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Invited Review

HIGHLIGHTED TOPIC | *Fatigue Mechanisms Determining Exercise Performance*

Convective oxygen transport and fatigue

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Amann M, Calbet JA. Convective oxygen transport and fatigue. *J Appl Physiol* 104: 861–870, 2008. First published October 25, 2007; doi:10.1152/japplphysiol.01008.2007.—During exercise, fatigue is defined as a reversible reduction in force- or power-generating capacity and can be elicited by "central" and/or "peripheral" mechanisms. During skeletal muscle contractions, both aspects of fatigue may develop independent of alterations in convective O_2 delivery; however, reductions in O_2 supply exacerbate and increases attenuate the rate of accumulation. In this regard, peripheral fatigue development is mediated via the O_2-dependent rate of accumulation of metabolic by-products (e.g., inorganic phosphate) and their interference with excitation-contraction coupling within the myocyte. In contrast, the development of O_2-dependent central fatigue is elicited *1*) by interference with the development of central command and/or *2*) via inhibitory feedback on central motor drive secondary to the peripheral effects of low convective O_2 transport. Changes in convective O_2 delivery in the healthy human can result from modifications in arterial O_2 content, blood flow, or a combination of both, and they can be induced via heavy exercise even at sea level; these changes are exacerbated during acute and chronic exposure to altitude. This review focuses on the effects of changes in convective O_2 delivery on the development of central and peripheral fatigue.

oxygenation; hypoxia; blood flow; exercise; hyperoxia

WHAT IS FATIGUE?

EXERCISE-INDUCED FATIGUE is defined as the reversible reduction in force- or power-generating capacity of the neuromuscular system (16, 47). Potentially, fatigue may originate in any of the elements that intervene in the planning, execution, and/or control of motor tasks. Classically, fatigue has been classified as "central" or "peripheral" (44, 46, 52, 53). Peripheral fatigue comprises processes at or distal to the neuromuscular junction, e.g., biochemical changes within the working muscle, leading to a failure to respond to neural excitation. Controversy exists about the extent to which significant failure of neuromuscular transmission, i.e., failure in the transmission of the neural signal, occurs during muscle fatigue in *healthy* humans (53). However, the reduction in force- or power-generating capacity can result from inadequate, or suboptimal, muscle activation—often, but not exclusively, in combination with failure of contractile mechanisms—resulting from a failure of the central nervous system (CNS) to excite—or "drive"—the motoneurons adequately (central fatigue). Several mechanisms that are not mutually exclusive have been suggested to underlie central and peripheral fatigue (2, 34, 44, 46, 52, 61, 95, 106), and the impaired motor performance is the result of a combination of various acute determinants of fatigue rather than just one aspect. Furthermore, insufficient O_2 delivery [blood flow × arterial O_2 content (Ca_{O_2})] may elicit fatigue by affecting both central and peripheral mechanisms (68, 105, 113).

The focus of this review is on factors causing changes in convective O_2 transport and their functional consequences on fatigue, rather than a discussion of diverse cellular mechanisms. We extend the definition of fatigue to include, as suggested by Enoka and Stuart (44), acute impairments of performance during exercise—as reflected in the failure to maintain a given force or power output (i.e., task failure)—which are attributable to mechanisms susceptible to alterations in convective O_2 transport.

How to Quantify Fatigue?

Methods to evaluate fatigue are numerous (23, 127, 133) and include techniques used to quantify biochemical changes known to cause reductions in force-generating capacity (41, 65, 71, 119). Assessment of neuromuscular functions are usually made *before* and immediately *after* fatiguing exercise, and the discrepancy between pre- vs. postexercise measures is used to quantify peripheral fatigue. These methods rely on the assumption that changes in neuromuscular function reflect fatigue induced during exercise and include either the assessment of effort-dependent contraction force [i.e., maximal voluntary contraction (MVC) force] or effort-independent force generated by evoked muscle contractions (i.e., force-frequency properties). Since the assessment of MVC force depends on the subject's voluntary effort (a major contributor to central fatigue), this method is not capable of exclusively quantifying

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peripheral fatigue, a disadvantage that is eliminated with evoked contractions. The determination of voluntary muscle activation (97) during MVC maneuvers can be used to reveal the contribution of the central component of fatigue. Peripheral fatigue is often quantified based on measurements of isometric contractions of a single muscle *before* and *after* exercise, whereas dynamic contractions of many muscles were used *during* exercise.

To determine the development of fatigue *during* exercise, electromyography (EMG) has been utilized (8, 13, 16, 42). Although electromyography has its shortcomings (11), it can be used to estimate the development of both central (16, 17, 42, 44, 52, 124) and peripheral (13, 42) fatigue *during* exercise. In the case of peripheral fatigue, EMG activity/neural drive at a constant work output increases progressively over time, presumably to compensate for fatiguing muscle fibers (Fig. 1). In the case of central fatigue, a fall in muscle force or power is secondary to a centrally mediated reduction in motor drive (reduction in EMG activity), resulting in reduced motor unit recruitment. Finally, the rate of development of fatigue has been estimated by means of the time to task failure—a typical indicator of muscular performance, which is defined as the point where the failure to maintain a given force or power (i.e., task) occurs.

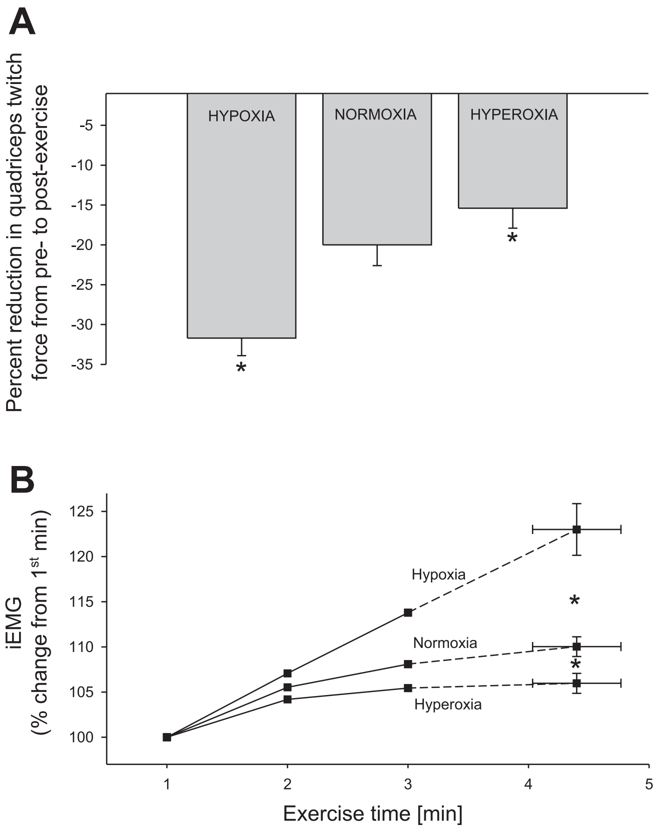

Fig. 1. Effects of constant-workload bicycling exercise for 4.5 ± 0.4 min at 314 ± 13 W (~94% of normoxic maximal O_2 uptake) on the development of locomotor (quadriceps) muscle fatigue under various conditions of convective O_2 transport [Hypoxia: inspiratory O_2 fraction (F_{IO_2}) 0.15, Sa_{O_2} 82%, arterial O_2 content (Ca_{O_2}) 18 ml O_2/dl; Normoxia: F_{IO_2} 0.15, Sa_{O_2} 95%, Ca_{O_2} 21 ml O_2/dl; Hyperoxia: F_{IO_2} 1.0, Sa_{O_2} 100%, Ca_{O_2} 24 ml O_2/dl]. *A*: exercise-induced reduction in potentiated quadriceps twitch force, which was assessed via supramaximal magnetic femoral nerve stimulation before and again 2 min after exercise. *B*: myoelectrical activity [integrated EMG (iEMG)] of vastus lateralis *during* exercise under the three different conditions. Values are normalized to the mean of the first minute. Mean value for iEMG during each muscle contraction (cycle revolution) was calculated and averaged over each 60-s period. Adapted from Amann et al. (8). $*P < 0.05$ vs. Normoxia.

CONVECTIVE O_2 TRANSPORT AND FATIGUE

Increases and decreases in systemic O_2 transport affect muscular performance and the rate of development of both central and peripheral fatigue. Blunted O_2 delivery exaggerates this rate, whereas an augmentation in O_2 delivery attenuates the rate of development (1, 6–9, 18, 24, 25, 32, 39, 43, 49–51, 71, 72, 81, 84, 85, 92, 107, 116–118, 120, 128, 136; see Figs. 1 and 2). The mechanisms by which changes in convective O_2 transport modify the rate of development of fatigue are complex, because the influences of altered O_2 supply occur throughout the organism. However, the highly sensitive effects of O_2 delivery on the rate of fatigue development are generally well accepted although not supported by all studies (14, 19, 22, 30, 45, 74, 82). By comparing the rate of decline in force-generating capacity during submaximal dynamic knee extensions in normoxia and hypoxia, Fulco et al. (50) reported a markedly faster rate of development of peripheral fatigue in hypoxia; however, the difference in exercise-induced reduction in MVC force was not significant between the two conditions until *minute 4* of exercise. These authors suggest that the failure to show greater reduction in MVC force under hypoxic conditions might be due to the use of high-intensity exercise of a duration shorter than 4 min (22, 30) or sustained static contractions in which muscle ischemia is likely to have markedly attenuated the effects of a reduced O_2 delivery on local muscle metabolism (19, 22). In support, studies on isolated canine muscle during which supramaximal electrical stimulation was used to evoke muscle contractions for 2–3 min under conditions of augmented as well as blunted O_2 delivery also reported no difference in end-exercise fatigue (73, 74). Thus under some experimental conditions, reduced oxygen delivery may accelerate the process leading to fatigue only when the duration of the exercise exceeds a certain threshold (>4 min). At lower exercise intensities under conditions of blunted Ca_{O_2}, compensatory increases in O_2 extraction fraction and blood flow are capable of maintaining adequate muscle O_2 supply and thus abolish or attenuate a potential difference in exercise-induced fatigue compared with normoxic conditions (12, 86, 87). At higher exercise intensities, cardiac output and leg blood flow approach their peak values and are no longer capable of compensating for the reduced Ca_{O_2}, and differences in fatigue resulting from alterations in O_2 delivery become more obvious.

Peripheral Fatigue

Alterations in O_2 delivery to the working muscles affect the development of peripheral fatigue during *whole body* exercise via its effects on relative exercise intensity and changes in intracellular metabolism. Both of these factors alter the rate of accumulation of metabolites (e.g., H^+, phosphates) known to cause failure of excitation-contraction coupling (ECC) within the muscle fiber, which has been identified as the main factor that evokes loss of tension development during the fatigue process occurring under conditions of high-intensity exercise (3, 46, 89, 91, 135). Briefly, ECC failure has been associated with an accumulation of metabolites that can directly inhibit the contractile apparatus (48, 55, 125) or disrupt the Ca^{2+} release and uptake pathways in the sarcoplasmic reticulum (2, 41, 46). Although the rate of development of peripheral fatigue is faster with reduced—and slower with increased—O_2 delivery to the working muscle, the key underlying mechanism of fatigue (i.e., perturbations of ECC via diminished Ca^{2+} release and inhibition of the contractile apparatus) are the same in conditions from hypoxia to hyperoxia (123).

Relative exercise intensity. Alterations in convective O_2 transport during *whole body* exercise precipitate a change in peak exercise capacity [peak workload and maximal O_2 uptake ($\dot{V}O_{2max}$)] and therefore a shift of a given *absolute* work load to a different *relative* intensity of exercise, i.e., higher in conditions of a reduced O_2 delivery to the working muscles and lower with an increased O_2 delivery (6–8, 51, 85, 94, 116, 117, 126). An increase in relative exercise intensity subsequent to a reduction in O_2 delivery is known to increase the percentage of type II fibers activated during dynamic muscular contractions (96). Furthermore, reductions in systemic and muscular O_2 delivery may affect fiber type contribution by attenuating the sensitivity of type III/IV muscle afferents to a given stimulus [their stimulation is associated with a preferential recruitment of O_2-dependent type I muscle fibers (10)]. Taken together, more type II fibers are activated under conditions of reduced O_2 transport to the working muscle to maintain a given constant workload. Since type II fibers are associated with an increased rate of accumulation of metabolites known to cause fatigue compared with type I fibers (42), the O_2 delivery-dependent change in relative exercise intensity might account for a significant proportion of the exaggerated rate of development of peripheral fatigue under conditions of reduced O_2 delivery to the muscle. This effect of altered O_2 delivery on the rate of development of peripheral muscle fatigue via alterations in relative work intensity as described above is not applicable when isolated isometric muscular contractions are utilized. This is due to the fact that maximal force output of the muscle under investigation is not affected by alterations in convective O_2 delivery under baseline resting conditions; hence, submaximal isometric muscular contractions at a given absolute force output are also carried out at the same relative work intensity when convective O_2 delivery is altered (35, 49, 50, 54, 81, 107, 136), and the difference in fatigue is mainly due to the effects of altered O_2 delivery on the rate of accumulation of metabolites known to cause fatigue.

Intracellular metabolism. Alterations in convective O_2 transport affect intracellular metabolism, including the rate of accumulation of metabolites that have been identified as major determinants of peripheral fatigue (1, 46, 71). Since the rate of accumulation of protons (1, 71, 75) and the hydrolysis of phosphocreatine and concomitant cytoplasmic inorganic phosphate (P_i) accumulation (65, 66, 71) are faster under conditions of reduced—and slower under conditions of increased—O_2 delivery to the working muscle, both metabolites have been considered to play a key role in the development of peripheral fatigue in conditions of altering systemic O_2 delivery. Although an increased $[H^+]$ is traditionally suggested as the main cause of skeletal muscle fatigue, recent in vitro studies have questioned the deleterious role of $[H^+]$ in metabolic fatigue of mammalian muscles at physiological temperatures (21, 108, 109), and the question regarding the relative contribution of protons to muscle fatigue remains controversial (88). More recently, increased P_i rather than acidosis appears to be the most important cause of peripheral fatigue during high-intensity exercise (134). Briefly, cytoplasmic P_i is thought to enter the sarcoplasmic reticulum and bind to Ca^{2+} to form a precipitate (CaP_i), thus reducing the amount of releasable Ca^{2+}, which results in perturbations of ECC (33, 41, 48). Overall, P_i appears to offer a more attractive explanation of the different rates of development of peripheral fatigue with alterations in systemic O_2 transport (134). For a more detailed reading on determinants of peripheral fatigue, we refer the reader to other reviews published as a part of this highlighted topic.

Causes of Alterations in Convective O_2 Transport and Associated Functional Consequences on Peripheral Fatigue

Alterations of convective O_2 transport to the working muscles in *healthy* humans are the result of changes in Ca_{O_2} and/or limb blood flow. First, alterations in Ca_{O_2} can result from changes in the inspiratory O_2 fraction (FI_{O_2}), inspiratory partial pressure of oxygen (PI_{O_2}; i.e., exposure to altitude), or hemoglobin concentration (i.e., anemia). In some, but not all, well-trained athletes, significant reductions in Ca_{O_2} can—even under sea-level normoxic conditions—result from a substantial high-intensity exercise-induced widening of the alveolar-arterial P_{O_2} difference combined with a blunted hyperventilatory response to exercise, resulting in a decrease in arterial P_{O_2} (Pa_{O_2}) and correspondingly arterial hemoglobin saturation (Sa_{O_2}) from rest, a phenomenon referred to as exercise-induced arterial hypoxemia (EIAH; see Ref. 38). It is important to notice that *severe* EIAH ($Sa_{O_2} < 88\%$) occurs only in a minority of athletes due to a reduction in Pa_{O_2}; more commonly, EIAH results from a rightward shift in the oxyhemoglobin dissociation curve mediated by acidosis and temperature (38). A mild level of EIAH (Sa_{O_2} 93–95%) is observed in most humans during sea level exercise, and a >3% reduction in Sa_{O_2} from rest has been shown to have a significant detrimental effect on $\dot{V}O_{2max}$ (63). Second, hyperventilation of heavy sustained exercise (>85% $\dot{V}O_{2max}$) causes substantial increases in respiratory muscle work, leading to diaphragm and expiratory muscle fatigue (37). Accumulation of metabolites in these muscles activates unmylenated group IV phrenic afferents, which in turn increase sympathetic vasoconstrictor activity in the working limb via a supraspinal reflex (37). The result is a work of breathing-induced reduction in limb blood flow, a corresponding reduction in O_2 delivery to the working muscles, and (presumably) an increase in blood flow to the respiratory muscles, indicating a competitive relationship for a limited cardiac output (62).

As a side note, a *severely* reduced convective O_2 transport to the working muscle via EIAH is experienced only by a subgroup of highly trained endurance athletes and can develop even at submaximal exercise intensities, whereas a reduction in convective O_2 transport via respiratory muscle fatigue and the subsequent reduction in blood flow to the working limb muscles occur in healthy untrained and trained subjects but only at sustained, high-intensity endurance exercise (>85% $\dot{V}O_{2max}$; see Ref. 7).

Ca_{O_2}. Alterations in Ca_{O_2} are followed by reciprocal changes in $\dot{V}O_{2max}$ and endurance performance (27); however, the effect on endurance is more accentuated than that on $\dot{V}O_{2max}$, especially after acclimatization to high altitude (80, 94, 122, 129).

The latter is likely due to a profound effect of Ca_{O_2} on muscle metabolism during submaximal exercise. For example, the blood lactate accumulation curve is shifted to the left, meaning that for a given absolute exercise intensity, the glycolytic rate and associated rate of accumulation of metabolites known to cause fatigue (e.g., H^+) is increased (28, 86). Even a relatively small reduction in Sa_{O_2} (5–8% from rest) associated with EIAH affects the magnitude of locomotor muscle fatigue during high-intensity endurance exercise (≥90% $\dot{V}O_{2max}$). Romer et al. (117) used two cycling exercise sessions at identical power output and duration, during which EIAH was either allowed to develop ($F_{I_{O_2}}$ 0.21; control) or prevented via small increases in $F_{I_{O_2}}$ (0.24–0.30). By preventing EIAH, end-exercise peripheral locomotor muscle fatigue was reduced by more than one-half compared with the level of peripheral quadriceps fatigue measured after the control trial (comparison of pre- vs. postexercise force-frequency curves). These effects of EIAH on locomotor muscle fatigue are reflected in a significant limitation to exercise performance (5-km cycling time trial) (6). Ca_{O_2}, and thus O_2 delivery to the working limbs, was increased by ~8% when the exercise-induced fall in Sa_{O_2} was prevented during the time trial via increases in $F_{I_{O_2}}$. Preventing this drop in Sa_{O_2} during the race resulted in a 2–5% reduction in the time to completion and an up to 5% increase in mean power output. However, although ventilatory muscle work was not directly measured in the study by Romer et al. (117), minute ventilation was significantly reduced when EIAH was prevented via increased $F_{I_{O_2}}$, and this alleviation in respiratory muscle work might have attenuated respiratory muscle fatigue, which in turn might have resulted in a higher limb blood flow compared with the condition when EIAH developed. Therefore, by preventing EIAH, O_2 delivery to the working muscle might have been increased—and therefore locomotor muscle fatigue reduced—due to the higher Sa_{O_2} (i.e., Ca_{O_2}) *and* the higher limb blood flow.

More recently Amann et al. (7) were able to isolate the independent effects of the ventilatory muscle work (and by extension limb blood flow) vs. Ca_{O_2} during heavy-intensity bicycle exercise in acute hypoxia on locomotor muscle fatigue (see Fig. 2). By contrasting normoxic vs. hypoxic Ca_{O_2} ($F_{I_{O_2}}$ 0.21 and 0.15; Ca_{O_2} ~20 ml O_2/dl and ~17 ml O_2/dl, respectively) at equal work rates and durations of exercise with very low levels of ventilatory work (via the use of a mechanical ventilator), they showed that low Ca_{O_2}—independent of any influence of work of breathing—exacerbated low-frequency quadriceps fatigue by over 50%.

Blood flow to working muscle. Increases in blood flow to the electrically stimulated in situ canine muscle per se can attenuate—and reductions exacerbate—the rate of fatigue during *long-term* contractions through a mechanism independent of alterations in O_2 and substrate delivery but probably related to alterations in intracellular environment, i.e., washout of local metabolites (12). However, changes in the rate of fatigue development due to alterations in blood flow are mainly via its effects on O_2 delivery rather than due to blood flow changes alone. This statement is based on the work by Hogan et al. (69, 70, 72), which is discussed in detail in the excellent review by Hepple (68). Briefly, the most compelling evidence stems from a study on electrically stimulated canine gastrocnemius muscle that yielded about 60% of $\dot{V}O_{2max}$ for this model (69). Under conditions of ischemia, muscle force rapidly fell; it recovered quickly upon restoration of normal blood flow and O_2 delivery, but not when normal blood flow alone was restored with deoxygenated blood (69). It is important to remark that upon reoxygenation the recovery of force was incomplete, remaining 24–33% below the control value (69).

Respiratory muscle work can cause skeletal muscle fatigue by reducing blood flow (see above), and thus O_2 delivery, to the working limb (62). The isolated effects of work of breathing-induced changes in limb blood flow on the development of

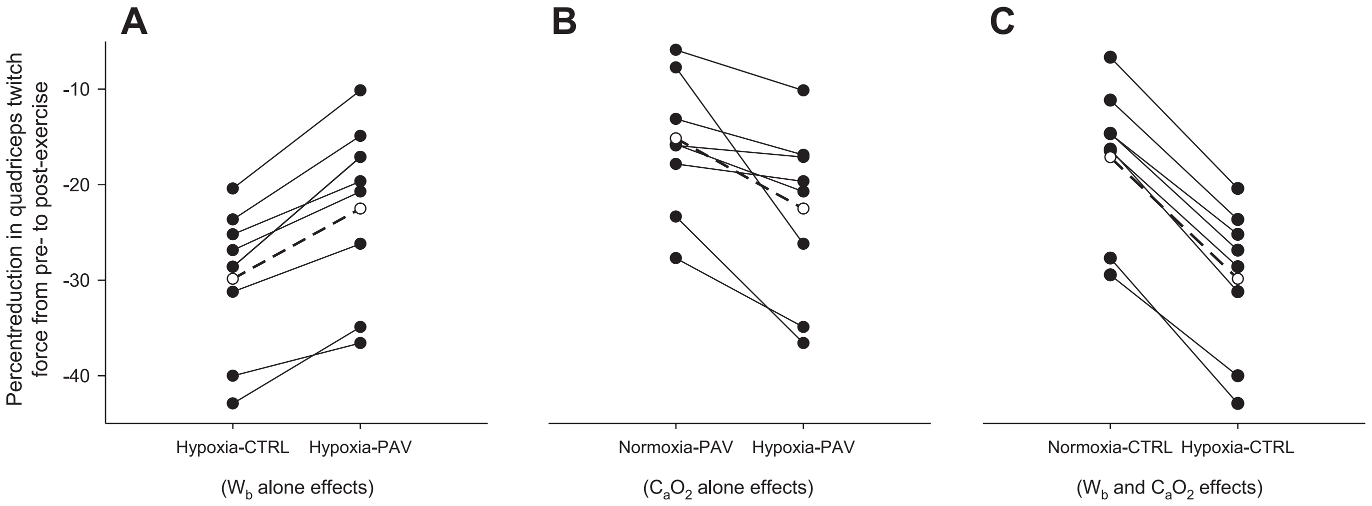

Fig. 2. Individual (●) and group mean (○) effects of constant workload bicycling exercise on the development of locomotor (quadriceps) muscle fatigue. All trials were conducted at identical work rate (273 ± 6 W) and identical duration (8.6 ± 0.2 min). A mechanical proportional assist ventilator (PAV) known to reduce inspiratory muscle work (W_b) by up to 70%, thereby increasing limb blood flow by more than 5% from control (62), and exposure to acute hypoxia ($F_{I_{O_2}}$ 0.15, Sa_{O_2} ~82%, Ca_{O_2} ~17 ml O_2/dl) were used to isolate and separate the independent effects of the two determinants of limb O_2 delivery (limb blood flow × Ca_{O_2}) on whole-body exercise-induced locomotor muscle fatigue. *A*: isolated effects of W_b (i.e., limb blood flow) in hypoxia on quadriceps fatigue. W_b was reduced by about 70%, whereas Ca_{O_2} was unchanged (~17 ml O_2/dl) from Hypoxia-Control (-CTRL) to Hypoxia-PAV. *B*: isolated effects of Ca_{O_2} on quadriceps fatigue. Ca_{O_2} was reduced from ~20 to ~17 ml O_2/dl, whereas W_b, and therefore limb blood flow, was unchanged from Normoxia-PAV to Hypoxia-PAV. *C*: exacerbating effects of reductions in Ca_{O_2} (~15%) combined with increases in W_b (~36%)—and therefore reductions in limb blood flow—on peripheral fatigue when exercising in hypoxia vs. normoxia. From Amann et al. (7).

peripheral locomotor muscle fatigue—independent of changes in Ca_{O_2}—were recently quantified by means of two trials of strenuous (>90% $\dot{V}O_{2max}$) cycling exercise of identical work rate, duration, and Ca_{O_2} (7, 118; see Fig. 2). When the exercise trial was performed with a mechanical ventilator capable of reducing force output of the inspiratory muscles by up to 70%, limb blood flow was increased by 5% or more and leg O_2 uptake ($\dot{V}O_2$) by 3% compared with the control conditions without ventilatory assistance (62). Exercise-induced peripheral quadriceps fatigue (pre- vs. postexercise force-frequency curves) was reduced by ~30% compared with control when both trials were performed in normoxia (118) and by over 35% when both trials were performed in acute hypoxia (7). In contrast, enhancing inspiratory muscle work by about 80% greater than during the control trial (via resistive loading)—and thus reducing limb blood flow by over 10% from control—almost doubled the amount of end-exercise quadriceps fatigue (118). Finally, it is important to mention that the work of breathing-induced change in limb blood flow and the consequential effect on peripheral fatigue is only apparent at exercise intensities greater than 80% of $\dot{V}O_{2max}$ (7), since it has been shown that those intensities, sustained to exhaustion, are necessary to elicit diaphragm fatigue, triggering the metaboreflex as described above (37). The documented effects of limb blood flow—as affected by normally occurring work of breathing—on the development of locomotor muscle fatigue during high-intensity whole body exercise are reflected in significant limitations to exercise performance (7, 64). The time to the limit of exhaustion was increased by ~14% when the normally occurring work of breathing was reduced by about one-half during strenuous constant workload cycling exercise in normoxia (64); when normally occurring work of breathing was reduced by about 70% during strenuous constant workload cycling exercise in acute hypoxia, time to exhaustion was increased by ~16% (7).

Central Fatigue

Central fatigue has been related to changes in extracellular neurotransmitter levels or exercise-induced alterations in the activity of different neurotransmitter systems (34, 95). However, under some experimental conditions it has been shown that central fatigue can also be elicited by low brain oxygenation, i.e., by insufficient O_2 delivery and/or low pressure gradient to drive the diffusion of O_2 from the capillaries to the mitochondria. The CNS is highly sensitive to reductions in oxygenation, and consequently cerebral oxygenation is strongly defended by several homeostatic mechanisms (98). Low brain oxygenation may cause a mismatch between brain O_2 demand and O_2 supply, leading to reduced interstitial (Pti_{O_2}) and cellular Po_2. The critical Po_2 levels in the brain capillaries and mitochondria remain unknown; there are no data on Pti_{O_2} in the cerebral white matter of healthy humans (83). In severely head-injured patients without intracranial hypertension or decreased cerebral perfusion, Pti_{O_2} ranges between 25 and 30 Torr (93). At a jugular venous oxygen saturation (Sjv_{O_2}) of 50% (considered clinically as the lower tolerable limit), brain Pti_{O_2} ranged from 3 to 12 Torr (the regression curve's best fit value being 8.5 Torr; see Ref. 83). An Sjv_{O_2} of 30% was associated with a brain Pti_{O_2} close to 0 Torr, and an Sjv_{O_2} of 70% corresponded to a brain Pti_{O_2} of 20 Torr (83). In one report on a series of 22 patients with severe head injuries, five of six patients with Pti_{O_2} values of 5 Torr or below died or stayed vegetative (132). In a later study these authors reported that even a local Pti_{O_2} value of less than 10 Torr for more than 10 min carried a statistically significant risk of death (131). Thus it is likely that if the Pti_{O_2} approaches or falls below 10 Torr during exercise, central fatigue will ensue due to impaired neuronal function, which will develop more easily the longer the low Pti_{O_2} is maintained.

Low Pti_{O_2} during exercise. Reduced Pti_{O_2} may be caused by reduced O_2 delivery, which may or may not be accompanied by hypoxemia (low Pa_{O_2}). Brain oxygen delivery is determined by the product of Ca_{O_2} × cerebral blood flow (CBF), and both factors are tightly controlled. A reduction in CBF is compensated by increasing cerebral O_2 extraction up to a limit of 0.60, beyond this point lowering CBF results in a reduction in cerebral $\dot{V}O_2$ (101). CBF is mainly regulated depending on brain metabolism, arterial blood pressure, Ca_{O_2}, Po_2, and Pco_2 (90, 112). Although some controversy remains, CBF increases with exercise intensity up to ~60% of $\dot{V}O_{2max}$, after which it decreases toward resting values and sometimes below resting values (67, 100). The reduction in CBF above 60% of $\dot{V}O_{2max}$ has been attributed to the development of hyperventilation-induced hypocapnia (15, 115), an effect that is exacerbated during exercise with hyperthermia (103), in part due to enhanced cerebral CO_2 reactivity (115). During exercise at a constant intensity eliciting fatigue between 5 and 10 min, middle cerebral artery blood velocity increases to a value 20–30% higher than basal at 90 s of exercise, and thereafter it declines to baseline values (59). Brain oxygenation [measured with near-infrared spectroscopy (NIRS)] shows a continuous decline to reach a nadir at exhaustion, while fractional O_2 extraction [calculated as $(Ca_{O_2} - Sjv_{O_2})/Ca_{O_2}$] is maintained close to 0.38, and it increases to 0.47 at exhaustion (59). When the exercise is started with a 1°C higher core temperature, exercise time is reduced and brain deoxygenation is accelerated, but at exhaustion similar levels of deoxygenation and brain O_2 extraction are reached compared with control conditions (59). At first glance, it seems that during high-intensity exercise at a constant intensity, brain deoxygenation could play a role as a mechanism causing central fatigue. Nevertheless, in these experiments the limit of cerebral O_2 extraction was not reached, and the calculated cerebral $\dot{V}O_2$ if anything increased toward the end of the exercise (59). Thus it seems that the reduction in brain oxygenation was not low enough to impair exercise capacity in these experiments.

Exercise-induced elevations in CBF occur primarily in the most active areas of the brain (36, 110). Pott et al. (110) showed that during unilateral handgrip exercise, middle cerebral artery blood velocity increased in the contralateral artery more than in the ipsilateral side. Logically, the areas activated during exercise, which have a higher O_2 demand, should be more vulnerable to a reduction in oxygen delivery and/or Pa_{O_2} during exercise. In agreement, it has been reported that brain oxygenation, measured with NIRS, declines at intensities above the respiratory compensation point, i.e., when arterial Pco_2 (Pa_{CO_2}) starts to decrease during progressive exercise to exhaustion (15). However, maneuvers that prevent a reduction in brain oxygen delivery during peak exercise at sea level, such as the prevention of hypocapnia (60) or the acute administration of a hyperoxic gas mixture (Fi_{O_2} 0.3–1.0) at exhaustion (9) do not prolong exercise time, suggesting that during peak exercise in normoxia, the deficit in cerebral oxygenation per se does not reach a level low enough to cause termination of exercise. An exception to this behavior may be the elite athlete (102) and other humans who show arterial hypoxemia and desaturation during exercise at sea level. For example, elite rowers, who showed marked arterial hypoxemia and 17% cerebral venous O_2 desaturation during exercise at sea level, attained higher performance when the exercise was performed with mild hyperoxia (F_{IO_2} 0.30), which was high enough to prevent arterial and cerebral desaturation (see Fig. 3) (102). However, since the whole exercise bout was performed with increased F_{IO_2}, this likely also delayed the development of peripheral fatigue (117). Moreover, the level of brain deoxygenation shown in these experiments is rather low compared with other studies (59), meaning that these subjects could likely tolerate even a higher degree of brain deoxygenation prior to exhaustion.

In conditions where the normal cardiac output response to exercise is blunted, such as in patients with atrial fibrillation (79), in subjects under β-blockade (77), or during exercise with hyperthermia (57, 58), the normal exercise-induced elevation of middle cerebral artery blood velocity is blunted (77, 79, 104). Although, theoretically, limited cerebral oxygenation could contribute to central fatigue during exercise with hyperthermia, other mechanisms are likely more important (31, 56, 130). In addition, it remains to be tested if preventing hypocapnia during exercise with hyperthermia results in enhanced cerebral perfusion and exercise capacity.

During exercise in severe acute hypoxia (F_{IO_2} 0.105), peak exercise cardiac output is reduced—along with peak work rate—when the exercise is performed with a large muscle mass (24) but not when the exercise recruits only one leg. Due to the very low Pa_{O_2} observed during whole-body exercise with severe acute hypoxia (~34 Torr), pulmonary ventilation is strongly stimulated, leading to very low Pa_{CO_2} values (~25 Torr, i.e., 8 Torr less than during peak exercise in normoxia; see Ref. 24). Cerebral blood flow drops between 2 and 3% per each 1 Torr drop in Pa_{CO_2} when Po_2 remains close to 100 Torr (78), and even if the effect of low Pa_{CO_2} on CBF may be attenuated by severe hypoxia (20, 111), the vasoconstricting effect of hypocapnia predominates over the vasodilatory action of hypoxemia (40, 111, 123). The reduced CBF combined with the reduction in Ca_{O_2} causes brain deoxygenation, which is more accentuated during intense exercise (126). The situation is further complicated by the very low Pa_{O_2}, which may lead to Pti_{O_2} values close to or below 10 Torr in some areas of the brain. Strong support for the role of low brain oxygenation in fatigue during exercise in severe acute hypoxia has been provided by the finding that, at the point of task failure, acute reoxygenation allows for immediate resumption of exercise (see below; see Refs. 9, 24).

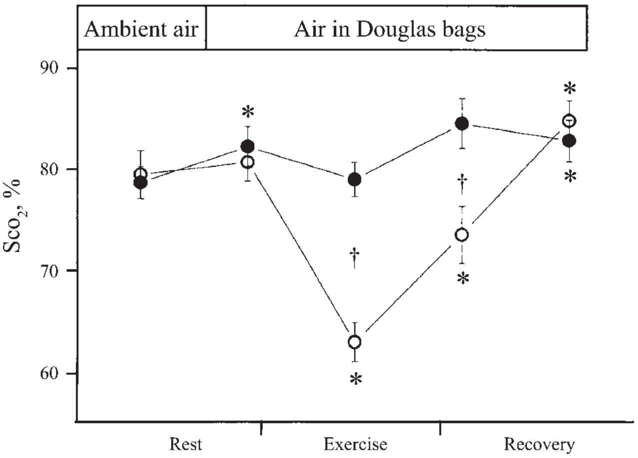

Fig. 3. Cerebral oxygenation (Sc_{O_2}) in ambient air, with an inspired O_2 fraction of 0.21 (●) or 0.30 (○) at rest, during 6 min of maximal rowing exercise, and at 2 and 4 min into recovery after exercise in elite rowers. Mean power output during the hyperoxic trial was 2.4% higher than during normoxia. $^*P < 0.05$ vs. control (rest); $^\dagger P < 0.05$ vs. trial with hyperoxia. From Nielsen et al. (102).

With altitude acclimatization, cerebral oxygenation at peak exercise is restored to sea level values due to higher cerebral blood flow and Ca_{O_2} (20, 99). Thus it is unlikely that insufficient brain oxygenation contributes to cause central fatigue during exercise at moderate altitude in acclimatized humans. However, at extreme altitudes the low Pa_{O_2} may cause a low $Ptio_2$ and by this mechanism limit O_2 diffusion in some regions of the CNS, even in the altitude-acclimatized human (76). The hypothesis that insufficient brain oxygenation contributes to fatigue during maximal exercise in chronic hypoxia is supported by the fact that in well-acclimatized humans at 5,000–5,260 m, acute reoxygenation at peak exercise enables the subjects to continue the exercise and even to increase workload (25, 82).

Is central command affected by hypoxia? The ability to generate maximal power as well as maximal force during *brief* efforts is preserved in severe acute (26) as well as chronic hypoxia (121). Similarly, various studies indicate the absence of a central mechanism limiting small muscle mass exercise in hypoxia (49, 54, 81, 107, 136). However, more recently it has been reported that during severe acute hypoxia (F_{IO_2} 0.10) handgrip MVC force is reduced, while maximal finger-typing frequency is not affected (114).

It has been suggested that hypoxia could also blunt the normal activation of the vasomotor areas of the brain, establishing a lower ceiling for cardiac output and heart rate (24). In turn, the latter could also cause peripheral fatigue due to reduced O_2 delivery to the locomotor and respiratory muscles, enhancing inhibitory feedback on central command.

The effects of low brain oxygenation during submaximal, long-duration whole body exercise on central command remain unknown. However, it has been argued that sensory afferent feedback, originating in the fatiguing locomotor muscle, to the CNS is one of the key determinants of the conscious (and/or subconscious) regulation of central motor drive (i.e., exercise performance), suggesting a strong link between "peripheral" (biochemical changes *within* the muscle) and "central" (reductions in CNS motor drive to the working muscle) fatigue (4, 6). Amann and Dempsey (4) have proposed that the magnitude of this inhibitory neural feedback is proportional to the rate of development of peripheral locomotor muscle fatigue (i.e., fatigue-related metabolic byproducts), which in turn is highly sensitive to muscle O_2 delivery (Fig. 1; see Ref. 8). Consequently, the rate of peripheral fatigue development acts as a dose-dependent trigger of central fatigue. When 5-km cycling time trials (power output voluntarily adjustable) were performed at different levels of arterial oxygenation, central motor drive and muscle power output were upregulated with increased Ca_{O_2} and downregulated with reduced Ca_{O_2}; however, the magnitude of peripheral muscle fatigue developed at end-exercise was identical (6; see Fig. 4). Since the rate of accumulation of peripheral fatigue (i.e., fatigue-causing metabolites) is enhanced with reduced Ca_{O_2} and slowed with increased Ca_{O_2}, the downregulation of central neural drive and consequently power output in the presence of reduced Ca_{O_2} ensured that the rate of development of peripheral fatigue was slowed and prevented from exceeding a sensory tolerance limit (52). Hence, end-exercise peripheral locomotor muscle fatigue was identical between the time trials of various levels of Ca_{O_2} and limited to a critical threshold (6). Based on this correlative evidence, peripheral locomotor muscle fatigue has been proposed as a sensed variable (6, 9, 29). However, how exactly the magnitude of fatigue and the associated metabolic milieu in the peripheral locomotor muscle is sensed and projected to higher brain areas where it might impose inhibitory effects on central motor drive remains to be solved (Fig. 5). These correlative data now need to be confirmed by a direct test of this hypothesis. This requires the determination of the true causal effect of specific interference with sensory input from working locomotor muscle by means of blocking somatosensory afferent feedback.

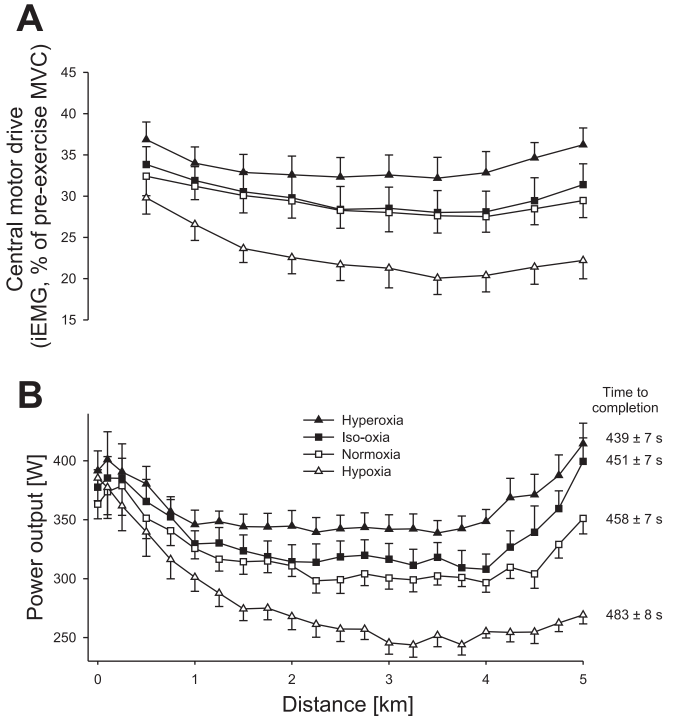

Fig. 4. Central motor drive and exercise performance during 5-km cycling time trials at various levels of Ca_{O_2}. *A*: effects of various Ca_{O_2} value on group mean central neural drive estimated via iEMG of vastus lateralis normalized to the iEMG obtained during pre-exercise maximal voluntary contractions (MVC). Each point represents mean iEMG of the preceding 0.5-km section. Mean iEMG during the time trial was significantly increased from hypoxia to hyperoxia ($P < 0.05$). *B*: group mean variations in power output during the 5-km time trial in four different conditions. End-exercise peripheral fatigue (estimated via changes in force output pre- vs. postexercise in response to supramaximal magnetic femoral nerve stimulation) was identical despite significant differences in exercise performance (i.e., time to completion and mean power output). Group mean power output was 356.5 ± 12.5 W, 331.0 ± 12.9 W, 313.8 ± 12.9 W, and 275.0 ± 9.7 W ($P < 0.05$) for Hyperoxia (FI_{O_2} 1.0, Sa_{O_2} 100%, Ca_{O_2} 24 ml/dl), Iso-oxia (FI_{O_2} 0.28, Sa_{O_2} 98%, Ca_{O_2} 23 ml/dl), Normoxia (FI_{O_2} 0.21, Sa_{O_2} 91%, Ca_{O_2} 21 ml/dl), and Hypoxia (FI_{O_2} 0.15, Sa_{O_2} 77%, Ca_{O_2} 18 ml/dl), respectively. $n = 8$. From Amann et al. (6).

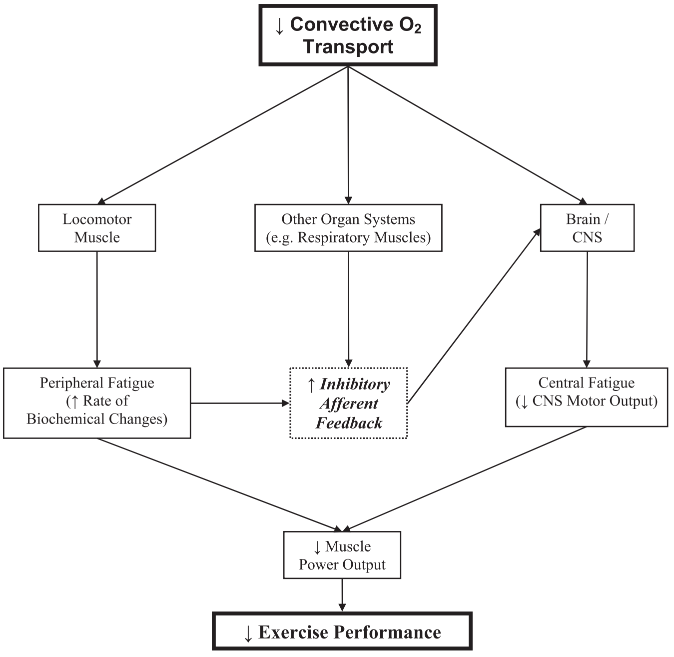

Fig. 5. Hypothetical scheme linking convective O_2 transport and exercise performance via its effects on fatigue. Alterations in convective O_2 transport occur throughout the organism and affect various organ systems. Consequently, various organs might affect exercise performance via inhibitory feedback mechanisms controlling central motor output. It has been proposed that peripheral muscle fatigue is carefully regulated via modulations of central nervous system (CNS) motor output to ensure muscle homeostasis during exercise from hyperoxia to moderate hypoxia (6). The relative importance of peripheral fatigue appears to diminish at more severe levels of hypoxia, and cerebral hypoxia might gain in relative influence regarding the termination of exercise (9). From Amann et al. (5).

Exceptions to this hypothesis have been shown to occur under conditions of critically low levels of brain oxygenation, i.e., exposure to extreme altitude or hyperventilation (see *Central Fatigue*). The O_2-dependent rate of development of peripheral fatigue and associated inhibitory effects of somatosensory afferent feedback on central motor drive has been shown to be crucial up to an acutely challenged level of Sa_{O_2} of >70% (6, 116), whereas below this level of Sa_{O_2}, O_2-sensitive sources of inhibition of central motor drive within the CNS appear to dominate the regulation of muscular performance (9, 24).

Summary

In many exercise models and environmental conditions, fatigue shows dependency on convective O_2 transport (Fig. 5). Reductions in O_2 supply exacerbate and increases attenuate the rate of fatigue development. Insufficient peripheral oxygenation elicits fatigue by facilitating the accumulation of metabolic byproducts, which interfere with excitation-contraction coupling within the myocyte. O_2-dependent central fatigue is mediated via *1*) the O_2-sensitive balance of ATP demand and supply in brain areas involved in the generation of central motor command, and/or *2*) inhibitory neural feedback to the CNS whose magnitude is proportional to the O_2-dependent accumulation of metabolic byproducts in the working locomotor muscles.

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