller lung volumes and airways, a lower resting lung diffusion capacity, and lower maximal expiratory flow rates compared men (McClaran *et al*., 1998; Guenette *et al*., 2007). Although the exact effects of these anatomical and morphologic gender differences remain elusive, they are considered as key contributors to the greater gas exchange disturbances and ventilatory limitations during exercise in females vs males.

Remaining issues - from a personal communication with Prof. Jerry Dempsey: “In the minority of trained individuals characterized by a reduction in S_aO_2 secondary to an excessive A-aDO_2 and the resulting fall in P_aO_2, it remains unresolved why the reductions in P_aO_2 already occur during submaximal exercise and why it only seems to occur in trained rather than untrained individuals – especially runners. The idea that we originally had (i.e. that the extraordinary demand for pulmonary O_2 transport exceeds the ordinary structural capacity of the lung in these athletes) does not apply under submaximal conditions because the athletes are not anywhere near maximal demands for O_2 transport and the ‘capacity’ of the lungs for gas exchange are not being challenged in the usual sense. The cause(s) of this arterial hypoxemia during submaximal exercise in the absence of hypoventilation in these types of endurance trained athletes remains a mystery to me. It is also a mystery to me that arterial hypoxemia occurs most often during running and only rarely during bicycle exercise. A further key unresolved issue is the huge variability in exercise-induced A-aDO_2 difference and oxyhaemoglobin desaturation amongst athletes. Many athletes are hardly affected even at maximal exercise, whereas others are characterized by a fall in P_aO_2 even during submaximal exercise which worsens at higher workloads.”

2. Exercise-Induced W_{resp} and Associated Metaboreflex-Mediated Impact on Q_L

A further threat to locomotor muscle O_2 delivery is W_{resp} associated with heavy sustained exercise (>85% VO_2max). The ventilatory response during heavy exercise, which is often accompanied and impaired by expiratory flow limitations and dynamic hyperinflation (Johnson *et al*., 1992), requires substantial increases in both inspiratory and expiratory muscle work, often leading to respiratory muscle fatigue. Even though diaphragm force, during tidal breathing, falls during the latter stages of sustained heavy exercise, alveolar ventilation is not compromised, presumably due to accessory muscle recruitment. However, fatiguing contractions and associated accumulation of metabolites in the inspiratory and

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expiratory muscles activate unmylenated group IV phrenic afferents (Hill, 2000) which reflexly increase sympathetic vasoconstrictor activity (St Croix *et al*., 2000) and vasoconstriction of the vasculature of the exercising limb (Harms *et al*., 1997) (Figure 1). The result is a reduction in Q_L, and (presumably) an increase in blood flow to the respiratory muscles, indicating a competitive relationship for a limited cardiac output (Manohar, 1986; Musch, 1993). These effects do not occur during exercise at intensities lower than ~80% VO_2max (Wetter *et al*., 1999). During intense exercise (>85% VO_2max) in the highly-trained subject, the respiratory muscles now require up to 15-16% of VO_2max and cardiac output (Harms *et al*., 1998b) – versus ≤10% in the untrained. Thus, in contrast to arterial desaturation, W_{resp} induced by heavy, sustained exercise has no effect on C_aO_2, but the reduction in O_2 transport is caused by reduced Q_L.

3. Intrathoracic Pressure Effects on Cardiac Output

The ventilatory response during high intensity exercise is associated with a substantial augmentation of negative and positive intrathoracic pressures. In the presence of expiratory flow limitation and hyperinflation in the well-trained young athlete, these inspiratory pressures may approach 95% and 30% of the maximum dynamic pressure available to the inspiratory and expiratory muscles, respectively (Johnson *et al*., 1992). The heart and great vessels are exposed to these substantial oscillatory pressures.

Recent studies in exercising humans and animals have used mechanical ventilation and threshold loads to reduce negative inspiratory or increase positive expiratory intrathoracic pressures, respectively. The results of these investigations suggest a substantial effect of these pressures on venous return, stroke volume, and cardiac output during exercise. For example, the normally occurring negative inspiratory intrathoracic pressures associated with high-intensity exercise have a significant facilitating contribution (up to 10%) to end-diastolic volume and subsequently stroke volume and cardiac output. Importantly, no additional effects on cardiac output are observed when negative inspiratory intrathoracic pressures are increased beyond normal by imposing additional inspiratory negative pressure via resistive loading (Harms *et al*., 1998b; Miller *et al*., 2007). In contrast, even small increases in positive intrathoracic pressures on expiration (5-10 cm H_2O) have been shown to decrease ventricular transmural pressure which reduces the rate of ventricular filling during diastole and thereby impairs stroke volume and cardiac output (Stark-Leyva *et al*., 2004; Miller *et al*., 2006). Increases in expiratory positive intrathoracic pressures of similar and even greater magnitudes occur during the transition from moderate to intense exercise in well-trained individuals and/or with the development of expiratory flow limitations (Johnson *et al*., 1992).

Taken together, negative inspiratory pressures during exercise appear to promote cardiac output via increasing ventricular preload and therefore stroke volume, whereas expiratory positive pressures during exercise limit cardiac output via increasing the ventricular afterload and thereby decreasing stroke volume. The net effect of intrathoracic pressure changes on cardiac output during high intensity exercise in well-trained endurance athlete will depend upon the degree to which the functional consequences of negative inspiratory pressures (i.e. facilitating cardiac output) balance the mechanical consequences of positive expiratory pressures (i.e. limiting cardiac output).

In summary, it should be emphasized that a threat to locomotor muscle O_2 transport secondary to arterial desaturation >4-5% from rest is experienced only by a subgroup of well-trained endurance athletes and can develop even at submaximal exercise intensities. However, the threat to O_2 delivery via the respiratory muscle metaboreflex occurs in all healthy subjects, but only at sustained, high-intensity endurance exercise (>85% VO_2max). Furthermore, the reduction in Q_L imposed by the respiratory muscle metaboreflex is

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potentially even further exacerbated via potentially negative effects of intrathoracic pressure excursions on cardiac output.

Respiratory System Limitations: Consequences for Endurance Performance and Fatigue

Consequences of Exercise-Induced Arterial Desaturation on Endurance Performance

The impact of arterial desaturation on endurance performance has been revealed by adding just sufficient O_2 to the inspired air to prevent the fall in S_aO_2 during exercise. The measurable threshold of S_aO_2-related limitations to peak aerobic power occurs at a desaturation of >4-5% from rest (Squires & Buskirk, 1982; Powers *et al*., 1989; Harms *et al*., 2000a). Beyond this threshold, a linear association between the changes in saturation and VO_2max is observed, such that each further 1% reduction in S_aO_2 causes a 1-2% reduction in peak aerobic power.

Similarly, exercise-induced arterial desaturation also limits endurance performance achieved during a time trial-like test modality (Koskolou & McKenzie, 1994; Nielsen *et al*., 2002). For example, Amann et al. (Amann *et al*., 2006) have recently demonstrated a significant limiting effect of arterial desaturation on 5-km cycling time trial performance (Figure 2). C_aO_2, and thus O_2 delivery, was increased by ~8% when the exercise-induced fall in S_aO_2 (to ~91%) was prevented by increasing the fraction of O_2 in the inspired air. This resulted in a substantial 2-5% reduction in the time to completion, and up to a 5% increase in mean power output.

Consequences of W_{resp} on Endurance Performance

The effects of the W_{resp} on endurance performance have been revealed by reducing the normally occurring W_{resp} during constant-load exercise via mechanical ventilatory assist or heliox breathing. At exercise intensities corresponding to ≤80% of VO_2max, significant 20-40% reductions in W_{resp} have no effect on endurance performance (Gallagher & Younes, 1989; Marciniuk *et al*., 1994; Krishnan *et al*., 1996). These observations are not surprising given the fact that blood flow redistribution between the respiratory muscles and the locomotor muscles only occurs at exercise intensities >85-90% of VO_2max (Harms *et al*., 1997) – and *not* at or below 80% of VO_2max (Wetter *et al*., 1999). However, when constant-load exercise is performed at intensities greater than 85-90% VO_2max, respiratory muscle unloading was found to significantly increase endurance time to exhaustion (Wilson & Welch, 1980; Johnson *et al*., 1996).

For example, during constant-load cycling at 90% VO_2max, a 60% reduction in W_{resp} resulted in increased limb vascular conductance and 3-4% increases in leg O_2 transport and uptake – even in the face of a reduced cardiac output (Harms *et al*., 1997). Time to exhaustion was increased by ~14% when W_{resp} was reduced by ~50%. This significant effect on exercise performance has indirectly been confirmed by increasing W_{resp} by ~28%, resulting in ~15% reduction in time to exhaustion (Harms *et al*., 2000b).

Consequences of Pulmonary System Limitations on the Development of Locomotor Muscle Fatigue

Even the relatively small reductions in O_2 transport associated with exercise-induced haemoglobin desaturation >5% from rest, or the high W_{resp}, exacerbate the rate of development of peripheral locomotor muscle fatigue during exercise (Amann & Calbet, 2008). For example, during constant-load exercise (>90% VO_2max), increases in locomotor muscle O_2 transport secondary to a ~60% reduction in W_{resp} (via proportional assist ventilation) alleviated end-exercise quadriceps fatigue by 25-30% compared to control

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exercise (Romer *et al*., 2006b) (Figure 3). Furthermore, when exercise-induced arterial desaturation was prevented during constant-load leg cycling (>90% VO_2max; via adding supplemental O_2 to the inspired air), end-exercise quadriceps fatigue was nearly 50% less compared to control conditions (Romer *et al*., 2006a). In contrast, no effect of maintaining resting S_aO_2 on peripheral fatigue was observed in those individuals who sustained haemoglobin saturation above 95% during the exercise (Romer *et al*., 2006a).

The effect of O_2 delivery on peripheral fatigue development has been shown to be a key determinant of endurance exercise performance (Amann *et al*., 2006; Amann *et al*., 2011). We recently proposed that exercise-induced alterations of locomotor muscle fatigue affect, in a dose-dependent manner, the firing rate – and thus the central projection – of group III/IV muscle afferents which are known to provide inhibitory feedback to the determination of central motor drive during exercise (Amann *et al*., 2006; Amann *et al*., 2009; Amann, 2011). In other words, acting via inhibitory feedback to higher motor areas, the highly O_2 delivery-sensitive peripheral locomotor muscle fatigue influences central motor drive and therefore exercise performance.

Exercise at Altitude

Additional respiratory limits to exercise performance at or near sea level occur during acute or chronic exposure to the hypoxia associated with altitudes beyond ~1500 m (Buskirk *et al*., 1967). Hypoxia aggravates the proposed threats to limb O_2 delivery in two ways. First, the alveolar-capillary diffusion limitation becomes more pronounced, due to a decreased P_AO_2 at any given alveolar ventilation. Second, acute, but especially chronic, hypoxic exposures potentiate the hyperventilatory response to exercise and markedly increase W_{resp} (Thoden *et al*., 1969; Amann *et al*., 2007). Therefore, hypoxia exacerbates the rate of development of peripheral locomotor muscle fatigue elicited via high intensity exercise and reduces exercise performance in two ways, namely, via reductions in S_aO_2 and increases in W_{resp} (Amann *et al*., 2007). For example, we recently studied identical submaximal constant-load bike exercise (273 W, 8.6 min) performed at sea-level and simulated altitude (inspiratory O_2 content = 0.15). Haemoglobin saturation was substantially lower during the exercise in acute hypoxia (~95% vs ~81%) whereas W_{resp} was about 40% higher compared to sea level (Amann *et al*., 2007). These drastic changes nearly doubled the rate of development of locomotor muscle fatigue during the cycling exercise and compromised the subjects' endurance performance (Amann *et al*., 2006).

Conclusion

Accumulating evidence over the past 25 years indicates a substantial role of the healthy respiratory system in limiting high-intensity endurance exercise in humans. This influence is mediated via the effects of the respiratory system on locomotor muscle O_2 delivery and associated consequences on the development of fatigue during exercise and an individual's aerobic capacity. Reductions in O_2 delivery are caused by the failure of the pulmonary system to maintain resting arterial oxygenation during exercise and/or a respiratory muscle metaboreflex which causes a sympathetically-mediated reduction in Q_L. Furthermore, intrathoracic pressure excursions associated with the high ventilatory work during intense exercise have been suggested to limit cardiac output. Taken together, the pulmonary system is a key – although highly variable – determinant of endurance performance in healthy individuals.

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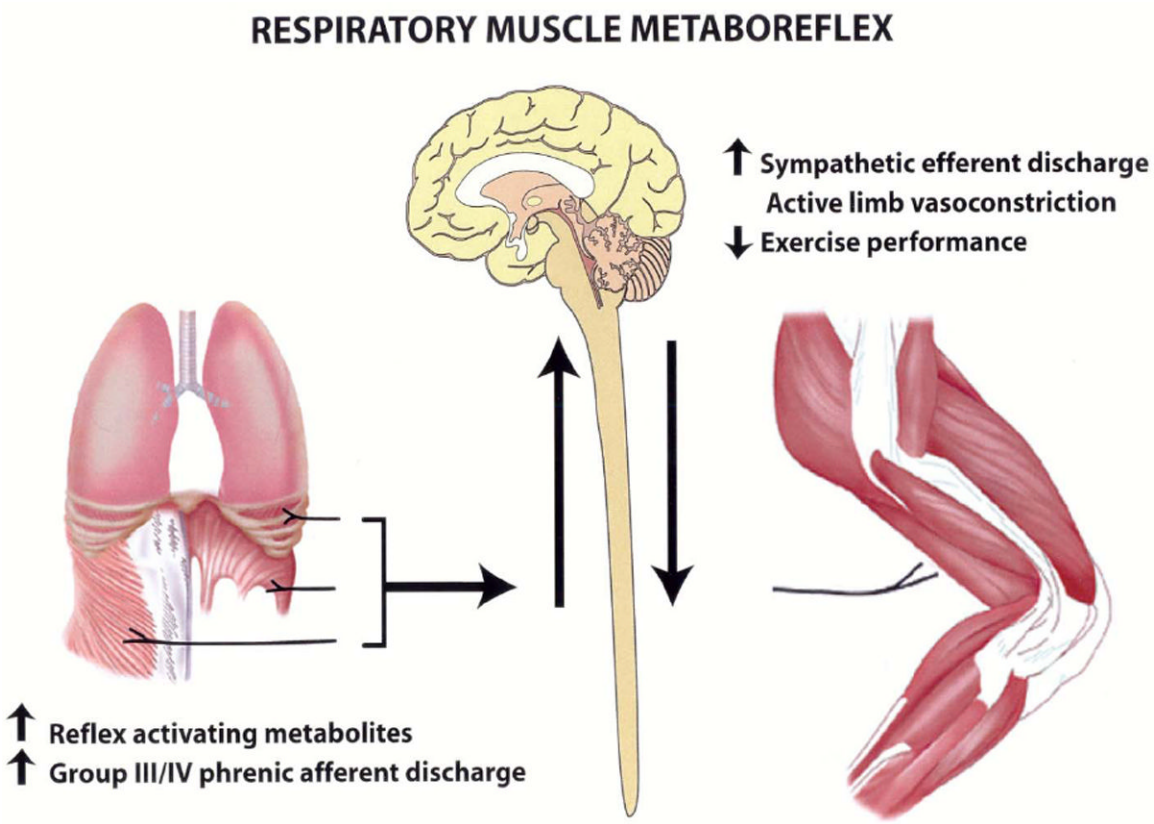

Figure 1.
Relationship between respiratory muscle work and leg blood flow. Fatigue related metabolite accumulation in respiratory muscles activate group III/IV phrenic afferents which reflexly cause increased sympathetic efferent discharge and limb vasoconstriction. This sequence facilitates locomotor muscle fatigue and limits endurance exercise performance. Adapted from (Dempsey *et al*., 2002).

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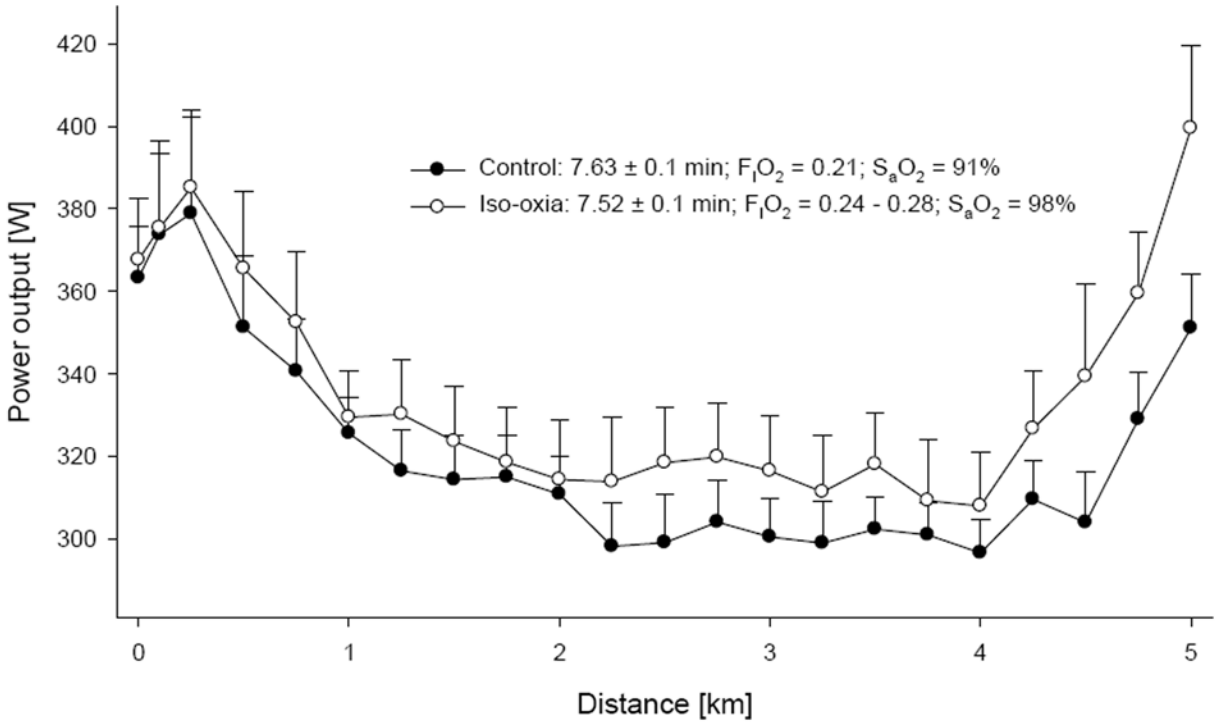

Figure 2.

Effect of exercise-induced arterial desaturation on 5 km cycling time trial performance. During the iso-oxic trial, S_aO_2 was maintained at resting levels (~98%) via progressive increases in inspiratory O_2 content (F_IO_2). Time to completion and mean power output (331 ± 13 W vs 314 ± 13 W) were significantly improved during the iso-oxic time trial. Adapted from (Amann *et al*., 2006).

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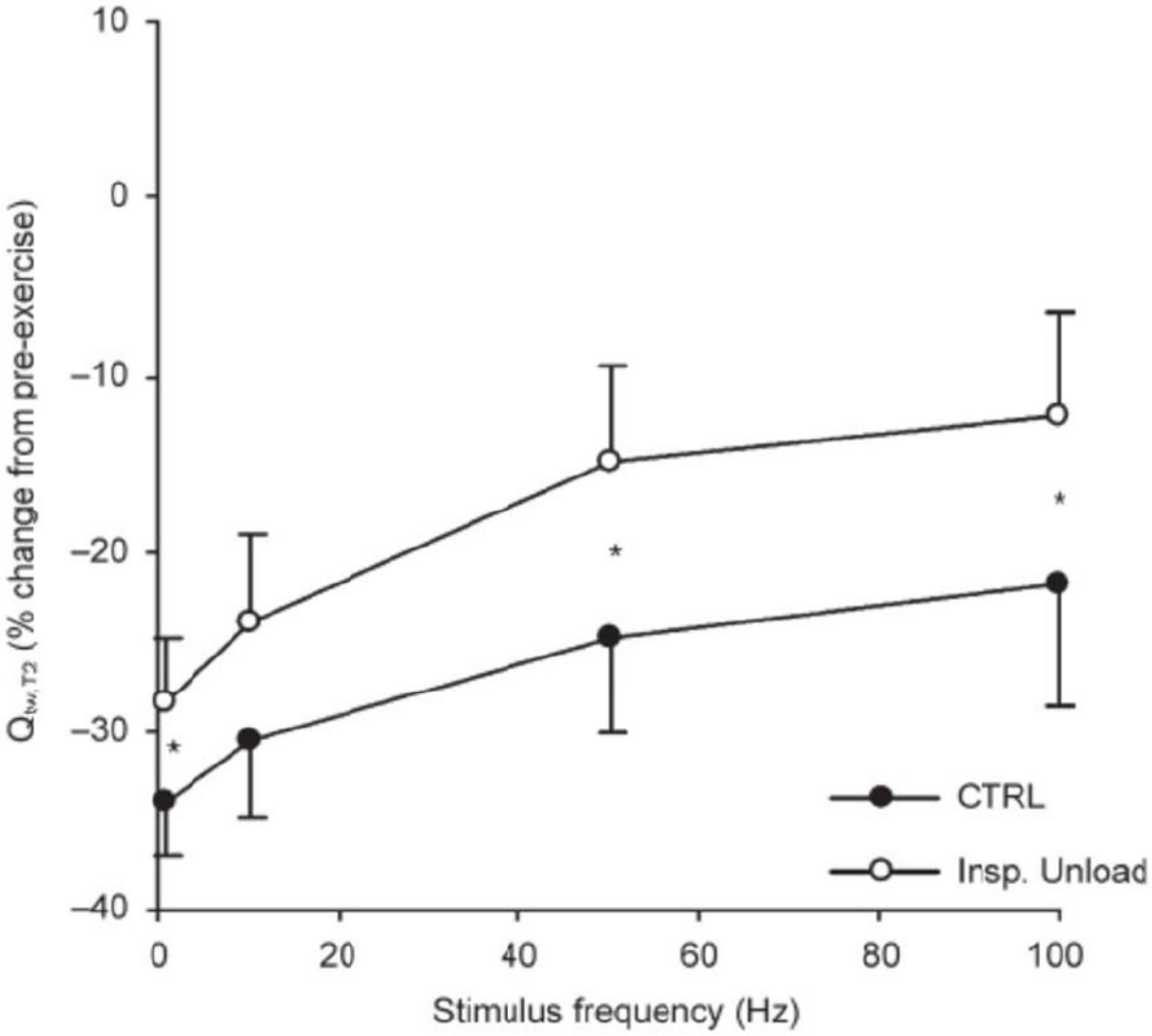

Figure 3.

Effects of a 60% reduction in inspiratory muscle work ('Insp. Unload') on the pre- to post-exercise change in the force-frequency curve of the quadriceps muscle. The y-axis represents the change for the second of the paired quadricep twitch amplitude ($Q_{tw,T2}$). The work rate and exercise time was identical during control exercise and inspiratory unloadin (≥90% VO_2max; 292 W, 13 min). Adapted from (Romer *et al*., 2006b).