Middle cerebral artery flow velocity and pulse pressure during dynamic exercise in humans

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1Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth; 2Institute for Exercise and Environmental Medicine, Presbyterian Hospital and The University of Texas Southwestern Medical Center, Dallas, Texas; and 3Copenhagen Muscle Research Center, Department of Anesthesia, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

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Ogoh, Shigehiko, Paul J. Fadel, Rong Zhang, Christian Selmer, Øivind Jans, Niels H. Secher, and Peter B. Raven. Middle cerebral artery flow velocity and pulse pressure during dynamic exercise in humans. Am J Physiol Heart Circ Physiol 288: H1526–H1531, 2005. First published December 9, 2004; doi:10.1152/ajpheart.00979.2004.—Exercise challenges cerebral autoregulation (CA) by a large increase in pulse pressure (PP) that may make systolic pressure exceed what is normally considered the upper range of CA. This study examined the relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) and systolic (V_s), diastolic (V_d), and mean (V_m) middle cerebral artery (MCA) blood flow velocity during mild, moderate, and heavy cycling exercise. Dynamic CA and steady-state changes in MCA V in relation to changes in arterial pressure were evaluated using transfer function analysis. PP increased by 37% and 57% during moderate and heavy exercise, respectively (P < 0.05), and the pulsatility of MCA V increased markedly. Thus exercise increased MCA V_m and V_s (P < 0.05) but tended to decrease MCA V_d (P = 0.06). However, the normalized low-frequency transfer function gain between MAP and MCA V_s and between SBP and MCA V_m remained unchanged from rest to exercise, whereas between DBP and MCA V_s increased from rest to heavy exercise (P < 0.05). These findings suggest that during exercise, CA is challenged by a rapid decrease rather than by a rapid increase in blood pressure. However, dynamic CA remains able to modulate blood flow around the exercise-induced increase in MCA V_m, even during high-intensity exercise.

CEREBRAL AUTOREGULATION (CA) maintains steady-state cerebral blood flow relatively stable over a range of perfusion pressures from 60 to 150 mmHg (21), but it takes ~3 s for CA to be established (1), explaining why the velocity (V) in basal cerebral arteries fluctuates in parallel with blood pressure throughout the cardiac cycle. Thus exercise presents a challenge to CA by the rapid and large increases in pulse pressure (PP). This is exemplified during rowing where the rapid fluctuations in blood pressure associated with each stroke result in similar fluctuations in middle cerebral artery (MCA) mean blood flow velocity (V_m) (17). Equally, during rhythmic resistance exercise fluctuations in arterial pressure with each muscle contraction are too rapid to be countered by CA (9). Despite such large changes in the MCA V waveforms with exercise, the averaged MCA V_m remains unchanged (9), slightly decreased (7), or increased when exercise does not cause large fluctuations in blood pressure (3, 16, 17). However, the MCA V_m may not fully reflect the dynamic control of CA (15, 24, 26, 27), and this may be relevant especially when PP increases systolic pressure beyond the CA range.

Dynamic CA is frequency dependent (10, 15, 24, 26, 27), and frequency-domain analyses of CA allows for evaluation of the influence of exercise-induced changes in arterial blood pressure on MCA V. Brys et al. (3) used frequency-domain analysis to evaluate dynamic CA between mean arterial pressure (MAP) and MCA V_m variability in the low-frequency (LF) domain. They found dynamic CA to be unaltered during incremental exercise to 150 W compared with rest. However, each stage of exercise was performed for just 3 min, raising some question as to whether steady-state conditions were reached (22).

During leg cycling exercise, PP may increase threefold with a large increase in systolic blood pressure (SBP) combined with a slight decrease or no change in diastolic blood pressure (DBP) (18). Considering that fluctuations in MCA V encompass both changes in systolic and diastolic blood flow velocities, we considered the potential differences that may be established during these two distinct phases of the MCA V profile, where increases in SBP may exceed the range of pressure counteracted by CA. This investigation examined dynamic CA using transfer function analysis between arterial blood pressure and MCA V_m, systolic blood flow velocity (V_s), and diastolic blood flow velocity (V_d) during three levels of steady-state cycle exercise. We hypothesized that as PP increases with workload, dynamic CA will be affected by the large increases in SBP.

METHODS

Six men and one woman with a mean age of 25 ± 1 yr, height of 184 ± 3 cm, and weight of 75 ± 2 kg (means ± SE) participated in this study. All subjects were free of any known 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 (01-386/02). Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 24 h before any experimental session. Before the experiments were performed, each subject visited the laboratory for familiarization with the techniques and procedures of the protocol.

Protocol. On the experimental day, the subjects arrived at the laboratory at least 2 h after a light meal. The subjects were seated in
a semirecumbent position on a bed that was modified to allow seated cycling exercise. Each subject performed three 8-min bouts of exercise at a steady-state heart rate (HR) of 90, 120, and 150 beats/min representing mild (EX90), moderate (EX120), and heavy (EX150) exercise. MCA Vm and middle cerebral artery mean blood flow velocity; CVCI, cerebrovascular conductance index; PaCO2, arterial PCO2. *Significantly different from rest (P < 0.05); †significantly different from EX90 (P < 0.05); ‡significantly different from EX120 (P < 0.05). Values are means ± SE.

Table 1. Steady-state cardiovascular and hemodynamic variables at rest and during mild, moderate, and heavy exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rest</th>
<th>EX90</th>
<th>EX120</th>
<th>EX150</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>66 ± 5</td>
<td>89 ± 2*</td>
<td>120 ± 3†</td>
<td>147 ± 5‡</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>88 ± 3</td>
<td>87 ± 3</td>
<td>95 ± 2*</td>
<td>106 ± 5‡</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>65 ± 4</td>
<td>75 ± 2*</td>
<td>89 ± 5‡</td>
<td>102 ± 4‡</td>
</tr>
<tr>
<td>MAP at MCA, mmHg</td>
<td>63 ± 3</td>
<td>63 ± 4</td>
<td>71 ± 2*</td>
<td>82 ± 5‡</td>
</tr>
<tr>
<td>MCA/Vm, cm/s</td>
<td>61 ± 3</td>
<td>64 ± 4</td>
<td>68 ± 2*</td>
<td>71 ± 5‡</td>
</tr>
<tr>
<td>CVCI, cm/s/mmHg</td>
<td>0.69 ± 0.03</td>
<td>0.73 ± 0.03</td>
<td>0.72 ± 0.04</td>
<td>0.67 ± 0.04</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>5.08 ± 0.14</td>
<td>5.12 ± 0.11</td>
<td>5.07 ± 0.11</td>
<td>4.88 ± 0.14†‡</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.00</td>
<td>7.40 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>7.37 ± 0.01‡‡</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>1.10 ± 0.24</td>
<td>0.89 ± 0.22</td>
<td>1.31 ± 0.25</td>
<td>4.42 ± 0.71‡‡</td>
</tr>
</tbody>
</table>

In addition, H(f) was normalized to the mean values of input (x) and output (y) variables as H(f) = Sxx(f)/Sxx(f)y, and the normalized gain was calculated as 20 log H(f) to express values in decibels. A value of 0 indicates that the output varies by the same fraction of the mean value as the input, a negative value indicates that it varies less, and a positive value indicates that it varies greater than the input.

The squared coherence function [MSC(f)] was estimated as:

\[ MSC(f) = \frac{|S_{xy}(f)|^2}{S_{xx}(f)S_{yy}(f)} \]

where \( S_{xy}(f) \) is the cross-spectrum of changes in x(t). The squared coherence function reflects the fraction of output power that can be linearly related to the input power at each frequency. Similar to a correlation coefficient, it varies between 0 and 1 and reflects the validity of transfer function analysis between two variables.

Analog signals of arterial blood pressure and the spectral envelope of MCA Vm were sampled at 100 Hz and digitized at 12 bits for off-line analysis. Beat-to-beat MAP, SBP, DBP, MCA Vm, MCA Vv, and MCA Vd were obtained from the analog signals. These beat-to-beat data were then linearly interpolated and resampled at 2 Hz for spectral analysis of dynamic CA (24). For an estimate of dynamic CA, using the transfer function, the cross-spectrum between changes in MAP and MCA Vm, SBP and MCA Vv, and DBP and MCA Vd were calculated and divided by the autospectrum of MAP, SBP, and DBP, respectively. Spectral power, mean value of transfer function gain, phase, and coherence function were calculated in the very-low frequency (VLF; 0.003–0.06 Hz), low-frequency (LF; 0.06–0.15 Hz), and high-frequency (HF; 0.15–0.40 Hz) ranges to reflect patterns of the dynamic pressure-flow relationship (24). These frequency ranges reflect patterns of the dynamic pressure-flow relationship, as identified by transfer function analysis (24, 25). Blood pressure fluctuations in the HF range are

![Fig. 1. Representative waveforms (solid line) and means (shaded line) of arterial blood pressure (ABP; top) and middle cerebral artery (MCA) blood flow velocity (V; bottom) from a subject at rest (left) and during heavy exercise (EX150; right).](http://ajpheart.physiology.org/)

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induced primarily by respiration, whereas those in the LF range are independent of the respiratory frequency and are dampened by CA (8). Furthermore, the VLF range of both flow and pressure variability appears to reflect multiple physiological mechanisms that confound interpretation. Thus we used the LF range of each variable for the spectral analysis to identify the dynamic CA during exercise (24). The transfer function gain and phase shift reflect the relative amplitude and time relationships, respectively, between the changes in perfusion pressure and blood flow over a specific frequency range. CA decreases the transmission effect of pressure on flow. Thus increased transfer function gain or decreased transfer function phase between pressure and flow can be interpreted as an increased effect of transmission, which suggests that dynamic CA is impaired.

Statistical analysis. One-way ANOVA with repeated measures was used to assess the differences in the steady-state hemodynamic variables, spectral power of arterial pressure and MCA $V$, and transfer function gain, phase, and coherence function in each frequency range between rest and the three exercise bouts (SigmaStat, Jandel Scientific Software, SPSS; Chicago, IL). A Student-Newman-Keuls test was employed post hoc when main effects were significant, i.e., $P < 0.05$, and data are expressed as means ± SE.

RESULTS

During EX90, MAP and MCA $V_m$ did not change significantly compared with rest, but PP increased (Table 1). However, the changes in MCA $V_m$ were associated with an increased MAP from rest to EX120 and EX150. During EX120 and EX150, MAP increased by 8% and 21% and MCA $V_m$ increased by 12% and 16%, respectively ($P < 0.05$). Thus CVCI did not increase during increasing exercise workload ($P = 0.224$). Arterial lactate increased and pH and $P_{aCO_2}$ decreased at EX150.

The amplitude of arterial pressure waveforms increased from rest to EX150 in association with similar increases in the amplitude of the MCA $V$ waveforms (Fig. 1). SBP increased during EX120 and EX150 ($P < 0.05$), whereas DBP was unchanged compared with rest (Fig. 2). MCA $V$ increased throughout exercise, and MCA $V_d$ tended to decrease from rest ($P = 0.06$). The steady-state changes in MCA $V_m$ in relation to those in MAP (MCA $V_m$/MAP) were unchanged during exercise. Likewise, the MCA $V$/SBP remained unchanged, but MCA $V_d$/DBP decreased throughout exercise, being significant from rest at EX120 and EX150. Also, MCA $V_d$/DBP during EX150 was decreased from EX90 ($P < 0.05$).

Spectral power analysis. The resting LF spectral power of MAP (5.0 ± 0.8 mmHg$^2$) and MCA $V_m$ (2.6 ± 0.6 cm/s$^2$) did not change significantly at any workload. For example, during EX120, MAP and MCA $V_m$ spectral power was 4.6 ± 0.7
mmHg² and 2.4 ± 0.9 cm/s², respectively. Similarly, LF spectral power of SBP and DBP was unchanged from rest to exercise. In contrast, the spectral power of HR variability was reduced at all workloads (rest: 5.9 ± 1.8 beats/min² vs. EX120 0.5 ± 0.1 beats/min² and EX150 0.3 ± 0.2 beats/min², P < 0.05).

Transfer function analysis. During exercise, the transfer function phase shift between arterial blood pressure and MCA V remained stable and did not differ from resting values (Figs. 3 and 4). Likewise, the normalized LF transfer function gain between MAP and MCA Vm as well as the normalized LF gain between SBP and MCA Vs remained unchanged from rest to exercise. However, there was a tendency for an increase in the MAP/MCA Vm normalized LF gain during EX150 (P = 0.08). Moreover, the normalized LF gain between DBP and MCA Vd increased from rest during EX90, EX120, and EX150 (P < 0.05). Importantly, the coherence between change in arterial blood pressure and MCA V remained above 0.5 during exercise, indicating that statistical significance was maintained.

DISCUSSION

The data provide novel insight into regulation of cerebral blood flow during the rapid and marked changes in blood pressure that occur within each heart beat during dynamic exercise. Although steady-state MCA Vm and Vs increased, dynamic CA appears unaltered by exercise. However, the normalized transfer function gain between DBP and MCA Vd increased from rest to heavy exercise. These findings suggest that during exercise, although CA is challenged by increases in PP, the ability of the cerebral vasculature to modulate blood flow around the exercise-induced increase in MCA Vm is maintained, but the cerebral circulation is less effective in responding to rapid decreases than it is to increases in blood pressure.

MCA V varies in response to fluctuations in arterial pressure (15). During exercise, the change in MCA V between systolic and diastolic flow velocity increases as PP increases. An increase in MCA Vm is in direct relation to workload and is likely a consequence of the increase in cerebral metabolism (5, 6) provided that there is a sufficient increase in cardiac output (13). The increase in MCA Vm from rest throughout exercise suggests that with increasing workload, the cerebral vasculature accommodates an increase in flow. More importantly, the unchanged transfer function gain between SBP and MCA Vs indicates that dynamic CA was functioning in maintaining the systolic phase of the MCA V around this higher flow velocity. However, the progressive decrease in MCA Vd from rest to exercise combined with the increasing normalized transfer function gain between DBP and MCA Vd suggests that dynamic CA was impaired in regulating the diastolic phase of the

![Fig. 3. Cross-spectral analysis in the spectrum from 0 to 0.3 Hz at rest (shaded line) and during EX150 (solid line). Group-averaged phase (top), normalized gain (middle), and coherence (bottom) between MAP and MCA Vm (left), SBP and MCA Vs (middle), and DBP and MCA Vd (right) are shown. Values are means; n = 7.](http://ajpheart.physiology.org/ by 10.220.32.247 on June 30, 2017)
exercise and especially from resistance exercise where gray outs or blackouts develop (4, 9).

A potential factor that may contribute to the impaired control of MCA $V_d$ during exercise is a dynamic shift in the CA curve to the right. CA is a dynamic process with temporal heterogeneity (10) and is subject to modulation (2, 26, 27). Levine et al. (14), in attempting to explain syncope during lower body negative pressure, speculated that sympathetic activation shifts the CA curve to the right. If a rightward shift in the CA curve occurs in response to sympathoexcitation, then, during exercise, it would serve as a protective mechanism during the exercise-induced systolic hypertension. However, a rightward shift of CA may be detrimental in the regulation of MCA $V_d$ during the diastolic phase and lead to impairment in MCA $V_d$ regulation. Clearly, the interaction between arterial baroreflex control of systemic blood pressure and CA becomes increasingly important during dynamic exercise.

A potential limitation of estimating MCA $V_d$ using transcranial Doppler ultrasonography is that vasoconstriction of the insonated vessel increases MCA $V_d$ at any given volume of flow. However, in humans, the MCA diameter appears to remain relatively constant under a variety of conditions (19, 20). Furthermore, even though Pott et al. (16) reported that the 50% increase in MCA $V_m$ that occurred during heavy exercise at $>80\%$ of maximal O$_2$ consumption may be confounded by MCA constriction, this was not the case for lower exercise workloads, which elicited a 30% increase in MCA $V_m$ and the finding during maximal exercise has not been reproduced (11). In the present study, during EX150, the increase in MCA $V_m$ approximated 17%. Thus we would contend that beat-to-beat changes in MCA $V_m$ reflected changes in flow. Another limitation is that heavy exercise may cause signal noise in the data acquisition of MCAV, but that appeared not to be the case from visual inspection of the MCA $V_d$ waveforms. In addition, the coherence remained above 0.5 during all conditions suggesting that there was little effect of signal noise on the validity of transfer function analysis during exercise. Finally, it is possible that the diastolic phase of the velocity profile may not be faithfully represented by the Doppler monitoring system. However, to insure that flow-velocity profile of the MCA $V_d$ was faithfully measured, we used transcranial Doppler equipment to measure the flow-velocity wave with a resonance frequency (RF) range of 12–25 Hz. This RF range has been identified to adequately encompass systolic and diastolic pressure wave monitoring using an arterial catheter and pressure transducer (12).

Pott et al. (17) reported that during the catch phase of the rowing stroke, MCA $V_m$ increased in parallel with MAP but during the return phase of the stroke MCA $V_m$ declined to a nadir even though MAP was stable. Together with the present data, these findings indicate that as PP increases and the pulse interval decreases with an increase in workload, dynamic CA becomes less able to regulate transient decreases in cerebral blood flow. These findings may prove important in understanding the decreases in cerebral perfusion that occur during recovery from dynamic exercise and especially from resistance exercise where grayouts or blackouts develop (4, 9).

**ACKNOWLEDGMENTS**

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**Fig. 4.** Group-averaged low-frequency (LF, 0.07–0.2 Hz) phase (A), LF gain (B), normalized LF gain (C), and LF coherence (D) between MAP and MCA $V_m$ (left), SBP and MCA $V_m$ (middle), and DBP and MCA $V_d$ (right) at rest and during EX90, EX120, and EX150. Values are means ± SE. *Significantly different from rest ($P < 0.05$); †significantly different from EX90 ($P < 0.05$); ‡significantly different from EX120 ($P < 0.05$).


