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Cerebral blood flow and metabolism during exercise

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Abstract

During exercise regional cerebral blood flow (rCBF), as blood velocity in major cerebral arteries and also blood flow in the internal carotid artery increase, suggesting an increase in blood flow to a large part of the brain. Such an increase in CBF is independent of the concomitant increase in blood pressure but is modified by the alteration in arterial carbon dioxide tension ($PaCO_2$). Also, the increase in middle cerebral artery mean blood velocity (MCA V_{mean}) reported with exercise appears to depend on the ability to increase cardiac output (CO), as demonstrated in response to beta-1 blockade and in patients with cardiac insufficiency or atrial fibrillation.

Near-infrared spectroscopy (NIRS) determined cerebral oxygenation supports the alterations in MCA V_{mean} during exercise. Equally, the observation that the cerebrovascular CO_2-reactivity appears to be smaller in the standing than in the sitting and especially in the supine position could relate to the progressively smaller CO.

In contrast, during exercise "global" cerebral blood flow (gCBF), as determined by the Kety–Schmidt technique is regarded as being constant. One limitation of the Kety–Schmidt method for measuring CBF is that blood flow in the two internal jugular veins depends on the origin of drainage and it has not been defined which internal jugular venous flow is evaluated. Such a consideration is equally relevant for an evaluation of cerebral metabolism during exercise.

While the regional cerebral uptake of oxygen (O_2) increases during exercise, the global value is regarded as being constant. Yet, during high intensity exercise lactate is taken up by the brain and its O_2 uptake also increases. Furthermore, in the initial minutes of recovery immediately following exercise, brain glucose and O_2 uptake are elevated and lactate uptake remains high.

A maintained substrate uptake by the brain after exercise suggests a role for brain glycogen in cerebral activation, but the fate of brain substrate uptake has not yet been determined.

Keywords: Arterial carbon-dioxide tension; Blood pressure; Cardiac output; Cerebral blood flow; Cerebral O_2 to carbohydrate uptake ratio; Oxygenation

Contents

Abbreviations: ACA, Anterior cerebral artery; CBF, Cerebral blood flow; CO, Cardiac output; CO_2, Carbon dioxide; F_1, First compartment flow; fMRI, functional magnetic resonance imaging; gCBF, global cerebral blood flow; Hb, Deoxygenated haemoglobin; HbO_2, Oxygenated haemoglobin; Hb_{total}, Total haemoglobin (sum of Hb and HbO_2); HR, Heart rate; ICA, Internal carotid artery; ISI, Initial slope index; MAP, Mean arterial pressure; MCA, Middle cerebral artery; NIRS, Near-infrared spectroscopy; NA, Noradrenaline; N_2O, Nitrous oxide; O_2, Oxygen; *P*, Doppler signal power; $PaCO_2$, Arterial CO_2 tension; PET, Positron emission tomography; $PetCO_2$, End tidal CO_2 tension; rCBF, regional cerebral blood flow; SPECT, Single photon emission computed tomography; TCD, Transcranial ultrasound Doppler; VO_2max, Maximal O_2 uptake; V_{mean}, Maximal frequency of Doppler shift mean blood velocity; V_{Iwmean}, The intensity weighted mean frequency of Doppler spectrum.

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1. Introduction

Since Kety and Schmidt (1945) developed the nitrous oxide (N_2O) method for measuring CBF, the "global" value (gCBF) and equally the brain metabolic rate have been determined in a variety of circumstances. It was concluded that gCBF is regulated to remain stable for as long as PaCO$_2$ is stable and blood pressure stays within the range of cerebral "autoregulation" with the range of mean arterial pressure (MAP) from 60 to 150 mm Hg (Lassen, 1959). Thus, exercise does not elevate gCBF, even though blood pressure increases (Madsen et al., 1993). Only in response to mental stimulation is gCBF increased, as is the metabolic rate of the brain (Madsen et al., 1995b) and, conversely, both are reduced during sleep (Madsen et al., 1991). As techniques were developed to evaluate clearance of radioactive substances from the brain, interest was directed to the regional changes in the brain during "activation" (Lassen et al., 1978). The brain was mapped with respect to the blood flow distribution following a given intervention and in contrast to the global evaluation of CBF, there appeared to be an increase in blood flow and in the metabolic rate corresponding to the cortical representation of the sensory input. During a hand movement there is an increase in blood flow as well as in O_2 uptake corresponding to the cortical representation of the sensory input (Raichle et al., 1976), but, as mentioned, during cycling neither flow nor the O_2 uptake change at the global level (Madsen et al., 1993). This discrepancy between a global and regional evaluation of CBF may be due to a relative insensitivity of the Kety–Schmidt technique as well as to the small cortical representation of the hand and the leg. In addition, any alterations in PaCO$_2$ during exercise may contribute to make a comparison between rest and exercise difficult, while PaCO$_2$ does not affect an evaluation of the regional flow distribution.

During supine rest the brain as a whole is estimated to receive ~750 ml min^{-1} of blood or ~55 ml (100) g^{-1} min^{-1} and a similar value is derived in a variety of situations by changing the diameter of the resistance of vessels in response to, e.g. a change in perfusion pressure (Paulson et al., 1990). Only when blood pressure increases beyond the range of cerebral "autoregulation", is there a proportional increase in gCBF and, conversely, blood flow decreases when blood pressure drops below ~60 mm Hg. Also, PaCO$_2$ has a strong effect on gCBF. CO_2 inhalation increases gCBF 20–30% per kPa PaCO$_2$. Besides the global influences of blood pressure and PaCO$_2$ on CBF, local metabolic regulation of regional perfusion is exhibited as flow is coupled specifically to discrete regions of the brain

activated during, e.g., motor or visual stimulation. Therefore, autoregulation, $PaCO_2$, and the local metabolic activity are integrated in the CBF response to a given stimulus including exercise. However, these factors do not seem to account fully for changes in CBF. For instance, with a reduced central blood volume developed during lower body negative pressure (Giller et al., 1992; Levine et al., 1994; Bonder et al., 1995; Schondorf et al., 1997; Zhang et al., 1997; 1998) or head-up tilt (Jørgensen et al., 1993b; Jordan et al., 1998), MCA V_{mean} is reduced and NIRS determined cerebral oxygenation decreases (Madsen et al., 1998b), although blood pressure is maintained at the level of supine rest. Also, in the awake dog, CBF is reduced during atrial fibrillation, even when the aortic pressure remains stable (Friedman et al., 1987).

The exercise CBF has been reviewed by Jørgensen (1995) with the main focus on the applicability of transcranial Doppler for CBF and she recently re-evaluated exercise CBF (Jørgensen et al., 1999). This review addresses whether CBF and cerebral metabolic rate increase out of proportion to changes in $PaCO_2$ and blood pressure during exercise. Additionally, the paper considers to what extent the ability of the subject to increase cardiac output influences brain circulation during exercise. Furthermore, we address whether cerebral metabolic rate changes during exercise and recovery including an evaluation of brain lactate uptake.

2. Cerebral blood flow

2.1. Kety–Schmidt technique

During exercise gCBF is reported to remain stable (Scheinberg et al., 1953, 1954; Zobl et al., 1965; Madsen et al., 1993), except in the study by Kleinerman and Sancetta (1955) where a reduction in gCBF was observed. Together these studies indicate that during exercise gCBF is related more to changes in $PaCO_2$ than to exercise per se (Fig. 1).

Scheinberg et al. (1953) measured gCBF during mild intensity cycling in patients with chronic pulmonary disease. Although MAP increased (91–101 mm Hg), the change in gCBF was not significant (53–58 ml $100g^{-1}$ min^{-1}) and $PaCO_2$ and arterial O_2 tension remained unchanged. Scheinberg et al. (1954) evaluated gCBF in healthy young subjects during brisk walking on a treadmill (120 m min^{-1}; 4% grade). During exercise gCBF did not differ from that measured during supine rest and there was no significant change in $PaCO_2$. However, MAP (61 mm Hg) was remarkably low. According to Scheinberg and Stead (1949) the standing position reduces gCBF by ~20%. Therefore, exercise could have increased gCBF from the resting level of the standing position to re-

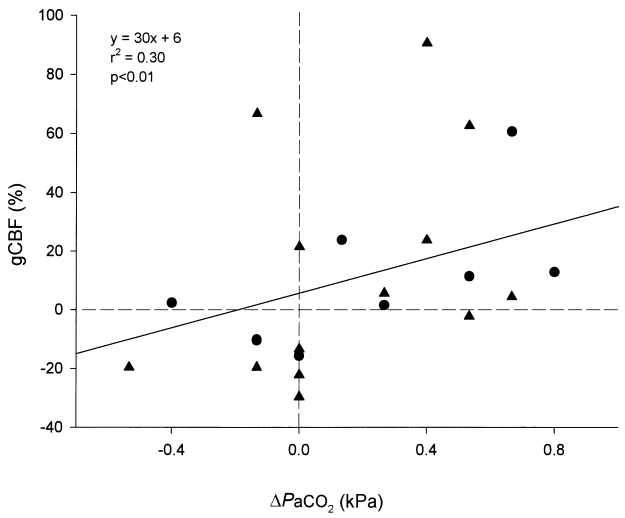

Fig. 1. Global cerebral blood flow (gCBF) related to the arterial carbon dioxide tension ($\Delta PaCO_2$) from rest to exercise. Data are from Scheinberg et al. (1953, ●; 1954, ▲).

establish the level of supine rest. Kleinerman and Sancetta (1955) obtained a 13% reduction in gCBF during mild cycling, but this reduction in flow is likely attributed to a lowered $PaCO_2$. Zobl et al. (1965) studied gCBF in healthy subjects and hypertensive patients during cycling. Although gCBF was not significantly different from rest to exercise, there was a slight rise in gCBF in both groups (16 and 10%, respectively). These small and nonsignificant rises in flow were manifest although arterial CO_2 content was reduced and there was an increase in MAP (92–105 mm Hg and 126–142 mm Hg, respectively). In the most recent study, Madsen et al. (1993) measured gCBF during cycling at a moderate intensity (~50% of maximal O_2 uptake; VO_2max) where the Kety–Schmidt technique in "desaturation mode" was used with application of ^{133}Xe rather than of N_2O as the tracer. To account for effects of a reduced $PaCO_2$ during exercise, Madsen et al. (1993) "corrected" gCBF using a cerebral CO_2 reactivity of 30% kPa^{-1} although the individual "CO_2 reactivity" was not determined. gCBF was 51 ml $(100)g^{-1}$ min^{-1} at rest and 47 ml $(100)g^{-1}$ min^{-1} during cycling (51 ml $(100)g^{-1}$ min^{-1} after the correction was made). In contrast, Hedlund et al. (1962) found an average increase in CBF of ~20% with a 77% increase in CO and a marked increase in systolic blood pressure (140–175 mm Hg). They calculated CBF from the injected radiolabeled erythrocyte (^{32}P) and blood sampling from the internal carotid artery (ICA) and the two internal jugular veins. The study was conducted in only four subjects and there was an increase in CBF of 10, 30 and 40%, respectively, in three subjects but a 5% reduction was found in the fourth subject and the authors did not find the increase

in CBF with exercise significant. These different results made interpretation difficult since $PaCO_2$ was not reported.

The cerebral CO_2 reactivity has not been evaluated during exercise. The plot of the data from Scheinberg et al. (1953; 1954) suggests that the same cerebral CO_2 reactivity exists during exercise (30% kPa^{-1}; Fig. 1) as at rest (Linkis et al., 1995), even though there is large scatter. Using this relationship, there is no reported change in gCBF during exercise.

The Kety–Schmidt technique (1945) is based on application of the Fick principle to the uptake of N_2O by the brain. During 10 min of inhaling a mixture of N_2O, O_2 and N_2, the arterial and internal jugular venous N_2O difference is repeatedly determined until the cerebral tissue is saturated with N_2O. After N_2O saturation, blood flow is calculated from the ratio of the N_2O uptake to the integrated a−v difference. This technique is limited by its applicability to steady state flow and it may be argued that such a steady state CBF is unlikely to be established during exercise since $PaCO_2$ increases during low intensity exercise and decreases to even below the resting level with hyperventilation during high intensity exercise (Fig. 2). It may be considered that the influence of $PaCO_2$ on CBF may depend on other factors such as MAP (Harper and Glass, 1965) and ideally the CO_2 reactivity should be determined during exercise.

A probably more serious problem with the Kety–Schmidt technique is the origin of the internal jugular venous drainage. To make jugular venous flow represent a global value for the brain, the two jugular veins must be equally representative for the whole brain. Yet, as pointed out >50 years ago by Himwich et al. (1947), the two jugular veins do not drain symmetrical portions of the brain. Brain scanning shows that the larger internal jugular vein is representative of cortical drainage while the other and usually smaller vein, drains blood largely from subcortical areas (Ferrier et al., 1993) (Fig. 3). In fact, blood flow into the two internal jugular veins and also the O_2 uptake of the brain (the a−v diff. for O_2 times the internal jugular venous flow), are different, depending on the origin of drainage (Ferrier et al., 1993; Lambert et al., 1996). Specifically, in hypertensive patients an elevated noradrenaline (NA) spillover originates from the subcortical area of the brain (Ferrier et al., 1993).

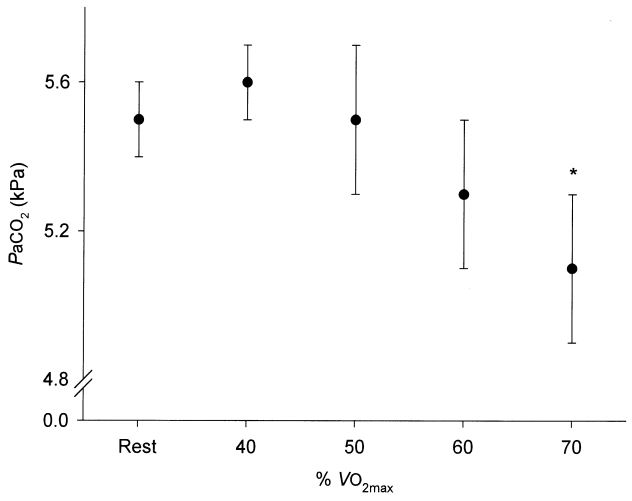

Fig. 2. Arterial carbon dioxide tension ($PaCO_2$) at rest and during incremental exercise. Values are means ± S.D. * denotes significant difference from rest. Data are from Ide et al. (2000a).

In the study of Ferrier et al. (1993), scanning showed that the superior sagittal sinus forms the right transverse sinus and tracks blood to the right jugular vein in ~50% of the subjects. Although the transverse sinus contains the bulk of cortical venous effluent, it also contains blood derived from some subcortical areas via the cavernous sinus. Yet, subcortical brain regions drain predominantly into the inferior sagittal and straight sinuses, which in turn form the transverse sinus generally on the opposite side to that derived from the superior sagittal sinus. The inferior sagittal sinus receives some cortical venous effluent from the falx cerebri. In ~25% of cases, the route of drainage of the superior sagittal sinus is into the left transverse sinus and left internal jugular vein and only in remaining 25% of the subjects is flow not lateralized. We obtained a brain scanning from 15 subjects. Eleven of the subjects were judged, from the peak count for radio-activity, to have a larger internal jugular venous flow to the right (Fig. 3; Ide, K., Eigtved, A., Nowak, M. and Secher, N.H., unpublished observations). An anatomical evaluation for the venous sinuses in the study of Bisaria (1985) supports this view. The drainage from the sagittal sinus can be divided into three types. In one type, the superior sagittal sinus drains into one lateral sinus and the straight sinus into the other with no connection between the two. In another type, the superior sagittal sinuses and the straight sinus fork and the fork from both sinuses join to form the lateral sinuses. In type three, the superior sagittal sinus joins to form the confluence of the sinuses.

2.2. Microspheres

With the use of radiolabeled microspheres Foreman et al. (1976) determined both total and regional CBF during moderate and severe exercise in swines. Severe exercise increased CO (91%) and MAP (102–139 mm Hg), while $PaCO_2$ was reduced (4.1 to 2.4 kPa). Exercise did not affect either total CBF or rCBF except in the cerebellum where the gray matter blood flow increased. Fixler et al. (1976) also found no change in total CBF with an increase in CO (128%) during exercise in the dog. In contrast, Gross et al. (1980) evalu-

ated rCBF during running and evaluated the role of hyperventilation per se on CBF with the use of doxapram in the dog. During exercise blood flow increased to the sensorimotor cortex by 30%; to the neocerebellar cortex by 39%; and to the paleocerebellar cortex by 29%, but again, when these regional changes in flow were integrated to express flow to the whole brain, there was found no significant change. This was the case although exercise increased MAP (95–124 mm Hg), but exercise also reduced $PaCO_2$ (3.9 to 2.9 kPa) which may have blunted an effect of exercise on regional blood flow to become significant for the brain as a whole (Fig. 1). Equally, doxapram increased MAP (to 134 mm Hg) but it reduced $PaCO_2$ (to 2.5 kPa) and therefore also total CBF.

2.3. Internal carotid artery blood flow

The ICA blood flow has been investigated during exercise by several authors. Samnegård and Carlens (1975) studied the ICA blood flow by an electromagnetic meter during cycling in both a sitting and in a supine position. Subjects were patients after arterial reconstruction of the carotid artery and the electromagnetic flow probe was implanted during surgery. In the sitting position cycling increased ICA blood flow by 8%, MAP (108–132 mm Hg), $PaCO_2$ (5.6–5.7 kPa) and CO (72%). Equally, in the supine position ICA blood flow increased by 11% as also MAP (120–143 mm Hg), $PaCO_2$ (5.6–5.9 kPa) and CO (85%). A similar conclusion was reached by Hellström et al. (1996) who measured ICA blood flow by duplex ultrasonography during incremental cycling in the supine position. ICA blood flow increased by 10% during mild exercise and reached a maximum of a 17% increase during moderate exercise in healthy subjects. Huang et al. (1991) studied ICA blood velocity and arterial diameter during mild to high intensity cycling both at

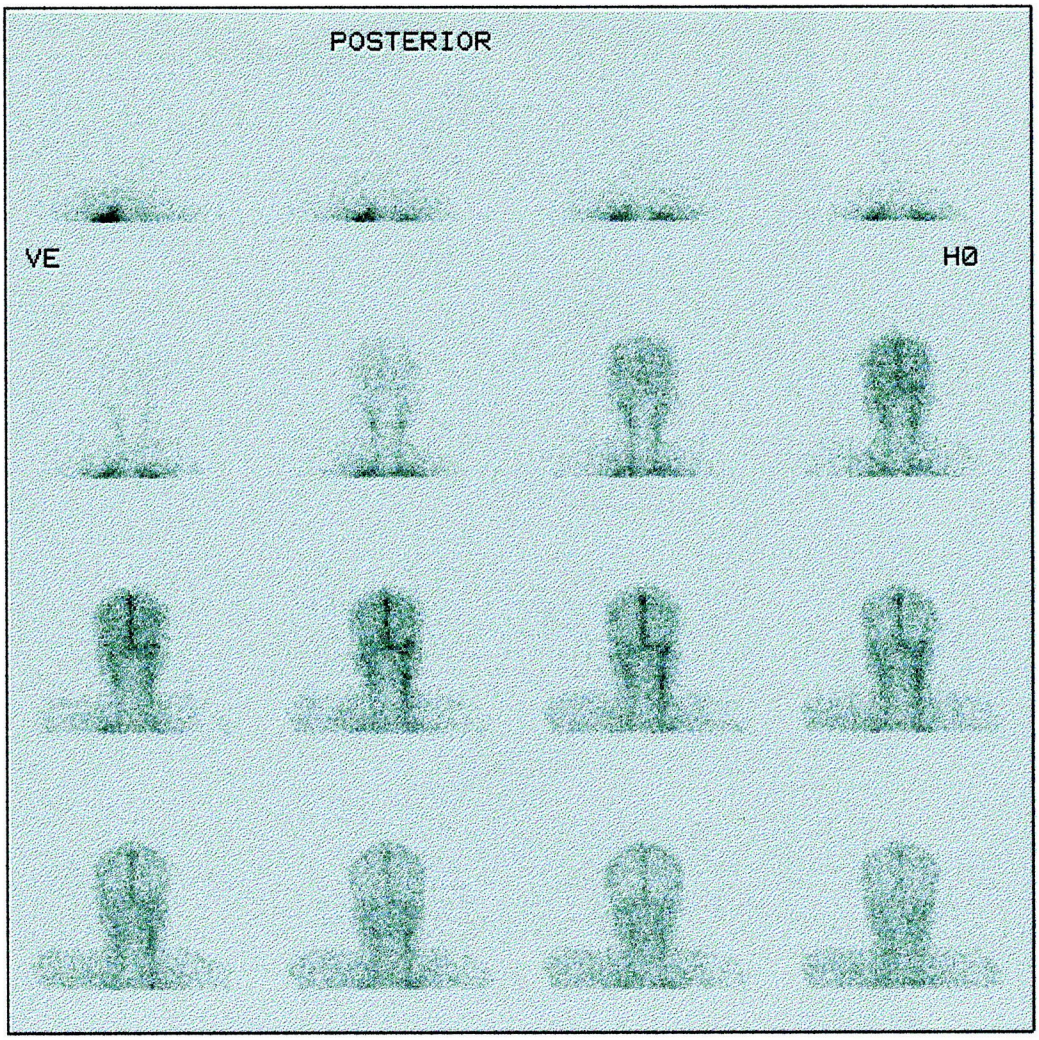

Fig. 3. Posterior view of the head during the transient of a bolus of technetium labelled human albumin. The predominant flow from the central sinus is to the right jugular vein. (Ide, K., Eigtved, A., Nowak, M. and Secher, N.H., unpublished observation).

sea level and at high altitude. During cycling at near maximal O_2 uptake, ICA V_{mean} increased by 22% at sea level and similarly by 17% at acute exposure to hypobaric hypoxia with no change in the ICA diameter. After acclimatisation to high altitude there was no change in the ICA V_{mean} from rest to exercise, although the exercise ICA V_{mean} was as high as in the other conditions and, therefore, the resting value appeared to be elevated. Subsequently, Huang et al. (1992) compared the exercise ICA V_{mean} at high altitude among high landers and sea level residents. Cycling at ~150 W increased ICA V_{mean} by 25% in the high landers and by only 14% in sea level residents and as this did not represent a statistically significant increase, although $PaCO_2$ level were not reported.

2.4. XE clearance technique

In humans cortical blood flow can be studied with the ^{133}Xe clearance technique. In the study of Globus et al. (1983) cortical blood flow did not change during supine cycling at 50% of maximal effort although both MAP (91 to 128 mm Hg) and CO (108%) increased. A drop in $PaCO_2$ of 0.5 kPa might have blunted the change in cortical blood flow related to regional cerebral metabolic activity. In contrast, others have found an increase in flow during exercise (Fig. 4). In the study of Hollman et al. (1986) the right hemispheric CBF increased by 27% during moderate exercise. The same group evaluated the left hemispheric CBF during cycling in two groups of subjects at different work loads. There were increases of 14% at low and 25% at moderate intensity cycling (Herholz et al., 1987). Thomas et al. (1989) found an equal increase in CBF during exercise as they expressed values both as the "initial slope index" (ISI) and as the "first compartment flow" (F_1). The ISI is assumed to represent an integration of cortical and white matter flow, while F_1 is assumed to reflect mainly cortical flow (Schroeder et al., 1986). The F_1 increased by 50% during cycling at 30% of VO_2max and remained elevated at subsequent higher work rates. The increase in ISI was, as expected, somewhat smaller than the increase in F_1; e.g. 26% increase at ~50% of VO_2max. Furthermore, Jørgensen et al. (1992b) studied cortical blood flow during cycling at four work rates corresponding to 0, 30, 60 and 150 W; the F_1 increased by 13, 30, 46 and 57% and the ISI increased by 5, 15, 25 and 42%, respectively. In a subsequent study Jørgensen et al. (1992a) found that the increase in ISI levelled off from moderate to high intensity cycling. In contrast to dynamic exercise and despite a similar increase in MAP as during dynamic exercise, ISI does not appear to change during static exercise (Rogers et al., 1990; Jørgensen et al., 1992a), suggesting that the exercise related increase depends on "movement". The increase in CO was not determined in any of these studies.

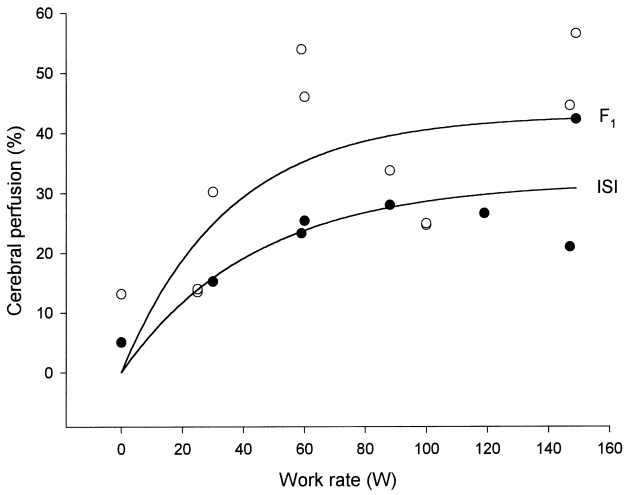

Fig. 4. Cortical brain blood flow as determined by the ^{133}Xe clearance technique during cycling. F1, first compartment flow; ISI, initial slope index. Data are from Hollman et al. (1986), Herholz et al. (1987), Thomas et al. (1989) and Jørgensen et al. (1992a,b).

2.5. Regional brain blood flow

With the development of flow methods based on clearance of radioactive substances it became possible to localise the areas associated with neuronal integration of a specific task (Lassen et al., 1978). Several methods including labelled inert gas clearance (^{133}Xe, ^{77}Kr), monitored by single detectors, γ-camera and single photon emission computerised tomography (SPECT) as well as flow tracers for SPECT and positron emission tomography (PET) are available. With the inert gas clearance technique, ^{133}Xe in saline is injected into the ICA (Roland et al., 1980) or alternatively ^{77}Kr is used by inhalation (Roland et al., 1982). The clearance of the isotope from the cerebral hemisphere is followed by extracranial scintillators. The technique was developed into SPECT where a tomograph with rotating detectors is added. By SPECT blood flow can be examined in one or several "slices" of the brain and also it is possible to study regional changes in flow, e.g. corresponding to the anterior, middle and posterior cerebral arterial territories. In comparison to SPECT, PET has a better spatial resolution (~4 mm in PET; ~7 mm in SPECT; Villringer and Dirnagl, 1995). The cortical activation associated with dynamic movement involves, according to the increase in rCBF, the supplementary motor and the primary sensorimotor areas (Orgogozo and Larsen, 1979). However, during a sustained contraction, the supplementary motor area is not activated and the primary sensorimotor area is activated to a lesser degree than during dynamic movement.

Roland et al. (1980) evaluated rCBF by labelled inert gas clearance technique both during planning of movement and during actual dynamic finger movement. ^{133}Xe in saline was injected into the ICA and the clearance of the isotope from as much as 254 regions of the cerebral hemisphere was measured by a γ-camera. Programming the movement increased blood flow in the supplementary motor area, while execution of the movement increased blood flow also in the contralateral sensorimotor area for the hand. In a subsequent study using PET, Roland et al. (1982) studied rCBF during dynamic finger movement. During movement blood flow increased bilaterally in the supplementary motor area by 30%, in the premotor area by 10% and contralaterally in the sensorimotor area for the hand by ∼30%, in the parietal opercula by 9% and in paracentral lobules by 20%. All the activated areas project to the nucleus caudatus and putamen and these regions are considered to contribute to programming and execution of movement. For sensory input to basal ganglia, there is a pathway in which the thalamus connects to caudate nucleus and putamen. The thalamus relays all sensory input, except olfactory input. The caudate nucleus sends output to the globus pallidus and to the substantia nigra and also the substantia nigra sends information to the caudate nucleus. The globus pallidus receives input from the putamen and the globus pallidus and the subthalamic nucleus projects mutually. Thus, a subcortical increase in blood flow was obtained in the globus pallidus in the contralateral hemisphere by 30% and in the ipsilateral hemishere by 14% and also in the head of caudate nucleus rCBF increased bilaterally by 13%, in the putamen by 15% and in the thalamic-subthalamic region by 10%.

Friedman et al. (1992) added the employment of SPECT with ^{133}Xe as the tracer during handgrip under local anaesthesia of the arm. The increases in blood flow to the contralateral sensorimotor area and to the supplementary motor area were attenuated by the axillary block in proportion to the degree of reduction in strength as previously indicated by the ICA injecting technique in a single individual (Orgogozo and Larsen 1979). On the other hand, during handgrip an increase in rCBF determined by PET was not affected by the axillary block (Nowak et al., 1999b). This difference may be explained by the fact that PET achieves a better spatial resolution than SPECT. Thus, sensory input from the working limb (arm) may be responsible for the bulk of the increase in rCBF but with PET it appears that it is also possible to detect same command related activation.

Studies have been directed to locate the cerebral activation associated with the cardiovascular and respiratory response to exercise (Williamson et al., 1996). The insular cortex has been implicated as an important site of cardiovascular regulation (Cechetto and Chen, 1992) and the superolateral primary motor cortex for the respiratory response (Fink et al., 1995). Thus, the left insular cortex is activated during active cycling, when HR is elevated to ∼100 beats min^{-1} (Williamson et al., 1997), while the right insular cortex may modulate cardiac sympathetic activity (Yoon et al., 1997; Nowak et al., 1999a, Fig. 5). During right leg exercise, both right and left superomedial primary cortex and superolateral primary cortex are activated. After cycling, when the ventilation is still elevated, only the activation in the bilateral superolateral primary areas is maintained (Fink et al., 1995).

2.6. Transcranial Doppler

Transcranial Doppler Ultrasound (TCD) is a non-invasive technique for the evaluation of cerebral perfusion with the advantage of continuous, real-time recording. TCD can determine cerebral perfusion in a variety of situations, including exercise with a large muscle mass as used during, e.g. cycling (Jørgensen et al., 1992a, 1992b; Linkis et al., 1995; Ide et al., 1998) and rowing (Pott et al., 1997a). Making use of the advantages of TCD, it was found that cerebral autoregu-

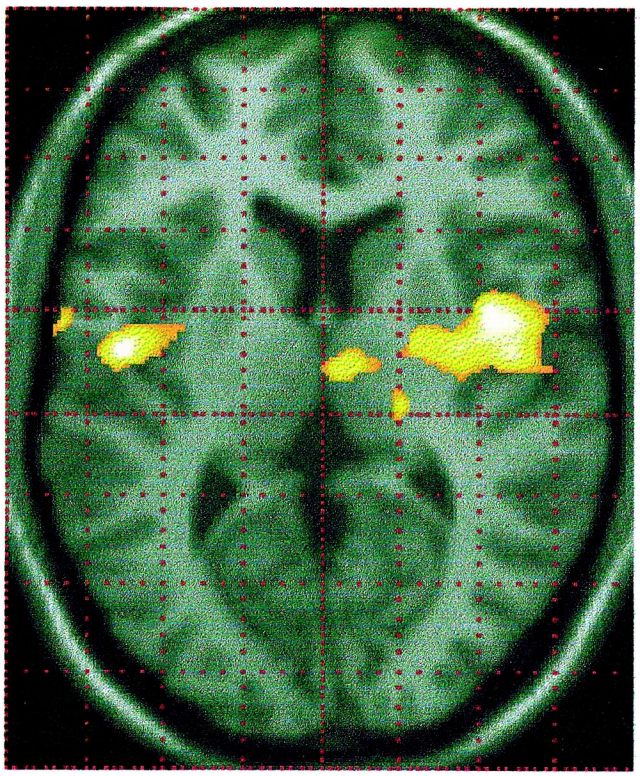

Fig. 5. PET determined changes in regional cerebral blood flow during rhythmic handgrip with the left arm. Activation is noted corresponding to the insular cortex on both sides of the brain. The figure was kindly provided by M. Nowak (1999a).

lation required a few seconds to be established (Aaslid et al., 1989). Thus, in the case of exercise, especially during the stroke in rowing or during weight lifting, where perfusion pressure (MAP minus central venous pressure) changes rapidly, the cerebral vessel cannot accommodate to the marked and rapid fluctuations in the perfusion pressure (Pott et al., 1997a). Compared to other techniques, the changes in MCA V_{mean} appear to be similar. The study by Hellström et al. (1996) determined ICA blood flow by duplex ultrasound simultaneously with MCA V_{mean}. Results showed that MCA V_{mean} is well followed by the changes in the ICA blood flow during cycling, without an exaggerated increase in MCA V_{mean} at maximal exercise. In addition, the change in cortical blood flow as determined by ^{133}Xe clearance technique is reflected by the changes in MCA V_{mean} during submaximal exercise where HR is below 150 beats min^{-1} (Jørgensen et al., 1992a, 1992b).

With TCD it is also possible to obtain some insight into the central neuronal integration of skeletal muscle control. The conclusions obtained by TCD (Jørgensen, 1995; Linkis et al., 1995) agree with those derived from a determination of CBF by intra-arterial injection of ^{133}Xe (Orgogozo and Larsen, 1979) and SPECT during muscle contractions with the hand (Friedman et al., 1991; 1992). During handgrip MCA V_{mean} increases on the contralateral side of the hand (Jørgensen et al., 1993a; Pott et al., 1997b; Ide et al., 1998) and during foot movement the increase in V_{mean} is most prominent corresponding to the contralateral anterior cerebral artery (ACA); and during cycling both ACA and especially MCA V_{mean} are enhanced bilaterally (Linkis et al., 1995).

These increases in V_{mean} appear to depend on afferent input from contracting muscle rather than on the cardiovascular effects, i.e. the increase in MAP and HR. Jørgensen et al. (1993a) studied MCA V_{mean} during handgrip with local anaesthesia of the arm. Even though MAP and HR increased to the same extent as during handgrip with the unblocked arm, the increase in MCA V_{mean} was eliminated by an auxillary blockade as previously shown for rCBF (Friedman et al., 1992).

A critical issue for the TCD technique is to what extent blood velocity reflects volume flow. The V_{mean} is calculated from maximal frequency of Doppler shift and it is assumed to record flow velocity in the centre of the vessel. If the flow is not laminar but complex, V_{mean} will not be proportional to the flow. On the other hand, the intensity of the power spectrum at any velocity should be related to the number of ultrasound scatters moving at that velocity. The intensity-weighted mean velocity (V_{IWmean}) provides a signal proportional to the overall flow despite the complexity of the flow pattern. Therefore, the V_{IWmean} would be preferred as an expression of the average flow velocity for the whole vessel. In situations where the head can remain motionless as is the case when a cuff around the leg is released and blood pressure drops (Aaslid et al., 1989), changes in the two expressions of flow velocity follow each other. This is equally the case during sitting rest while the subjects is on hypocapnic (Poulin et al., 1998) or hypercapnic conditions (Poulin and Robbins, 1996). However, there is still another problem. When the cross-sectional area of vessel insonated is changing, neither V_{mean} nor V_{IWmean} can reflect the blood flow. To circumvent this problem, Poulin and Robbins (1996) evaluated the change in MCA flow index, which is derived by V_{IWmean} multiplied by cross-sectional area with the total power of the Doppler signal (P), in addition to two expressions of flow velocity during various conditions including hypoxia, hypercapnia and combined hypoxia and hypercapnia. On the whole V_{mean} and V_{IWmean} change similarly and they reflect MCA flow index with no change in P, suggesting an unchanged cross-sectional area during manoeuvres. However, during the hypoxia and hypercapnia condition, the change in V_{mean} was larger than V_{IWmean} and during the recovery period V_{mean} and V_{IWmean} underestimate the MCA flow index. These trends are even clearer during exercise. During cycling at 40% VO_2max, the increase in V_{IWmean} is smaller (8%) than V_{mean} (14%), although the MCA flow index did not change because of a fall in P (Poulin et al., 1999). A concern using the V_{IWmean} and MCA flow index is its dependency on high quality of Doppler power, thereby these are affected more than V_{mean} by a movement related artefact (Newell et al., 1994).

3. Factors influencing cerebral artery blood velocity

3.1. Arterial diameter

A major limitation of TCD is that any vasoconstriction of the insonated vessel would be expected to increase blood velocity at a given volume flow and this will lead to misleading results. Pott et al. (1997b) evaluated whether sympathetic nervous activation relates to the changes in MCA V_{mean}. During muscle ischaemia following rhythmic hand grip, sympathetic activation did not change the luminar diameter of a peripheral artery (the dorsalis pedis artery), an arterial vessel of similar size to the MCA. Yet, MCA V_{mean} returned to the basal level, confirming the earlier observation made by Jørgensen et al. (1992a). However, sympathetic activity and/or an elevated plasma NA level may induce constriction of MCA during submaximal and especially maximal exercise. Pott et al. (1996) concluded that a 50% increase of MCA V_{mean} during exercise at $>80\%$ of VO_2max may reflect MCA con-

striction when compared with the 20% increase of MCA V_{mean} observed in athletes during low level exercise, as the increase in venous NA was as much as ~12 nmol L^{-1}.

A constriction of MCA by 0.2–0.4 mm will induce an elevation V_{mean} >20% at an unchanged volume flow and this magnitude is below the spatial resolution achievable by current imaging technique (~5 mm, Pott et al., 1997b). Doppler power was used as the cross-sectional area changes in MCA in the study by Poulin et al. (1999). They observed a fall in P during cycling, suggesting a reduced diameter and specifically such a phenomenon was seen during systole. The possible causes of the fall in P are a movement related vessel loss by Doppler probe, flow reversal, or flow separation across the vessel (Poulin et al., 1999). An increase in blood pressure during exercise may provoke a decrease in arterial diameter as a myogenic response (Rubanyi et al., 1990), thereby resulting the fall in Doppler power. However, this regulatory mechanism is primary acting in the relatively smaller vessels (Bevan and Bevan, 1993). Therefore, it is not certain whether this fall in P is indicating a reduced diameter of MCA or a change in the arterial pulse wave form and frequency or if simply it represents an artefact. Although it is not determined, it would be likely that the basal cerebral vessels dilate in response to the increasing pressure during systole as is the case for peripheral arteries like the temporal, the radial (Iversen et al., 1995) and the dorsalis pedis artery (Williamson et al., 1994; Olesen et al., 1995; Pott et al., 1997a,b).

3.2. $PaCO_2$

At rest, CBF is controlled by cerebral autoregulation and influenced by changes in $PaCO_2$. Especially, exercise with a large muscle mass such as cycling is associated with dramatic change in $PaCO_2$ (Fig. 2) and changes in gCBF during exercise often appear to be "correlated" with changes in $PaCO_2$ (Scheinberg et al., 1953, 1954; Kleinerman and Sancetta, 1955). Equally, the increase in MCA V_{mean} during exercise is influenced by $PaCO_2$ (alternatively expressed as $PetCO_2$) as shown by Moraine et al. (1993). MCA V_{mean} increased by up to 40% with increase in work rate from low to moderate intensity cycling, while $PetCO_2$ increased from 5.9 to 7.4 kPa. At subsequent higher work intensities MCA V_{mean} then declined toward the resting level with hyperventilation (Moraine et al., 1993). The study by Imms et al. (1998) also showed the change in MCA V_{mean} related to changes in CO_2 tension during static hand grip at 40% of maximal voluntary contraction for 2 min. MCA V_{mean} increased by 17% in the subjects whose $PetCO_2$ was stable and there was no rise in MCA V_{mean} in the subjects whose $PetCO_2$ was decreased by 1.1 kPa. In the study of Linkis et al. (1995) the changes in MCA V_{mean} during cycling was related by the individually determined cerebrovascular CO_2 reactivity at rest (23% kPa^{-1}). During 15 min of cycling the initially increase in MCA V_{mean} by 7 min was normalised gradually to pre-exercise level. However, when the values were related to $PaCO_2$ this tendency disappeared. Thus, the increase in MCA V_{mean} during cycling is masked by $PaCO_2$.

3.3. MAP

Whether MAP influences CBF or MCA V_{mean} during exercise is less well elucidated. As mentioned above, the study of Jørgensen et al. (1993a), using an auxillary blockade, indicated that the increase in MCA V_{mean} during handgrip depends on cerebral metabolic activity rather than on cardiovascular effects. In contrast, Herholz et al. (1987) suggested that the linear increase in hemispheric blood flow as determined by the ^{133}Xe clearance technique in relation to work rate results from the combination of the increased MAP and local metabolic activity. Also cerebrovascular CO_2 reactivity is affected by the blood pressure. The CO_2 "reactivity" is ~15% kPa^{-1} in the normotensive and apparently smaller (~10% kPa^{-1}) in the mild hypotensive dogs (Harper and Glass, 1965). Therefore, during exercise CBF may be influenced by MAP when the vessel tone is attenuated by local metabolic activity or $PaCO_2$. However, during exercise an increase in MAP due to cuff occlusion does not affect the increase in CBF (Olesen, 1971). Also the increase in MAP induced by way of blocking the afferent input from the arterial baroreceptor with stellate ganglion block does not affect the changes in MCA V_{mean} during exercise (Ide et al., 2000a). Thus, as for gCBF (Fig. 6), MAP does not appear to influence MCA V_{mean} during exercise.

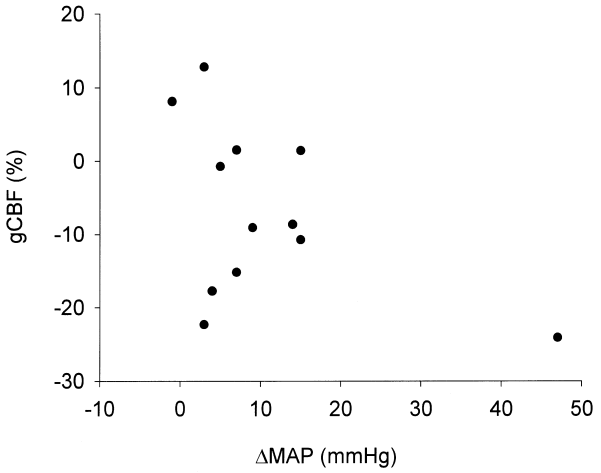

Fig. 6. MAP and gCBF during exercise. Data are from Madsen et al. (1993).

3.4. Cardiac output

In contrast to MAP, CO may affect CBF when there is competition for perfusion between different organs. Hellström et al. (1997) compared the changes in MCA V_{mean} during exercise with one leg and with two legs in heart failure patients and healthy subjects. In the healthy similar age control subjects, MCA V_{mean} increased by 20% during one-legged exercise and this increase was maintained during two-legged exercise. In contrast, in the heart insufficient patients, MCA V_{mean} increased nonsignificantly (8%) during one-legged exercise and MCA V_{mean} decreased to below the resting value during two-legged exercise and this was the case although there was no difference in $PaCO_2$ between the two groups of subjects. Although CO was not determined, these results, along with the data on patients with atrial fibrillation (Ide et al., 1999a) support that the ability to increase CO is of importance for brain circulation during exercise. In some patients with atrial fibrillation the ability to increase CO is limited (Fig. 7) and equally such patients exhibit only a small, or no increase in MCA V_{mean} during exercise (Ide et al., 1999a, Fig. 8). Thus, during cycling the subjects with the highest increase in CO also showed the greatest increase in MCA V_{mean} (Ide et al., 1999a, Fig. 9). The effect of an attenuated increase in CO during exercise on MCA V_{mean} is also demonstrated experimentally in healthy subjects with cardioselective beta-1 blockade (Ide et al., 1998). With metoprolol induced attenuation of CO during cycling, the increase in MCA V_{mean} is by only 12% compared to

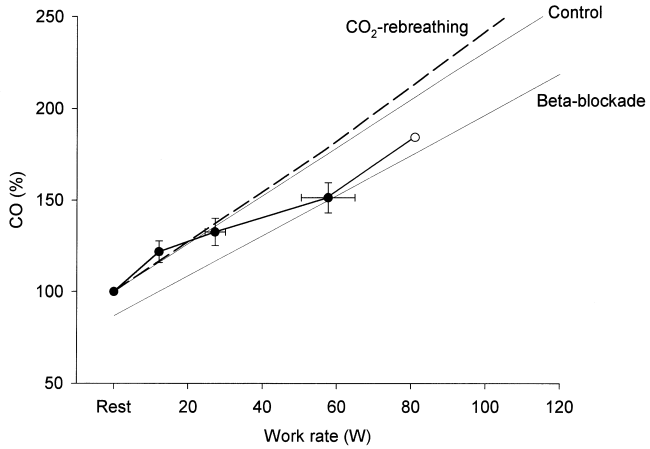

Fig. 7. Cardiac output estimated by model flow analysis during incremental exercise in patients with atrial fibrillation (Ide et al., 1999a). Closed symbol, $n = 5$; open symbol, $n = 3$. Values from young healthy subjects with (beta-1 blockade) and without beta-1 blockade are also shown (control; Ide et al., 1998). Broken line, CO_2-rebreathing-determined CO in a group of subjects with similar age (McElvaney et al., 1989).

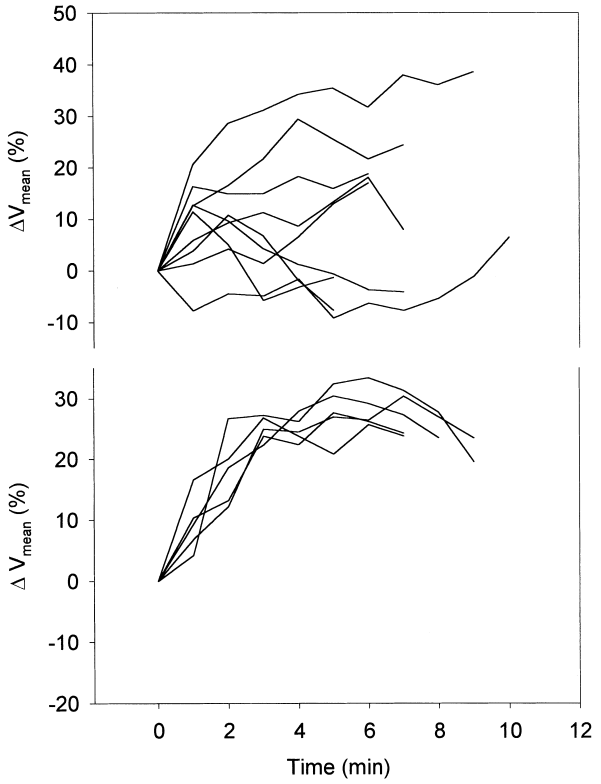

Fig. 8. Middle cerebral artery mean blood velocity (ΔV_{mean}) during cycling in patients with atrial fibrillation (upper panel) and in aged control subjects (lower panel). Data are from Ide et al. (1999a).

22% during control exercise (Fig. 10; Ide et al., 1998). In contrast, beta-1 adrenergic blockade does not affect the increase in MCA V_{mean} during rhythmic handgrip where the demand for an elevated CO is minimal. One of the possible explanations for the attenuated increase in MCA V_{mean} during cycling with beta-1 blockade and in patients with heart insufficiency is that an aug-

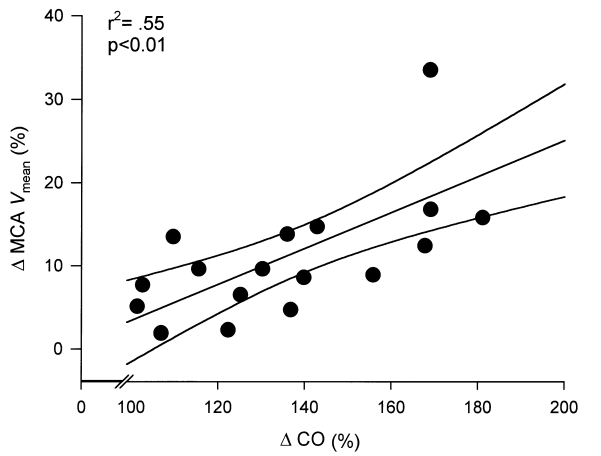

Fig. 9. Middle cerebral artery mean blood velocity (MCA V_{mean}) and cardiac output in patients with atrial fibrillation during incremental cycling. Data are from Ide et al. (1999a).

mented sympathetic nerve activity mediated vasoconstriction in the brain, as seen in working skeletal muscle (Pawelczyk et al., 1992; Magnusson et al., 1997). Thus, a sympathetic block applied on the level of the neck (a stellate ganglion block) restored the reduction in MCA V_{mean} during cycling with beta-1 blockade in healthy subjects. The increase in MCA V_{mean} on the contralateral side of the stellate block was reduced with beta-1 blockade, while the ipsilateral MCA V_{mean} was not different from the control (Ide et al., 2000a, Fig. 11).

In patients with neurogenic orthostatic hypotension due to autonomic failure, the cerebrovascular CO_2-reactivity in the supine position is even larger than in age and gender-matched control subjects. However, in the patients, the cerebrovascular CO_2-reactivity becomes smaller in the sitting and especially in the supine position (Harms et al., 1998), suggesting a progressive decline in CO during posture affects the cerebrovascular responsiveness to CO_2.

4. Cerebral oxygenation

4.1. Functional magnetic resonance imaging (fMRI)

The fMRI evaluates the different magnetic properties of deoxygenated haemoglobin (Hb) and oxygenated haemoglobin (HbO_2; van Zijl et al., 1998). It is consistently found that oxygenation increases corresponding to the activated area in the brain (Ogawa et al., 1993). The conclusion to be drawn is that in con-

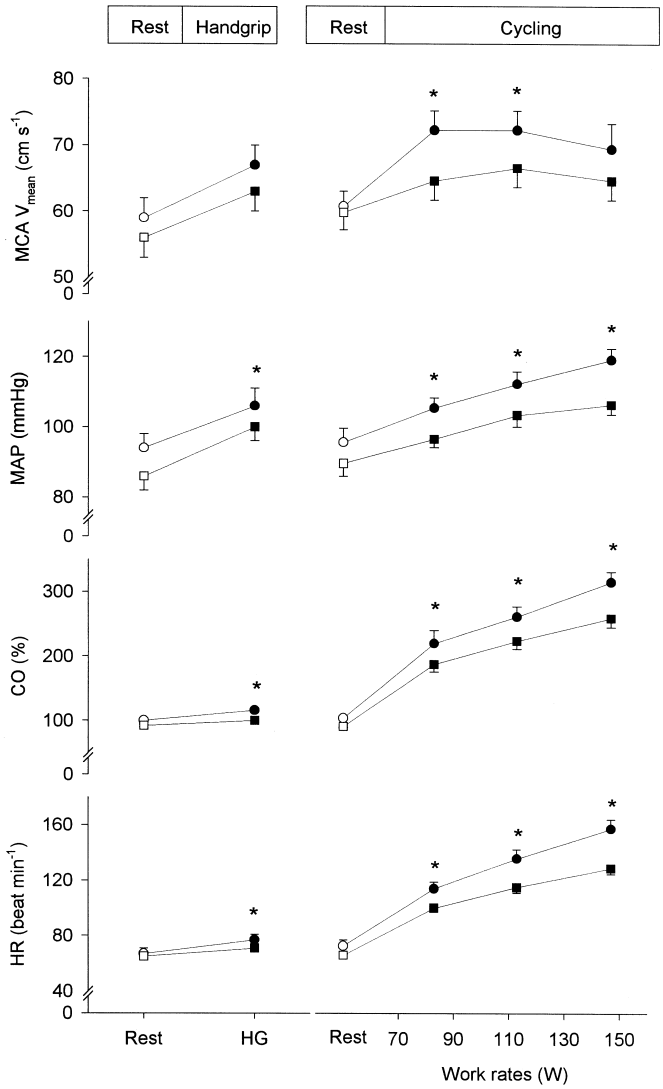

Fig. 10. Middle cerebral artery mean blood velocity (MCA V_{mean}), mean arterial pressure (MAP), cardiac output (CO) and heart rate (HR), responses to handgrip and cycling with (squares) and without (circles) beta-1 blockade. Data are from Ide et al. (1998). The closed symbol denotes the difference from rest and * indicates difference from control.

trast to skeletal muscle that demonstrate a reduced venous O_2 saturation during exercise (Boushel et al., 1998b; MacDonald et al., 1999), the increase in rCBF appears to be larger than the regional metabolic O_2 demand. Ramsey et al. (1996) validated fMRI in comparison with PET technique. In response to the cerebral activation associated with finger movements, CBF increased in the contralateral primary sensorimotor cortex detected with both PET and fMRI and the size of activated areas were highly correlated. A recent study by Kinahan and Noll (1999) compared PET and fMRI during a motor task and showed that for the centre of activation, there is an ~10 mm difference between the techniques, despite similar pattern of activation. This result corresponds to the fact that fMRI is more sensitive to the signal change in the draining veins (Jørgensen et al., 1999).

4.2. Near infrared spectroscopy

With the use of near-infrared (NIR) light it is possible to penetrate the scalp to a depth sufficient to assess the content of Hb and HbO_2 in the human adult brain (Madsen and Secher, 1999). The cerebrovascular response to changes in CO_2 during hyperventilation and 5% CO_2 inhalation has been evaluated with cerebral oxygenation determined by near infrared spectroscopy (NIRS) and the response was related to cerebral perfusion determined by transcranial Doppler (Smielewsky et al., 1995). Hoshi and Tamura (1993) evaluated the response in cerebral oxygenation to a mental task, as well as to visual and auditory stimulation. The time course of oxygenated blood supply varied with each brain region, depending on the type of stimulation. In response to a motor task, Obrig et al. (1996) demonstrated an increase in HbO_2 and a decrease in Hb, supporting that cerebral oxygenation exceeds the increase in O_2 demand during motor stimulation. Also, Hirth et al. (1997) observed the increases in cerebral oxygenation determined by NIRS and in the cerebral perfusion as expressed by transcranial Doppler simultaneously. In confirmation of the experience from fMRI, cerebral activation results in an elevated cerebral oxygenation.

Within the sample volume, haemoglobin is contained in arterioles, capillaries and venules and the exact proportions of these components cannot be determined. From anatomical studies of the brain, the

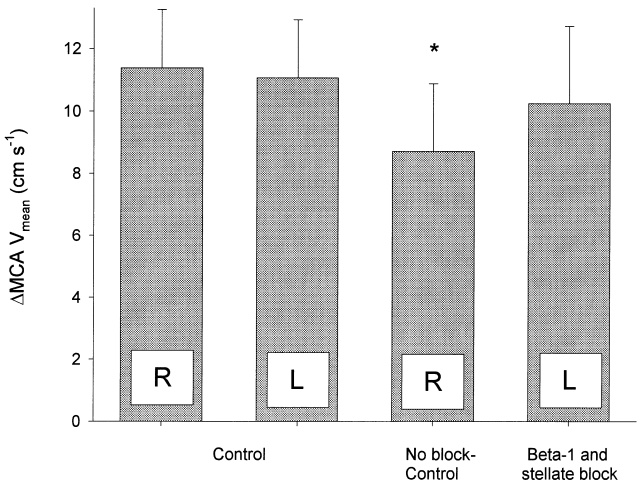

Fig. 11. Middle cerebral artery mean blood velocity (ΔMCA V_{mean}) from rest to exercise following pharmacological interventions (beta-1 adrenergic and stellate ganglion blockade). * denotes difference from control; $p < 0.05$. Data are from Ide et al. (2000a).

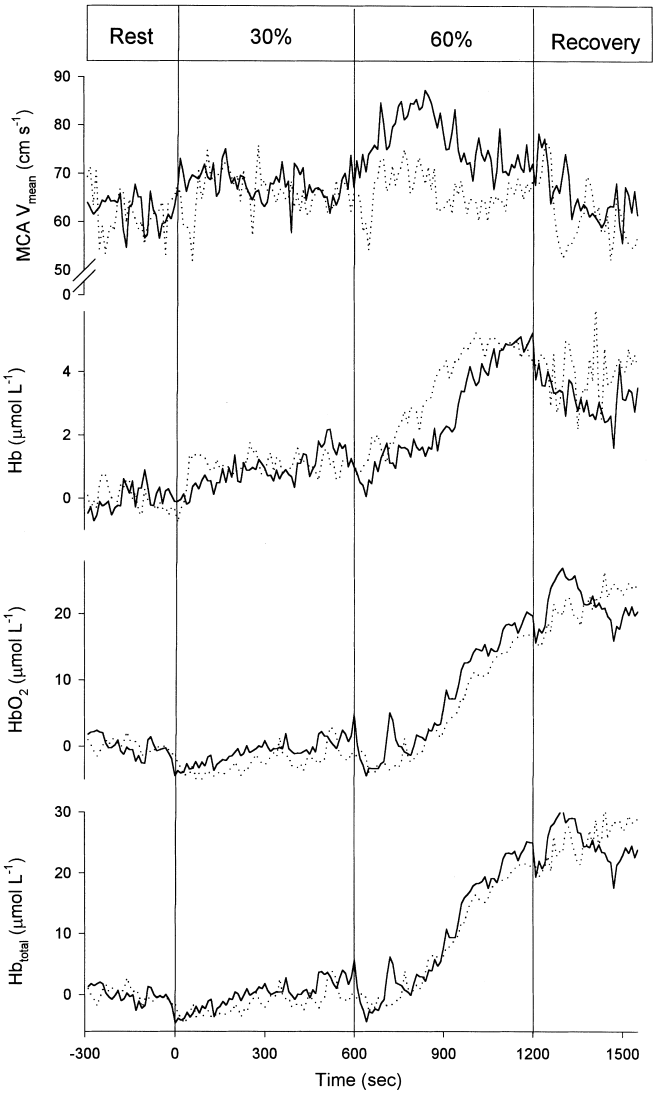

Fig. 12. Middle cerebral artery mean blood velocity (MCA V_{mean}) determined by transcranial Doppler and cerebral oxygenation determined by near-infrared spectroscopy at rest, during exercise with (dotted line) and without (solid line) beta-1 blockade and recovery in one subject. Data are from Ide et al. (2000a).

venule to total vessel volume-ratio range from two-thirds to four-fifths (Mchedlishvili, 1986). Only ~5% of the blood is situated in the capillaries and ~20% in the arterioles. Most of the haemoglobin determined by NIRS is therefore "post-cellular". During exercise the arterial O_2 content increases and changes in cerebral HbO_2 and total Hb (Hb_{total}) determined by NIRS do not reflect only changes in perfusion, since tissue oxygenation is determined by arterial O_2 content and blood flow. Thus, an increase in HbO_2 does not always reflect an increase in flow. In fact, when an increase in blood volume is induced by the jugular venous occlusion, NIRS determined HbO_2 and Hb_{total} increase (Elwell et al., 1997). Alternatively, during cardiopulmonary bypass and deep hypothermic circulatory arrest in piglets, the cooling of the body was associated with the increase in HbO_2 and Hb_{total} despite a reduction in CBF (Nomura et al., 1996). In addition, the increase in MCA V_{mean} was normalised immediately to the pre-exercise level during the recovery after cycling as $PaCO_2$ decreased, although cerebral HbO_2 and Hb_{total} reached the highest values (Fig. 12; Ide et al., 2000a). Nevertheless, during submaximal exercise, cerebral oxygenation state, at least partly, reflects the changes in cerebral perfusion. During cycling the increase in MCA V_{mean} is followed by changes in cerebral HbO_2 and Hb_{total} as determined by NIRS and with beta-1 adrenergic blockade the increase in MCA V_{mean} was reduced and HbO_2 and Hb_{total} followed such reduction even though haematocrit and arterial O_2 content were not affected.

During exhaustive exercise as rowing arterial O_2 saturation decreases to ~90% and arterial O_2 desaturation induces cerebral deoxygenation (Nielsen et al., 1999). Interestingly, supplementation of 30% O_2 reversed cerebral oxygenation, although muscle oxygenation was not affected.

5. Cerebral metabolism

5.1. Regional cerebral metabolism

Dynamic movement is associated with cortical activation and increases in blood flow to the supplementary motor area and the primary sensorimotor area (Orgogozo and Larsen, 1979). Apparently, such regional flow changes are accompanied by a much smaller increase in regional metabolism. As determined by PET corresponding to sensorimotor area for the hand, regional O_2 uptake increases during hand movement (Raichle et al., 1976). Also, the glucose uptake increases in the mesial frontal and contralateral sensorimotor and premotor areas during complex finger movement (Guenther et al., 1994). Furthermore, the cerebral metabolic rate for glucose determined after running indicates an involvement of the posterior cingulate, parahippocampal gyri, the hypothalamus, the temporoparietal, the posterior parietal, the prefrontal, the premotor and the primary motor cortex (Tashiro et al., 1998). In contrast, during repetitive wrist movement such as cycling (Herzog et al., 1991), the cerebral metabolic rate does not change, despite the increase in flow to the contralateral sensorimotor cortex region by ~40%, to the same region on the ipsilateral side by

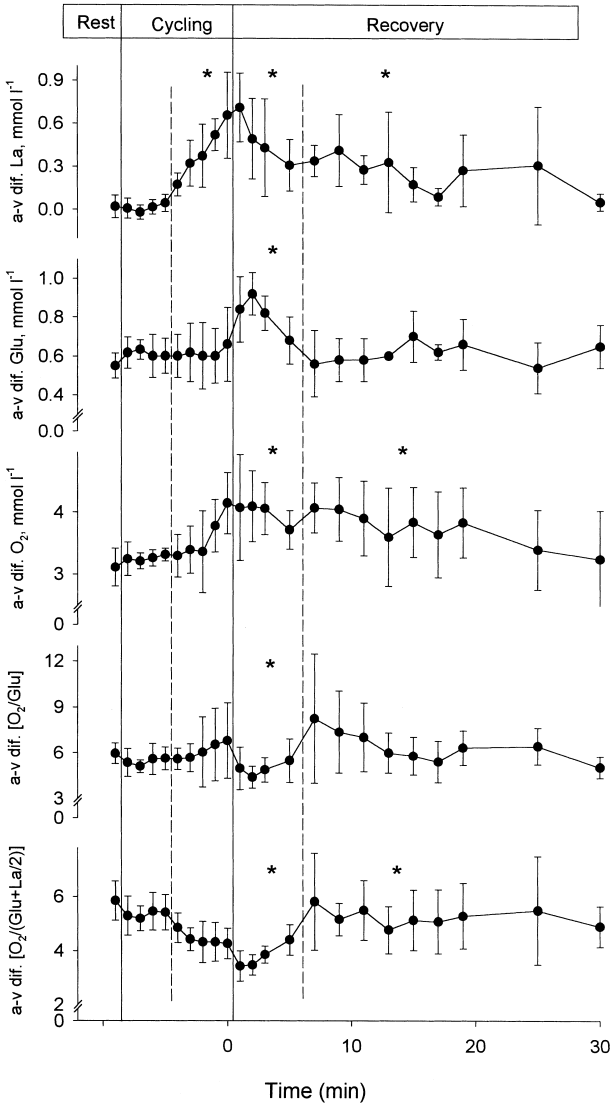

Fig. 13. Arterial to internal jugular venous difference at rest, during exercise and in the immediate recovery. Data are mean ± S.D for six subjects. Arterial to jugular venous differences [(a−v) dif.] of lactate (La), glucose (Glu) and O_2 and the molar ratios of the brain uptake of O_2 to glucose [(a−v) dif. O_2/Glu] and to carbohydrate [(a−v) dif. O_2/(Glu + La/2)]. ″). Data at rest were compared with the average values during exercise below and above the lactate threshold and during the first five and the last 25 min of recovery. * indicates significant difference from rest. Data from Ide et al. (2000b).

~20% and to the medial frontal cortex by 30% (Hallett et al., 1994).

5.2. Global cerebral metabolism

The traditional view is that CBF is relatively unaffected by a marked increase in CO associated with exercise and also that the global cerebral metabolic rate do not reflect the regional changes. Thus, during cycling at mild to moderate intensity, brain O_2 uptake remained unchanged (Scheinberg et al., 1953; Zobl et al., 1965; Madsen et al., 1993). Therefore, the brain is taken to be a metabolically stable organ (Zobl et al., 1965). On the other hand, during vigorous exercise on the treadmill there is a reported increase in brain O_2 uptake (Scheinberg et al., 1954). Also, there appears to be an increased O_2 uptake by the brain when exercise approaches a near maximal exercise intensity and this increase appears to be maintained during the early recovery from exercise (Fig.13; Ide et al., 2000b). The study by Fox and Raichle (1986) showing that the regional cerebral O_2 uptake changes only little in comparison with the increase in regional and global glucose uptake in response to brain stimulation (Madsen et al., 1995b), suggests that the brain possesses a capacity for anaerobic metabolism. At least these results indicate that for an evaluation of the metabolic response of the brain to, e.g. exercise, an evaluation based only on the O_2 uptake is insufficient. In addition to O_2, glucose and lactate may offer broader information about the brain's metabolic response during exercise. It was reported that there is a trend towards an increase in glucose uptake during exercise (Scheinberg et al., 1954) and the increase is pronounced in the first minutes after the cessation of exercise (Ide et al., 2000b). In addition to glucose, the brain takes up lactate (Ahlborg and Wahren 1972; Ide et al., 1999b, 2000a,b) which may be used as an energy substrate, when the plasma lactate level increases during intense exercise and also the lactate uptake is maintained during immediate recovery period (Ide et al., 2000b).

When glucose is oxidised to CO_2 and water, the O_2 to glucose uptake should be close to six. Yet, in response to brain stimulation, the brain uptake of glucose increases in excess of the O_2 uptake. Therefore, the O_2 to glucose uptake ratio decreases (Fox et al., 1988) and the ratio stays reduced even after the cessation of brain stimulation (Madsen et al., 1995a; 1995b). When lactate is taken into consideration, a similar observation has been obtained for the O_2 to carbohydrate ratio during both exercise and recovery (Fig. 13; Ide et al., 2000b). The metabolic fate of "the excess" carbohydrate uptake of the brain is not known. However, it is reasonable to assume that lactate could substitute for glucose as substrate. Thus, in the rat, brain activation reduces the cerebral glycogen content by ~15% (Madsen et al., 1995a). Brain tissue, including neurons (Dringen et al., 1993) and the astrocytes (Tildon et al., 1993), possess the capacity to take up and utilise lactate as an energy source. Therefore, if lactate substitutes for glucose as an energy fuel, it may be that some glucose is refilled into the glycogen pool of the brain. Especially during the first minutes of recovery from exercise an increase in brain uptake of glucose and lactate suggests an important role for brain glycogen stores in the metabolic response to physiological activation with subsequent repletion.

6. Conclusion

During dynamic exercise with a large muscle mass the increase in middle cerebral artery mean blood velocity as determined by transcranial Doppler is lowered if the ability to increase cardiac output is limited as is the case with beta-1 blockade in healthy humans and in some patients with atrial fibrillation and cardiac insufficiency. The lowered MCA V_{mean} during cycling with beta-1 blockade recovers following the block of the sympathetic fibres at the neck, suggesting that such a reduction in MCA V_{mean} during exercise is by way of sympathetic nervous system. Although it is still controversial if blood velocity of the major cerebral arteries in the brain reflects actual flow, data obtained by other techniques including ^{133}Xe clearance, internal carotid artery blood flow with duplex ultrasound Doppler technique are comparable. The near infra-red spectroscopy determined cerebral oxygenation is increased during exercise and equally reduced by beta-1 adrenergic blockade, supporting the changes in MCA V_{mean}.

During intense exercise brain seems to take up lactate and its O_2 uptake also increases. Yet, brain carbohydrate uptake including glucose and lactate exceeds the O_2 uptake, even though O_2 availability determined by NIRS increases. Such an uncoupling between carbohydrate uptake and O_2 uptake is even larger in the initial minutes of recovery from exercise.

7. Future perspective

In order to clarify whether CBF is affected by the ability to increase CO during exercise with a large muscle mass, a more sophisticated technique than TCD is needed. PET, fMRI, SPECT are unsuitable for that purpose but they are limited by the fact that they require the experiment to be conducted in a scanner. Rather the ^{133}Xe clearance technique for the cortical brain blood flow and the duplex ultrasound Doppler for the internal carotid artery blood flow could be applied. Alternatively, a new technique using near-in-

frared spectroscopy combined with cardiac output determination by indocyanine green dye is being developed (Roberts et al., 1993; Boushel et al., 1998a). For the use of the Kety–Schmidt technique, two jugular veins should be assessed in order to evaluate gCBF. An evaluation of the origin of venous drainage using dynamic brain scanning will give further insight. Internal jugular venous blood flow by the thermo-dilution technique may be also useful. This technique has better time resolution compared with the Kety–Schmidt technique and be repeatedly measured. Equally, such a consideration is relevant for an evaluation of cerebral metabolism. As in the rat neocortical brain regions are able to utilise keton bodies to a greater extent than mesencephalic structures (Hawkins et al., 1986), there may be differences in the metabolic activity between cortical and subcortical brain regions. Using a radio labeled tracer, it could be evaluated whether the lactate taken up by brain during and after exercise is oxidised or not. It should also be evaluated whether the decreasing ratio O_2 to substrate uptake by the brain after exercise is associated with repletion of the brain glycogen level.

Acknowledgements

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