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Inadequate Cerebral Oxygen Delivery and Central Fatigue during Strenuous Exercise

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NYBO, L. and P. RASMUSSEN. Inadequate cerebral oxygen delivery and central fatigue during strenuous exercise. *Exerc. Sport Sci. Rev.*, Vol. 35, No. 3, pp. 110–118, 2007. *Under resting conditions, the brain is protected against hypoxia because cerebral blood flow increases when the arterial oxygen tension becomes low. However, during strenuous exercise, hyperventilation lowers the arterial carbon dioxide tension and blunts the increase in cerebral blood flow, which can lead to an inadequate oxygen delivery to the brain and contribute to the development of fatigue.* **Key Words:** central nervous system, cerebral blood flow, cerebral metabolism, hypoxia, mitochondria

INTRODUCTION

Fatigue emerges during exercise as increased difficulty in retaining a required power or as impairment in the ability to produce force and power. The development of fatigue is complex and determined by an intricate interplay between psychological and physiological factors. Even in well-motivated subjects, the relative importance of muscular/peripheral and central factors seems to vary markedly depending on the mode, intensity, and duration of the exercise, besides the nutritional status of the subjects and the environmental setting. Some physiological factors may relate directly or indirectly to homeostatic disturbances in the skeletal muscles, whereas other factors may directly affect the central nervous system (CNS) and its ability to activate the skeletal muscles via the alpha motor neurons.

Previously, the "central fatigue hypothesis" has focused mainly on changes in extracellular neurotransmitter levels or exercise-induced alterations in the activity of different neurotransmitter systems, with the serotonin, dopamine, and ammonia-glutamate-glutamine "hypotheses" as the most dominant (3,20,24). The present review discusses the possibility that, during some exercise conditions, fatigue can be provoked or modulated by inadequate oxygen delivery to the brain and subsequently low cerebral capillary and mitochondrial oxygen tension (PO_2). In turn, this could influence the function of neurons and astrocytes and thereby the ability to maintain motor activation. Although it is recognized that this impairment can occur during exercise at high altitude, it may also arise as a consequence of exercise-induced arterial hypoxemia (EIAH) or exercise conditions where hyperventilation-induced hypocapnia lowers cerebral blood flow (CBF). Hypocapnia may be provoked by exercise at intensities above the ventilatory threshold and, especially, exercise with hyperthermia, which may lower the cerebral perfusion by 20%–30% (23,24).

At rest, the brain is protected against hypoxia-induced reductions in arterial oxygen delivery because CBF increases when the arterial oxygen tension becomes low. When exercise and hypoxemia are combined, however, hyperventilation-induced reductions of the arterial carbon dioxide tension ($PaCO_2$) may become so pronounced that it blunts the increase in CBF, and therefore, increased perfusion fails to compensate for the lower arterial oxygen content. Anecdotes from athletes experiencing blackout or fainting immediately after completing maximal exercise support the idea that oxygen delivery to the brain may become critically low, and studies of maximal rowing in subjects with EIAH show that the cerebral oxygenation falls during such exercise. Although athletes rarely faint during exercise studies in the laboratory, studies with different combinations of strenuous exercise and impaired oxygen delivery to the brain indicate that the CNS function may be

compromised and that mitochondrial oxygen tension (P_{mito}) in the brain may become critically low. At rest and during moderate exercise, the brain is well perfused, and moderate reductions in CBF/cerebral oxygen delivery may be compensated for by increased extraction. However, a relatively high capillary oxygen tension is required to maintain the mitochondrial PO_2 at an adequate level. The main questions raised in the present review are the following: 1) How large reduction in cerebral oxygen delivery and subsequent lowering of the mitochondrial PO_2 can the brain tolerate before it begins to influence motor performance and contribute to the development of so-called central fatigue? 2) Which exercise conditions cause such reductions, and how can we monitor and evaluate whether cerebral oxygenation levels are sufficient?

LOW PO_2 AND MOTOR PERFORMANCE

Reductions in the arterial oxygen content (CaO_2) lowers maximal work rate and impairs exercise endurance during whole-body exercise. Because changes in CaO_2 influences oxygen delivery to all tissues, including the skeletal muscles and the brain, it may be difficult to determine whether performance deteriorates as direct effect of the low PO_2 in some of the most active brain regions or whether central motor output becomes reduced secondary to feedback from the muscles and from the increased cardiorespiratory stress that accompanies exercise with a low atmospheric oxygen tension. At moderate hypoxia, the reduced work rate during maximal whole-body exercise is influenced by feedback from the working muscles. Reduced oxygen delivery to exercising muscles accelerates the accumulation of muscle metabolites, and these fatigue-related and sensory fiber-stimulating substances may activate group 3 and 4 muscle afferents and contribute to inhibitory feedback to the CNS during fatiguing exercise. In contrast, during severe hypoxia, afferent feedback seems to be of minor importance because epidural anesthesia (blocking or reducing feedback from group 3 and 4 muscle afferents) has no effect on performance or perceived exertion during maximal exercise, when the inspired oxygen fraction was lowered to approximately 10% (17).

Further support for a direct effect of reduced cerebral oxygen delivery on motor performance is provided by the study presented in Figure 1. In that study, cerebral oxygen delivery was varied by providing low, normal, or high PO_2 in the inspired air either with normal, high, or reduced arterial CO_2 tension, and motor performance was evaluated as maximal handgrip strength. When oxygen delivery was reduced by more than 15% below control levels, as a separate effect of either hyperventilation-induced reduction in CBF or inhalation of air with a low PO_2, the maximal handgrip strength decreased concurrently with an increase in lactate spillover from the brain, which indicated that cerebral oxygen levels became inadequate to support optimal aerobic metabolism (Fig. 1 and "Cerebral Metabolism and Mitochondrial PO_2" section). Although low arterial PO_2 or hyperventilation-induced alkalosis may have influenced the ability of the muscles to produce a maximal
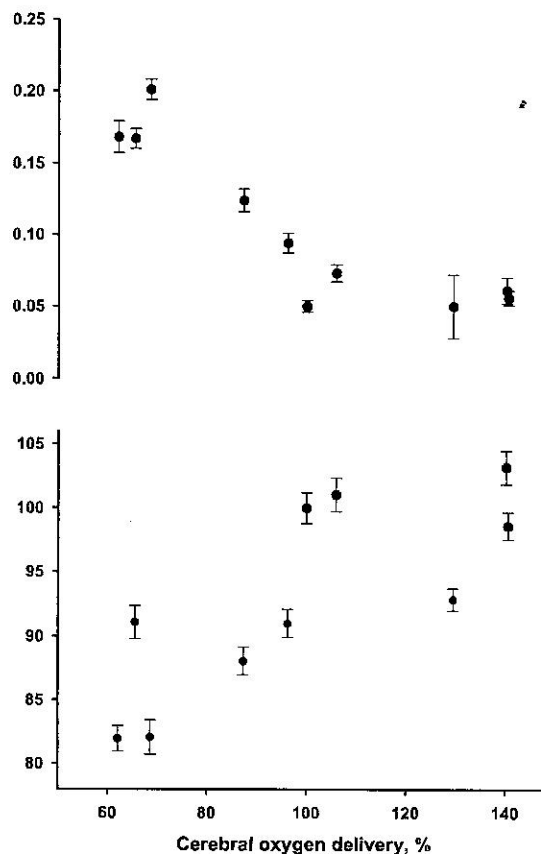

Figure 1. Cerebral lactate release (*top*) and maximal voluntary handgrip force (*bottom*) as a function of cerebral oxygen delivery (percent control). Alterations in central blood flow (CBF) (induced by CO_2 breathing, hyperventilation, or normal ventilation) were combined with different levels of CaO_2 and PaO_2 (10%, 21%, or 100% oxygen in the inspired air) to vary the cerebral oxygen delivery from approximately 60% to approximately 140% of control (supine rest; see 29 for details). Data are mean ± SE for 12 subjects.

force, the energy used in the skeletal muscles during a brief maximal contraction is delivered mainly by anaerobic metabolism (net adenosine triphosphate (ATP) and creatine phosphate degradation). It is likely, therefore, that the impaired motor performance observed in the study by Rasmussen et al. (29) relates to central fatigue arising subsequently from inadequate oxygen delivery to the brain.

Central fatigue may not always appear during a single brief maximal voluntary contraction (MVC), and it may be necessary to use a protocol with repeated or sustained maximal contractions. Both for hypoglycemia- and hyperthermia-induced central fatigue (see 24 for review), well-motivated subjects are capable to establish a maximal neural drive to the muscle for a brief period, despite pronounced fatigue, whereas the ability to sustain a high firing rate of the alpha motor neurons for more than a few seconds becomes markedly impaired. Accordingly, MVC of a small and rested muscle group may be unaffected by exposure to moderate altitude (6), whereas others have reported (4,7) on the effect of extreme simulated altitude: "in some

subjects, the responses to stimuli interpolated during repeated MVC provided evidence of central fatigue at altitude." If a period of rest is allowed between or before brief maximal efforts, there may be enough time for replenishment of brain glycogen and restoration of high-energy phosphate compounds in the relevant brain areas. In contrast, low mitochondrial oxygen tension during sustained motor activation may not allow for adequate maintenance of neuronal and astrocytic homeostasis, and eventually, this will impair the ability to maintain a high level of neuronal firing.

FACTORS COMPROMISING CEREBRAL OXYGEN DELIVERY DURING EXERCISE

Because sustained static and dynamic exercise requires continuous or frequent repetitive neuronal firing in several motor areas, the brain seems to be more vulnerable to hypoxia during exercise. Furthermore, an elevated CBF does not compensate for a low arterial Po_2 during strenuous exercise because pronounced hyperventilation will lower arterial carbon dioxide tension (Pco_2) and cause constriction (less vasodilation) of the arterioles in the brain. This seems irrational because the primary function of the cerebral circulation is to ensure homeostasis in the brain by providing oxygen for mitochondrial respiration and removal of waste products from the cerebral metabolism. Cerebral autoregulation, metabolic regulation, and CO_2 (hydrogen ion; H^+)–mediated vasodilatation are the most important mechanisms to ensure that CBF remains adequate. However, CO_2 reactivity seems to dominate, and during exercise associated with hyperventilation-induced reductions of the arterial CO_2 tension, CBF may decline despite increased metabolic activity in motor areas of the brain (24). Both at rest and during exercise, the cerebral perfusion is influenced strongly by $Paco_2$, and the cerebral CO_2 reactivity (percentage change in CBF per millimeters of mercury change in $Paco_2$) may even increase from approximately 3%–4% at rest to 4%–5% during exercise (13,23,28). It is not unusual to see reductions of the arterial Pco_2 by 6–10 mm Hg during maximal exercise and exercise with hyperthermia, which, in turn, may reduce global CBF by 30% compared with moderate intense exercise at a normal temperature response (23,28).

Cerebral blood flow is distributed heterogeneously and largely depends on the neuronal activity in the different regions of the brain. Dynamic exercise is associated with activation of several areas of the brain, and when the intensity does not exceed the ventilatory threshold (and arterial Pco_2 remains fairly stable), flow to these activated areas will increase linearly with the exercise intensity (13,30). When the intensity exceeds the ventilatory threshold, both global and regional CBF decline as $Paco_2$ decreases (Fig. 2). Although neuronal activity and metabolic needs keep increasing in the motor areas, regional CBF will decline as exercise intensity increases toward maximum, and regional CBF (e.g., to the motor cortex) may return to similar levels as at rest. According to equation 1 in "Cerebral Metabolism and Mitochondrial Po_2" section,
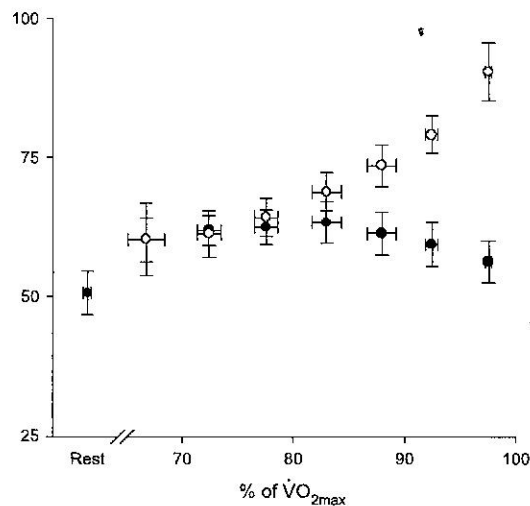

Figure 2. Middle cerebral artery blood flow velocity during incremental exercise, with (open symbols) and without (solid symbols) "adjustments" for arterial carbon dioxide tension (Rasmussen, P., H.H. Stie, B. Nielsen, et al., unpublished manuscript/observations, 2005). Data are mean ± SE for 7 subjects.

this uncoupling of metabolism and flow will cause a reduction in the mitochondrial Po_2 in the activated motor areas.

However, exercise causes hemoconcentration (secondary to increased filtering of plasma in the muscle capillaries) and, based on the assumption that the arterial saturation remains unchanged, CaO_2 may increase by 5%–10% during exercise. Therefore, with a normal atmospheric (and arterial) Po_2, the exercise-induced hemoconcentration causes the oxygen delivery to motor areas of the brain to be slightly higher during maximal exercise compared with that during rest but lower than that during submaximal exercise and lower than would be expected on the basis of the neuronal activity in the activated motor areas (14). Nonetheless, oxygen supply seems to be sufficient to support the aerobic metabolism in the brain during maximal exercise (Table). However, in subjects with severe EIAH, which may lower the arterial Po_2 to less than 70 mm Hg and saturation to less than 88%, the cerebral oxygen delivery may be disturbed to an extent where it begins to influence aerobic metabolism in the brain as P_{mito} may be reduced by approximately 10 mm Hg. Similarly, low atmospheric and arterial Po_2 when exercising at a high altitude may reduce the cerebral capillary oxygenation levels and limit mitochondrial Po_2 to support the cerebral metabolism. At rest, lactate spillover increases when the cerebral oxygen delivery is reduced by more than approximately 15% and the mitochondrial Po_2 decreases by more than 6–7 mm Hg (Fig. 1; see 29). It is more difficult to use increased lactate spillover as an indicator of inadequate oxygen delivery during strenuous exercise because the brain begins to metabolize lactate during high intensity exercise (2). Although endogenous lactate production in some brain areas may increase with strenuous exercise, it is likely that such an increase will be hidden by the high arterial lactate

TABLE. Comparisons of cerebral mitochondrial oxygen tension, cerebral metabolism, oxygen uptake, delivery, capillary saturation, and tension at rest during submaximal exercise and in response to strenuous exercise conditions.

	Normal Values at Rest	Submaximal Exercise with Normal PaO_2	Maximal Exercise with Normal PaO_2	Maximal Exercise in Subjects with Severe EIAH[a]	Exercise at High Altitude (or Low F_1O_2)	Submaximal Exercise with Hyperthermia	Maximal Exercise with Hyperthermia
Delta change in cerebral mitochondrial oxygen tension	—	Increases ~5 mm Hg	Decreases ~5 mm Hg	Decreases ~10 mm Hg	Decreases by up to 13 mm Hg	Decreases ~5 mm Hg	Decreases ~6 mm Hg
Capillary oxygen saturation (%) and tension (mm Hg)	Saturation ~80; P_{cap} ~40–45 mm Hg	Saturation ~80; P_{cap} ~45 mm Hg	Saturation ~70; P_{cap} ~40 mm Hg	Saturation ~65; P_{cap} ~34 mm Hg	Saturation ~44; P_{cap} ~25 mm Hg	Saturation ~77; P_{cap} ~40 mm Hg	Saturation ~74[b]; P_{cap} ~38 mm Hg
Cerebral oxygen delivery and/or CBF	O_2 delivery ~400 μmol 100 g^{-1} min^{-1}, with a CBF of 50 mL min^{-1} (100 g cerebral tissue)$^{-1}$	20% increase in oxygen delivery to active motor areas — no change in global CBF	10% increase in delivery to motor cortices but reduced delivery to the whole brain	The global cerebral oxygen delivery may decrease by ~25% as combined effect of reduced arterial saturation and lowered flow. Slight or no reduction in delivery to activated motor areas.	20–25% reduction in delivery to active motor areas, although regional flow increases by 30%–40%	Oxygen delivery and global CBF decreases by ~20% compared with rest. Regional CBF to motor cortex initially increases but becomes reduced as hyperventilation lowers $PacO_2$.	Similar CBF response during hyperthermia and control trial in the present study.[c] MCA V_{mean} at exhaustion equal to rest.
Cerebral oxygen consumption	150 μmol (100 g)$^{-1}$ min^{-1}	Unchanged, or slightly increased, compared with rest.	Increased in the active motor regions — no or slight increase in global CMR.	Unchanged, or slightly increased, compared with rest.	Reduced by 10%–12%.	Increases by 7%.	No change compared with maximal exercise with normal temperature response but increased compared with rest.[c]
Cerebral extraction fraction	~35%	~35%	46%	48%	39%	43%	46%
Cerebral metabolic changes		No changes in net lactate turnover.	Marked lactate uptake by the brain as lactate uptake and metabolism increases when the arterial becomes elevated.	Marked lactate uptake by the brain.	No lactate uptake despite high arterial levels, which normally causes an uptake during strenuous exercise.	Increased glucose uptake — no change in lactate release.	Marked lactate uptake by the brain — not different from maximal exercise with normal temperature response.
References	(16,19,29)	Unpublished observations	(9)	(22,26), Rasmussen et al., unpublished manuscript/observations.	Observations from study with a PaO_2 of 76 mm Hg (F_1O_2 = 10% ~ 6000 m above sea level and ~5000 m 12	(23,25)	(9)

[a]Estimated on the basis of results from Nielsen et al. (22) with trained rowers experiencing a reduction in SaO from 98% to 92% during maximal exercise. However, because jugular venous saturation was not reported for the trained subject in that study, data have been combined with recent results from study in our laboratory, where similar levels of SaO have been obtained with inhalation of air with 17% oxygen.

[b]Calculated from the arterial and venous blood values reported by the authors in accordance to equation 2. However, the authors observe an almost 40% decrease in near-infrared spectroscopy (NIRS)–determined saturation (tissue oxygenation), which is much larger than those reported in any other study and may relate to the algorithm used by the NIRS device in this study to convert the raw NIRS signal to an absolute saturation level.

[c]This study reports a marked increase in the global oxygen uptake from rest to maximal exercise and a quite large global CBF and oxygen uptake in the resting condition. However, it should be considered that CBF was evaluated with duplex Doppler and measured as arterial inflow (carotid artery), although such methodology has not been evaluated against Kety-Schmidt during exercise (see "Cerebral Metabolism and Mitochondrial Po2" section).

CMR indicates cerebral metabolic rate.

levels and the marked increase in the cerebral uptake of carbohydrates (including both blood glucose and lactate) in response to brain activation (2).

Although exercise with superimposed hypoxia may compromise cerebral autoregulation and the ability to increase and to maintain an adequate cardiac output seems to influence the CBF response to exercise, the influence of changes in CBF arising secondary to changes in mean arterial pressure are of minor importance for maintenance of oxygen delivery to the brain. Thus, compared with the relatively large changes in CBF and arterial oxygen content with changes in arterial CO_2 and O_2 tension, the influence of arterial blood pressure is much smaller, and because mean arterial pressure increases during exercise, this would support rather than compromise oxygen delivery to the brain.

CEREBRAL METABOLISM AND MITOCHONDRIAL Po_2

Because the brain relies on aerobic metabolism, it is clear that the oxygen tension within the mitochondria is critical for the cerebral function. However, it is not clear what the critical Po_2 level is. Thus, impairment of the mitochondrial oxidation has been observed in the range of approximately 0.5–20 mm Hg (depending on the methodology used for evaluation of P_{mito}), and the physiological level in a resting human is estimated to range from close to zero and up to 40 mm Hg (5,27). Obviously, it is not possible to measure P_{mito} directly in vivo, and the wide range of the reported values for P_{mito} may relate to the methodological differences and difficulties; however, it may also relate to large differences within the brain. Although, the regional CBF is matched largely to the metabolic activity, flow and energy turnover are distributed heterogeneously in the brain, and there may be relatively large differences across brain regions. P_{mito} depends on the balance between oxygen supply and use and the oxygen conductance from the capillary to the mitochondria (L). Thus, the mitochondrial oxygen tension is determined by the capillary Po_2, the oxygen use (cerebral metabolic rate (CMR); $CMRO_2$), and L as expressed by equation 1 (8,29):

$$P_{mito} = P_{Cap} - \frac{CMRO_2}{L} \qquad [1]$$

As the brain lacks capillary recruitment, O_2 diffusibility (L) remains stable at any measured blood flow level and is determined at the lowest capillary oxygen tension, where P_{mito} is assumed to approach zero. P_{Cap} can be estimated from measurement of arterial and cerebral venous blood,

$$P_{Cap} = P_{50_a}^{Hb} \sqrt[h_a]{\frac{S_aO_2 + S_vO_2}{2 - S_aO_2 - S_vO_2}} \qquad [2]$$

where $P_{50_a}^{Hb}$ is the Po_2 when hemoglobin is half saturated, and h_a is Hill coefficient for arterial blood.

The average oxygen consumption may be calculated on the basis of the cerebral a-v difference for oxygen and CBF. However, it may not be simple to estimate flow during strenuous whole-body exercise, and interpretation and comparison of results from different studies require care, including consideration of whether a regional or a global CBF has been estimated. Mixed cerebral venous blood may be obtained from the internal jugular vein, but this blood may not be representative of all brain regions, and it provides only a measure of the average oxygen tension and saturation of the blood leaving the brain. Venous blood from active brain areas may have different oxygen content. Nevertheless, this method may provide the best functional estimate of changes in P_{mito} in exercising subjects. The calculation does not allow for an absolute determination of the cerebral P_{mito}, but it provides a useful indication of changes in the average cerebral P_{mito} relative to a basal level and thus the global oxygen state of the brain. As illustrated in Figure 1, it seems that a reduction in the average P_{mito} by more than 6–7 mm Hg — either induced by arterial hypoxia or reduced CBF — is associated with impaired cerebral aerobic metabolism (as increased lactate spillover indicates that aerobic pyruvate metabolism cannot match the required glycolytic rate). In addition, there is a reduced ability to activate the motor neurons at this P_{mito} level, implying that a drop by more than 6–7 mm Hg in P_{mito} or a reduction in cerebral oxygen delivery by more than 15% needs to be prevented for optimal motor function of the brain. Brain cells can survive for a relatively long time on anaerobic energy turnover; glycolytic metabolism by the astrocytes may protect against cell damage, and for a limited period, it may postpone fatigue. However, anaerobic metabolism of a glucose molecule only produces energy for resynthesis of 2 ATP, whereas aerobic metabolism of glucose is much more efficient and may provide up to 36 ATP. Thus, even if the brain cells could get rid of the produced lactate and maintain the lactate dehydrogenase–catalyzed conversion of pyruvate to lactate and concomitant interconversion of the reduced form of nicotinamide adenine dinucleotide to the oxidized form, NAD+ (as required to allow for further breakdown of glucose to pyruvate via the Embden-Meyerhof pathway), the brain would have to increase its glucose uptake substantially. In accordance, the cerebral glucose uptake increases during hypoxia and maximal exercise (2,29). However, during hypoxia, the increase is modest (2), and the enhanced cerebral uptake and anaerobic metabolism of glucose are not sufficient to maintain optimal function of the brain as judged from the impaired motor activation after 10-min exposure to hypoxia (29).

These observations have been made in resting subjects, and the tolerable reduction in P_{mito} may be even lower when the brain is activated by strenuous exercise, which raises the metabolism in the involved motor areas of the brain. Thus, the P_{mito} depends on the integration of supply and demand, and increased regional $CMRO_2$ will lower the cerebral P_{mito} (equation 1) unless flow in the active brain area increases to compensate for the increased use. To maintain P_{mito}, or at least avoid critically large reductions of P_{mito} in the active brain areas, the capillary oxygen tension and saturation must be kept at a relatively high level, and this requires that the increase in flow is proportionally larger than the increase in metabolism. There is practically no capillary recruitment in the brain; the oxygen extraction

rises linearly with distance as the blood traverses the capillary network from arterial to venous ends, and the capillary geometry is such that all segments of the capillary bed supply equal amounts of brain tissue (15). Therefore, compared with muscle tissue, the maximal extraction fraction is much lower for the brain.

Capillary Oxygen Tension and Saturation

As described by equation 2, the oxygen saturation and tension of the capillaries may be estimated on the basis of arterial and cerebral venous blood sampling. With this methodology, the lowest capillary saturation level consistent with unimpaired metabolic function of the brain is estimated to approximately 70%, corresponding to a capillary Po_2 between 35 and 40 mm Hg (depending on temperature, pH, and CO_2 level). In resting subjects with a normal PaO_2, the highest extraction fraction (a-v difference for oxygen divided by arterial oxygen content) seems to be 55%–60%. Presyncope symptoms emerge during head-up tilt when the jugular venous saturation becomes reduced by approximately 15% (19), corresponding to a oxygen extraction fraction of approximately 55%. However, the global cerebral oxygen extraction rarely exceeds 50% during exercise (Table). Because physical or mental activation of the brain involves increased energy turnover in the active regions, whereas other regions may have unchanged or a decreased metabolic rate, the mixed venous blood may not reflect oxygen extraction in the activated brain regions. Furthermore, the highest obtainable global extraction fraction during hypoxia may become even lower because the Po_2 gradient between the capillary and mitochondria will be too low to allow for sufficient oxygen flux/diffusion from blood to the mitochondria. Accordingly, the CMR for oxygen declines during exercise with severe hypoxia, and oxygen delivery to the brain becomes inadequate, although the oxygen extraction fraction is below 50% (Table).

Cerebral metabolism and oxygenation can be estimated noninvasively by determining capillary-oxygenation-level–rdependent (COLD) monitoring with near-infrared spectroscopy (NIRS). Near-infrared spectroscopy works by emitting light at a defined wavelength into the tissue; after absorbance by hemoglobin that depends on its conformal state, some of the emitted light reaches to an optode, and oxygenation can be calculated according to a modified Lambert-Beer law. Near-infrared spectroscopy can be applied over any region of the skull; however, for subject's comfort, the forehead is usually preferred. The penetration depth of NIRS remains unknown *in vivo* but is likely restricted to a few centimeters. Although NIRS is a relative measure, it faithfully tracks the capillary oxygenation level as estimated from arterial and jugular venous blood saturation (29). The COLD signal, nonetheless, still depends on the chosen algorithm, and the signal may vary some 5% from "true" blood oxygenation, depending on the apparatus (29). Therefore, NIRS provides a rough estimate of capillary oxygen saturation, and the COLD signal is usually converted to hemoglobin oxygen saturation to provide a useful measure of the relation between oxygen availability and demand.

Cerebral Oxygen Uptake and Metabolism

Comparison of the CMR for oxygen during different exercise conditions could indicate whether oxygen delivery has been adequate to support the aerobic metabolism. Although global and regional $CMRO_2$ may be determined with various methods during strenuous exercise, the estimate is associated with a host of problems. The rigorous movements associated with strenuous exercise preclude the use of advanced imaging techniques such as functional magnetic resonance imaging and positron emission tomography.

Therefore, evaluations of cerebral metabolism during whole-body exercise have concentrated on measurements of CBF and the arteriovenous differences across the brain. However, the cerebral circulation receives blood from both the carotid and spinal arteries, making evaluation of the inflow troublesome. Furthermore, the venous drainage goes to both the spinal venous plexus and the internal jugular veins. The internal jugular vein is relatively easily catheterized and, therefore, used for sampling of cerebral venous blood but may not represent venous blood from all regions of the brain. To further complicate the evaluation, contribution to the drainage of each vein depends on body position; it is asymmetrical and may vary between subjects (29). Despite these problems, the standard has been considered the Kety-Schmidt method, which derives CBF based on Fick principle — that is, wash out of a freely diffusible tracer determined from arterial and internal jugular venous blood samples (25). Although the evaluation of the CBF with the Kety-Schmidt technique provides a measure of jugular venous flow, the method can provide useful values of global CBF at rest and during submaximal exercise (18). However, a major difficulty with this method for determination of CBF and calculation of the $CMRO_2$ during maximal exercise is the time resolution of the method. The Kety-Schmidt method requires approximately 30 min of tracer infusion, followed by at least 10 min of blood sampling, which is not compatible with maximal whole-body exercise.

Alternatively, CBF can be evaluated continuously by ultrasound Doppler sonography in the carotid artery or the basal cranial arteries. The exercise response in the basal arteries is similar to that in the carotid arteries (9), thereby indicating some relation between changes in regional and global CBF. However, determination of flow or flow velocities in the basal cerebral arteries estimates regional rather than global CBF, and data from studies using different methods for evaluation of CBF must be interpreted with caution (18). A crucial assumption in the interpretation of Doppler-derived flow velocity data is an unchanged caliber of the insonated vessel; however, it seems that vascular tone (vessel diameter) is regulated distally to the basal cerebral vessels, and in general, CBF velocities obtained by transcranial ultrasound Doppler seems to reflect regional CBF (13).

When evaluated with the Kety-Schmidt technique, whole-brain blood flow and $CMRO_2$ seem to be unchanged during exercise compared with those during rest, although the 10%–25% increase in flow derived by ultrasound Doppler assessment of the arterial inflow to the brain or in

the basal cerebral vessels indicates that flow to large parts of the brain increases in response to motor activation (10,11,13). However, even if global or regional CBF and $CMRO_2$ may be determined, an unchanged or even elevated $CMRO_2$ does not necessarily imply that oxygen delivery has been adequate. It may be argued that oxygen delivery is not sufficient to allow for a further increase in the $CMRO_2$, which may be required during periods with intense neuronal firing (e.g., mentally demanding exercise).

RESPONSES DURING STRENUOUS EXERCISE

During submaximal exercise, oxygen delivery to the brain seems to be more than adequate because P_{mito} increases. There is an unchanged lactate release and global metabolic rate during such exercise. However, P_{mito} and capillary oxygen saturation during strenuous exercise (Table) declines when hyperventilation-induced hypocapnia lowers or blunts an increase in CBF. During the three conditions where PaO_2 and arterial oxygen saturation (SaO_2) remain fairly unchanged (i.e., maximal exercise and submaximal and maximal exercise with hyperthermia), the drop in P_{mito} is limited to 5–6 mm Hg; therefore, it is below the level where P_{mito} begins to restrict the cerebral metabolic function and motor performance. The 5- to 6-mm Hg drop in P_{mito} is close to the reduction that may be tolerated without impairment in cerebral function, as confirmed by that lack of a change in lactate spillover from the brain during submaximal exercise with hyperthermia and during maximal exercise with or without hyperthermia, and the marked lactate uptake by the brain when the arterial lactate concentration rises. When cerebral oxygen delivery becomes inadequate to support aerobic metabolism during exercise with severe hypoxia, the brain does not take up lactate, although the arterial concentration increases to similar levels as during maximal exercise. The reduction in P_{mito} during submaximal exercise with progressive hyperthermia is similar to that of maximal exercise, but arterial lactate remains low (~2 mM), and there is no change in lactate balance across the brain. Taken together, these observations indicate that a reduction in cerebral P_{mito} of 5–6 mm Hg may be tolerated without impaired aerobic energy turnover and, consequently, without changes in anaerobic metabolism of glucose in the brain.

The observation of a 7% increase in the $CMRO_2$ during exercise with hyperthermia, despite an approximately 20% reduction in CBF, provides support of an adequate oxygen delivery to the brain. On the other hand, the cerebral temperature at exhaustion, which is higher by 1.5°C–2°C if we compare with normothermic exercise and increased by approximately 3°C compared with rest, would predict an even greater increase in the $CMRO_2$. Assuming a Q_{10} of 2, (which is the normal Q_{10} temperature coefficient for metabolic processes including the cerebral metabolism (24)), $CMRO_2$ should increase by at least 13% compared with that in control exercise. Therefore, it cannot be excluded that low oxygen delivery during submaximal exercise with hyperthermia restricts an even larger increase in the $CMRO_2$, and the blackout or fainting occasionally

experienced by hyperthermic athletes may relate to inadequate oxygen delivery to the brain. However, the central fatigue arising with hyperthermia during submaximal exercise is probably largely related to a direct inhibitory effect of high brain temperature on motor outflow (24). Likewise, factors other than cerebral oxygen delivery seems to be of greater importance for the development of fatigue during maximal exercise. When maximal exercise is performed during hyperthermic conditions, cerebral oxygenation may decline at a faster rate than that during normothermic conditions (9), and that could be involved with the reduced time to exhaustion; however, it seems more likely that the marked reduction in cardiac output and subsequent impairment of oxygen delivery to the exercising muscles is the factor involved with reduced performance during maximal exercise with hyperthermia.

In contrast, when arterial hypoxia is superimposed either during exposure to high altitude or as consequence of EIAH, the reduction in P_{mito} is so pronounced that inadequate oxygen delivery to the brain may become a significant factor influencing the development of fatigue. As calculated from the data by Imray et al. (12) during exercise on Chacaltaya at 5260 m above sea level and by Rasmussen et al. (unpublished manuscript/observation, 2006) during simulated altitude (~6000 m), the reductions in cerebral oxygen delivery, cerebral oxygenation, and P_{mito} are likely to impair both the cerebral metabolism and motor performance. During exercise with severe arterial hypoxia, the brain does not display a net uptake of lactate, despite increases in arterial lactate to similar levels as during maximal exercise with normoxia, indicating that the cerebral oxygen status does not allow for an uptake and metabolism of lactate, and it is likely that endogenous lactate production by the brain becomes so large that the lactate gradient between the blood and the brain disappears. Furthermore, during acute hypoxia, the exercise $CMRO_2$ is lower than that during exercise with normal PaO_2 when both compared with the same absolute exercise intensity or matched to exercise, resulting in similar arterial lactate levels, cardiovascular stress, and perceived exertion (Rasmussen, Nybo, Peterson, et al., unpublished manuscript/observation, 2006). In contrast, acclimatized subjects exhibited no difference in CBF, oxidative metabolism, or lactate release when exercise performed on Chacaltaya was compared with rest or submaximal exercise at sea level (21). The differences between this study (21) and those by Imray et al. (12) and Rasmussen et al. (unpublished manuscript/observation, 2006) may relate to the differences between acute exposure and responses in acclimatized subjects, but it may also relate to the differences in exercise intensities. The workload in the study by Moller et al. (21) was rather low, and it seems that cerebral oxygen delivery in acclimatized subjects may be adequate at rest and low exercise intensities but becomes challenged as maximal workload is approached (Fig. 3).

When subjects with EIAH perform maximal exercise, the cerebral oxygen delivery may decrease by approximately 25% because of the combined effect of reduced arterial saturation and lowered CBF, and this may cause reductions in P_{mito} from 6 and up to 13 mm Hg, depending on the level of arterial hypoxemia and hyperventilation-induced reduction
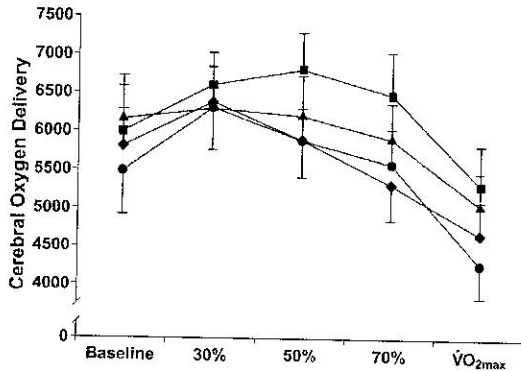
Figure 3. Changes in cerebral oxygen delivery at different altitudes (■, 150 m; ◆, 3,610 m; ●, 4,750 m; ▲, 5,260 m). (Reprinted from Imray, C.H., S.D. Myers, K.T. Pattinson, A.R. Bradwell, C.W. Chan, S. Harris, P. Collins, and A.D. Wright. Effect of exercise on cerebral perfusion in humans at high altitude. *J. Appl. Physiol.* 99:699–706, 2005. Copyright © 2005 The American Physiological Society. Used with permission.)

of CBF. In endurance-trained subjects, SaO_2 may decrease to below 88% and hyperventilation-induced reductions in $PaCO_2$ by 8–10 mm Hg during maximal exercise (22), and P_{mito} is reduced by more than 10 mm Hg and to such an extent that it impairs motor performance. Similarly, Nielsen et al. (22) reported that well-trained rowers experiencing a drop in SaO_2 from 98% to 92% during maximal exercise also displayed reduced NIRS-determined COLD from 80 to 65 mm Hg; however, cerebral desaturation was prevented, and performance improved when oxygen supplementation was provided and the arterial oxygen saturation maintained. Although the improvement in performance may relate to enhanced oxygen delivery to the exercising muscles and prevention of muscle fatigue (1), the reduction in cerebral oxygen saturation and P_{mito} is of such magnitude that it may affect motor performance during maximal exercise in subjects with EIAH. Therefore, oxygen supplementation may also contribute to improved performance by preventing central fatigue arising secondary to reductions of P_{mito}.

CONCLUSIONS

In summary, strenuous exercise conditions that cause hyperventilation-induced restrictions of CBF may compromise oxygen delivery to active brain areas and lower the cerebral P_{mito}, but reductions in cerebral oxygenation become relevant for the development of central fatigue primarily when arterial hypoxemia is superimposed. Under such conditions, the mitochondrial oxygen tension may decline by more than 10 mm Hg as compared with rest, and it is no longer adequate to support the cerebral metabolism and maintain motor function.

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