Cerebral blood flow velocity during and after sustained isometric skeletal muscle contractions in man

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1. Twenty-seven young subjects used their right hand to perform sustained, isometric contractions at 40% of maximum for 2 min while lying supine.
2. During the last 30 s of exercise, mean arterial blood pressure increased by $38 \pm 4$ mmHg (mean $\pm$ S.E.M.) and heart rate by $27 \pm 2$ beats/min.
3. Nineteen of the subjects respired eucapnically during exercise, increasing ventilation by $4.1 \pm 0.5$ litres/min. Eight subjects hyperventilated ($7.1-19.6$ litres/min) and decreased end-tidal $PCO_2$ by $8.2$ to $15.1$ mmHg during the last minute of exercise.
4. In the eucapnic subjects mean flow velocity in the right (i.e. contralateral to the activated cortex) middle cerebral artery increased by $11.4 \pm 1.0$ cm/s, a change of 17%, during the contraction. This represents an increase in volume flow to the territory of this vessel, but an increase in global flow to the brain cannot be inferred.
5. In the eight subjects who hyperventilated during exercise, there was no rise of flow velocity in the middle cerebral artery, and in some subjects there was a fall during the first 2 min of recovery. These findings suggest that if subjects hyperventilate during handgrip exercise there could be a fall in volume flow to many regions of the brain during and after the exercise.

INTRODUCTION

Blood flow through the brain is controlled to maintain optimal respiratory gas tensions in intracranial tissues, with cerebral vessels being particularly sensitive to small variations in arterial $PCO_2$. Raising alveolar $PCO_2$ ($PACO_2$) by breathing a CO$_2$-rich gas mixture dilates the cerebral vessels and increases blood flow, while lowering $PACO_2$ by hyperventilation causes vasoconstriction and may endanger the oxygen supply [1, 2]. A reduced arterial oxygen content increases cerebral blood flow [3], but breathing 100% oxygen does not reduce cerebral perfusion [4].

Cerebral blood flow is largely independent of arterial blood pressure, since autoregulation occurs over the physiological range of blood pressures [1].

During mild and moderate dynamic exercise both alveolar and arterial $PCO_2$ are unchanged, although reductions may occur during efforts above the anaerobic threshold [5]. In contrast, during isometric contractions sustained towards exhaustion, there may be quite marked hyperventilation in some subjects with profound falls in $PACO_2$ [6-8]. Since this type of exercise also causes marked elevations of blood pressure [6, 7, 9], it may have conflicting influences on cerebral blood flow.

It would seem important to investigate cerebral blood flow in subjects who hyperventilate during isometric exercise and to continue monitoring during recovery since at the end of the contraction blood pressure falls quickly back to control levels while the reduced $PACO_2$ recovers more slowly [7]. These studies are of practical importance because a reduction of cerebral blood flow may lead to postural instability and possibly to falling if the subjects were standing during exercise. In this study on supine subjects, cerebral blood flow was assessed by measuring flow velocity in the middle cerebral artery, using a non-invasive Doppler ultrasound technique, during 2 min of sustained handgrip contraction.

METHODS

The subjects were 21 males and 6 females aged 18 to 38 years. None had a history of cardiovascular or respiratory disease and none was taking medication. All were familiar with respiratory monitoring equipment but none had previously performed handgrip exercise experiments. Control data obtained over...
Table 1. Resting data for 27 subjects (means ± S.D.)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
<td>91 ± 10</td>
</tr>
<tr>
<td>Ventilation (litres/min)</td>
<td>7.9 ± 1.3</td>
</tr>
<tr>
<td>End-tidal PCO₂ (mmHg)</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>mCAV (cm/s)</td>
<td>68 ± 13</td>
</tr>
<tr>
<td>Cerebrovascular resistance index (mmHg.s⁻¹cm⁻¹)</td>
<td>1.38 ± 0.29</td>
</tr>
</tbody>
</table>

5 min before exercise were within normal limits (Table 1).

The studies were carried out in accordance with the declaration of Helsinki (1989) of the World Medical Association and were approved by the ethics committee of the West Lambeth (Teaching) Health Authority. All subjects gave their informed consent before testing.

The subjects reclined semi-supine on a couch with their right hand resting on a handgrip dynamometer. After instrumentation, the subject performed a series of maximal handgrip contractions at intervals of 1 min; the largest being taken as maximum. Forty percent of the maximum voluntary contraction (40% MVC) was indicated on a monitor to the subject, who practised sustaining the effort.

**Experimental protocol**

During a 5 min control period, continuous recordings were made of arterial blood pressure, heart rate, ventilation, fractional CO₂ in the airway and mean flow velocity in the right middle cerebral artery. The subject then maintained a handgrip contraction at 40% MVC for 2 min. All variables were monitored throughout exercise and for the first 5 min of recovery.

**Hyperventilation**

After 20 min of recovery, 12 subjects voluntarily hyperventilated to lower PACO₂. A target tidal volume of between 1000 and 1500 ml, derived from the output of the pneumotachograph, was demonstrated to the subject on a monitor. The subject inspired to this volume 12 times a minute for 2 min in response to verbal commands. All variables were monitored during a 5 min control period, through the period of hyperventilation and for 5 min of recovery.

**Monitoring**

Arterial blood pressure and heart rate were measured with a Finapres blood pressure monitor (Ohmeda 2300). The cuff was attached to the middle phalanx of the middle finger of the left hand which was supported on a bench some 20 cm below the level of the aortic valve. The pressure trace and the derived heart rate were displayed on a Grass 79D Polygraph. Mean arterial blood pressure (MABP) was calculated in the conventional manner and corrected for the height difference between the finger cuff and the aortic valve.

Ventilation was measured with an integrating pneumotachograph (Mercury Electronics) and the tidal volume displayed on the recorder. The pneumotachograph was calibrated with a large Perspex syringe for volumes of 250 to 2500 ml.

Airway CO₂ was measured with a Leybold Heraeus Binos 1 meter from a fine catheter placed in the mouthpiece of the pneumotachograph. End-tidal CO₂ was taken as the peak level reached during expiration. The end-tidal partial pressure of CO₂ was calculated assuming a core temperature of 37°C.

Blood flow velocity in the right middle cerebral artery was measured using transcranial Doppler ultrasound (Eden Medizinische Elektronik TC2-64). The probe, liberally coated with conducting jelly, was initially hand-held against the skull, and when an optimal signal was obtained it was held in place with a head band. Time was often required to obtain an adequate signal and the experiment only commenced when the operator was satisfied with the waveform and the level of the resting velocity. Mean flow velocity was recorded every 10 s, but values were only accepted if all waveforms on the screen (sweep duration 4 s) were satisfactory.

**Statistical methods**

The significance of changes from control values was determined by analysis of variance and a post hoc t-test [10]. To show differences between a small subgroup, the data for which were often not normally distributed, and a larger group for which the data were normally distributed, it was demonstrated that most data points for the former fell outside the 95% confidence limits of the latter. Relationships between two or more variables were demonstrated by regression analysis.

**RESULTS**

**Responses to handgrip contraction**

In all subjects there were progressive rises in both MABP and heart rate during the 2 min of sustained handgrip contraction at 40% MVC (Fig. 1). These changes are similar to those described by others [6, 9, 11]. After the contraction heart rate returned to pre-exercise control levels within 60 s, but MABP was persistently elevated by around 4 mmHg throughout recovery.

There were variable increases of ventilation during handgrip exercise (Fig. 2). During the last 30 s of exercise the increases ranged from 0.2 to
19.6 litres/min. The data were not normally distributed; the median increase was 4.9 litres/min. The effects on end-tidal $P_{\text{CO}_2}$ ($P_{\text{ETCO2}}$) were likewise highly variable, ranging from an increase of 3.4 mmHg to a fall of 15.1 mmHg (median -2.1 mmHg).

The subjects have been divided into a subgroup of 19 who ventilated eucapnically during exercise with a mean increase of ventilation of 4.06 ± 0.52 litres/min and no change in $P_{\text{ETCO2}}$ (0.92 ± 0.42 mmHg), and a group of eight subjects who increased ventilation by 8 litres/min or more during the last minute of exercise (mean 13.00 ± 1.69 litres/min; 25 degrees of freedom; $P<0.001$) and whose $P_{\text{ETCO2}}$ decreased by more than 5 mmHg (mean -10.38 ± 1.02 mmHg; $P<0.001$). Data for the larger subgroup have been plotted as means with 95% confidence limits and individual points plotted for the hyperventilating subjects (Fig. 2). Ventilation by the eucapnic subjects was still raised during the first 30 s of recovery, and subsequently declined to about 1 litre above the precontraction level. Some of the subjects who hyperventilated during exercise continued to breathe at well above control levels during the first 2 min of recovery. Low $P_{\text{ETCO2}}$ during and after exercise did not appear to suppress ventilation.

Mean flow velocity in right middle cerebral artery (mMCAV) during handgrip exercise

Blood flows continuously in the middle cerebral artery, with the peak velocity at systole being about 50% greater than the mean velocity through the cycle. Assuming that the diameter of this major vessel does not change in response to changes of MABP or $P_{\text{CO}_2}$ (see Discussion), then in a given subject, mMCAV will be proportional to blood volume flow. The value obtained at rest, 68 ± 13 cm/s (mean ± S.D.; Table 1) is slightly higher than those reported previously [4, 12, 13].

In the 19 subjects who ventilated eucapnically during handgrip exercise, mMCAV increased progressively through the 2 min of exercise to reach a value of 11.4 ± 1.0 cm/s (mean ± S.E.M., $P<0.001$; Fig. 3) above the control level, an increase of about 17%.

For the eight subjects who hyperventilated during exercise the mean change was significantly lower (1.7 ± 2.7 cm/s, $P<0.001$), with two subjects having small reductions of velocity. Based on data for all
Fig. 3. Changes in mean blood flow velocity in the right middle cerebral artery (mMCAV) during and after 2 min of isometric handgrip exercise at 40% MVC (indicated by bar). For the 19 subjects who ventilated without a change in $PETCO_2$ the data are shown as means (○) with the 95% confidence intervals indicated by dashed lines. Individual data points are shown for the eight subjects who hyperventilated during exercise (●).

Subjects during the last 30 s of exercise, the change of flow is related to changes of MABP and $PETCO_2$ by the multiple regression equation:

$$\text{AmMCAV} = 5.276 + 0.174\text{AMABP} + 0.929\Delta PETCO_2$$

(1)

($r = 0.578, P < 0.001; 95\% \text{ confidence interval for } b_1 = 0.058 - 0.290; \text{ for } b_2 = 0.511 - 1.347$).

This equation predicts that during the last 30 s of exercise, a subject who breathed eucapnic (i.e. $\Delta PETCO_2 = 0$) and whose increase of MABP equalled the mean for all subjects (38.1 mmHg; Fig. 1), would increase mMCAV by 11.9 cm/s. This represents an increase of 17.5% in response to a blood pressure change of 41.9%, and suggests that some degree of autoregulation of cerebral blood flow is occurring.

After exercise in the eucapnic subjects mMCAV returned to control levels within 30 s. In the hyperventilating subjects the changes in mMCAV were variable after exercise, with pronounced falls in some subjects. The change of mMCAV during the 2 min after exercise is related to the change in $PETCO_2$:

$$\text{AmMCAV} = 1.166\Delta PETCO_2 - 0.721$$

(2)

($r = 0.610, n = 25, P < 0.01; \text{ Fig. 4}$).

The change of flow velocity in these subjects is also related to the blood pressure change by the equation:

$$\text{AmMCAV} = -2.635 + 0.415\text{AMABP} + 1.126\Delta PETCO_2$$

(3)

($r = 0.707, P < 0.001; 95\% \text{ confidence interval for } b_1 = 0.065 - 0.765; \text{ for } b_2 = 0.550 - 1.702$).

Equation 3 predicts that subjects who hyperventilate during isometric exercise and continue doing so into recovery, and have a 4 mmHg increase in MABP (Fig. 1) and a 10 mmHg fall in $PETCO_2$, will reduce mMCAV by 12.2 cm/s (18%) after the contraction. No subjects reported symptoms related to a reduction of cerebral blood flow.

Cerebrovascular resistance index

From MABP and mMCAV an index of vascular resistance in the cerebral circulation may be calculated. This is based on the following assumptions:

(i) The pressure drop from arterial inflow of the brain to venous efflux is the same as that between the right atrium and the ascending aorta.

(ii) The filling pressure of the heart approximates to zero. This seems reasonable since all subjects were young and healthy, there were no episodes of breath-holding during exercise, and in a previous study [11] central venous pressure did not increase from resting levels during isometric exercise.

(iii) During exercise there is no change in the internal diameter of the middle cerebral artery (see Discussion).

The resistance index for all subjects was $1.38 \pm 0.29 \text{mmHg} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$ (Table 1) and in the eucapnic subjects increased by $0.27 \pm 0.05 \text{mmHg} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$ (mean ± S.E.M.; Fig. 5), a change of 20%, during the final 30 s of exercise. This suggests that pressure autoregulation of blood flow is occurring in the smaller vessels of the cerebral circulation.

During the first minute of recovery resistance returned to control levels, but subsequently increased slightly at the time when MABP was raised and $PETCO_2$ was a little below normal (Figs 1a and 2b). In the hyperventilating subjects the changes
Cerebral blood flow in isometric exercise

Fig. 5. Changes in cerebral resistance index during and after 2 min of isometric handgrip exercise at 40% MVC. For 19 subjects who hyperventilated without a change in PETCO₂, the data are shown as means (○) with the 95% confidence limits indicated by dashed lines. Individual data points are shown for eight subjects who hyperventilated during exercise (●).

during and after exercise were variable, but five of the eight subjects had greater changes than the eucapnic subjects at the end of exercise. During the first 30 s after exercise four out of five subjects for whom data was obtained had resistance indices above the upper confidence interval of the eucapnic group.

Responses to voluntary hyperventilation

These studies were performed to determine the sensitivity of the cerebral circulation to reductions of PACO₂ in the absence of exercise, and to compare this sensitivity in the two subgroups of subjects. In eight subjects who ventilated eucapnically during handgrip exercise, 2 min hyperventilation lowered PETCO₂ by 12.2 ± 1.1 mmHg (mean ± S.E.M.) and mMCAV by 23.6 ± 2.5 cm/s (35%). Similar changes occurred in four subjects who had hyperventilated during exercise. The regression coefficients for the sensitivity of the cerebral circulation to CO₂ were almost identical:

Eucapnic subjects:

\[ \Delta \text{mMCAV} = 1.727\Delta P_{ETCO₂} - 0.701 \]  \hspace{1cm} (4)

\( r = 0.600, n = 49, P < 0.001 \).

Hyperventilating subjects:

\[ \Delta \text{mMCAV} = 1.582\Delta P_{ETCO₂} - 1.503 \]  \hspace{1cm} (5)

\( r = 0.538, n = 28, P < 0.01 \).

DISCUSSION

Do cerebral flow velocity measurements represent cerebral blood flow?

Changes of mMCAV will only quantitatively represent changes in blood flow to the region of the brain that this vessel supplies if the diameter of this major vessel is unchanged during isometric exercise. It is also necessary to consider whether local changes of flow velocity are representative of global changes of both velocity and of flow. Three factors may affect vascular dimensions and blood flow in the territory of the middle cerebral artery during and after handgrip exercise. These are changes in PACO₂, changes of MABP and local changes associated with activation of brain tissue. Since the subjects were exercising the right upper limb it might be expected that greater, locally induced changes would occur in the left cortex, but Friedman et al. [14], who measured regional cerebral blood flow by a ¹³³Xe uptake and washout technique, found small (10%) bilateral increases of flow in the premotor and motor sensory regions.

The change of flow velocity (1.655 cm/s) described in this study for each 1 mmHg drop of Pco₂ during hyperventilation represents a change of 2.43%, similar to the value of 2.8% found by Kirshen et al. [15]. The magnitude of flow changes described in man (3.15% [2]), in the monkey (2.13% [16]) and in the dog (2.78% [17]) are very similar to these changes of velocity and suggest that CO₂ exerts its effects on vessels distal to the middle cerebral artery. Since the flow measurements were for the whole brain, estimations of mMCAV may be used to assess global changes in cerebral blood flow when these are caused by alterations of Pco₂. Direct measurement of changes in diameter of the middle cerebral artery when the human brain was exposed during surgery [18] indicated a change of 0.17% for each 1 mmHg change in Pco₂. This represents a change of 0.34% in the cross-sectional area of the vessel, and if no other factor changed, volume flow would change by the same amount. This is less than 15% of the flow change described above for a unit change in Pco₂. Recently, Poulin and Robbins [19] have used a power-weighted Doppler index to measure flow in man and confirmed that middle cerebral artery dimensions do not change during CO₂ breathing.

From direct observations of pial vessels in the cat and studies of pressure changes in vascular segments, Kontos et al. [20] suggested that much of the change in vascular resistance during pressure autoregulation occurred in the larger cerebral arteries. In man, Giller et al. [18] measured a 2.8% change in diameter of larger cerebral vessels for a 20 mmHg change in MABP. This would change the cross-sectional area of the vessel by 5.5%. If blood flow were to remain constant when blood pressure increased, then flow velocity would increase by 5.5%.

It must be emphasized that these were both experiments in which the skull was open, and studies by Aaslid et al. [21] using a power-weighted Doppler index suggest that flow velocity does accurately assess volume flow during pressure autoregulation.

Is there an increase in cerebral blood flow during isometric handgrip exercise?

During 2 min of isometric exercise in 19 subjects mMCAV increased by 11.4 ± 1.0 cm/s (17.5%),
blood flow. Previous studies \cite{11, 12, 14} showed no
This statement cannot be extrapolated to global
change in hemispheric or global flow during isomet-
rical exercise, but Friedman et al. \cite{14} showed small
increases of flow in the territory of the middle cere-ral artery.

These changes were bilateral during single-limb
exercise, and are consistent with our finding of
increased mMCAV to the cortex contralateral to
that directly activated during exercise.

Does hyperventilation during isometric exercise reduce
cerebral blood flow?

In eight subjects who reduced PET\textsubscript{CO\textsubscript{2}} by between
8 and 15 mmHg during handgrip exercise, mMCAV
did not increase \cite{16, 18} during exercise and in some subjects there were marked falls
during recovery. From studies on voluntary hyper-
ventilation in the absence of handgripping, it could
be predicted that a decrease in PET\textsubscript{CO\textsubscript{2}} of 10 mmHg
would reduce mMCAV by 16.5 cm/s. Allowing for
the increase in mMCAV seen in eucapnic subjects
during exercise, an overall fall of around 5 mmHg
might be expected. That the actual fall is smaller
suggests some interaction of blood pressure auto-
regulation of cerebral blood flow with the responses
to CO\textsubscript{2}. During the period after contraction, when
MABP had almost returned to control levels
(+4 mmHg), but PET\textsubscript{CO\textsubscript{2}} was still reduced in some
subjects, mMCAV was also reduced. Interestingly,
the regression coefficient for change of mMCAV
was lower \cite{18, 20} than that during voluntary hyperventilation in the
cerebral circulation are likely to be global, in regions
where flow is not increased by local factors during
exercise, there may be a marked fall in volume
flow in the hyperventilating subjects during and after
exercise. None of these subjects experienced dizziness
or other signs of reduced cerebral blood flow.

ACKNOWLEDGMENT

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