Regulation of middle cerebral artery blood velocity during dynamic exercise in humans: influence of aging

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1Department of Medical Pharmacology and Physiology, 2Dalton Cardiovascular Research Center, University of Missouri, Columbia; and 3Harry S. Truman Memorial Veterans Hospital, Department of Veterans Affairs Medical Center, Columbia, Missouri; and 4Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas

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Fisher JP, Ogoh S, Young CN, Raven PB, Fadel PJ. Regulation of middle cerebral artery blood velocity during dynamic exercise in humans: influence of aging. J Appl Physiol 105: 266–273, 2008. First published May 8, 2008; doi:10.1152/japplphysiol.00118.2008.—Although cerebral autoregulation (CA) appears well maintained during mild to moderate intensity dynamic exercise in young subjects, it is presently unclear how aging influences the regulation of cerebral blood flow during physical activity. Therefore, to address this question, middle cerebral artery blood velocity (MCAV), mean arterial pressure (MAP), and the partial pressure of arterial carbon dioxide (PaCO2) were assessed at rest and during steady-state cycling at 30% and 50% heart rate reserve (HRR) in 9 young (24 ± 3 yr; mean ± SD) and 10 older middle-aged (57 ± 7 yr) subjects. Transfer function analysis between changes in MAP and mean MCAV (MCAVmean) in the low-frequency (LF) range were used to assess dynamic CA. No age-group differences were found in PaCO2, at rest or during cycling. Exercise-induced increases in MAP were greater in older subjects, while changes in MCAVmean were similar between groups. The cerebral vascular conductance index (MCAVmean/MAP) was not different at rest (young 0.66 ± 0.04 cm·s⁻¹·mmHg⁻¹ vs. older 0.67 ± 0.03 cm·s⁻¹·mmHg⁻¹; mean ± SE) or during 30% HRR cycling between groups but was reduced in older subjects during 50% HRR cycling (young 0.67 ± 0.03 cm·s⁻¹·mmHg⁻¹ vs. older 0.56 ± 0.02 cm·s⁻¹·mmHg⁻¹; P < 0.05). LF transfer function gain and phase between MAP and MCAVmean was not different between groups at rest (LF gain: young 0.95 ± 0.05 cm·s⁻¹·mmHg⁻¹ vs. older 0.88 ± 0.06 cm·s⁻¹·mmHg⁻¹; P > 0.05) or during exercise (LF gain: young 0.80 ± 0.05 cm·s⁻¹·mmHg⁻¹ vs. older 0.72 ± 0.07 cm·s⁻¹·mmHg⁻¹ at 50% HRR; P > 0.05). We conclude that despite greater increases in MAP, the regulation of MCAVmean is well maintained during dynamic exercise in older healthy middle-aged subjects.

cerebral blood flow; transfer function; leg cycling; blood pressure

CEREBRAL AUTOREGULATION (CA) refers to the ability of the cerebral vasculature to maintain blood flow relatively constant over a wide range of perfusion pressures via changes in cerebrovascular resistance (44). Exercise presents a potential challenge to CA, not only due to rapid and robust fluctuations in arterial blood pressure but also due to increases in sympathetic nerve activity, cardiac output, and cerebral metabolism (26, 47, 50). Although CA appears well maintained during mild- to moderate-intensity dynamic exercise in young individuals (4, 38, 40), it is presently unclear how aging influences the regulation of cerebral blood flow during physical activity. This is an important question considering age-related alterations in peripheral circulatory control have been reported at rest (12, 33, 35) and during exercise (12, 45, 48). Indeed, exaggerated sympathetic vasconstrictor tone and blunted vasodilator responsiveness have been demonstrated in dynamically exercising skeletal muscle of older individuals (12, 13, 31, 45). Whether these peripheral vascular changes with age are manifest in the cerebral circulation and alter CA is currently unknown. In addition, the resultant exaggerated pressor response to exercise may present an additional challenge to the regulation of cerebral blood flow during physical activity in older individuals (9, 14, 15).

Although age-related alterations in the control of cerebral blood flow have not always been found under resting conditions (6, 7, 34, 54), several studies have observed impairments in cerebral vascular function at rest in older compared with younger subjects (17, 24). Moreover, Heckmann and colleagues (21) recently suggested that cerebral autoregulatory mechanisms demonstrated a delayed responsiveness to exercise in older subjects. These authors noted that cerebrovascular resistance increased more slowly in older compared with younger subjects in response to increases in cerebral blood flow at the onset of a short bout (3 min) of supine leg cycling. Although this is suggestive of an age-related impairment in cerebral vascular control, a potential caveat is that both young and older subjects performed exercise at similar absolute workloads. Considering that peak work rate and aerobic capacity typically decrease with age (15), it is plausible that the older subjects were exercising at a greater relative intensity. Because cerebral blood flow responses to exercise have been shown to be proportional to exercise intensity (40), this may explain the greater increase in cerebral blood flow at exercise onset in the older subjects. In addition, since exercise was performed for only 3 min, it is probable that these results were not representative of steady-state exercise conditions.

Given this background, the present study was designed to investigate middle cerebral artery blood velocity (MCAV), mean arterial pressure (MAP), and the cerebral vascular conductance index at rest and during low- and moderate-intensity steady-state cycling in healthy young and older middle-aged subjects. In addition, dynamic CA was assessed using transfer function analysis between changes in MAP and mean MCAV (MCAVmean) in the low-frequency range (4, 38–40). We tested the hypothesis that dynamic CA would be impaired in older subjects during dynamic exercise in association with greater increases in blood pressure compared with younger subjects.

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METHODOLOGY

Nine young and ten older middle-aged subjects were recruited from the University of Missouri community and the surrounding area (Table 1). Both young and older subjects were recreationally active, but importantly none were competitive athletes. All experimental procedures and protocols conformed to the Declaration of Helsinki and were approved by the University of Missouri-Columbia Health Sciences Institutional Review Board and the Research and Development Committee of the Harry S. Truman Memorial Veterans Hospital. Each subject gave written informed consent. Before participation each subject completed a medical health history questionnaire, and a blood chemistry screening was performed after a 12-h overnight fast. No subjects had a history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease, and none were using prescribed or over-the-counter medications. Although hormonal status of the women participants was not directly assessed, all older women were postmenopausal and not taking any hormone replacement, and young women performed the main steady-state exercise protocol (described below) around the early follicular phase of the menstrual cycle, in which plasma estrogen and progesterone concentrations are generally low (20). Subjects were requested to abstain from caffeinated beverages for 12 h and strenuous physical activity and alcohol for at least 24 h before experimental sessions. On experimental days, the subjects arrived at the laboratory a minimum of 2 h following a light meal. All subjects were familiarized with the equipment and procedures before any experimental sessions.

Experimental Measurements

Heart rate (HR) was continuously monitored using a lead II electrocardiogram (ECG; Q710, Quinton Instruments, Bothell, WA). Beat-to-beat blood pressure was measured using finger photoplethysmography (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) obtained from the middle finger of the left hand, which was supported at the level of the right atrium on an adjustable padded bedside table. In addition, brachial artery blood pressure was measured using an automated sphygmomanometer with toe clips (Angio V2, Lode, Groningen, The Netherlands). Subjects were instrumented with a 12-lead ECG, and blood pressure was measured with the aforementioned automated sphygmomanometer. Following a 3-min warm up period of cycling at 60 rpm, the workload was increased by 25 W every minute. Peak responses were determined at the power output where the subject could no longer maintain a pedal frequency of 60 rpm despite strong verbal encouragement. All subjects gave a maximal rating of perceived exertion (i.e., 19–20) at exhaustion.

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/Women, n/n</td>
<td>6/3</td>
<td>6/4</td>
</tr>
<tr>
<td>Age, yr</td>
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<tr>
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<td>Height, cm</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Cholesterol, mg/dl</td>
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<td>Triglycerides, mg/dl</td>
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<tr>
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<td>53±17</td>
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<td>Glucose, mg/dl</td>
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<td>102±12*</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>13±3</td>
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<td>Na⁺, meq/l</td>
<td>139±2</td>
<td>140±2</td>
</tr>
<tr>
<td>K⁺, meq/l</td>
<td>4.0±0.3</td>
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</tr>
</tbody>
</table>

Values are means ± SD. BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urea nitrogen. *Significantly different from young (P < 0.05).

Experimental Procedures

Incremental maximal exercise test. To exclude the possibility of any exercise-induced arrhythmias or blood pressure abnormalities, and to ascertain peak HR for the determination of steady-state workloads, all subjects performed a continuous incremental maximal exercise test. Subjects were seated in a semirecumbent position on a medical exam table equipped with an electrically braked cycle ergometer with toe clips (Angio V2, Lode, Groningen, The Netherlands). Subjects were instrumented with a 12-lead ECG, and blood pressure was measured with the aforementioned automated sphygmomanometer. Following a 3-min warm up period of cycling at 60 rpm, the workload was increased by 25 W every minute. Peak responses were determined at the power output where the subject could no longer maintain a pedal frequency of 60 rpm despite strong verbal encouragement. All subjects gave a maximal rating of perceived exertion (i.e., 19–20) at exhaustion.

Cerebral vascular responses to steady-state exercise. After 3–5 days from the incremental maximal exercise test, subjects returned to the laboratory to perform two bouts of cycling at steady-state HRs corresponding to 40% and 50% of HR reserve (HRR), representing low- and moderate-intensity exercise (1). Following instrumentation for the measurement of HR, arterial blood pressure, and cerebral blood flow velocity, subjects rested quietly for 15 min. For the assessment of PaCO₂, subjects then respired through a low-resistance mouthpiece (model 2700, Hans Rudolph, Kansas City, MO) attached to the metabolic measurement system for 3 min while a nose clip was worn to prevent nasal breathing. For each exercise bout, subjects maintained a pedal frequency of 60 rpm, and the workload was gradually increased until the target HR was achieved (~3–5 min), after which 15 min of steady-state cycling was performed. During the last 2 min of exercise, breath-by-breath samples were taken for the determination of PaCO₂. Before the cessation of exercise, subjects were asked to provide a rating of perceived exertion. Each exercise bout was separated by a minimum of 30 min to allow full recovery and the reestablishment of baseline HR and MAP. The order of the low- and moderate-intensity trials was randomized. Throughout the test, subjects were reminded to keep their upper limbs relaxed to aid blood pressure measurements, and their head facing forward to prevent movement artifacts in the transcranial Doppler signal.

Transfer Function Analysis for Dynamic CA

Five-minute steady-state data segments at rest and during low- and moderate-intensity cycling were used for transfer function analysis to identify indexes of dynamic CA. Beat-to-beat values of MAP and MCAV̇mean were obtained by integrating analog signals within each cardiac cycle, then linearly interpolated and resampled at 2 Hz for spectral analysis (38, 40, 41, 55, 56). For an estimate of dynamic CA using the transfer function, the cross-spectrum between changes in MAP and MCAV̇mean were calculated and divided by the autospectrum of MAP. Transfer function gain measurements reflect the relative amplitude relationship between changes in MAP and MCAV̇mean over a particular frequency range and were used to quantify the ability of the cerebral vascular bed to buffer changes in cerebral blood velocity induced by transient alterations in blood pressure (55, 56). Transfer
function phase measurements were used to determine the temporal relationship between changes in MAP and MCAVmean over a particular frequency range (55, 56).

From the temporal sequences, the frequency-domain transforms were computed with a fast Fourier transformation algorithm. The transfer function H(f) between the two signals was calculated as H(f) = Sxx(f)/Sxx(f), where Sxx(f) is the autospectrum of the input signal and Sxx(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 $[\text{Re}(H(f))]$ and imaginary $[\text{Im}(H(f))]$ components of the complex transfer function:

$$|H(f)| = \left[\text{Re}(H(f))^2 + \text{Im}(H(f))^2\right]^{1/2}$$

$$\Phi(f) = \tan^{-1}\left[\frac{\text{Im}(H(f))}{\text{Re}(H(f))}\right]$$

Additionally, the transfer function H(f) was normalized to the mean values of input ($x$) and output ($y$) variables as $H^*(f) = S_{xy}(f)/S_{xx}(f)y$, and the normalized gain was calculated as 20 log|$H^*(f)$| to express values in decibels.

The squared coherence function $[\text{MSC}(f)]$ was estimated as:

$$\text{MSC}(f) = \left[S_{yy}(f)/\left[S_{xx}(f)S_{yy}(f)\right]\right]$$

where $S_{xx}(f)$ is the autospectrum of MCAVmean. The squared coherence function reflects the fraction of output power that can be linearly related to the input power at each frequency. Similarly to a correlation coefficient, it varies between 0 and 1, with a coherence of >0.5 taken as suggestive of a stable relationship between two oscillations reflecting the statistical reliability of transfer function analysis between input and output.

Spectral power of MAP and MCAVmean, and transfer function gain, phase, and coherence were calculated in the very low (VLF; 0.02–0.07 Hz), low (LF; 0.07–0.20 Hz) and high (HF; 0.20–0.30 Hz) frequency ranges. The arterial blood pressure fluctuations in the HF range, such as those induced by respiration, are transferred to MCAVmean whereas arterial blood pressure fluctuations in the VLF and LF ranges are independent of the respiratory frequency and are dampened by autoregulatory mechanisms (11). Thus the dynamic buffering capacity of the cerebral vasculature is dependent on the frequency of the fluctuations in perfusion pressure. As such, we used the VLF and LF ranges of each variable to identify dynamic CA at rest and during exercise (27, 40, 41, 56).

**Statistical Analysis**

Statistical comparisons of physiological variables were made utilizing a repeated-measures two-way ANOVA. A Student-Newman-Keuls test was employed post hoc to investigate significant main effects and interactions of group (young vs. older) and condition (rest vs. low exercise vs. moderate exercise). Statistical significance was set at $P < 0.05$. Analyses were conducted using SigmaStat (Jandel Scientific Software, SPSS, Chicago, IL) for Windows.

**RESULTS**

**Subject Characteristics**

The mean age difference between young and older subjects was 33 yr. There were no significant age-group differences in body weight, body mass index, triglycerides, high-density lipoprotein (HDL), blood urea nitrogen, or electrolytes (Table 1). Total cholesterol, low-density lipoprotein (LDL), and glucose tended to be higher in the older subjects; however, values were not substantially greater than the upper limit for healthy individuals. All subjects had normal resting and maximal exercise ECGs, and, as expected, the peak HR response to the incremental exercise test was significantly higher in younger subjects (young 185 ± 3 beats/min vs. older 160 ± 4 beats/min; mean ± SE; $P < 0.05$).

**Steady-State Cardiovascular Measures**

All measurements were performed in the semirecumbent position. At rest there were no significant age-group differences in HR, systolic blood pressure (SBP), MAP, MCAVmean, CVCi, or $\text{PaCO}_2$ ($P > 0.05$); however, resting DBP was significantly higher in the older compared with younger subjects ($P < 0.01$; Table 2). During both low- and moderate-intensity steady-state leg cycling, the SBP and MAP responses were greater in older subjects ($P < 0.01$; Table 2 and Fig. 1A). Likewise, DBP was significantly greater in older individuals during exercise ($P < 0.01$). Overall, DBP remained the same or slightly increased in the older group during low- and moderate-intensity cycling, whereas it progressively decreased from rest in the younger group. Indeed, during moderate-intensity cycling, DBP was significantly lower than rest in the younger subjects ($P < 0.05$; Table 2). Pulse pressure was significantly increased during low- and moderate-intensity exercise, and no age-group differences were found (Table 2 and Fig. 1B). For the group, MCAVmean increased slightly but

<p>| Table 2. Steady-state physiological measurements at rest and during low- and moderate-intensity leg cycling in young and older subjects |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>MAP, mmHg</th>
<th>Pulse Pressure, mmHg</th>
<th>Heart Rate, beats/min</th>
<th>MCAVmean, cm/s</th>
<th>CVCi, cm·s⁻¹·mmHg⁻¹</th>
<th>$\text{PaCO}_2$, mmHg</th>
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<td></td>
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<tr>
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<td>92±2</td>
<td>67±5</td>
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<tr>
<td>Young</td>
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<td>99±2*†</td>
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<td>0.005</td>
<td>0.244</td>
<td>0.001</td>
<td>0.942</td>
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Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; MCAVmean, middle cerebral artery mean blood velocity; CVCi, cerebral vascular conductance index; $\text{PaCO}_2$, estimated arterial carbon dioxide tension; Ex, exercise. *Significantly different from young ($P < 0.05$). †Significantly different from rest ($P < 0.05$). ‡Significantly different from Low Ex ($P < 0.05$).
significantly during low- and moderate-intensity cycling ($P < 0.05$), but no differences were observed between older and younger subjects ($P > 0.05$; Table 2 and Fig. 1C). CVCi was not altered from rest in the young individuals during either low- or moderate-intensity cycling ($P > 0.05$). Similarly, no changes in CVCi were observed in the older individuals during low-intensity exercise. However, a significant reduction in CVCi was observed during moderate-intensity exercise in the older subjects ($P < 0.01$), leading to a significant age-group difference (Fig. 1D). No differences in $P_aCO_2$ were found between the young and older subjects; however, $P_aCO_2$ was slightly but significantly reduced from rest during moderate-intensity exercise ($P < 0.05$; Table 2). The RPE values obtained during low-intensity (young 9 ± 1 vs. older 9 ± 1; mean ± SE; $P > 0.05$) and moderate-intensity cycling (young 13 ± 1 vs. older 13 ± 1; $P > 0.05$) were similar in young and older subjects ($P > 0.05$).

Spectral Analysis and Transfer Function Analysis

No significant age-group differences were found in the VLF and LF $MCAV_{mean}$ power spectral density (PSD) at rest or during exercise ($P > 0.05$; Table 3). Similarly, VLF and LF MAP PSD were not different between young and older subjects. However, the VLF MAP PSD exhibited a condition effect with a significant difference between the low- and moderate-intensity exercise bouts (Table 3). The VLF and LF transfer function gain between MAP and $MCAV_{mean}$ were not significantly different between the young and older subjects ($P > 0.05$; Fig. 2). The LF transfer function gain decreased significantly during low- and moderate-intensity cycling ($P < 0.05$), but no differences were observed between older and younger subjects ($P > 0.05$; Table 2 and Fig. 1C). CVCi was not altered from rest in the young individuals during either low- or moderate-intensity cycling ($P > 0.05$). Similarly, no changes in CVCi were observed in the older individuals during low-intensity exercise. However, a significant reduction in CVCi was observed during moderate-intensity exercise in the older subjects ($P < 0.01$), leading to a significant age-group difference (Fig. 1D). No differences in $P_aCO_2$ were found between the young and older subjects; however, $P_aCO_2$ was slightly but significantly reduced from rest during moderate-intensity exercise ($P < 0.05$; Table 2). The RPE values obtained during low-intensity (young 9 ± 1 vs. older 9 ± 1; mean ± SE; $P > 0.05$) and moderate-intensity cycling (young 13 ± 1 vs. older 13 ± 1; $P > 0.05$) were similar in young and older subjects ($P > 0.05$).

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Spectral Analysis and Transfer Function Analysis

No significant age-group differences were found in the VLF and LF $MCAV_{mean}$ power spectral density (PSD) at rest or during exercise ($P > 0.05$; Table 3). Similarly, VLF and LF MAP PSD were not different between young and older subjects. However, the VLF MAP PSD exhibited a condition effect with a significant difference between the low- and moderate-intensity exercise bouts (Table 3). The VLF and LF transfer function gain between MAP and $MCAV_{mean}$ were not significantly different between the young and older subjects ($P > 0.05$; Fig. 2). The LF transfer function gain decreased significantly during low- and moderate-intensity cycling ($P < 0.05$), but no differences were observed between older and younger subjects ($P > 0.05$; Table 2 and Fig. 1C). CVCi was not altered from rest in the young individuals during either low- or moderate-intensity cycling ($P > 0.05$). Similarly, no changes in CVCi were observed in the older individuals during low-intensity exercise. However, a significant reduction in CVCi was observed during moderate-intensity exercise in the older subjects ($P < 0.01$), leading to a significant age-group difference (Fig. 1D). No differences in $P_aCO_2$ were found between the young and older subjects; however, $P_aCO_2$ was slightly but significantly reduced from rest during moderate-intensity exercise ($P < 0.05$; Table 2). The RPE values obtained during low-intensity (young 9 ± 1 vs. older 9 ± 1; mean ± SE; $P > 0.05$) and moderate-intensity cycling (young 13 ± 1 vs. older 13 ± 1; $P > 0.05$) were similar in young and older subjects ($P > 0.05$).
from rest during both low- and moderate-intensity cycling ($P < 0.05$), whereas the VLF transfer function gain was only different from rest during moderate exercise (Fig. 2). Overall, similar age-group and condition effects were found for the normalized VLF and LF transfer function gains (Table 3). An age-group difference was found in the VLF coherence between MAP and MCA$_V$mean with younger subjects exhibiting lower values under all conditions (Fig. 2). In contrast, the LF coherence was not different between young and older subjects at any time point studied ($P > 0.05$), but progressively decreased from rest to low-intensity ($P < 0.01$) and from low- to moderate-intensity exercise ($P < 0.05$; Fig. 2). However, LF coherence values remained above 0.5 under all conditions. The VLF and LF phase between MAP and MCA$_V$mean was not significantly different between the young and older subjects ($P > 0.05$) or between rest and exercise ($P > 0.05$; Fig. 2).

**DISCUSSION**

The present study is the first to examine the regulation of cerebral blood flow during steady-state dynamic exercise in healthy older middle-aged subjects. First, we found that despite greater increases in blood pressure during exercise in older individuals, no differences in MCA$_V$mean were observed between young and older subjects. Second, no significant age-group differences were found in the VLF or LF transfer function gain or phase between MAP and MCA$_V$mean during low- or moderate-intensity cycling, indicating that the ability of the cerebral vasculature to respond to spontaneous fluctuations in MAP (i.e., dynamic CA) was preserved with age during exercise. Collectively, these data suggest that the regulation of MCA$_V$mean is well maintained during dynamic exercise in healthy older middle-aged subjects.

Cerebral blood flow is influenced by neurogenic, neurohumoral, endothelial, as well as metabolic factors (26, 47, 50). As such, exercise presents a potential challenge to CA, not only due to the rapid and robust fluctuations in arterial blood pressure but also due to increases in sympathetic nerve activity, cardiac output, and cerebral metabolism (26, 47, 50). In the present study, we hypothesized that this may be particularly true in older individuals, considering previous reports of age-related alterations in peripheral circulatory control during exercise (12, 45). Indeed, aging-induced impairments in metabolic vasodilatation and exaggerated sympathetic vasoconstriction have been reported in the vasculature of dynamically exercising skeletal muscle and are believed to contribute to age-related reductions in exercising muscle blood flow (12, 13, 31, 45, 48). In addition, exaggerated pressor responses to exercise may present an additional challenge to the regulation of cerebral blood flow during physical activity in older individuals (9, 12, 14, 15). However, despite greater exercise-induced increases in blood pressure in the older subjects, our results indicate that during low- and moderate-intensity steady-state cycling, MCA$_V$mean responses were similar in young and older individuals. In this regard, the slight but significant
increases in MCAV_{mean} observed during steady-state cycling are in agreement with previous studies in young subjects and likely are requisite to meet the demands of exercise-induced increases in cerebral metabolism (10, 23, 30, 40, 41, 50, 53). Thus, in contrast to age-related impairments in peripheral blood flow, the regulation of cerebral blood flow appears to be well maintained during dynamic exercise with age.

Of note, we found that the cerebral vascular conductance index was significantly reduced in older subjects during the moderate-intensity cycling bout, suggesting that cerebral vasoconstriction occurred. Although the cause for this decrease in cerebral vascular conductance is unclear, we suggest that this response may be normal and necessary to offset the greater blood pressure response to exercise (ΔMAP from rest: young 9 ± 3 mmHg vs. older 23 ± 2 mmHg; \( P < 0.05 \)). In this regard, a comparison of the moderate-intensity cycling bout in the young to the low-intensity cycling bout in the older subjects, in which MAP responses to exercise were closely matched (ΔMAP from rest: young 9 ± 3 mmHg vs. older 10 ± 2 mmHg; \( P < 0.05 \)), indicates very similar cerebral vascular conductance responses (see Table 2). Thus we interpret the greater decrease in conductance in the older subjects during moderate exercise as a normal CA response. However, other factors cannot be completely discounted, including an enhanced activation of sympathetic outflow directed to the cerebral vasculature (8). At present, sympathetic neural control of the cerebral circulation is controversial; however, it is known that cerebral arteries are richly innervated with sympathetic nerve fibers (36, 37), and a direct effect of sympathetic activation on cerebral blood flow has been reported in several disease states (25, 29). Considering previous reports have suggested an exaggerated exercise-induced sympathoexcitation in older individuals (46, 52), it is plausible that an exaggerated sympathetically mediated cerebral vasoconstriction occurs in older individuals at moderate to high exercise intensities (8). In addition, although no age-group effect was found, the lower \( \text{PaCO}_2 \) during moderate-intensity exercise in older subjects may have contributed to the significant decrease in cerebral vascular conductance from rest. Further studies in this area are warranted.

Along with consideration of static CA, we also assessed dynamic measures of CA at rest and during exercise. Indeed, recent studies have emphasized the importance of evaluating dynamic CA using frequency-domain analysis in order to more fully examine the ability of the cerebral vasculature to rapidly respond to changes in perfusion pressure (18, 42, 55, 56). However, we found no significant age-group differences in either the VLF or LF transfer function gain between MAP and MCAV_{mean} during low- or moderate-intensity cycling. These data indicate that the ability of the cerebral vasculature to respond to spontaneous fluctuations in MAP was preserved in healthy older subjects during exercise. Thus similar to the static measurements made, no age-related alterations in dynamic CA was found. These findings are in agreement with previous studies reporting that dynamic CA was maintained in healthy older subjects at rest and during various laboratory stressors (6, 7, 34, 54). In contrast, the only other paper to examine aging effects on cerebral vascular responses during exercise indicated that cerebral autoregulatory mechanisms demonstrated a delayed responsiveness in older subjects (21). These authors found a delayed increase in cerebrovascular resistance in older individuals in response to increases in cerebral blood flow at the onset of a short bout (3 min) of supine leg cycling. The reason for the conflicting findings between these previous data and the present results is unclear; however, differences in exercise workloads between young and older subjects (absolute vs. relative) and time points studied (onset vs. steady state) likely contributed. In this regard, the findings of the present study indicate that compared with younger subjects exercising at the same relative intensities, the regulation of cerebral blood flow is well maintained during steady-state dynamic exercise in healthy older middle-aged subjects.

In the present study, in addition to the LF range between MAP and MCAV_{mean}, we also utilized the VLF range to more completely assess dynamic CA. Although the majority of studies have focused on the LF range (4, 27, 34, 40, 41), recent studies suggest that CA may be more active in the VLF range than in the LF range (32, 56). Thus we considered the possibility that changes in the VLF range may be important when moving from rest to exercise and possibly contribute to age-related changes in cerebral blood flow control. However, similar to the LF range, no age-group differences were found in the VLF gain or phase between MAP and MCAV_{mean}. Interestingly, the VLF and LF transfer function gains decreased from rest to exercise in both the young and older subjects. These findings are indicative of improved dynamic CA and suggest that during low- to moderate-intensity dynamic exercise, for any given change in blood pressure, smaller oscillations in MCAV_{mean} occur, an effect that appears unaltered with age. Although it remains to be determined if CA is more active in the VLF or in the LF range in humans, the relatively consistent responses between the VLF and LF ranges at rest and during exercise clearly indicate a preserved dynamic CA with aging.

It should be noted that the coherence values for the VLF range tended to be lower than those for the LF range, particularly in the younger subjects. Although these lower values are consistent with previous studies (27, 41, 54–56), the reason for this finding is unclear. Overall, the coherence analysis and interpretation should be considered. Coherence functions have primarily been used to indicate the strength of the linear relationship between MAP and MCAV_{mean} and validate the measurements of transfer function being made (4, 27, 34, 38, 40, 41, 54–56). Thus, when coherence is high (>0.5), MAP and MCAV_{mean} vary closely together and the transfer function gain can be used to evaluate the effectiveness of CA. Indeed, in the present study, LF coherence values remained above 0.5 under all conditions in both young and older subjects. However, other ideas have recently evolved with regard to the coherence function, particularly in the VLF range. It has been suggested that at these very low frequencies (<0.07 Hz) the fluctuations in MCAV_{mean} are more independent of changes in arterial pressure (low coherence) because the cerebral vasculature can effectively buffer such slow changes in blood pressure, and thus fluctuations in MCAV_{mean} can occur independently of blood pressure (27, 56). In fact, some researchers have proposed that a low coherence value is suggestive of an effective CA (27). However, the usage of the coherence in this way requires further validation, and therefore, as in previous studies (4, 27, 34, 38, 40, 41), we have relied on the LF transfer function gain as our primary index of dynamic CA.
Several potential limitations in the design and interpretation of the present investigation should be considered. First, it is realized that changes in MCAV\textsubscript{mean} are only proportional to changes in cerebral blood flow if middle cerebral artery diameter remains unchanged. Although we cannot completely rule out that changes in vessel diameter influenced the MCAV\textsubscript{mean} measurements, previous studies in humans directly measuring middle cerebral artery diameter have demonstrated that the diameter remains relatively constant under a variety of experimental conditions and to various stimuli (19, 49). Furthermore, during dynamic exercise it has been demonstrated that MCAV\textsubscript{mean} increases in parallel with the inflow of the ipsilateral internal carotid artery (22) and with cerebral blood flow determined using the "initial slope index" of the \textsuperscript{133}Xenon clearance method, which is considered to represent the average cerebral blood flow (30). Indeed, a recent review of the literature reported that the diameter of large cerebral arteries does not change significantly during exercise and that the regulation of cerebral blood flow takes place in the smaller arteries (50). Thus we would contend that the changes in MCAV\textsubscript{mean} reported in the present investigation likely reflect changes in cerebral blood flow (50).

Another potential limitation of the present study is the small sample size and the possibility that sex differences and in turn hormone status may have influenced our results as both men and women were included. Although the number of subjects is similar to previous studies that employed a within-between subject design to examine the influence of aging, we cannot completely discount the potential that differences may have been detected with a larger number of subjects (i.e., type II error). In addition, since all older women were postmenopausal and not taking any hormone replacement and young women completed the steady-state exercise protocol around the early follicular phase of the menstrual cycle in which plasma estrogen and progesterone concentrations are generally low (20), further studies are needed to examine the influence of sex hormones on CA in women.

The mean age of the older subjects in the present study (57 ± 7 yr) was more indicative of a middle-aged group. Although we did not observe any differences in CA, this age range is similar to that of previous investigations reporting age-related alterations in peripheral blood flow control as well as changes in cardiovascular responses to exercise (13–15, 17, 35, 51, 54). Thus we believe the results of the present study provide novel insight into the regulation of cerebral blood flow during dynamic exercise as one advances in age. However, we would caution readers in extrapolating our findings to subjects over 70 yr of age. In addition, the results of the present study are specific to steady-state dynamic exercise at low and moderate relative intensities, and thus the potential for age-related differences at higher exercise intensities or when comparing at absolute workloads cannot be dismissed. Nonetheless, the intensities studied were chosen because they are an integral part of the recommended exercise prescription for healthy older adults (16).

In summary, we found that despite greater increases in blood pressure during exercise in older individuals, no differences in MCAV\textsubscript{mean} were observed between young and older subjects. Furthermore, we observed no significant age-group differences in dynamic CA during low- or moderate-intensity steady-state dynamic exercise performed at an equivalent relative intensity in young and older individuals. Thus the ability of the cerebral vasculature to respond to spontaneous fluctuations in MAP was preserved with age during exercise. Collectively, these data suggest that the regulation of MCAV\textsubscript{mean} is well maintained during dynamic exercise in healthy older middle-aged subjects.

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GRANTS

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REFERENCES


