Dynamic cerebral autoregulation remains stable during physical challenge in healthy persons

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Cerebral autoregulation normally ensures that cerebral blood flow (CBF) remains relatively constant despite fluctuations in blood pressure (BP), provided that mean BP remains within the range of autoregulation, usually from 50 to 170 mmHg (6, 21, 37). If BP exceeds these limits, CBF increases, initially in a curvilinear relation, and then follows BP passively in a linear relation (21, 31). During increasing levels of physical effort, cerebral perfusion is not only driven by increasing BP and heart rate (HR) but also has to adjust to high levels of sympathetic activity and to altered metabolism with changes in PO2 and PCO2. With increasing muscle metabolism, PO2 in the blood decreases, whereas PCO2 increases, unless augmented respiration compensates for the higher O2 demand and production of CO2 (17, 35, 54). Cerebral autoregulation has to counterbalance all the cardiovascular and metabolic responses to physical effort. Although some studies suggest that CBF velocity (CBFV) and CBF remain stable despite physical effort (15), several others found an increase in CBFV (14, 17, 30) as well as regional CBF (10, 55) and global CBF during exercise (24, 51).

During cardiovascular changes as they occur with increasing physical challenge, cerebral autoregulation can be evaluated by analyzing the quality of dynamic BP filtering, i.e., the extent to which the transfer of BP oscillations onto CBFV is dampened. Cerebral autoregulation can be compared with a high-pass filter (11). Rapid BP fluctuations in the high-frequency (HF) range (0.15–0.50 Hz), such as those induced by breathing, are transferred to CBFV, whereas slow BP fluctuations in the low-frequency (LF) range (0.04–0.14 Hz) are dampened by autoregulatory mechanisms (11). Because cerebral autoregulation is a frequency-dependent phenomenon (56), its function can be determined by comparing BP and CBFV oscillations in the frequency domain (11, 46, 56). If autoregulation is functioning effectively during exercise, spontaneously occurring changes in BP should only minimally influence CBF, as indicated by a low coherence between BP and CBFV or by a negligible change in the phase shift and gain between BP and CBFV fluctuations (1, 6, 56).

This study was performed to determine the effects of physical effort on cerebral autoregulation in young, healthy persons by means of transcranial Doppler sonography (TCD) and by calculation of cerebrovascular resistance (CVR), gain, and phase shift changes between oscillations in BP and CBFV during exercise. We hypothesized that during increasing levels of physical effort dynamic cerebral autoregulation and CVR would adapt to ensure an adequate CBF response to...
the metabolic and cardiovascular effects of physical effort.

METHODS

Subjects. Forty healthy young adults (24 men, 16 women) aged 20–42 yr (mean age 27.9 ± 5.4 yr) participated in the study. We excluded volunteers with a history of cardiovascular or neurological diseases or persons who were taking medication influencing the autonomic nervous system. All participants were asked not to consume nicotine, caffeine, or alcohol for at least 18 h before testing. The study protocol was approved by the Institutional Review Board of New York University School of Medicine, and each subject gave informed written consent according to the Declaration of Helsinki.

Procedures. Participants were tested after a resting period of at least 40 min to ensure cardiovascular stability. The participants were seated on a semirecumbent bicycle ergometer (CatEye Ergosicer, Osaka, Japan) with a backrest inclination of 55°. The procedure consisted of a 10-min baseline followed by levels of physical effort at 50, 100, and 150 W with 3 min duration of each step.

At rest and during ergometric challenge, we continuously monitored beat-to-beat radial artery systolic, diastolic, and mean BP (BPsys, BPdia, BPMean) at the level of the wrist with applanation tonometry (Colin Pilot, San Antonio, TX). The tonometer consists of an array of 32 equally spaced piezoresistive pressure transducers, an automated positioning system, signal conditioning, and initial as well as intermittent calibration by oscillometric cuff measurement of brachial artery BP (27).

HR was monitored with a standard five-lead electrocardiogram with superficial skin electrodes (Colin Pilot). Respiratory frequency was monitored with a calibrated two-belt chest-abdomen inductance plethysmograph (Respitrace Caltronic, Ayrda, NY, USA). Transcutaneous oxygen saturation was measured at the right index finger with a pulse oximeter (Nellcor, Pleasanton, CA) using the principle of light absorption characteristics of oxygenated and deoxygenated hemoglobin (48). End-expiratory Pco2 was monitored via nasal cannulas and analyzed by the Colin Pilot monitor. Systolic, diastolic, and mean CBFV (CBFVsys, CBFVdia, CBFVmean) at the left and right proximal middle cerebral arteries (MCAs) were studied with TCD (Multidop XL; DWL, Sipplingen, Germany). The MCA was insonated through the temporal window with an adjustable positioning system. After the Doppler signal was optimized, the probe was attached to the skull in a fixed angle by using a headband with an adjustable positioning system.

Data acquisition and analysis. All data were digitized by an analog-to-digital converter at a sampling rate of 300 Hz, fed to a computer, manually cleaned of artifacts by linear interpolation, and stored for off-line analysis. A C-language program identified all the QRS complexes in each recording, located the peak of each R wave, and calculated consecutive RR intervals. From the continuous waveforms of BP (systolic, diastolic, and mean), CBFV (systolic, diastolic, and mean), respiration, end-tidal CO2 levels, and oxygen saturation, beat-to-beat mean values were automatically calculated and interpolated linearly between adjacent values to construct a corresponding continuous time series. The signals recorded during baseline (resting conditions) were analyzed during a 60-s interval that ended 30 s before the onset of physical exercise to ensure that baseline values were not biased by preparatory activities. During physical exercise, signals were analyzed from the last 60 s of each of the 3-min exercise levels (50, 100, and 150 W) to ensure cardiovascular stability.

From the 60-s epochs at rest and during the three exercise levels, we calculated means and standard errors of all biosignals. We compared CBFVsys, CBFVdia, and CBFVmean values between the left and right MCAs and intended to further analyze CBFV values of the left MCA only, provided there was no difference between values of the left and right side (t-test, P > 0.5).

CVR was calculated as the mean arteriolar blood pressure at brain level (BPmean_brain) divided by CBFVmean (45). We estimated BPmean_brain as the difference between BPmean at heart level and the hydrostatic pressure (BPhydro) effect at the level of transcranial insonation. We determined the vertical length (h) between the insonation site and the fourth intercostal space in the midclavicular line (heart level). The hydrostatic pressure of the blood column between heart and insonation levels was calculated as BP = σ · a · g · h, where σ is the specific density of blood (1.06 g/cm3) and g is gravitational acceleration (9.81 m/s2). The angle α was used to correct for the height reduction caused by the semisupine position of our bicycle ergometer with a backrest inclination of 55° (α = sin 55°) (26).

Spectral analysis. Oscillations in BPmean and CBFVmean were characterized by applying power spectral analysis to these signals by means of an autoregressive algorithm with a linear detrending option and model order estimation according to Akaike information criteria (9). The autoregressive algorithm, in contrast to the fast Fourier transformation, allows for identification of the frequencies and powers of the relevant oscillations with relatively small amounts of data (3, 19, 38). However, the autoregressive spectral analysis gives reliable spectral estimates only for stationary signals. To verify stationarity of analyzed HR, BP, and CBFV recordings at different levels of physical activity, we compared mean values and standard deviations of the signals averaged for the first and second half of each epoch (3). Stationarity was assumed if the mean values of the signals from the first and second half of an epoch did not differ by >10% and if there was no statistical difference between the standard deviations (3).

The spectral and cross-spectral analysis was applied on the same 1-min segment used for calculation of time domain parameters. We identified peaks of oscillations in the LF (0.04–0.14 Hz) and HF (0.15–0.50 Hz) ranges. LF oscillations in HR at rest are considered to be mediated by combined sympathetic and parasympathetic activity (16, 33, 39, 44), whereas there is a predominance of sympathetic activity during stressful conditions (16, 44). In contrast, LF fluctuations of the BP signal are mostly related to fluctuations in sympathetic outflow (20, 42, 50a). HF oscillations in HR are associated with respiratory sinus arrhythmia and reflect parasympathetic activity (16, 33, 39, 44), whereas fluctuations of the BP and CBFV signal in the HF range are primarily a mechanical consequence of respiration-induced increases in venous return (20, 42, 50a). We normalized the powers of HR oscillations as percentage values by dividing the LF or HF power by the sum of the LF and HF powers and multiplying by 100 (4, 36).

To assess dynamic autoregulation at rest and during increasing physical effort, we calculated the LF BP-CBFV gain and phase shift angle between BP and CBFV fluctuations in the LF band, provided there was significant coherence between both signals (11, 43, 46, 56).

The coherence between two oscillations in a given frequency spans from 0 (i.e., no association) to 1 (i.e., maximal
CEREBRAL AUTOREGULATION DURING EXERCISE

Table 1. Time-domain and frequency-domain results

<table>
<thead>
<tr>
<th></th>
<th>At Rest (n = 40)</th>
<th>At 50 W (n = 40)</th>
<th>At 100 W (n = 40)</th>
<th>At 150 W (n = 35)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>72.4 ± 1.9</td>
<td>107.5 ± 2.5</td>
<td>131.6 ± 3.2</td>
<td>153.7 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPmean, mmHg</td>
<td>80.8 ± 1.9</td>
<td>91.1 ± 2.5</td>
<td>95.6 ± 2.6</td>
<td>97.8 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPmean_brain, mmHg</td>
<td>78.3 ± 1.9</td>
<td>88.7 ± 2.5</td>
<td>93.1 ± 2.6</td>
<td>95.4 ± 3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBFVmean, cm/s</td>
<td>64.1 ± 2.2</td>
<td>75.2 ± 2.3</td>
<td>82.3 ± 3.0</td>
<td>80.2 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVR, mmHg·s·cm⁻¹</td>
<td>1.25 ± 0.05</td>
<td>1.20 ± 0.05</td>
<td>1.18 ± 0.05</td>
<td>1.22 ± 0.06</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>End-tidal CO₂, mmHg</td>
<td>40.6 ± 0.8</td>
<td>45.7 ± 0.6</td>
<td>48.5 ± 0.9</td>
<td>45.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>satO₂, %</td>
<td>97.2 ± 0.14</td>
<td>97.2 ± 0.12</td>
<td>97.2 ± 0.12</td>
<td>97.1 ± 0.13</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Respiration, min⁻¹</td>
<td>16.3 ± 0.6</td>
<td>20.2 ± 0.6</td>
<td>22.3 ± 0.9</td>
<td>28.7 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF HR, % of total</td>
<td>60.8 ± 3.8</td>
<td>73.0 ± 4.0</td>
<td>75.4 ± 3.1</td>
<td>77.7 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HF HR, % of total</td>
<td>39.2 ± 3.8</td>
<td>27.0 ± 4.0</td>
<td>24.6 ± 3.1</td>
<td>22.3 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF BPmean, mmHg²</td>
<td>5.08 ± 0.55</td>
<td>7.88 ± 0.71</td>
<td>8.85 ± 1.33</td>
<td>10.02 ± 1.19</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HF BPFmean, mmHg²</td>
<td>1.07 ± 0.18</td>
<td>1.79 ± 0.23</td>
<td>2.31 ± 0.38</td>
<td>2.47 ± 0.37</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LF CBFVmean, cm²/s²</td>
<td>5.19 ± 0.70</td>
<td>6.09 ± 0.65</td>
<td>5.54 ± 0.63</td>
<td>5.84 ± 0.78</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>HF CBFVmean, cm²/s²</td>
<td>1.11 ± 0.16</td>
<td>2.03 ± 0.29</td>
<td>2.84 ± 0.33</td>
<td>2.94 ± 0.44</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>CA LF gain, cm·s⁻¹·mmHg⁻¹</td>
<td>0.95 ± 0.08</td>
<td>0.94 ± 0.07</td>
<td>0.93 ± 0.07</td>
<td>0.94 ± 0.09</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Normalized LF gain, dB</td>
<td>0.01 ± 0.04</td>
<td>-0.01 ± 0.04</td>
<td>-0.02 ± 0.03</td>
<td>0.00 ± 0.03</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CA phase shift,°</td>
<td>37.1 ± 3.0</td>
<td>36.6 ± 4.6</td>
<td>46.0 ± 5.5</td>
<td>47.6 ± 11.7</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE; n = no. of subjects at the various levels of exercise. HR, heart rate; BPmean, mean blood pressure; CBFVmean, mean cerebral blood flow velocity; satO₂, oxygen saturation; CVR, cerebrovascular resistance; BPFmean_brain, mean blood pressure at brain level; HF, high frequency; LF, low frequency; CA, cerebral autoregulation.

With increasing physical effort, there was a significant increase in HR, respiratory frequency, BP, and CBFV (RANOVA, P < 0.001; Table 1). HR and respiratory frequency correlated with the levels of exercise in an almost linear relation, with a Spearman correlation coefficient of r = 0.86 for HR and r = 0.74 for respiratory frequency. The correlation was lower between the levels of challenge and the values of BP (r = 0.43) and CBFV (r = 0.36).

End-expiratory P CO₂ levels at 50, 100, and 150 W were significantly higher than baseline P CO₂ values (t-test, P < 0.01). However, at 150-W challenge P CO₂ decreased and was lower than at 100 W. In contrast, transcutaneous O₂ saturation remained stable at all levels of exercise and did not differ from baseline values (t-test, RANOVA, P > 0.05).

There was no difference between the CVR values at baseline and during exercise (t-test). There was no difference between the CVR values at baseline and during exercise (t-test) (Fig. 1).

Comparison of mean values of HR, BP, and CBFV averaged from the first and second half of each epoch

**RESULTS**

**Time domain analysis.** All participants completed the 50- and 100-W exercise levels, but five participants were unable to complete the 150-W level. Comparison of CBFVsys, CBFVdia, and CBFVmean in both MCAs showed no significant differences (t-test, P > 0.05). Therefore, we used the values recorded from the left MCA for further calculations and for spectral analysis.
for each biosignal and at each level of physical activity showed that the mean values did not change by >10%. Moreover, there was no significant difference between the standard deviations calculated for each signal from the first and second half of each epoch of physical activity (t-test, P > 0.05).

**Frequency domain analysis.** Similar to the increase of HR, BP, CBFV, and respiratory rate, there was a significant and almost linear increase of the normalized LF powers of HR (t-test, RANOVA, P < 0.001) and the LF powers of BP (Wilcoxon, Friedman, P < 0.005; Table 1, Fig. 2). In contrast, there was only a slight, nonsignificant increase of LF powers of CBFV (Wilcoxon, Friedman, P > 0.05; Table 1). The normalized HF power of HR, i.e., the parameter of parasympathetically mediated HR oscillations, decreased significantly with exercise (t-test, RANOVA, P < 0.001; Table 1). In contrast, the increase of respiration resulted in the expected increase of the mechanically induced HF powers of BP and CBFV (Wilcoxon, Friedman, P < 0.005; Table 1).

At 50-, 100-, and 150-W exercise levels, the LF cross-spectral phase shift angle between BP and CBFV as well as LF BP-CBFV gain and the gain normalized by the individual BP-CBFV relations remained stable and did not differ significantly from the baseline values (t-test, RANOVA, P > 0.05; Table 1).

**DISCUSSION**

As expected (17, 25, 30), we observed an exercise-induced increase in BP as well as an increase in CBFV. Exercise also significantly increased the power of LF oscillations of BP, most likely related to increased sympathetic drive (42, 50a). However, it is possible that other factors contributed to the increase in LF BP oscillations. Although the LF oscillations in BP and in CBFV were in a constant phase relationship, mechanical effects of increased ventilation and rhythmic muscle contraction during pedaling cannot be excluded. In contrast, the increase of LF power of CBFV modulation during exercise was less pronounced, suggesting that the LF oscillations of BP were not fully transmitted onto CBFV modulation (11, 12). These results suggest that dynamic cerebral autoregulation, i.e., the ability of the cerebral resistance vessels to restore CBF after rapid BP changes, remains intact during physical exercise. During lower body negative pressure (LBNP), a stimulation that also increases cardiovascular sympathetic activity, we observed that enhanced BP oscillations were not transmitted onto CBFV, although there was a reduction in mean CBFV during LBNP (8). These findings corroborate the conclusion of the current study that intact interaction of the various mechanisms of cerebral autoregulation and of metabolic changes during physical effort ensure buffering of LF BP oscillations and thus protect brain tissue from hypo- or hyperperfusion, even at relatively high levels of cardiovascular stress.

Although various mechanisms, including the myogenic autoregulatory response (Bayliss effect), might contribute to adequate filtering of LF BP oscillations...
during physical exercise, we assume that the autonomic neural control of cerebral circulation is probably the most important factor of dynamic autoregulation. As recently demonstrated by Zhang et al. (57), removal of autonomic neural activity by ganglion blockade decreased phase shift and increased gain between LF BP and CBFV oscillations, suggesting a significant role of autonomic activity in the regulation of beat-to-beat changes in CBF.

Physical exercise stresses every component of the cardiovascular system. The increased metabolic demands of the exercising muscles results in local vasodilatation to ensure adequate blood perfusion and cause a decrease in total peripheral resistance (49). Simultaneously, cardiac output and HR both increase substantially (28, 54) along with an increase in BP. Although an exercise-induced increase in CBF was observed in previous studies (24, 51), these findings seem to be at odds with the traditional concept of cerebral autoregulation, which postulates that CBF should remain constant over a range of perfusion pressures. Most likely, the CBFV increase during exercise might be related to the increase in end-tidal CO₂. Another possibility is that an enhanced cerebral metabolic demand for O₂ might induce or contribute to the increase in CBFV. There is, however, considerable controversy as to whether the metabolic activity of the brain increases during physical exercise. Ide et al. (24) showed that, although cerebral metabolic activity does increase during exercise, the extent of the cerebral perfusion increase is in excess of that required to fulfill the cerebral metabolic demand for O₂. Moreover, PCO₂ increased significantly with higher levels of exercise. Because CO₂ is one of the strongest metabolites affecting CBF, the increase in CBFV is probably largely due to the dilating effects of CO₂ on cerebral vessels in the presence of exercise-induced increase in BP. In addition to systemic CO₂ increases, there might even be local, cerebral increases of CO₂ during exercise, as exercise induces functional changes of brain metabolism (18). CBFV might have increased by far more if autoregulation had been compromised in our study participants.

The variables assessed to evaluate the integrity of dynamic cerebral autoregulation—the LF gain between BP and CBFV oscillations and the phase shift between BP and CBFV oscillations—demonstrated that dynamic cerebral autoregulation remained stable during increasing levels of physical exercise despite the autonomic, mechanical, and metabolic effects of increasing physical effort (7, 15, 24, 28, 32, 35, 41, 50, 53). In our study, not only did the absolute gain remain stable but we also observed no change in normalized LF gain value. Because CVR is calculated as pressure divided by flow, the normalized LF gain value takes into account changes in CVR at which the variation occurs (6). Thus a stable normalized gain value indicates that the same amount of BP variation was transferred into cerebral circulation regardless of the mean values of BP and CBFV. Therefore, it is most likely that dynamic cerebral autoregulatory mechanisms act independently of static resistance changes.

One methodological point that must be addressed is the signal stationarity versus the length of an analyzed segment. To make an analysis on a quite stationary exercise segment (which is a requirement for autoregression), the 1-min segment length was chosen based on a trade-off between increasing accuracy of the spectral estimate and loss of signal stationarity. Another aspect that must be considered is whether our results were influenced by changes in the diameter of the insonated artery. A constriction of the MCA due to enhanced sympathetic vasoconstrictor tone during exercise could theoretically explain the observed increase in the measured CBFV. However, several studies have indicated that there is minimal or no major change in the diameter of the proximal MCA during a variety of stimuli (13, 23, 29, 34, 47). Moreover, the increase of CO₂ during exercise would override a vasoconstricting effect of an increased sympathetic activity (23, 52). We assume that our findings of increased CBFV are

![Cross-spectral analysis](image-url)
mainly due to dilatation of the downstream resistance vessels in response to the CO₂ increase during exercise. To conclude, our study showed no significant increase of LF CBFV oscillations as well as stable LF BP-CBFV gain and phase shift angle despite the increase of sympathetically mediated HR and LF oscillations of BP during exercise. These results suggest that the mechanisms of cerebral autoregulation adequately counterbalance increased sympathetic outflow during physical exercise.

DISCLOSURES

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