

**HIGHLIGHTED TOPIC | *Fatigue Mechanisms Determining Exercise Performance*****Cerebral blood flow and metabolism during exercise: implications for fatigue****Neils H. Secher, Thomas Seifert, and Johannes J. Van Lieshout***Department of Anesthesia, The Copenhagen Muscle Research Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; and Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

**Secher NH, Seifert T, Van Lieshout JJ.** Cerebral blood flow and metabolism during exercise, implications for fatigue. *J Appl Physiol* 104: 306–314, 2008. First published October 25, 2007; doi:10.1152/jappphysiol.00853.2007.—During exercise: the Kety-Schmidt-determined cerebral blood flow (CBF) does not change because the jugular vein is collapsed in the upright position. In contrast, when CBF is evaluated by  $^{133}\text{Xe}$  clearance, by flow in the internal carotid artery, or by flow velocity in basal cerebral arteries, a  $\sim 25\%$  increase is detected with a parallel increase in metabolism. During activation, an increase in cerebral  $\text{O}_2$  supply is required because there is no capillary recruitment within the brain and increased metabolism becomes dependent on an enhanced gradient for oxygen diffusion. During maximal whole body exercise, however, cerebral oxygenation decreases because of eventual arterial desaturation and marked hyperventilation-related hypocapnia of consequence for CBF. Reduced cerebral oxygenation affects recruitment of motor units, and supplemental  $\text{O}_2$  enhances cerebral oxygenation and work capacity without effects on muscle oxygenation. Also, the work of breathing and the increasing temperature of the brain during exercise are of importance for the development of so-called central fatigue. During prolonged exercise, the perceived exertion is related to accumulation of ammonia in the brain, and data support the theory that glycogen depletion in astrocytes limits the ability of the brain to accelerate its metabolism during activation. The release of interleukin-6 from the brain when exercise is prolonged may represent a signaling pathway in matching the metabolic response of the brain. Preliminary data suggest a coupling between the circulatory and metabolic perturbations in the brain during strenuous exercise and the ability of the brain to access slow-twitch muscle fiber populations.

ammonium; central fatigue; cerebral blood flow; cerebral metabolic ratio; glucose; glycogen; lactate; oxygen; temperature

DURING EXERCISE, THERE IS hyperbolic relationship between work intensity and endurance, and A. V. Hill used the relationship to demonstrate that energy turnover can be taken to represent a continuous provision of energy supplemented by an energy store (56). Yet, it is the brain that makes the decision when to slow down or to stop exercise, and from that perspective fatigue is of central origin. Obviously, cerebral metabolism becomes affected if exercise has a duration that lowers blood glucose (74), and, equally, the low  $\text{O}_2$  tension faced during mountaineering (47) affects brain function. Perturbation of cerebral metabolism is, however, not restricted to situations where the arterial glucose and  $\text{O}_2$  levels are reduced. Recent investigations (3, 65, 70, 90) indicate that also at sea level maximal exercise may be associated with so-called central fatigue as indicated by lower voluntary activation than the force elicited during evoked contractions.

The purpose of this review is to address cerebral metabolism in response to activation by exercise and to identify changes and circumstances that determine the inability of the central nervous system to access the motoneurons projecting to the working muscles. Because evaluation of cerebral metabolism depends critically on the method used for determination of cerebral blood flow (CBF) and because the noninvasive transcranial Doppler (TCD) method is applied widely for human exercise studies, methods applied to assess CBF are addressed in some detail.

**CBF DURING EXERCISE**

Traditionally, assessment of brain metabolism is based on determination of CBF and concentration of relevant metabolic substances across the brain. CBF is determined by the Kety-Schmidt method with evaluation of the uptake, or the elimination of an inert gas (nitric oxide or xenon) over the brain by arterial and jugular venous sampling until a new steady state is reached. With that method no consistent change in CBF during exercise is found and, accordingly, the cerebral metabolic rate for  $\text{O}_2$  ( $\text{CMRO}_2$ ) does not change (62). The stability of CBF and  $\text{CMRO}_2$  in awake humans is in contrast to regional CBF

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(rCBF) and metabolism during cerebral activation. With such evaluations, a distinct increase in both rCBF and regional metabolism has become synonymous with cerebral activation as visualized by single-photon emission tomography, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). The motor tasks involved in exercise have been associated with an increase in rCBF as demonstrated by Olesen (77) and confirmed in numerous follow-up studies. Similarly, an increase in CBF during brain activation elicited by exercise has been shown with near-infrared spectroscopy (NIRS) (42) that, based on a different physical principle from fMRI, also evaluates the ratio between oxyhemoglobin and hemoglobin.

Further support for the dynamic behavior of the CBF response to exercise is the finding that CBF increases during exercise as shown both by  $^{133}\text{Xe}$  clearance (49, 51, 99) and the TCD-determined mean flow velocity ( $V_{\text{mean}}$ ) in large basal cerebral arteries (49, 51), and with little elevation in mean arterial pressure during dynamic exercise, the increase in flow represents an almost as large increase in cerebral vascular conductance. Regarding the evaluation of cerebral perfusion with TCD, the concern has been raised whether the diameter of the basal cerebral arteries remains stable during exercise. If sympathetic activation elicits vasoconstriction in basal cerebral arteries, an increase in  $V_{\text{mean}}$  could represent a compensation for a reduced vessel diameter, aiming to maintain flow. However, during exercise,  $V_{\text{mean}}$  of the middle cerebral artery (MCA) increases in parallel with the inflow of the internal carotid artery (34, 38, 39) and with the “initial slope index” of the  $^{133}\text{Xe}$  clearance-determined CBF, which is considered to represent the average value (Fig. 1). Thus the diameter of large cerebral arteries does not change significantly during exercise, and regulation of CBF takes place in the smaller arteries (28). Changes in CBF evaluated with TCD are tracked, at least quantitatively, by NIRS-determined cerebral oxygenation ( $\text{cO}_2\text{Hb}$ ). Thus, if the  $V_{\text{mean}}$  and  $\text{cO}_2\text{Hb}$  change in parallel, it is difficult not to accept that also CBF is changed in that direction, and that is confirmed by clinical evaluation (61, 103). Also,  $V_{\text{mean}}$  in basal cerebral arteries reports the regional rather than the global distribution of CBF during exercise. During

right-handgrip exercise, MCA  $V_{\text{mean}}$  increases only for the contralateral side (50) when there is no coactivation of the contralateral hand, and when one foot is moved,  $V_{\text{mean}}$  increases in the contralateral anterior cerebral artery (55). In contrast, during cycling  $V_{\text{mean}}$  increases bilaterally in the medial and anterior cerebral arteries. If the increased flow velocity in basal cerebral arteries was a compensation for global cerebral sympathetic vasoconstriction, the  $V_{\text{mean}}$  response to exercise would have been equal among the different branches of the internal carotid artery. It should be noted, however, that  $V_{\text{mean}}$  reports the velocity associated with the maximal frequency of the Doppler shift (“the envelope”) rather than the intensity-weighted mean flow velocity or the total signal power. This is so because a small change in insonation angle of the artery is of no consequence for the reported maximal velocity, whereas the average flow velocity is affected by the insonation. Thus exercise-related changes in flow velocity are largely lost when focus is not on  $V_{\text{mean}}$  (29, 85).

Together these inflow evaluations of CBF during exercise by the determination of  $V_{\text{mean}}$ ,  $^{133}\text{Xe}$  clearance, and internal carotid flow examine a dynamic aspect of CBF that remains undetected when CBF is assessed with the Kety-Schmidt method, suggesting a fixed CBF of  $\sim 45 \text{ mg} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$  (62) vs. a consistent  $\sim 25\%$  increase in flow rate to the brain [50% when gray matter flow (first-compartment flow) is evaluated; 49, 51, 99; Fig. 1]. The most likely reason for this discrepancy in the ability to track the CBF response to dynamic exercise is that the internal jugular vein used in the Kety-Schmidt method for assessment of the arterial-venous differences for an inert gas collapses when the subject is upright (21, 30, 31) and the brain circulation is no longer sensitive to perturbations in central venous pressure (83, 88). In the upright posture assumed in exercise studies, the venous drainage of the brain becomes dependent on spinal veins of the vertebral plexus (2, 11, 12, 100, 101), and even in the supine position a predominantly nonjugular drainage pattern is found in  $\sim 6\%$  of subjects (5, 22). Evaluation of CBF with the Kety-Schmidt method is complicated further by the asymmetry of the venous drainage from the brain.

The hemispheres are drained by the larger right internal jugular vein, whereas the smaller left vein drains deeper structures of the brain of importance for evaluation of metabolism. For example, there is selective enhanced norepinephrine spillover from deep structures of the brain in patients with arterial hypertension (26). However, the interindividual variability in the venous drainage of the brain is considerable, and in some individuals the left internal jugular vein is larger and, accordingly, drains the hemispheres. For a detailed evaluation of CBF based on the Kety-Schmidt method, the venous drainage of the two internal jugular veins needs to be evaluated, e.g., by labeling of the red blood cells by technetium and following their passage through the brain by a gamma camera (44).

#### REGULATION OF CBF DURING EXERCISE

With an increase in CBF during exercise, the mechanisms that may drive the enhanced flow are of interest. In the era of the Kety-Schmidt method, regulation of CBF was a debate dominated by the  $\text{CO}_2$  reactivity of CBF and cerebral autoregulation. Both mechanisms are relevant to the CBF response to exercise because of marked changes in mean arterial pressure (MAP) and the arterial  $\text{CO}_2$  tension ( $\text{PaCO}_2$ ) (88).

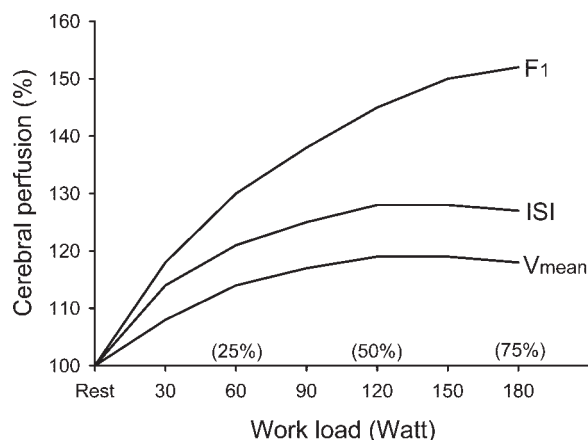


Fig. 1. Parallel changes in middle cerebral artery flow velocity (MCA  $V_{\text{mean}}$ ) and the  $^{133}\text{Xe}$  clearance-determined initial slope index (ISI) of cerebral blood flow at various levels of dynamic exercise. First-compartment flow ( $F_1$ ) is considered to represent gray matter flow. Values are expressed relative to rest (modified from Ref. 51) with indication of the approximate relative workload.

The influence of  $\text{PaCO}_2$  on CBF during exercise is of importance at different exercise intensities. Moderate exercise is associated with a small increase in  $\text{PaCO}_2$  that would be considered to support the increase in CBF and MCA  $V_{\text{mean}}$  (49). On the other hand, intense exercise is associated with a reduction in  $\text{PaCO}_2$  because ventilation increases exponentially with work rate as pH decreases (66). Accordingly, intense exercise is accomplished despite a decreasing CBF and MCA  $V_{\text{mean}}$  (49, 51, 55, 88) that interferes with adequate oxygenation of the brain (Fig. 2).

The second important influence on CBF consists of cerebral autoregulation that maintains CBF more or less stable within a range of MAP between 60 and 150 mmHg (78). Accordingly, the increase in  $V_{\text{mean}}$  during dynamic exercise is not explained by the elevated in MAP. For instance, during postexercise muscle ischemia, MCA  $V_{\text{mean}}$  returns to the resting level (49), whereas MAP is maintained at the exercise level, or even increases if metaboreceptors in the exercising muscles are

excited further by inflating thigh cuffs before the end of exercise, and, therefore, cerebral vascular conductance becomes elevated (91). The fact that  $V_{\text{mean}}$  is maintained during postexercise muscle ischemia, although sympathetic activity increases markedly, supports the theory that MCA  $V_{\text{mean}}$  is not influenced by sympathetic activity under physiological circumstances (82). The steadiness of both the  $^{133}\text{Xe}$  clearance-determined CBF and MCA  $V_{\text{mean}}$  during static exercise in the face of an increase in MAP similar to what is found during dynamic exercise (49, 89) is another indication that it is not the increase in MAP per se that influences CBF. It should be noted that owing to the latency of cerebral autoregulation mechanisms, it takes  $\sim 3\text{--}5$  s to offset the effects of changes in MAP (46) and with rapid fluctuations in MAP in response to, e.g., posture change (102), weight lifting (58), and rowing (81), MCA  $V_{\text{mean}}$  changes in parallel. In the same way, the initial rise in MCA  $V_{\text{mean}}$  with the marked increase in MAP at the onset of static exercise is dominated by the Valsalva-like maneuver (48, 83) that is carried out to support the spine especially during leg contractions.

Specifically, the large increase in systolic blood pressure during intense exercise is of concern because it often exceeds the level considered to represent the upper limit of cerebral autoregulation. Yet, dynamic cerebral autoregulatory capacity appears sufficient to limit the systolic increase in MCA velocity (75), whereas the reduction in diastolic velocity is large in relation to the fluctuations in blood pressure during rowing (81) and in the recovery from exercise (76).

Whole body exercise is associated with an  $\sim 10$  fold increase in plasma catecholamine concentrations (37), and whether sympathetic activity influences CBF is of direct relevance to exercise but at the same time is controversial. A relationship between MCA  $V_{\text{mean}}$  and cardiac output (CO) is found by demonstrating that both the MCA  $V_{\text{mean}}$  and the NIRS-determined  $\text{cO}_2\text{Hb}$  decrease in association with the reduction in CO that occurs when changing position from supine to standing. This reduction in cerebral perfusion takes place even though MAP increases (102), further indicating an important role of sympathetic activation for regulation of CBF. The reduction in cerebral perfusion has been alleged to cause the associated postural decrease in  $\text{Pco}_2$ , but the decrease in  $\text{PaCO}_2$  accounts for only approximately one-half of the orthostatic influence on MCA  $V_{\text{mean}}$  (45, 97). In support of this theory, both MCA  $V_{\text{mean}}$  and  $\text{cO}_2\text{Hb}$  increase when the standing position is supplemented by a leg-crossing maneuver that attenuates sympathetic activity by enhancing CO (102).

Of more direct relevance for exercise are the observations made during manipulation of CO. During exercise,  $\beta$ -adrenergic blockade with metoprolol attenuates the increase in CO (4), e.g., from 19 to 15 l/min (79), and also concomitantly the increase in MCA  $V_{\text{mean}}$ , typically to one-half of the normal response to exercise (75). However, the normal 25% increase in MCA  $V_{\text{mean}}$  returns if, during exercise with metoprolol, sympathetic activity to the brain is eliminated by blocking the stellate ganglion (40). Similarly, in patients with cardiac insufficiency, there is a direct relationship between the increase in MCA  $V_{\text{mean}}$  and the ability to increase CO during exercise (33, 41). The importance of this relationship is illustrated when comparing one- with two-legged exercise. During one-legged exercise, patients with cardiac insufficiency demonstrate the

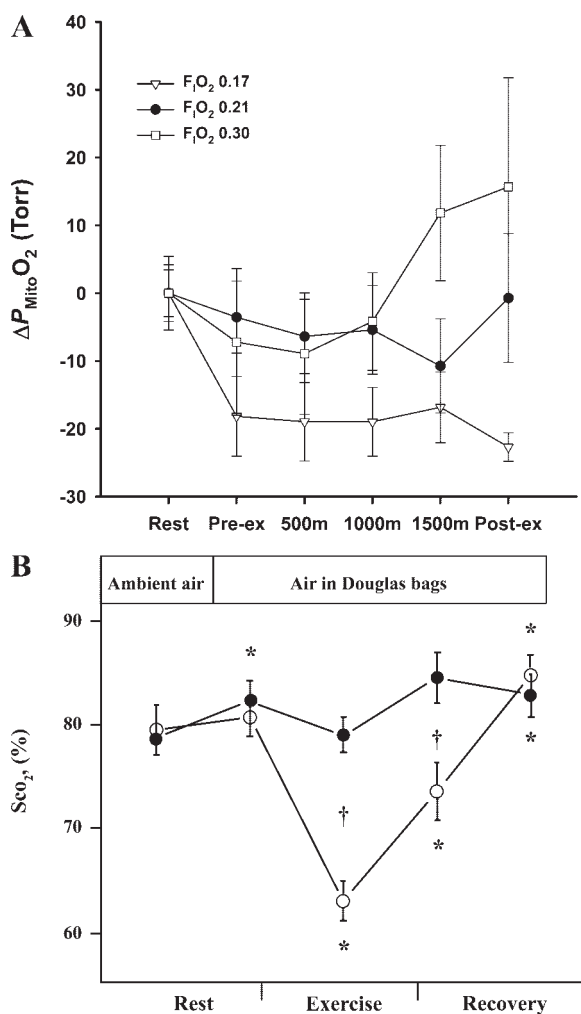


Fig. 2. Changes in calculated cerebral mitochondrial  $\text{O}_2$  tension ( $\Delta P_{\text{Mito O}_2}$ ) during 2,000-m all-out ergometer rowing at 3 levels of inspired  $\text{O}_2$  fraction ( $F_{\text{I O}_2}$ ) (104). Also shown is the effect of breathing 30%  $\text{O}_2$  (●) on the near-infrared spectroscopy-determined frontal lobe oxygenation ( $\text{ScO}_2$ ) during ergometer rowing (bottom; 65). Breathing 30%  $\text{O}_2$  enhanced work capacity by 3% compared with breathing 21% oxygen (○). Pre-ex, before exercise; Post-ex, after exercise. \*Compared with rest,  $P < 0.05$ ; †compared with breathing 21% oxygen,  $P < 0.05$ .



normal increase in MCA  $V_{\text{mean}}$ , which is attenuated, or eliminated, during two-legged exercise (35).

### CEREBRAL OXYGENATION

The increase in cerebral oxygenation during activation by exercise (42) is in contrast to the progressive reduction in muscle oxygenation with workload. Also, brain function deteriorates when its average oxygenation becomes reduced more than 10% (32, 61, 102, 103), whereas skeletal muscles maintain their activity despite  $O_2$  saturation below 10% (4). Brain activation seems to be associated with surplus perfusion reflected in high values for fMRI- and NIRS-determined oxygenation, and there may be good reasons why that is necessary. The capillaries within skeletal muscle are positioned in direct contact to the muscle cells, but for the brain, there is a barrier between the capillaries and the neurons. Cerebral capillaries are not different from those in other vascular beds, but within the brain, the capillaries are protected by extension of the astrocytes covering the entire capillary network and constituting the blood-brain barrier. The diffusion distance for  $O_2$  becomes critical when the brain is activated resulting in a high  $O_2$  consumption. An increase in rCBF to match the enhanced neuronal metabolism is required to create an elevated  $O_2$  gradient, because within the brain and, in contrast to skeletal muscles, there is no capillary recruitment.

Changes in  $O_2$  tension in brain capillaries and mitochondria tension can be mathematically derived during activation, including exercise (86). Maximal exercise is, despite the increase in capillary oxygenation, associated with a reduced mitochondrial  $O_2$  tension as CBF becomes affected by the reduction in  $P_{aCO_2}$  in addition to a decline in arterial  $O_2$  content during whole body exercise (66, 67; Fig. 2). However, even during maximal whole body exercise, cerebral mitochondrial  $O_2$  tension does not become as low as established during submaximal exercise with a 10% inspiratory  $O_2$  fraction (73).

To what extent a reduction in the cerebral mitochondrial  $O_2$  tension during maximal whole body exercise affects brain function remains to be established. In humans, the supraspinal contribution to exercise-induced fatigue may be isolated by cerebral cortex electromagnetic stimulation to quantify the muscular force that still may be recruited at fatigue onset. Making use of this technique following exhaustive ergometer rowing, there is little indication of affected cerebral function, and, in fact, after exercise there is facilitation of the brain's influence on the motoneurons to become attenuated following exercise under hypoxic conditions (9). On the other hand, when under those conditions cerebral hemoglobin desaturates, the ability for slow contractions becomes affected, although there is no influence on fast movement (86). Whereas that observation is awaiting confirmation, it does suggest that motoneurons controlling slow-twitch muscle fibers are more susceptible to hypoxia than those controlling fast-twitch muscle fibers. In other words, it is the ability to perform graded, or refined, movement that is affected mostly by hypoxia. As demonstrated immediately following strenuous exercise, some level of central fatigue is developed indicated by both electrical (70) and electromagnetic femoral nerve stimulation (3, 90). Also, supplementation of  $O_2$  enhances performance with an increase in cerebral rather than muscle oxygenation (Fig. 2) (65). Interestingly, fatigue does not affect the electromechanical activation

of the muscle that, in fact, seems to be enhanced (63). Thus central fatigue is a manifestation of the inability to maintain rather than inability to generate force (92, 95), and that is what would be expected when the contribution of the slow-twitch muscle fibers to the contraction becomes less important as demonstrated during partial neuromuscular blockade and in patients with myasthenia gravis (96) (Fig. 3).

### CEREBRAL METABOLISM

Given the uncertainty on how to express changes in CBF, and thereby in  $CMRO_2$ , during exercise, it is advantageous that changes in cerebral metabolism can be expressed independently of those in CBF. Cerebral activation is associated with a reduction in the metabolic ratio, defined as the ratio of the  $O_2$  and glucose uptake as demonstrated for visual stimulation by Fox and Raichle (27). Normally, the brain takes up  $O_2$  and carbohydrate in a ratio of six to one, reflecting combustion of the six carbon atoms in glucose. Thus a cerebral metabolic ratio (CMR) of six indicates that for the brain carbohydrate oxidation matches its uptake. The balance in cerebral aerobic metabolism is supported by two fundamental observations. First, a person becomes unconscious within seconds after the brain is deprived from its  $O_2$  supply following a cardiac arrest. The other contention is that the brain's capacity to develop significant anaerobic metabolism is limited by phosphocreatine and glycogen stores compared with skeletal muscles. The first notion is obvious: the capacity of the brain for anaerobic metabolism has to be reconsidered. The brain glycogen content is confined to the astrocytes, in humans reaching 5–6 mM (glucosyl units) in gray and white matter and 13 mM within the hippocampus, with only marginally lower levels for the pig (16). Thus, for the astrocytes that take up <50% of the brain's volume, the glycogen level approaches that in skeletal muscles. Anaerobic metabolism likely plays a pivotal role in providing enhanced energy turnover to sustain cerebral activation (80), although, as in skeletal muscles, it cannot support prolonged activity. Moreover, the brain may release a small amount of lactate at rest and especially during hypoxemia or in response to cerebral hypoperfusion when MAP has become extremely low (25).

The work of Fox and Raichle (27) supports the notion that variation in cerebral metabolism is larger than indicated by a Kety-Schmidt-determined  $CMRO_2$ . In the PET-based evaluation by Fox and Raichle, the resting CMR was as low as 4.1, and in the visual cortex it decreased further to 2.8 during exposure to a flashing light. In a follow-up study, Madsen et al. (60) found the CMR based on arterial and jugular venous blood sampling to decrease to 5.4 during a mental task. However, such a decrease in the CMR for the whole brain seems trivial compared with that developed during exercise (14).

Following arterial and internal jugular venous catheterization needed to determine the CMR from blood samples, values of 5.7, or even lower immediately after catheterization, are observed and have been demonstrated to recover gradually toward 6 during the following resting period. The CMR decreases in response to the anxiety associated with catheterization and with the expectations involved in participating in a physiological experiment. This may have been contributing to the very low initial value reported by Fox and Raichle (27) when the subjects were confined in a PET scanner.

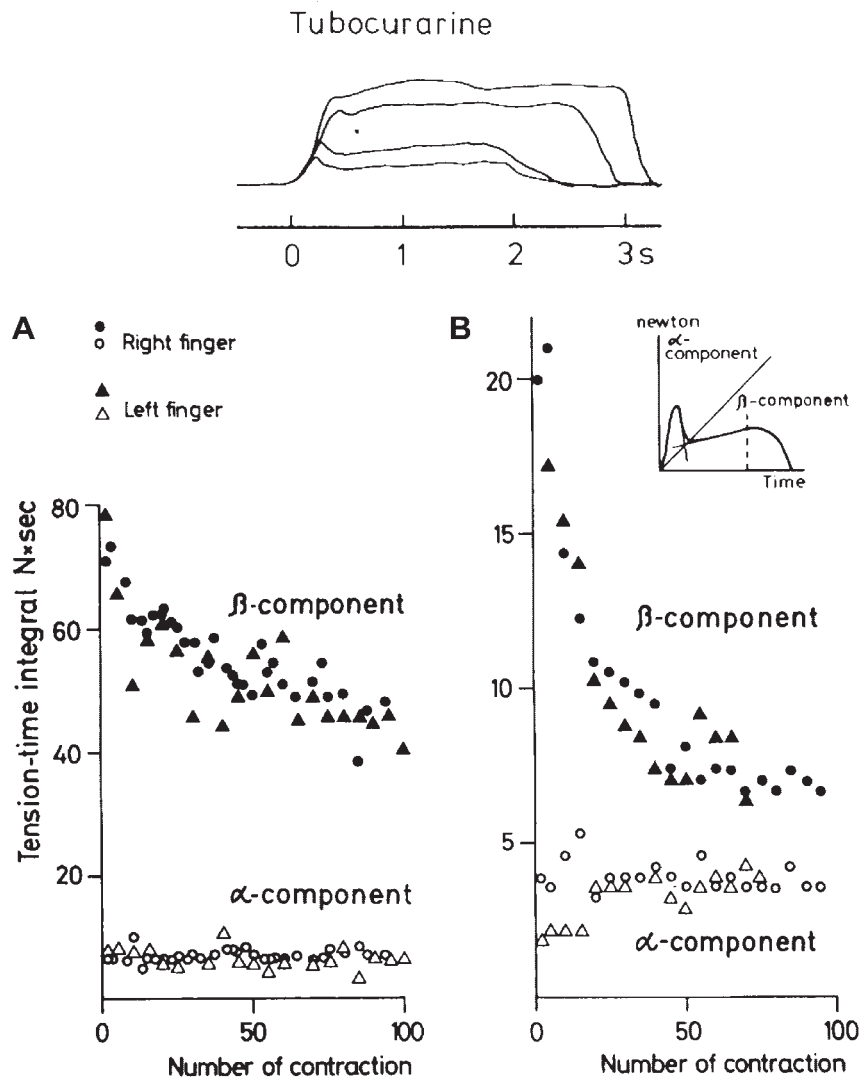


Fig. 3. Contraction pattern developed during repeated maximal voluntary contractions and during partial neuromuscular blockade with tubocurarine, which affects mainly slow-twitch muscle fibers. Partial neuromuscular blockade (*top*) and quantification of the contractions developed during repeated maximal contractions in a patient with myasthenia gravis (*bottom; A*) and a normal subject (*bottom; B*) (modified from Refs. 95, 96 with permission). Under all 3 circumstances, a reduction in strengths affects the ability to maintain rather than to initiate the contraction because the slow-twitch muscle fiber contribution to force generation is attenuated and ultimately lost.

During submaximal exercise, the CMR remains relatively stable until the workload becomes demanding (43, 71). Only then, for instance during an incremental test to exhaustion, the CMR declines reaching a nadir of, e.g., 4.7 (43). Whether the workload becomes demanding depends not only on its absolute level as observed following neuromuscular blockade, where strength can deliberately be reduced to any level until paralysis of all skeletal muscles. In that situation, an otherwise trivial submaximal workload becomes demanding and as soon as it requires maximal effort, the CMR decreases markedly (15). Similarly, when exercise is made difficult and painful by hindering leg blood flow with thigh cuff, the CMR declines (17). Both the apparent influence from the drive to exercise and the associated pain affect brain metabolism, although their separate contributions do not seem as large as observed during control maximal exercise. It supports the theory that many cerebral areas need to be activated for the expression of the global CBF response. Also the reduction in the CMR progresses as more muscles are involved in exercise to a record low level of 1.7 during exhaustive ergometer rowing (104). Maximal ergometer rowing often involves a “2,000-m” all-out

effort, and in that situation, the reduction in the CMR already manifests at the onset of exercise.

At rest, the arterial lactate level is  $<1$  mM and of little or no importance for the CMR. However, as blood lactate increases with work rate, lactate is taken up by the brain in proportion to its arterial concentration (20, 43) that, during rowing, may exceed 30 mM (64). Thus, with increasing lactate concentration during exercise, lactate is integrated in the CMR ( $O_2$  uptake/uptake of glucose +  $\frac{1}{2}$  uptake of lactate) (43), whereas the contribution of pyruvate is negligible (87). Integration of lactate in the CMR is supported by the finding that the lactate taken up by the brain during exercise does not accumulate in spinal fluid or within the brain tissue in humans, at least not above the detection level of proton magnetic resonance spectroscopy ( $\sim 2.5$  mM; 20), confirming data in the rat (59). Thus lactate is established as a substrate for the neurons (80) both from glycolysis in astrocytes and, apparently, also for lactate taken up from blood (20, 43) as confirmed in preliminary data with evaluation by labeled lactate. Integrating the lactate taken up by the brain during exercise implies an excess carbohydrate uptake of 10–15 mmol (glucosyl units) compared with what

can be accounted for by the  $O_2$  uptake. Such an uptake of carbohydrate is of the same order of magnitude as the brain's glycogen level (16). Thus, during exercise, brain uptake of lactate appears to supplement, or to replace, its uptake of glucose (52).

The reduction in the CMR during activation of the brain is not well understood. Brain uptake of carbohydrate during exercise is not associated with arterial-to-venous differences for relevant hormones, including insulin, insulin-like growth factor, and cortisol (19), and it does not depend on the  $O_2$  availability (104). However, the concentration of norepinephrine increases in the cerebrospinal fluid and the only intervention that has been shown to affect the CMR is the administration of the nonselective  $\beta$ -adrenergic blocking agent propranolol in the rat (94) as confirmed by preliminary human exercise data (Fig. 4). On the other hand, the cardioselective  $\beta$ -adrenergic blocking agent metoprolol does not affect the CMR during exercise (18).

The observation that the CMR is low following catheterization and decreases in proportion to work rate and muscle mass involved in exercise and, thus, in proportion to the lactate level, may well indicate that the CMR decreases in response to the exponential increase in plasma epinephrine with work rate (53), similar to lactate. If so, it may be that there is a sex difference in the level that the CMR reaches during maximal exercise (1). One avenue to explore the influence of epinephrine on the CMR would be to evaluate the response to static exercise. Static exercise involving a  $>30\%$  of maximal voluntary contraction hinders muscle blood flow (7) and is, therefore, associated with a low lactate level in blood, whereas there is no restriction in the release of epinephrine from the adrenal gland. Prolonged exercise also offers an opportunity to separate the epinephrine and blood lactate concentrations. During prolonged exercise, there is little or no increase in blood lactate as the muscle glycogen store becomes depleted, but the CMR decreases when exercise has lasted for so long that it becomes demanding. The decrease in the muscle glycogen level, intolerable heat stress, dehydration, or, eventually, a decreasing blood glucose level may all be involved (Fig. 5; 69, 71). Taken together, the hypothesis emerges that the CMR decreases by adrenergic stimulation of cerebral metabolism, and with the high  $Na^+-K^+$ -ATPase activity in the brain under the influence

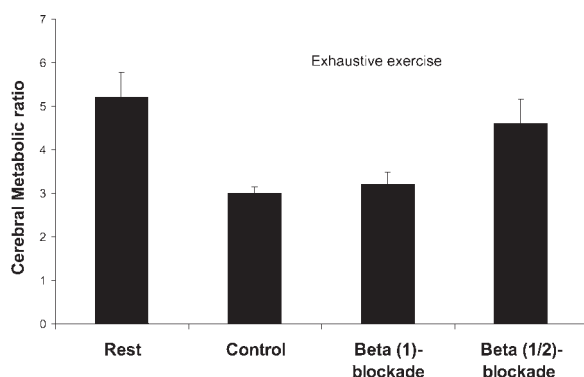


Fig. 4. Changes in the cerebral metabolic ratio [uptake of oxygen/(uptake of glucose +  $\frac{1}{2}$  lactate)] at rest and during exhaustive exercise in humans without administration of propranolol and with administration of metoprolol ( $\beta_1$ -blockade) or propranolol ( $\beta_1$ - and  $\beta_2$ -blockade). Values are means  $\pm$  SE for 7 subjects. Data ( $n = 7$ ; from Ref. 16) for exhaustive exercise are after administration of metoprolol ( $\beta_1$ -blockade; means  $\pm$  SE).

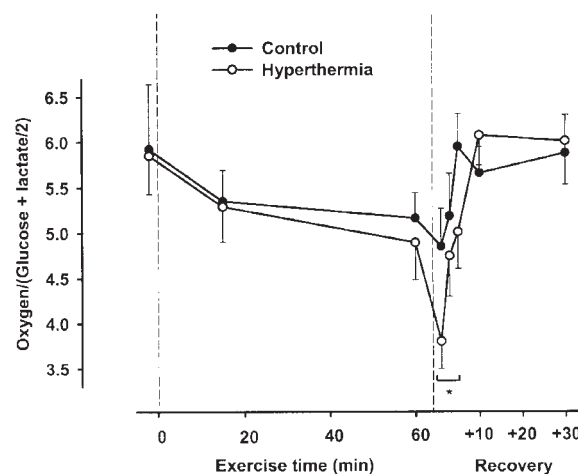


Fig. 5. Cerebral metabolic ratio during and after exercise with a normal (control) or elevated (hyperthermia) core temperature. Values are means  $\pm$  SE for 8 subjects. Blood lactate was  $<2$  mM when the cerebral metabolic ratio decreased (71). \*Different from rest and the corresponding value in the control trial,  $P < 0.05$ .

of epinephrine (8, 12), disturbance in brain metabolism during exercise may relate to the energy available for glycolysis to regulate membrane potentials.

Another indicator of the brain glucose metabolism during exercise is the cytokine interleukin-6 (IL-6) that increase markedly in the circulation during exercise with the main contributor being the working skeletal muscles (23). Glucose ingestion during exercise, however, attenuates the release of IL-6 from the muscles as soon as glucose uptake in the working muscles becomes enhanced (24). In a similar way, the release of IL-6 from the brain during exercise may reflect an energy crisis within the brain because the release of IL-6 from the brain is larger during a subsequent exercise trial (72). It is still unknown whether carbohydrate supplementation affects the release of IL-6 from the brain during prolonged exercise, whereas IL-6 does not seem to respond to short-lasting maximal exercise (19). In addition, intense exercise does not affect the brain handling of tumor necrosis factor or heat shock protein, and their cerebrospinal fluid concentration does not change in response to exercise (98). Also, there is no uptake or release of brain natriuretic peptide from the brain during exercise (93).

Insight to brain metabolism during exercise may also be obtained by determination of brain-derived neurotrophic factor (BDNF). At least at rest, administration of glucose eliminates the release of BDNF from the brain (54), whereas during prolonged exercise, administration of glucose attenuates the tryptophan concentration and its cerebral uptake and, maybe, also the synthesis of serotonin in the brain (6). Together these results indicate that ingestion of glucose (and fluid) during prolonged exercise prevents accumulation of serotonin within the brain, and provision of branched-chain amino acids in preparation for, or during, prolonged exercise has been proposed; however, as yet, there is no convincing evidence available for a positive effect. During prolonged exercise, fatigue may relate to accumulation of ammonia in the brain. Ammonia is produced by skeletal muscles and taken up by the brain in proportion to its arterial concentration and accumulates within the brain as indicated by the concentration in the cerebrospinal



fluid, and the perceived effort is related to such accumulation of ammonia (68).

The brain may be challenged to accelerate its metabolism during activation in response to a mental effort, including exercise. The brain has the capability to provide, at least some, enduring anaerobic metabolism. Even at rest a small amount of lactate is released (0.04 mmol/min) from the brain. Furthermore, during exercise in hypoxia, there may be no uptake of lactate in the brain, although the blood lactate level is enhanced (73). This observation suggests that lactate is taken up by the brain according to the blood lactate level but that uptake is compensated for by an equal release of lactate.

In regard to central fatigue, it seems also likely that the amount of magnesium in the brain, which enhances CBF (57), has an important role for stabilizing brain metabolism during exercise. At least in the gerbils, injection of magnesium sulfate increases the amount of brain glucose and pyruvate, and at the same time it attenuates the increase in lactate during forced swimming (10). In many situations, an elevated pyruvate level enhances metabolism when it is challenged, e.g., during reperfusion of ischemic organs. During strenuous exercise, local depletion of magnesium in the brain would then be an indication of impaired brain metabolism and, hence, reduced physical performance. However, in preliminary data, there appears to be maintained magnesium balance over the brain during short-lasting maximal exercise. It appears that plasma magnesium level should not be low when participating in demanding exercise.

## CONCLUSIONS

From the era of the Kety-Schmidt evaluation of CBF, brain metabolism seemed to remain stable during exercise. This is in sharp contrast to the dynamics of cerebral metabolism revealed by determination of arterial inflow to the brain. Also the earlier consideration that brain metabolism relies only on oxygenation of glucose has changed dramatically by the finding that during intense exercise, the brain may take up as much lactate as glucose, and, together, the carbohydrate uptake by the brain is much larger than can be accounted for by the uptake of O<sub>2</sub>. In addition, brain metabolism may be limited by depletion of glycogen within the astrocytes. Electromagnetic stimulation of the brain provides an avenue for elaboration on functional consequences linked to deviations in brain metabolism associated with central fatigue. What emerges is that oxygenation of the brain is challenged during intense exercise and that besides arterial deoxygenation, also heat, accumulation of ammonia, and the reduction in PaCO<sub>2</sub> associated with maximal exercise challenge the ability of the brain to get access to the neurons projecting to the working muscles. Also in that regard there is emerging evidence to suggest an inability to recruit especially slow-twitch muscle fibers.

## ACKNOWLEDGMENTS

We thank Prof. Børn Quistorff and Dr. Stefanos Volianitis for review of the manuscript.

## GRANTS

This review was supported by A. and E. Danielsen's Foundation and by the Danish Ministry for Research.

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