

Effects of the exercise in the cerebral blood flow and metabolism. A review

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ABSTRACT

Lucas-Cuevas, A.G., Priego, J.I., Pérez-Soriano, P. & Llana-Belloch. S. (2015). Effects of the exercise in the cerebral blood flow and metabolism. A review. *J. Hum. Sport Exerc.*, 10(1), pp.150-160. In recent years it has been shown that cerebral blood flow is affected by intense exercise, what may even lead to a reduction in the cognitive capacity. This statement is contrary to the traditional belief that cerebral blood flow remains constant and unaltered even when exercise is performed. During physical exercise of moderate intensity, cerebral blood flow increases in the cerebral areas responsible for movement. Moreover, recent studies have observed that cerebral blood flow decreases during high-intensity exercise as a consequence of a local hyperventilation and vasoconstriction of the areas with lower cerebral activity. Traditionally, the glucose has been considered as the main and unique source of energy for the brain. However, new studies are suggesting that as the intensity of exercise increases, the glucose uptake decreases in favour of an increase in the lactate uptake. Finally, Hyperthermia may also play a major role in the cerebral regulation system, since it can provoke central fatigue as well as hypoglycaemia. **Key words:** BRAIN, BLOOD CIRCULATION, OXYGEN CONSUMPTION, HYPERTHERMIA, GLUCOSE UPTAKE, LACTATE.

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INTRODUCTION

Many studies have investigated how physical exercise affects cerebral blood flow (CBF). One of the most important protective mechanisms of the cerebral flow is its capacity to maintain the CBF within a broad range of cerebral perfusion pressures (Paulson, Strandgaard, & Edvinsson, 1990). Although some years ago it was believed that physical exercise did not provoke any effects on a cerebral level, recent studies show that the cerebral dynamic autoregulation is influenced by physical exercise of high intensity (Ogoh et al., 2005), what in some cases has resulted in a reduction of the individual cognitive capacities (Brisswalter et al., 1997).

On this basis, the present work aims to show how physical exercise may affect CBF. This review will be presented in three parts:

Influence of physical exercise on CBF, focusing on the changes that different intensities of exercise provoke on CBF.

Influence of physical exercise on cerebral cellular metabolism, focusing on the effects that physical exercise has on the cerebral metabolism of glucose and lactate.

Influence of Hyperthermia on CBF and cerebral cellular metabolism during exercise.

MATERIAL AND METHODS

The systematic search was focused on the literature pertaining to the effect of exercise on the CBF, cerebral cellular metabolism and in health of patients with cerebral palsy.

For this systematic review, an extensive literature search was conducted using MEDLINE (PubMed), Scopus, Science Direct and Google Scholar electronic database with no year, gender, age or type of article restriction. The key words used in the online search included “cerebral”, “flow”, “exercise”, “brain”, “glucose”, “lactate”, “cerebral metabolism”, and “cerebral circulation”. Boolean operators, ‘OR’ and ‘AND’ were used to combine within and between the search terms of the subject areas.

The search strategy and article screening process are illustrated in Figure 1. Our search yielded 1324 articles, and a final selection of 56 articles which were considered relevant was done to fit the objectives of the study.

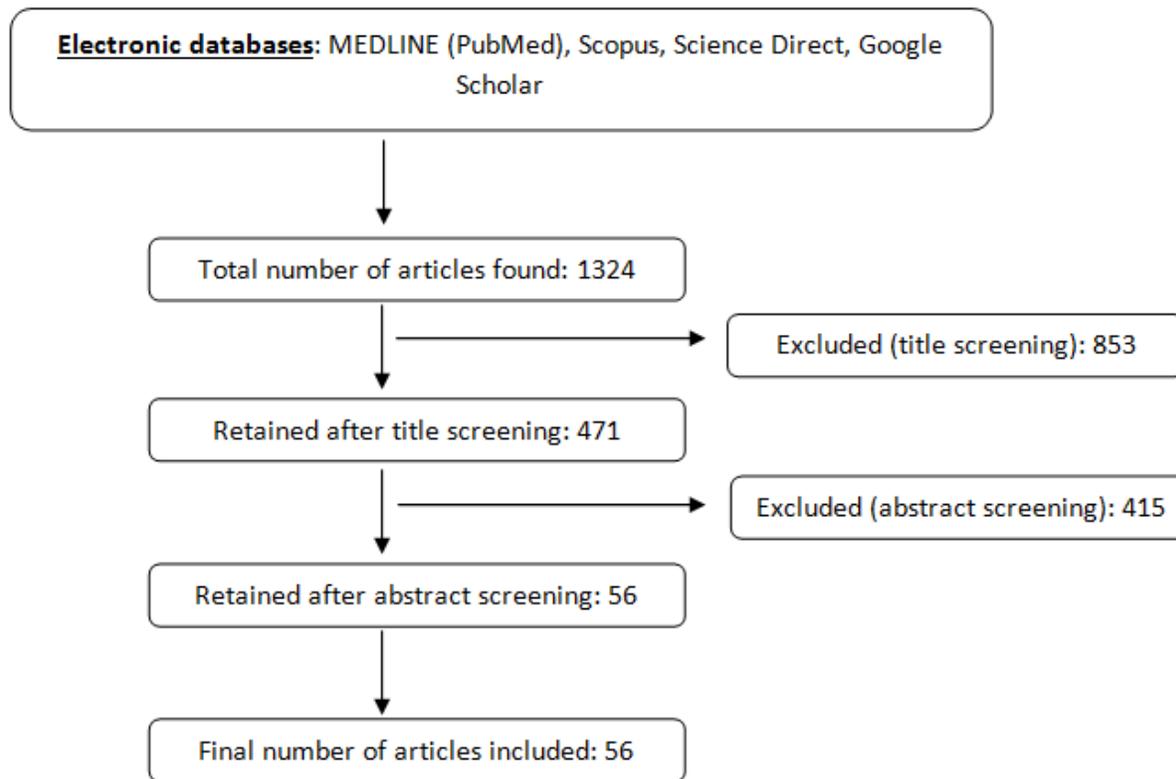


Figure 1. Search process

RESULTS

1. Physical exercise influence on cerebral blood flow

It has been traditionally believed that CBF, unlike the behaviour of blood flow in other organs, remains constant and unaltered regardless the activity being performed by the individual (Lassen, 1959, 1974). However, recent studies have observed that during physical exercise, both the cerebral activity and cerebral metabolism increase, resulting in a higher CBF (Madsen et al., 1993; Marsden et al., 2012; Ogoh & Ainslie, 2009).

Controversy exists regarding the effect of physical exercise on blood flow, which could be a consequence of the different techniques used to determine “global” CBF (gCBF). A very common technique is Kety-Schmidt, carried out for the first time in the 1940s. This technique allows to quantify the CBF via the artery-jugular differences of oxygen (Kety & Schmidt, 1948). Originally, N₂O concentration was sequentially determined in arterial and jugular samples after breathing a mix of gases including a low concentration of N₂O (Kety & Schmidt, 1948). Nowadays, based on the same theory, the value of CBF is quantified using Xenon, Krypton, or similar indicators, together with tomographic techniques such as the PET and SPECT (Poca et al., 2005). Constant values of gCBF during physical exercise have been observed using the Kety-Schmidt technique (Ide & Secher, 2000; Madsen et al., 1993). However, this finding may be controversial because the Kety-Schmidt technique bases its analysis on the blood flow within the two internal jugular veins, which depends on the origin of the drainage and it may not be properly defined which one of the jugular venous flow is evaluated (Ide & Secher, 2000). This limitation may explain why some of the studies previously mentioned did not observe any variation of the CBF during exercise (Madsen et al., 1993). When

the intensity of the exercise elevates up to 60% of VO_{2max} , CBF values also increase (Ogoh & Ainslie, 2009; Sato & Sadamoto, 2010). However, it has been observed that physical exercise higher than 60-70% VO_{2max} leads to a reduction in CBF via cerebral hyperventilation and vasoconstriction of specific cerebral areas (probably of those with lower cerebral activity during exercise), what results in lower values of $PaCO_2$ (Ogoh & Ainslie, 2009; Smith et al., 2012). This finding supports the theory that CBF decreases during physical exercise despite the elevated metabolic cerebral demand (Ogoh & Ainslie, 2009).

Some authors indicate that during physical exercise, the blood flow augments locally in those areas involved in integrating sensory input, maintenance of equilibrium and coordination of exercise (Delp et al., 2001; Williamson et al., 1999). The regional cerebral blood flow (rCBF) is increased during exercise as well as blood velocity in the in the major cerebral arteries and the internal carotid artery (Ide & Secher, 2000; Sato & Sadamoto, 2010; Willie et al., 2011). For this reason, exercise induces a increase of CBF in the occipital regions than in the temporal and frontal regions (Willie et al., 2011). This phenomenon results in greater blood flow in most of the brain (Ide & Secher, 2000). On this basis, transcranial Doppler measures have shown an increase of 20% in the average velocity of the blood flow in the cerebral artery during dynamic exercise (Linkis et al., 1995; Madsen et al., 1993), whereas no changes were observed in the anterior cerebral artery (Jorgensen, Perko, & Secher, 1992).

1.1. Role of blood flow and VO_2 demand

Although the vasodilatory effects of the acute hypoxia tend to initially increase the CBF when the individual is at rest, it is unclear how the hypoxia affects the CBF autoregulation during exercise (Ainslie et al., 2007). Due to the cerebral oxygenation, the CBF should increase during physical exercise as a response to the higher demand of O_2 (Ide, Horn, & Secher, 1999). However, it is questioned whether the general metabolic activity actually increases during exercise (Ide et al., 1999). Several studies addressing cycling have not register any significant change in the cerebral metabolic rate of oxygen ($CMRO_2$) (Madsen et al., 1993; Zobl et al., 1965). On the other hand, Scheinber et al. (Scheinberg et al., 1954) observed an increase in $CMRO_2$ during high-intensity exercise on a treadmill. The heterogeneity of the CBF was demonstrated when Kleinschmidt and colleagues (Kleinschmidt et al., 1996) observed that an individual showed reduced deoxyhemoglobin and increased oxyhemoglobin values when developing a task involving the movement of a finger against a resistance. When several groups of muscles are involved in the same exercise, certain areas of the brain may suffer a reduction in CBF, since it seems that the global cerebral blood flow of O_2 is not affected by the exercise (Madsen et al., 1993). Although $CMRO_2$ has been considered an important variable when studying the cerebral metabolic activity, it has been suggested that $CMRO_2$ may not be the most adequate indicator (Ide et al., 1999) because different studies have observed that CBF increases at a greater rate than $CMRO_2$ (Fox & Raichle, 1986).

1.2. Effect of Cardiac Output on CBF

Querido and Sheel (2007) observed that those types of exercise involving a large muscle mass lead to an increase of the cardiac output, resulting in a higher velocity of the CBF. Other authors have also found in patients with heart failure and atrial fibrillation that the increase of the cardiac output seems to affect the velocity of blood flow in the medial cerebral artery during exercise (Ide & Secher, 2000). These findings suggest that cardiac output may be playing a major role in the CBF response during exercise (Querido & Sheel, 2007).

1.3. Effect of Blood Pressure on CBF

Not only those studies which registered changes of CBF during exercise but also those which did not find any modification have observed slight increases of blood pressure (Hedlund, Nylin, & Regnström, 2008). It

is widely known that blood pressure plays a significant role in the increase of blood flow during exercise (Querido & Sheel, 2007). However, the cerebral blood flow autoregulation can be impaired when acute hypotension occurs such as during the diastole in high-intensity exercise (Querido & Sheel, 2007). During exercise, O₂ blood pressure may decrease, what affects the O₂ cerebral supplies (Dempsey, Hanson, & Henderson, 1984; Nielsen et al., 1998). This phenomenon is observed during the hyperventilation associated to exercise, which involves a reduction of the CO₂ blood pressure (Linkis et al., 1995). In this situation, if the CO₂ reduction is accompanied by a constriction of the cerebral vessels, the hyperventilation will decrease the cerebral perfusion (Linkis et al., 1995).

1.4. Effect of hyperthermia on CBF

Hyperthermia reduces CBF at rest (Brothers et al., 2009; Fan et al., 2008; Nelson et al., 2011) and during prolonged exercise (Nybo et al., 2002). The induced hyperthermia reduces the central activation because a maximal muscle contraction is voluntarily maintained, a mechanism that is commonly associated with central fatigue (Nybo & Nielsen, 2001a). An alteration of the cerebral perfusion can also provoke presyncopal symptoms during exercise in hot environments (Nybo et al., 2002).

Moreover, blood flow velocity in the medial cerebral artery decreases progressively during exercise with hyperthermia compared to control groups of exercise without hyperthermia (Nybo & Nielsen, 2001b). This reduction of the flow velocity in the medial cerebral artery is associated with an induced hyperventilation that provokes a decrease in the partial pressure of CO₂ (PaCO₂), what indicates that gCBF may also become lower (Nybo et al., 2002). However, other studies have not find any proof of this mechanism, what highlights the need to measure CBF precisely in order to know the actual behaviour of cerebral irrigation during prolonged exercise with hyperthermia (Nybo et al., 2002).

2. Influence of physical exercise on cellular metabolism

The brain needs a large energy requirements and it consumes 20% of total oxygen uptake and 25% of glucose when it only have the 2% of total body mass in human (Attwell et al., 2010; Bolduc, Thorin-Trescases, & Thorin, 2013; Faraci, 2011). For this reason, in the last decade numerous studies have gained interested about how exercise affects the cerebral glucose consumption.

Different results have been found depending on the intensity of the exercise (Dalsgaard et al., 2004; Kemppainen et al., 2005). It was firstly demonstrated that during exercise there is a local increase of glucose consumption in the brain, especially in the areas responsible for locomotion (Ide et al., 2004; Vissing, Andersen, & Diemer, 1996). However, other studies indicate that the global energetic metabolism in the brain remains unaltered during the transition from rest to moderate exercise, due to the fact that the greater activation of the motor areas of the brain is compensated with a lower activation in other cerebral areas (Nybo & Secher, 2004). Kemppainen et al. (2005) demonstrated that the increase in the intensity of the activity produces a decrease of glucose captation.

It is important to understand the behaviour of the glucose and lactate metabolic consumption in the brain during exercise. The glucose and lactate uptake as energetic substrates in response to physical exercise increase at a greater rate compared to O₂ uptake (Madsen et al., 1993; Nybo & Secher, 2004), implying that during exercise the anaerobic cerebral metabolism is greater than the aerobic cerebral metabolism as expressed by the Cerebral Metabolic Rate.

2.1. Cerebral Metabolic Rate: relationship between lactate and glucose consumption

The brain possesses a capacity for anaerobic metabolism (Fox & Raichle, 1986), providing an important means to enhance energy turnover to sustain cerebral activation during high-intensity exercise (Pellerin, 2005). However, as blood lactate increases during anaerobic exercise, lactate uptake in the brain depends on its arterial concentration (Ogoh & Ainslie, 2009). A variable commonly studied when addressing cerebral metabolism is the cerebral metabolic rate (CMR). CMR is a value that indicates changes in cerebral metabolism independently of those in CBF (Secher, Seifert, & Lieshout, 2008). CMR value can be calculated from the following equation:

$$\text{CMR} = \text{O}_2 \text{ uptake} / [\text{glucose uptake} + 1/2 \text{ lactate uptake}]$$

CMR reductions are associated with a greater cerebral activation (Secher et al., 2008). During an increment of exercise workload, the CMR decreases gradually (Ogoh & Ainslie, 2009). Cerebral lactate uptake, together with glucose uptake, is larger than O₂ uptake, as reflected by the decrease in CMR (Quistorff, Secher, & Lieshout, 2008). CMR also decreases when plasma lactate is not high, as during prolonged exercise, cerebral activation associated with mental activity, or exposure to a stressful situation (Quistorff et al., 2008). Additionally, low CMR values in sport performance could be associated with central fatigue (Secher et al., 2008).

High-intensity exercise is associated with metabolic alterations that could reduce CMR (Dalsgaard et al., 2004; Seifert & Secher, 2011) and produce central fatigue (Nybo & Secher, 2004). This central fatigue could involve the depletion of the glycogen cerebral reserves since intense exercise increases the glucose uptake (Nybo & Secher, 2004). Traditionally, the brain was believed to depend completely on glucose as energetic supply, and CMR values were close to 6 (Ahlborg & Wahren, 1972; Madsen et al., 1995). However, some studies observed that glucose uptake decreased when the intensity of exercise increased (Kemppainen et al., 2005). This suggests that the brain is likely to be using other energetic substrates during high-intensity exercise.

Evidence suggests that this substrate is lactate (Dalsgaard et al., 2004; Ide et al., 2004; Quistorff et al., 2008). During maximal exercise, the human brain is able to take the lactate produced by the muscles and use it to reduce CMR by 30-40% (Dalsgaard et al., 2004; Ide & Secher, 2000). In-vitro studies in neurons observed they have higher affinity to consume lactate compared to glucose during neuronal activation (Larrabee, 1995; Schurr et al., 1999). In addition, the magnitude of the use of lactate as energy substrate is proportional with exercise intensity (Kemppainen et al., 2005; Willie & Smith, 2011). On the other hand, global glucose uptake was reduced in humans at rest when they were exposed to higher levels of lactate, suggesting that the brain is capable of using exogenous lactate (Smith et al., 2003). Moreover, it has been observed that during high-intensity exercise there is not lactate accumulation in the cerebrospinal fluid of the brain, what indicates that lactate may be metabolised (Dalsgaard et al., 2003).

Some studies suggest that the potential use of lactate as cerebral substrate is clear when the lactate infusion suppresses the hypoglycaemic symptoms (King et al., 1998; Veneman et al., 1994) and reduces the cerebral glucose uptake during euglycemia (normal glucose concentrations) (Smith et al., 2003). After exhaustive exercise, the greater absorption of glucose and lactate in relation to oxygen, observed as a response to a reduction of CMR, indicate that glucose and lactate are either stored or metabolised since they are not released from the brain during a recovery period of 1 hour (Dalsgaard et al., 2004; Ide & Secher, 2000). Furthermore, restoration of the brain glycogen stores may require periods three times longer than the time used in the depletion of those same stores (Dienel, Wang, & Cruz, 2002).

Kemppainen et al. (2005) observed that during exercise, the glucose uptake decreased in the dorsal cingulate cortex, effect that was more pronounced in individuals with higher exercise capacity (37% vs 20%). These results demonstrated two hypotheses: 1) as the intensity of exercise increases, cerebral glucose uptake decreases in favour of other substrates such as lactate to maintain the neuronal activity during high-intensity exercise (Kemppainen et al., 2005; Querido & Sheel, 2007); and 2) training could result in local metabolic adaptations in the frontal cortical regions leading to more pronounced reductions of glucose uptake observed in individuals with higher exercise capacity (Kemppainen et al., 2005). This evidence suggests that subjects with higher exercise capacity experience adaptations in the involved cortical areas, which would result in a greater use of lactate.

2.2. Hyperthermia effect

Nybo and Secher (2004) reported significant changes in cell metabolism during exercise at high temperatures. During exercise with hyperthermia, the excessive heat accumulation in the brain as a consequence of the concomitant restriction of the cerebral blood flow may lead to an increase of temperature over 40°C, resulting in a disruption of the brain capacity to maintain the maximal motor activity during exercise (Nybo & Secher, 2004). If this effect remains for a prolonged time, it could lead to hypoglycaemia (Nybo & Secher, 2004). Hypoglycemia (low content of glucose in blood) may provoke an increase in the perception of effort and reduce the uptake of brain glucose, what could lead to the onset of fatigue due to a restriction in the uptake of other substrates by the brain (Nybo & Secher, 2004) (Figure 2).

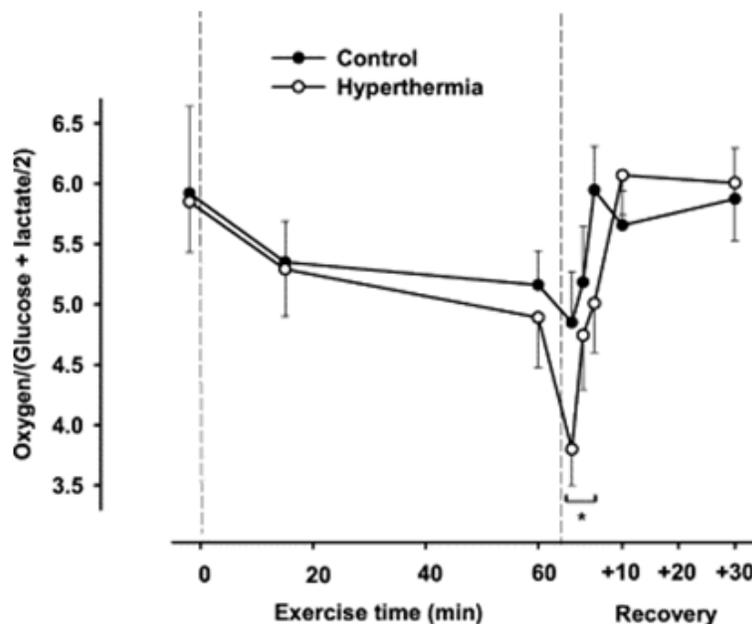


Figure 2. CMR values during and after exercise in subjects with and without hyperthermia. The values are the mean of 8 subjects. (Extracted from Nybo et al., 2001b)

CONCLUSIONS

In summary, the conclusions of this review are as follows:

1. High-intensity exercise not only causes changes in cardiorespiratory and locomotor systems, but also at a cerebral level.
2. Medium-intensity exercise appears to increase cerebral blood flow, but as the intensity of exercise increases, the cerebral blood flow is reduced to initial values. This may be due to other mechanisms such as hyperventilation or compensatory vasoconstriction of those areas with lower cerebral activity during exercise.
3. Flow and metabolic consumption locally increases in the motor areas of the brain, specifically in those involved during the exercise.
4. In response to exercise, the brain increases glucose and lactate uptake at a greater rate than VO_2 uptake. Furthermore, as the exercise intensity increases, lactate uptake is greater than glucose uptake, highlighting the important role that the anaerobic metabolism plays during exercise.
5. Physical exercise under hyperthermia can produce circulatory disorders and reduce cerebral blood flow resulting in lower glucose uptake by the brain.

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REFERENCES

1. Ahlborg, G., & Wahren, J. (1972). Brain substrate utilization during prolonged exercise. *Scand J Clin Lab Invest*, 29(4), pp.397-402.
2. Ainslie, P.N., Barach, A., Murrell, C., Hamlin, M., Hellems, J., & Ogoh, S. (2007). Alterations in cerebral autoregulation and cerebral blood flow velocity during acute hypoxia: rest and exercise. *Am J Physiol Heart Circ Physiol*, 292(2), pp.H976-H983.
3. Attwell, D., Buchan, A.M., Charpak, S., Lauritzen, M., MacVicar, B.A., & Newman, E.A. (2010). Glial and neuronal control of brain blood flow. *Nature*, 468(7321), pp.232-243.
4. Bolduc, V., Thorin-Trescases, N., & Thorin, E. (2013). Endothelium-dependent control of cerebrovascular functions through age: exercise for healthy cerebrovascular aging. *Am J Physiol Heart Circ Physiol*, 305(5), pp.H620-633.
5. Brisswalter, J., Arcelin, R., Audiffren, M., & Delignieres, D. (1997). Influence of physical exercise on simple reaction time: Effect of physical fitness. *Percept Mot Skills*, 85(3), pp.1019-1027.
6. Brothers, R.M., Wingo, J.E., Hubing, K.A., & Crandall, C.G. (2009). The effects of reduced end-tidal carbon dioxide tension on cerebral blood flow during heat stress. *J Physiol*, 587(15), pp.3921-3927.
7. Dalsgaard, M.K., Nybo, L., Cai, Y., & Secher, N.H. (2003). Cerebral metabolism is influenced by muscle ischaemia during exercise in humans. *Exp Physiol*, 88(2), pp.297-302.
8. Dalsgaard, M.K., Quistorff, B., Danielsen, E.R., Selmer, C., Vogelsang, T., & Secher, N.H. (2004). A reduced cerebral metabolic ratio in exercise reflects metabolism and not accumulation of lactate within the human brain. *J Physiol*, 554(2), pp.571-578.
9. Delp, M.D., Armstrong, R.B., Godfrey, D.A., Laughlin, M.H., Ross, C.D., & Wilkerson, M.K. (2001). Exercise increases blood flow to locomotor, vestibular, cardiorespiratory and visual regions of the brain in miniature swine. *J Physiol*, 533(3), pp.849-859.

10. Dempsey, J.A., Hanson, P.G., & Henderson, K.S. (1984). Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol*, 355(1), 161–175.
11. Diemel, G.A., Wang, R.Y., & Cruz, N.F. (2002). Generalized sensory stimulation of conscious rats increases labeling of oxidative pathways of glucose metabolism when the brain glucose–oxygen uptake ratio rises. *J Cereb Blood Flow Metab*, 22(12), pp.1490-1502.
12. Fan, J.L., Cotter, J.D., Lucas, R.A., Thomas, K., Wilson, L., & Ainslie, P.N. (2008). Human cardiorespiratory and cerebrovascular function during severe passive hyperthermia: effects of mild hypohydration. *J Appl Physiol*, 105(2), pp.433-445.
13. Faraci, F.M. (2011). The Robert M. Berne Distinguished Lecture: Protecting against vascular disease in brain. *Am J Physiol Heart Circ Physiol*, 300(5), pp.H1566.
14. Fox, P.T., & Raichle, M.E. (1986). Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A*, 83(4), pp.1140-1144.
15. Hedlund, S., Nylin, G., & Regnström, O. (2008). The behaviour of the cerebral circulation during muscular exercise. *Acta Physiol Scand*, 54(3-4), pp.316-324.
16. Ide, K., Horn, A., & Secher, N.H. (1999). Cerebral metabolic response to submaximal exercise. *J Appl Physiol*, 87(5), pp.1604-1608.
17. Ide, K., Schmalbruch, I.K., Quistorff, B., Horn, A., & Secher, N.H. (2004). Lactate, glucose and O₂ uptake in human brain during recovery from maximal exercise. *J Physiol*, 522(1), pp.159164.
18. Ide, K., & Secher, N.H. (2000). Cerebral blood flow and metabolism during exercise. *Prog Neurobiol*, 61(4), pp.397-414.
19. Jorgensen, L.G., Perko, G., & Secher, N.H. (1992). Regional cerebral artery mean flow velocity and blood flow during dynamic exercise in humans. *J Appl Physiol*, 73(5), pp.1825-1830.
20. Kempainen, J., Aalto, S., Fujimoto, T., Kalliokoski, K.K., Laangsjö, J., Oikonen, V., ... Knuuti, J. (2005). High intensity exercise decreases global brain glucose uptake in humans. *J Physiol*, 568(1), pp.323-332.
21. Kety, S.S., & Schmidt, C.F. (1948). The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *J Clin Invest*, 27(4), pp.476.
22. King, P., Kong, M.F., Parkin, H., MacDonald, I.A., Barber, C., & Tattersall, R.B. (1998). Intravenous lactate prevents cerebral dysfunction during hypoglycaemia in insulin-dependent diabetes mellitus. *Clin Sci (Lond)*, 94(2), pp.157.
23. Kleinschmidt, A., Obrig, H., Requardt, M., Merboldt, K.D., Dirnagl, U., Villringer, A., & Frahm, J. (1996). Simultaneous recording of cerebral blood oxygenation changes during human brain activation by magnetic resonance imaging and near-infrared spectroscopy. *J Cereb Blood Flow Metab*, 16(5), pp.817-826.
24. Larrabee, M.G. (1995). Lactate metabolism and its effects on glucose metabolism in an excised neural tissue. *J Neurochem*, 64(4), pp.1734-1741.
25. Lassen, N.A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiol Rev*, 39(2), pp.183-238.
26. Lassen, N.A. (1974). Control of cerebral circulation in health and disease. *Circulation Research*, 34(6), pp.749-760.
27. Linkis, P., Jorgensen, L.G., Olesen, H.L., Madsen, P.L., Lassen, N.A., & Secher, N.H. (1995). Dynamic exercise enhances regional cerebral artery mean flow velocity. *J Appl Physiol*, 78(1), pp.12-16.
28. Madsen, P.L., Hasselbalch, S.G., Hagemann, L.P., Olsen, K.S., Bülow, J., Holm, S., ... Lassen, N.A. (1995). Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation:

- evidence obtained with the Kety–Schmidt technique. *J Cereb Blood Flow Metab*, 15(3), pp.485-491.
29. Madsen, P.L., Sperling, B.K., Warming, T., Schmidt, J.F., Secher, N.H., Wildschiodtz, G., ... Lassen, N.A. (1993). Middle cerebral artery blood velocity and cerebral blood flow and O₂ uptake during dynamic exercise. *J Appl Physiol*, 74(1), pp.245-250.
 30. Marsden, K.R., Haykowsky, M.J., Smirl, J.D., Jones, H., Nelson, M.D., Altamirano-Diaz, L.A., ... Willie, C.K. (2012). Aging blunts hyperventilation-induced hypocapnia and reduction in cerebral blood flow velocity during maximal exercise. *Age*, 34(3), pp.725-735.
 31. Nelson, M.D., Haykowsky, M.J., Stickland, M.K., Altamirano-Diaz, L.A., Willie, C.K., Smith, K.J., ... Ainslie, P.N. (2011). Reductions in cerebral blood flow during passive heat stress in humans: partitioning the mechanisms. *J Physiol*, 589(16), pp.4053-4064.
 32. Nielsen, H.B., Madsen, P., Svendsen, L.B., Roach, R.C., & Secher, N.H. (1998). The influence of PaO₂, pH and SaO₂ on maximal oxygen uptake. *Acta Physiol Scand*, 164(1), pp.89-87.
 33. Nybo, L., Møller, K., Volianitis, S., Nielsen, B., & Secher, N.H. (2002). Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J Appl Physiol*, 93(1), pp.58-64.
 34. Nybo, L., & Nielsen, B. (2001a). Hyperthermia and central fatigue during prolonged exercise in humans. *J Appl Physiol*, 91(3), pp.1055-1060.
 35. Nybo, L., & Nielsen, B. (2001b). Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol*, 534(1), pp.279-286.
 36. Nybo, L., & Secher, N.H. (2004). Cerebral perturbations provoked by prolonged exercise. *Prog Neurobiol*, 72(4), pp.223-261.
 37. Ogoh, S., & Ainslie, P. N. (2009). Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol*, 107(5), pp.1370-1380.
 38. Ogoh, S., Dalsgaard, M.K., Yoshiga, C.C., Dawson, E.A., Keller, D.M., Raven, P.B., & Secher, N.H. (2005). Dynamic cerebral autoregulation during exhaustive exercise in humans. *Am J Physiol Heart Circ Physiol*, 288(3), pp.H1461-H1467.
 39. Paulson, O.B., Strandgaard, S., & Edvinsson, L. (1990). Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*, 2(2), pp.161-192.
 40. Pellerin, L. (2005). How astrocytes feed hungry neurons. *Mol Neurobiol*, 32(1), pp.59-72.
 41. Poca, M.A., Sahuquillo, J., Monforte, R., & Vilalta, A. (2005). Métodos globales de monitorización de la hemodinámica cerebral en el paciente neurocrítico: fundamentos, controversias y actualizaciones en las técnicas de oximetría yugular. *Neurocirugía*, 16(4), pp.301-322.
 42. Querido, J.S., & Sheel, A.W. (2007). Regulation of cerebral blood flow during exercise. *Sports Med*, 37(9), pp.765-782.
 43. Quistorff, B., Secher, N.H., & Lieshout, J.J.V. (2008). Lactate fuels the human brain during exercise. *FASEB J*, 22(10), pp.3443-3449.
 44. Sato, K., & Sadamoto, T. (2010). Different blood flow responses to dynamic exercise between internal carotid and vertebral arteries in women. *J Appl Physiol*, 109(3), pp.864-869.
 45. Scheinberg, P., Blackburn, L.I., Rich, M., & Saslaw, M. (1954). Effects of vigorous physical exercise on cerebral circulation and metabolism. *Am J Med*, 16(4), pp.549-554.
 46. Schurr, A., Miller, J.J., Payne, R.S., & Rigor, B.M. (1999). An Increase in Lactate Output by Brain Tissue Serves to Meet the Energy Needs of Glutamate-Activated Neurons. *J Neurosci*, 19(1), pp.34-39.
 47. Secher, N.H., Seifert, T., & Lieshout, J.J.V. (2008). Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol*, 104(1), pp.306-314.

48. Seifert, T., & Secher, N.H. (2011). Sympathetic influence on cerebral blood flow and metabolism during exercise in humans. *Prog Neurobiol*, 95(3), pp.406-426.
49. Smith, D., Pernet, A., Hallett, W. A., Bingham, E., Marsden, P.K., & Amiel, S.A. (2003). Lactate; A Preferred Fuel for Human Brain Metabolism In Vivo. *J Cereb Blood Flow Metab*, 23(6), pp.658-664.
50. Smith, K.J., Wong, L.E., Eves, N.D., Koelwyn, G.J., Smirl, J.D., Willie, C.K., & Ainslie, P.N. (2012). Regional cerebral blood flow distribution during exercise: Influence of oxygen. *Respir Physiol Neurobiol*, 184(1), pp.97-105.
51. Veneman, T., Mitrakou, A., Mookan, M., Cryer, P., & Gerich, J. (1994). Effect of hyperketonemia and hyperlacticacidemia on symptoms, cognitive dysfunction, and counterregulatory hormone responses during hypoglycemia in normal humans. *Diabetes*, 43(11), pp.1311-1317.
52. Vissing, J., Andersen, M., & Diemer, N.H. (1996). Exercise-induced changes in local cerebral glucose utilization in the rat. *J Cereb Blood Flow Metab*, 16(4), pp.729-736.
53. Williamson, J.W., McColl, R., Mathews, D., Ginsburg, M., & Mitchell, J.H. (1999). Activation of the insular cortex is affected by the intensity of exercise. *J Appl Physiol*, 87(3), pp.1213-1219.
54. Willie, C.K., Cowan, E.C., Ainslie, P.N., Taylor, C.E., Smith, K.J., Sin, P.Y.W., & Tzeng, Y.C. (2011). Neurovascular coupling and distribution of cerebral blood flow during exercise. *J Neurosci Methods*, 198(2), pp.270-273.
55. Willie, C.K., & Smith, K.J. (2011). Fuelling the exercising brain: a regulatory quagmire for lactate metabolism. *J Physiol*, 589(4), pp.779-780.
56. Zobl, E.G., Talmers, F.N., Christensen, R.C., & Baer, L.J. (1965). Effect of exercise on the cerebral circulation and metabolism. *J Appl Physiol*, 20(6), pp.1289-1293.