Dynamic cerebral autoregulation during exhaustive exercise in humans

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Ogoh, Shigehiko, Mads K. Dalsgaard, Chie C. Yoshiga, Ellen A. Dawson, David M. Keller, Peter B. Raven, and Niels H. Secher. Dynamic cerebral autoregulation during exhaustive exercise in humans. Am J Physiol Heart Circ Physiol 288:H1461–H1467, 2005. First published October 21, 2004; doi:10.1152/ajpheart.00948.2004.—We investigated whether dynamic cerebral autoregulation is affected by exhaustive exercise using transfer-function gain and phase shift between oscillations in mean arterial pressure (MAP) and middle cerebral artery (MCA) mean blood flow velocity ($V_{\text{mean}}$). Seven subjects were instrumented with a brachial artery catheter for measurement of MAP and determination of arterial PCO$_2$ ($\text{PaCO}_2$) while jugular venous oxygen saturation ($\text{SvO}_2$) was determined to assess changes in whole brain blood flow. After a 10-min resting period, the subjects performed dynamic leg-cycle ergometry at 168 ± 5 W (mean ± SE) that was continued to exhaustion with a group average time of 26.8 ± 5.8 min. Despite no significant change in MAP during exercise, MCA $V_{\text{mean}}$ decreased from 70.2 ± 3.6 to 57.4 ± 5.4 cm/s, $\text{SvO}_2$ decreased from 68 ± 1 to 58 ± 2% at exhaustion, and both correlated to $\text{PaCO}_2$ (5.5 ± 0.2 to 3.9 ± 0.2 kPa; $r = 0.47$; $P = 0.04$ and $r = 0.74$; $P < 0.001$, respectively). An effect on brain metabolism was indicated by a decrease in the cerebral metabolic ratio of O$_2$ to [glucose + one-half lactate] from 5.6 to 3.8 ($P < 0.05$). At the same time, the normalized low-frequency gain between MAP and MCA $V_{\text{mean}}$ was increased ($P < 0.05$), whereas the phase shift tended to decrease. These findings suggest that dynamic cerebral autoregulation was impaired by exhaustive exercise despite a hyperventilation-induced reduction in $\text{PaCO}_2$.

Although acute changes in ABP are transmitted to the cerebral circulation, under normal conditions the cerebral blood flow tends to return to its original value within a few seconds (1, 26). This is usually referred to as dynamic CA, and it correlates well with assessments of static autoregulation (26, 37). During mild to heavy exercise, dynamic CA is maintained and may reflect a balance between the influence of sympathetic activity and $\text{PaCO}_2$ (5). However, it remains unknown whether dynamic CA becomes enhanced during exhaustive exercise when $\text{PaCO}_2$ decreases. To test this question, subjects exercised to exhaustion on a bicycle ergometer while beat-to-beat measurements of middle cerebral artery (MCA) mean blood flow velocity ($V_{\text{mean}}$) and mean arterial pressure (MAP) were made and analyzed using linear dynamic analysis (26, 39, 41). At the same time, jugular venous oxygen saturation ($\text{SvO}_2$) values were determined to assess changes in whole brain blood flow.

METHODS

Seven men with a mean age of 23 ± 2 yr, height of 180 ± 10 cm, and weight of 72 ± 9 kg (means ± SD) were recruited to participate in the study. All subjects were free of cardiovascular and pulmonary disorders and were not using prescribed or over-the-counter medications. Each subject provided written informed consent as approved by the Ethics Committee of Copenhagen (KF 01-369/97). Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 24 h before the experiment.

Protocol. The subjects arrived at the laboratory after fasting overnight. After catheterization, they were seated in a semirecumbent position on a modified Krogh cycle ergometer. After a 10-min resting period, the subjects began cycling at 10 W, which was subsequently adjusted to the target heart rate (HR) of 160 beats/min, i.e., to 168 ± 5 W (mean ± SE), which was continued until they could no longer maintain a pedaling frequency of 60 rpm despite strong verbal encouragement.

Measurements. A catheter (1.1 mm inner diameter, 20 gauge) was placed in the brachial artery of the nondominant arm, and ABP was measured using a Bentley transducer (Uden) positioned at the level of the right atrium and connected to a pressure-monitoring system (model M1275A; Hewlett-Packard). Beat-to-beat data of cardiovascular variables were acquired and collected using a personal computer with customized software. The HR, stroke volume (SV), and thus cardiac output (Q) were calculated from the blood pressure waveform using the Model flow method incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO TPD; Biomedical Instrumentation; Amsterdam, The Netherlands). Model flow measurement provides a reliable estimate of changes in Q during exercise in healthy young humans (36), and SV and Q were expressed relative to rest. Arterial blood samples were obtained with subjects at rest and exerci-
cising and were stored in ice water until analysis for pH, arterial Po$_2$ (PaO$_2$), oxygen saturation (SaO$_2$), and glucose and lactate levels (model ABL725I; Radiometer; Copenhagen, Denmark). In addition, a catheter (2.2 mm, 14 gauge) was placed in the right internal jugular vein for measurement of internal jugular venous pressure, venous pH, venous Po$_2$ (PvO$_2$) and venous Pco$_2$ (PvCO$_2$), oxygen saturation (SvO$_2$), and glucose and lactate levels. The MCA V$_{mean}$ was obtained by transcranial Doppler ultrasonography (Multi-Dop X; DWL; Sipplingen, Germany) with a 2-MHz probe placed over the temporal window and fixed with an adjustable headband and adhesive ultrasonic gel (Tensive; Parker Laboratories; Orange, NJ). Cerebral vascular resistance index (cVR) was expressed as (MAP at MCA level) - (jugular venous pressure)/MCA V$_{mean}$. The MAP at the MCA level took into consideration the vertical distance from the fourth intercostal space in the midclavicular line (heart level) to the Doppler probe (i.e., hydrostatic the vertical length $\times 0.77$ mmHg/cm). To evaluate changes in brain activation, the cerebral metabolic ratio (CMR$_{b}$) was calculated from the arteriovenous differences across the brain for O$_2$/glucose + one-half lactate) as previously described (7).

Data analysis. Analog signals of ABP and the spectral envelope of MCA V$_{mean}$ were sampled at 100 Hz and digitized at 12 bits for offline analysis. Beat-to-beat MAP and MCA V$_{mean}$ values were obtained by integrating analog signals within each cardiac cycle and were linearly interpolated and resampled at 2 Hz for spectral analysis of dynamic CA (39). When subjects were at rest or exercising, dynamic CA was calculated as the transfer-function gain and phase shift between fluctuations in MAP and MCA V$_{mean}$ (39). The transfer gain and phase shift reflect the relative amplitude and time relationship between the changes in MAP and MCA V$_{mean}$ over a specified frequency range. From the temporal sequences of MAP and MCA V$_{mean}$, the frequency-domain transformations were computed with a fast Fourier transformation algorithm. The transfer function H(f) between the two signals was calculated as $H(f) = S_x(f)/S_y(f)$, where $S_x(f)$ is the autospectrum of changes in MAP and $S_y(f)$ is the cross-spectrum between the two signals. The transfer function magnitude $|H(f)|$ and phase spectrum $\phi(f)$ were obtained from the real part $H_r(f)$ and imaginary part $H_i(f)$ of the complex function

$$|H(f)| = \left[|H_r(f)|^2 + |H_i(f)|^2\right]^{1/2}$$

$$\phi(f) = \tan^{-1}(H_i(f)/H_r(f))$$

Moreover, the transfer function $H(f)$ was normalized to the mean values of input (x) and output (y) variables as $H'(f) = [S_x(f)/|S_y(f)|]$, and the normalized gain was calculated as $20 \log H'(f)$ to provide values in decibels. A value of 0 indicates that the output varied by the same fraction of the mean value as the input, and a negative or positive value indicate that the output varied less or more, respectively, than the input.

The squared coherence function MSC(f) was estimated as

$$\text{MSC}(f) = |S_x(f)|^2/[S_x(f)S_y(f)]$$

where $S_x(f)$ is the autospectrum of changes in MCA V$_{mean}$. The squared coherence function reflects the fraction of output power (MCA V$_{mean}$) that can be linearly related to the input power (MAP) at each frequency. Similar to a correlation coefficient, this value varies between 0 and 1.

Spectral power of MAP, MCA V$_{mean}$, mean value of transfer function gain, phase, and coherence function were calculated in the very-low-frequency (VLF), 0.02 to 0.07 Hz), low-frequency (LF, 0.07 to 0.20 Hz), and high-frequency (HF, 0.20 to 0.30 Hz) ranges to reflect different patterns of the dynamic pressure-flow relationship (39, 40). The ABP fluctuations in the HF range, including those induced by the respiratory frequency, are transferred to MCA V$_{mean}$, whereas ABP fluctuations in the LF range are independent of the respiratory frequency, and the LF transfer function reflects CA mechanisms (8, 39). Furthermore, the VLF range of both the flow and the pressure variabilities appears to reflect multiple physiological mechanisms that confound interpretation. Thus we used the LF range for the spectral analysis to identify the dynamic CA during exercise.

Resting measurements were made during a 3-min data collection segment, whereas during exercise, the data segments of minutes 6–9 and 12–15 and the 3-min period before exhaustion were used. The power spectra, transfer function gain, phase, and coherence of the minute 12–15 segment could be calculated for only five subjects, because in two subjects the period before exhaustion overlapped.

Statistical analysis. One-way ANOVA (SigmaStat; Jandel Scientific Software; SPSS; Chicago, IL) with repeated measures was used to assess the differences in the steady-state hemodynamic variables, spectral power of HR, MAP and MCA V$_{mean}$, transfer function gain, phase, and coherence function in each frequency range between rest and the three exercise segments. A Student-Newman-Keuls test was employed post hoc when main effects were significant, i.e., $P < 0.05$. Data are expressed as means ± SE, and the relationships between $S_{V_O2}$ and MCA V$_{mean}$ and PaCO$_2$ are described using linear regression analysis.

RESULTS

Exercise increased ABP, HR, SV, and Q (Table 1), and exhaustion was reached after 26.8 ± 5.8 min. HR continued to increase with time from 5 min (166 ± 4 beats/min) to exhaustion (185 ± 3 beats/min; $P < 0.05$), whereas SV and Q did not change significantly during exercise.

Blood gas variables. Throughout exercise, arterial lactate concentrations increased and pH decreased ($P < 0.05$), whereas PaO$_2$ remained stable (Table 1). However, $S_{vO2}$ decreased at the beginning of exercise ($P < 0.05$), whereas $S_{vO2}$ increased at minute 5 ($P < 0.05$) and then decreased to a value smaller than at rest ($P < 0.05$). Thus the arteriovenous difference (a-v diff) in oxygen saturation across the brain decreased at the beginning of exercise ($P < 0.05$) and then increased at 15 min and at exhaustion to values similar to those obtained at rest. The a-v diff across the brain for lactate demonstrated a small release at rest ($-0.45 ± 0.25$ mmol/l), however, at 15 min and at exhaustion, an uptake occurred (a-v diff, 1.06 ± 0.23 and 1.00 ± 0.24 mmol/l, respectively; $P < 0.05$). Thus the cerebral metabolic ratio of O$_2$ to (glucose + one-half lactate) decreased from 5.6 ± 0.7 at rest to 3.0 ± 0.4 and 3.8 ± 0.7 at 15 min and at exhaustion, respectively ($P < 0.05$).

MAP, MCA V$_{mean}$, $S_{vO2}$, and PaCO$_2$ values. Representative changes in MAP and MCA V$_{mean}$ during exercise are outlined for one subject in Fig. 1. Despite no significant change in MAP throughout exercise to exhaustion, MCA V$_{mean}$ decreased gradually toward exhaustion. The increase in MAP from rest to exercise was 23.5 ± 3.2% at 5 min, 19.4 ± 3.8% at 15 min, and 18.3 ± 4.3% at exhaustion ($P < 0.05$), whereas the changes in MCA V$_{mean}$ were 19.7 ± 5.3, 12.8 ± 7.5, and −2.0 ± 9.0%, respectively (Table 1; $P < 0.05$). Thus CVR index tended to increase from 1.16 ± 0.06 mmHg·s·cm$^{-1}$ at rest to 1.51 ± 0.23 mmHg·s·cm$^{-1}$ ($P = 0.11$) at exhaustion. There was a small increase in PaCO$_2$ at the beginning of exercise, but PaCO$_2$ decreased to below the resting value at exhaustion ($P < 0.05$). Thus during exercise, the reduction in MCA V$_{mean}$ was related to the decrease in PaCO$_2$. (MCA V$_{mean} = 33 ± 6.8 \times \text{PaCO}_2$; $r = 0.47$; $P = 0.04$; Fig. 2A). Similarly, $S_{vO2}$ decreased from 68 ± 1 to 58 ± 2% at exhaustion and was also related to the decrease in PaCO$_2$. ($S_{vO2} = 34 ± 5.0 \times \text{PaCO}_2$; $r = 0.74$; $P < 0.001$; Fig. 2B).

Spectral and transfer function analyses. During exercise to exhaustion, there were no significant changes in the spectral
power of MCA $V_{\text{mean}}$ across all frequency ranges; the same held for the spectral power of MAP with the exception of the HF range at exhaustion (Table 2; $P < 0.05$). The transfer function phase shift tended to decrease over time (Figs. 3 and 4), but at minutes 12–15 and at exhaustion, the transfer function gain as well as the normalized values for each frequency range increased from the resting values ($P < 0.05$). The coherence between MAP and MCA $V_{\text{mean}}$ decreased compared with rest, but there was no significant difference between the values obtained during exercise (Fig. 4). Despite this, throughout exercise, the coherence remained >0.5, i.e., it remained statistically significant.

**DISCUSSION**

The main finding of the present investigation was that the effectiveness of dynamic CA was reduced by exhaustive exercise despite a reduction in $P_{\text{ACO}_2}$, and a presumed marked increase in sympathetic activity. Furthermore, the slope of the linear relationship between MCA $V_{\text{mean}}$ and $P_{\text{ACO}_2}$ throughout the range of $P_{\text{ACO}_2}$ (5.5 to $\sim$3.9 kPa) that was developed by exercise to exhaustion appeared to be markedly less than at rest, i.e., 12 vs. 29%/kPa (12).

The CA maintains a constant cerebral blood flow and is considered to operate within a MAP range of 60–150 mmHg as long as $\dot{Q}$ and $P_{\text{ACO}_2}$ remain stable (28). However, cerebral blood flow is highly sensitive to alterations in $P_{\text{ACO}_2}$ (1, 8, 9, 12, 14, 27, 31). For example, at rest, increases in $P_{\text{ACO}_2}$ dilate the cerebral resistance vessels and promote blood flow, whereas a decrease causes vasoconstriction of the cerebral resistance vessels (14, 17, 31), which consequently produces marked changes in MCA $V_{\text{mean}}$ without changes in diameter (12, 14, 31). The relationship between MCA $V_{\text{mean}}$ and $P_{\text{ACO}_2}$ is unclear and has been reported to be linear (12), sigmoidal (31), and exponential (14). The cerebral metabolic demand for oxygen also contributes to changes in MCA $V_{\text{mean}}$ (4). Throughout exercise to exhaustion, $\text{ SvO}_2$ decreased and correlated to the decrease in $P_{\text{ACO}_2}$ (see Fig. 2B), which suggests that...
**Figure 2.** Relationships between MCA $V_{mean}$ and arterial PCO$_2$ (PaCO$_2$; A) and venous O$_2$ saturation (SvO$_2$) and PaCO$_2$ (B) at rest and during exercise. Values are means ± SE.

PaCO$_2$ maintains its ability to cause vasoconstriction of the cerebral resistance vessels during exhaustive exercise. With both MAP and Q remaining stable during exercise, the relationship between individual MCA $V_{mean}$ and PaCO$_2$ ranging from 5.5 to 3.9 kPa was linear (see Fig. 2A), but the slope was approximately half of that found both at rest (12) and during exercise combined with the administration of CO$_2$ to the inspired air (24). Moreover, during exercise, MCA $V_{mean}$ was higher than expected for a given PaCO$_2$.

The cerebral metabolic rate of oxygen remains stable during cerebral activation (23). Therefore, during the initial 5 min of exercise, a decrease in the a-v diff in blood oxygen saturation across the brain indicates enhanced perfusion (see Table 1). However, at 15 min of exercise and at exhaustion, the a-v diff in blood oxygen saturation across the brain was not significantly different from that at rest, which suggests normalization of cerebral blood flow. In addition, the a-v diff of lactate concentration across the brain indicated increased uptake as the subject became tired particularly at exhaustion. Moreover, the cerebral metabolic ratio decreased during exercise to exhaustion. These results substantiate the hypothesis that cerebral metabolism is enhanced by intense exercise. Ide and co-workers (13, 15) found that changes in Q independent of MAP affect MCA $V_{mean}$. However, in the present study, both Q and MAP remained stable during exhaustive exercise, and the

Table 2. Power spectra of beat-to-beat variability of mean arterial pressure and MCA mean blood flow velocity at rest and during exercise

<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>At Rest</th>
<th>6–9 Min</th>
<th>12–15 Min</th>
<th>3 Min Before Exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mmHg$^2$</td>
<td>5.57±1.30</td>
<td>3.44±0.38</td>
<td>2.25±0.33</td>
<td>3.35±0.88</td>
</tr>
<tr>
<td>Very low</td>
<td>5.96±1.96</td>
<td>2.85±0.86</td>
<td>2.98±0.79</td>
<td>4.09±0.66</td>
</tr>
<tr>
<td>Low</td>
<td>0.60±0.14</td>
<td>0.42±0.11</td>
<td>0.52±0.13</td>
<td>1.07±0.29</td>
</tr>
</tbody>
</table>
| High | 0.69±0.13 | 0.52±0.09 | 0.97±0.24 | 2.70±0.75$^{*}$
| MCA mean blood flow velocity, cm/s$^2$ | 3.79±0.46 | 5.80±1.38 | 7.98±1.52 | 6.84±1.28 |
| Very low | 5.81±1.66 | 3.09±0.59 | 5.35±0.77 | 8.02±1.90 |
| Low | 0.69±0.13 | 0.52±0.09 | 0.97±0.24 | 2.70±0.75$^{*}$

Values are means ± SE; $n = 7$ subjects at rest and during 6–9 minutes exercise and 3 min before exhaustion; $n = 5$ subjects during 12–15 min exercise. $^{*}P < 0.05$, different from rest; $^{+}P < 0.05$, different from 5 min; $^{\ddagger}P < 0.05$, different from 15 min.

**Figure 3.** Cross-spectral analysis of the entire spectrum from 0.02 to 0.3 Hz at rest, 6–9 min, 12–15 min, and exhaustion. Group-averaged phase (A), gain (B), and normalized gain (C) between MAP and MCA $V_{mean}$ are shown. LF, low frequency. Values are means; $n = 7$ subjects.

The cerebral metabolic rate of oxygen remains stable during cerebral activation (23). Therefore, during the initial 5 min of exercise, a decrease in the a-v diff in blood oxygen saturation across the brain indicates enhanced perfusion (see Table 1). However, at 15 min of exercise and at exhaustion, the a-v diff in blood oxygen saturation across the brain was not significantly different from that at rest, which suggests normalization of cerebral blood flow. In addition, the a-v diff of lactate concentration across the brain indicated increased uptake as the subject became tired particularly at exhaustion. Moreover, the cerebral metabolic ratio decreased during exercise to exhaustion. These results substantiate the hypothesis that cerebral metabolism is enhanced by intense exercise. Ide and co-workers (13, 15) found that changes in Q independent of MAP affect MCA $V_{mean}$. However, in the present study, both Q and MAP remained stable during exhaustive exercise, and the
be expected to enhance dynamic CA (1, 8, 9, 27). However, the transfer function gain was increased, which indicates impairment of dynamic CA. The impairment in dynamic CA may be related to the altered milieu of cerebral vessels associated with the efflux of metabolites into the vascular tissue related to increased brain metabolism (7). In the systemic circulation, such increases in metabolites have been found to alter vasomotor tone (18). However, brain metabolism may not be the only reason that dynamic CA becomes impaired during exercise.

Another possible explanation for impaired dynamic CA is acute hyperammonemia during exhaustive exercise. In patients with acute liver failure, sympathetic regulation of cerebral blood flow is impaired (20), and CA becomes impaired in response to stepwise hypotensive stimuli (21), which may be related to ammonia-induced perturbations of brain metabolism (6, 25). Similarly, intense exercise increases the blood content of ammonia, which easily penetrates the blood-brain-barrier (2). Thus impaired dynamic CA and reduced responsiveness of MCA $V_{\text{mean}}$ to changes in $P_{\text{CO}_2}$ could result from elevated ammonia in the brain during exhaustive exercise.

The range or set point of the function representing both static and dynamic CA is influenced by the prevailing perfusion pressure (35). In chronic hypertension, the limits of the CA function curve are shifted to the higher MAP (28), whereas chronic cerebral hypoperfusion shifts the curve to a lower pressure (38). Acute exposure to orthostatic stress such as head-up tilt and lower body negative pressure results in a downward (3) or rightward (41, 42) shift in the CA curve. Levine et al. (22) speculate that sympathetic activation during lower body negative pressure shifts the CA curve to the right and compromises CA during orthostatic hypotension and may contribute to symptoms of presyncope. However, it has been reported (13) that during heavy exercise, the prospect of hyperperfusion of the brain was prevented by sympathoexcitation and may be reflective of a rightward shift in the CA function curve. In the present investigation, although a rightward shift in the CA curve may have been present especially at exhaustion, dynamic CA was impaired. This impairment was associated with the hyperventilatory response to metabolic acidosis producing hypocapnia; therefore, we conclude that the interaction between sympathoexcitation and decreases in $P_{\text{CO}_2}$ are changed by exhaustive exercise via an unidentified mechanism.

**Potential limitations.** Estimating changes in cerebral blood flow via MCA $V_{\text{mean}}$ could be influenced by changes in diameter of the insonated vessel. However, MCA diameter remains relatively constant under a variety of conditions (32, 34). Nonetheless, sympathetic activity may induce constriction of MCA during submaximal and, more particularly, during maximal exercise (16). However, sympathetic activation produced during muscle ischemia after rhythmic handgrip exercise does not change the luminal diameter of a systemic conduit artery (30). Pott et al. (29) suggested that the 50% increase of MCA $V_{\text{mean}}$ during strenuous exercise (at >80% of maximal work capacity) may reflect MCA constriction when compared with the only 20% increase of MCA $V_{\text{mean}}$ observed in athletes during low-workload exercise. However, these differences can be explained by the increase in sympathoexcitation producing greater constrictions of the cerebral resistance vessels at the

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**Fig. 4.** Group-averaged low-frequency (0.07–0.2 Hz) transfer function phase (A), gain (B), normalized gain (C), and coherence (D) between MAP and MCA $V_{\text{mean}}$ at rest and during exercise. Values are means ± SE. *P < 0.05, different from rest; †P < 0.05, different from 6 to 9 min.
higher workload without changing the MCA diameter. Hence, we contend that the beat-to-beat changes in MCA $V_{\text{mean}}$ during steady-state exercise primarily reflect changes in flow, which is confirmed by the changes in $S_{\text{VO}}$. It should also be noted that during intense exercise, the MAP profile includes a considerable increase in pulse pressure. Considering that the fluctuations in MCA $V_{\text{mean}}$ encompass changes in both peak systolic and diastolic flow velocities, it is important to consider the potential differences that may occur during these two distinct phases of the MCA $V_{\text{mean}}$ profile. This is particularly important with regard to the increase in the systolic pressure wave that must be countered by CA.

In conclusion, the relationship between MCA $V_{\text{mean}}$ and $P_{\text{ACO}}$, appears to be linear throughout the range of $P_{\text{ACO}}$ that was produced by subjects’ exercise to exhaustion. However, the slope of the relationship curve was markedly less during exercise than at rest, and despite the large reduction in $P_{\text{ACO}}$ resulting from hyperventilation, dynamic CA was impaired.

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