Assessment of Cerebrovascular Dynamics and Cognitive Function with Acute Aerobic Exercise in Persons with Multiple Sclerosis

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Background: Cognitive dysfunction in multiple sclerosis (MS) may partially stem from inadequate cerebral blood flow. Cerebral blood flow and cognitive function improve with aerobic exercise in healthy adults. The effect of aerobic exercise on cerebrovascular hemodynamics and cognitive performance in persons with MS is unclear. The acute effect of aerobic exercise versus quiet rest on cerebrovascular hemodynamics and cognitive performance in relapsing-remitting MS was examined.

Methods: Sixteen adults with relapsing-remitting MS underwent cerebrovascular hemodynamics and cognitive performance testing before, 2 minutes after, and 30 minutes after aerobic exercise (20-minute treadmill walking, 60% peak oxygen consumption) and a time-matched seated control. Brachial blood pressure was obtained via an oscillometric cuff. Right middle cerebral artery (MCA) blood velocity was measured via transcranial Doppler and used to calculate mean velocity, pulsatility index (PI), and conductance. Carotid artery stiffness was measured via ultrasonography and tonometry. Cognitive performance (accuracy, reaction time) was assessed using a modified flanker task.

Results: Exercise elicited significant increases in mean pressure and carotid artery stiffness and decreases in MCA conductance at 2 minutes after exercise, which subsided by 30 minutes ($P < .05$). Exercise did not significantly alter MCA PI. Flanker reaction time decreased during posttesting in both conditions ($P < .05$). There were no condition × time interactions for cognitive performance.

Conclusions: Persons with MS seem resilient to exercise-induced acute changes in MCA PI despite transient carotid stiffening, potentially via reductions in MCA conductance. These data suggest that changes in cognitive performance after acute aerobic exercise are not directly related to transient cerebrovascular responses in persons with MS. Int J MS Care. 2021;23:162-169.

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease affecting approximately 1 million adults in the United States and 2.5 million worldwide. It results in a heterogeneous array of outcomes that can compromise quality of life.$^1$ One of the most common and impactful results of MS is cognitive dysfunction, affecting nearly two-thirds of persons with MS.$^2$ Cognitive dysfunction typically manifests as impaired information processing speed, learning and memory, and/or executive function.$^{2,3}$ Although

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there may be multiple mechanisms contributing to cognitive dysfunction in MS, cerebrovascular dysfunction may play an underappreciated role in this setting. Reduced cerebral blood flow is associated with MS disease severity and progression. As such, cerebral hypoperfusion has been recognized as a contributor to the pathophysiology of MS and a potential mechanism underlying the cognitive dysfunction in this population. The brain is a high-flow organ that requires continuous, adequate blood flow, the disruption of which may impair cognitive function by 1) acutely reducing oxygen delivery to active neurons and 2) over time giving way to mitochondrial dysfunction and neuronal and white matter damage. Indeed, reduced resting cerebral blood flow and an inability to increase cerebral blood flow during times of neural activity are associated with cognitive dysfunction in MS. This suggests that altered cerebral blood flow may be a mechanism of cognitive dysfunction in MS that has direct effects (hypoperfusion and reduced blood flow to active neurons) and indirect effects (brain lesions, atrophy, and structural integrity) on cognition.

Cerebral blood flow is dependent on the elastic buffering function of the large extracranial arteries (such as the carotid). Stiffening of the large elastic extracranial arteries impairs their ability to damp pulsatile hemodynamics, increasing propagation of pulsatile energy into the fragile cerebrovascular and damaging brain structures. Brain health and cognitive function may be modulated in part by large extracranial arteries such as the carotid. Persons with MS may have increased arterial stiffness, thereby rendering them vulnerable to excessive pulsatility- and hypoperfusion-mediated cognitive dysfunction. Identifying approaches that simultaneously improve cerebral blood flow, de-stiffen the large extracranial arteries, and slow cognitive decline may have the potential to attenuate disability progression in MS.

Regular aerobic exercise is a pluripotent behavior for improving cerebral blood flow and extracranial artery stiffness, ultimately improving brain health and slowing cognitive decline. Aerobic exercise may thus be a promising means of directly and indirectly improving cognitive function in MS. Exercise acutely improves cognitive function and chronically improves function and slows rates of cognitive decline in adults without MS. Acute exercise increases cerebral blood flow, and cardiorespiratory fitness, a surrogate for aerobic exercise training, is cross-sectionally associated with improved arterial stiffness, cerebral blood flow, and cognitive function. These potential benefits suggest that exercise may be an ideal means to improve cognitive performance and manage cognitive dysfunction in patients with MS. Recent reviews acknowledge the potential of behavioral preventive measures such as exercise to protect the brain and cognitive function in MS. Data suggest that acute aerobic exercise acutely improves aspects of executive function in individuals with MS. Acute vascular and cognitive responses to a single bout of aerobic exercise seem to predict training responses in the general population. As such, examining the effects of acute exercise is a critical first step in determining the efficacy of using exercise as a therapeutic intervention in combating and rehabilitating cognitive dysfunction in persons with MS. An understanding of the acute effects of exercise on cerebrovascular and cognitive function in MS will help lay the framework for subsequent work in determining the potential role that therapeutic exercise interventions may have on brain health in MS.

The purpose of this study was to examine the effect of acute aerobic exercise on carotid artery stiffness, cerebrovascular hemodynamics, and cognitive performance in adults with MS. We hypothesized that cerebral blood flow would increase and offset transient increases in carotid stiffness and cerebral pulsatility and that cognitive performance would improve after a single bout of aerobic exercise.

Methods

Participants

Physically inactive adults with relapsing-remitting MS aged 30 to 55 years were recruited from the community for this study. Physical inactivity was assessed via self-report and was defined as less than 60 minutes of moderate-to-vigorous activity per week. All the participants had an Expanded Disability Status Scale score between 0 and 4, had not undergone medication changes during the previous 3 months (Table S1, which is published in the online version of this article at ijmsc.org), were relapse free for longer than 30 days before enrollment, and fulfilled the McDonald criteria for relapsing-remitting MS as confirmed by their physician. Exclusion criteria included progressive presentations of MS (determined by participants’ physicians); self-reported cardiovascular, metabolic, or other neurologic diseases; major depressive symptoms (assessed via the Hospital Anxiety and Depression Scale); pregnancy; and smoking. This study was approved by the University of Illinois at Chicago institutional review board and conformed to the standards outlined in the Declaration of Helsinki. All the participants provided written informed consent before study participation.

Study Design

This study involved three visits (about 7-10 days between individual visits) to examine the effects of acute aerobic exercise, compared with a control condition, on cerebrovascular hemodynamics and cognitive performance in individuals with MS. Participants were instructed to fast for more than 4 hours and to abstain from alcohol and exercise for 24 hours and from caffeine the morning of testing. Visit 1 included a
Symbol Digit Modalities Test task, cognitive task familiarization (V̇O₂peak). Experimental visits 2 and 3 included cerebrovascular and cognitive measures at baseline and immediately (2 minutes) and 30 minutes after a 20-minute bout of 1) acute aerobic exercise and 2) quiet, seated rest, in a randomized, counterbalanced order (Figure S1). Participants were block randomized to either the exercise or the quiet seated rest (ie, sham) condition using the randomization feature in Excel (Microsoft Corp) (blocks of 4). For the exercise trial, participants stood up, walked approximately 1.5 m to the treadmill, and underwent a 3- to 5-minute warm-up, followed by 20 minutes of walking at a heart rate that corresponded with 60% V̇O₂peak from the maximal exercise trial. Immediately after the end of the exercise bout, participants returned to the seated position for posttesting. For the control trial, participants remained in the seated position on completion of seated baseline testing for 20 minutes of seated rest. Conversation during each trial was limited and ceased within 5 minutes of each measurement.

Peak Oxygen Consumption
Participants underwent an incremental walking treadmill test. Walking speed was individualized based on participant walking ability. The test began at 0% grade at a self-selected pace and increased to a brisk walking pace, after which speed was kept constant while grade increased 2% every 2 minutes until volitional fatigue. The V̇O₂peak was assessed as the highest recorded 20-second epoch. Peak effort was defined as achieving three of the following: 1) an increase in V̇O₂ less than 200 mL/min despite an increase in workload, 2) respiratory exchange ratio of at least 1.1, 3) peak heart rate within 10 beats per minute of age-predicted maximum, and 4) peak rating of perceived exertion of at least 17 (Borg scale).

Measurements
Cerebrovascular and Hemodynamic
Cerebrovascular measurements were obtained with participants in a semirecumbent position. Heart rate was measured continuously via a three-lead electrocardiogram integrated into a continuous data acquisition platform (Biopac Systems). Whereas cerebral blood velocity and heart rate were monitored continuously, the remaining hemodynamic measurements were obtained in the following order: brachial blood pressure, carotid artery stiffness, carotid blood pressure.

Cerebral Blood Velocity
Cerebral blood velocity was measured in the right middle cerebral artery (MCA) using a 2-MHz transcranial Doppler probe (TOCM Neurovision, Multigon Industries Inc) secured with a headset to the temporal window. The MCA blood velocities were recorded at 500 kHz using a data acquisition system (Biopac Systems) and stored offline for subsequent analyses. Baseline MCA blood velocities were calculated by averaging 5 minutes of data after the initial 15-minute rest/instrumentation period. Postmeasurements were calculated by averaging minutes 2 to 4 and minutes 30 to 32 after the exercise/control condition. The MCA pulsatility index (PI) and conductance were calculated as (systolic – diastolic)/mean velocity and mean velocity/brachial mean pressure, respectively. End-tidal carbon dioxide (CO₂) was measured simultaneously using a fitted mask (Hans Rudolph Inc) and a gas analyzer (CO2100C, Biopac Systems) to account for the effects of CO₂ on cerebral hemodynamics. End-tidal CO₂ was integrated into the data acquisition system and averaged at the same intervals as cerebral blood velocity.

Brachial Blood Pressure
Brachial blood pressure was measured using an automated oscillometric cuff (Omron Healthcare). Pressures were obtained in duplicate and averaged at baseline, with a third measurement obtained if values differed by more than 5 mm Hg. A single blood pressure measurement was obtained immediately after the cerebral blood velocity measurement period for both 2 and 30 minutes post. Mean pressure was calculated as one-third systolic + two-thirds diastolic pressure.

Carotid Artery Stiffness and Pressure
The right common carotid artery was imaged longitudinally 1 to 2 cm upstream of the bifurcation using a 7.5- to 13-MHz linear array probe (ProSound α7, Aloka). The distance from the near to far wall lumen-intima interface was continuously traced using eTracking to generate a distension waveform.56 Carotid stiffness indices were calculated by calibrating the distension waveforms with ipsilateral carotid systolic and diastolic pressures obtained via applanation tonometry (AtCor Medical) immediately after ultrasound imaging. Carotid pressure waveforms were ensemble averaged from a 10-second epoch and calibrated to brachial mean and diastolic pressures. Regional β-stiffness index and Young’s elastic modulus (Ep) were calculated as $\beta = \ln(P_{Max}/P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$ and $Ep = (P_{Max} - P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$, where $P$ and $D$ correspond to carotid pressure and diameter, respectively, and maximum (systolic) and minimum (diastolic) values during the cardiac cycle. Carotid stiffness and pressure were obtained in duplicate and averaged for each time point.

Cognitive Performance
A modified flanker task was used to interrogate processing speed, executive function, and attention/inhibitory control. This task has been used in previous acute exercise studies on cognitive performance in MS and has been described previously in detail.32,33 All the participants were familiarized with the task on visit 1 to minimize practice effects. Familiarization included an explanation, a 20-item practice to ensure greater than 50% correct, and a full (200 stimuli) task practice. Participants were instructed to identify the direction (left vs right) of the central target arrow using the keyboard while ignoring the flanking arrows. The task lasted approximately 5 minutes and included 100 congruent (ie, <<<<<) and 100 incongruent (ie, >>>>>) stimuli presented in white (3-cm tall) on a black background. Reaction time was computed as the time from stimulus display onset to participant/button response in milliseconds and coded based on the type of stimulus (ie, incongruent or congruent). Interference was calculated as mean incongruent – mean congruent reaction time. Accuracy was calculated as number of hits/total number of attempted trials. Participants did not receive biofeedback during cognitive testing procedures.

Statistical Analyses
All the data are reported as mean ± SD, and statistical significance was established a priori as $P < .05$. Data normality was assessed using the Shapiro-Wilk test. Nonnormally distributed data were natural-log transformed to meet normality assumptions but are reported as raw data for interpretation. We examined the effect of exercise on cerebrovascular
hemodynamics and cognitive function using a two-way condition (exercise vs seated-control) × time (baseline, 2 minutes post, 30 minutes post) repeated-measures analysis of variance. Significant time main effects and interactions were further explored using Bonferroni-corrected post hoc tests. Data that violated sphericity assumptions in the repeated-measures analysis of variance (heart rate, time, and interaction; MCA variables, time) were interpreted with Greenhouse-Geisser–adjusted $P$ values. All flancker hit rates and flancker interference data were nonnormally distributed, even when logarithmically transformed, and were, therefore, analyzed using 1) Wilcoxon signed rank tests to determine condition effects (control vs exercise) and condition × time interactions (change in accuracy post-pre) and 2) Friedman tests to determine time effects (pre-exercise vs postexercise measures). Nonparametric analyses were corrected for multiple comparisons using a Bonferroni correction factor because these analyses could not be run simultaneously.

Results

Sixteen adults with relapsing-remitting MS (12 women) participated in this study. Table 1 shows their descriptive characteristics.

### Acute Exercise Bout

Mean ± SD walking speed during the acute exercise bout was 2.6 ± 0.7 (range, 1.5-3.7) mph. Mean ± SD heart rate achieved during exercise was 111 ± 15 (range, 85-140) beats per minute.

### Cerebrovascular Hemodynamics

Condition × time interactions were detected for brachial systolic pressure ($F_{2,30} = 8.87, P = .011$) and mean pressure ($F_{2,30} = 4.84, P = .002$), carotid systolic pressure ($F_{2,30} = 5.26, P = .011$), and heart rate ($F_{1,3,17.6} = 10.08, P = .003$) (Table 2). Brachial mean pressure increased gradually by 30 minutes post during the control condition, while mean pressure increased from baseline to 2 minutes post in the exercise condition and was greater than the control condition at 2 minutes post ($P < .05$). Similar observations were made for brachial and carotid systolic pressure. Brachial and carotid systolic pressure and mean pressure values were not different from baseline at 30 minutes after exercise. Heart rate during the exercise condition increased from baseline to 2 minutes post, was higher than control at 2 minutes post, and recovered to baseline levels by the 30 minutes after the measurement period ($P < .05$). Brachial diastolic pressure increased from baseline to 30 minutes post in both conditions (time effect: $F_{2,30} = 5.27, P = .011$). No main effects were detected for end-tidal CO$_2$.

Condition × time interactions were detected for carotid diameters (systolic: $F_{2,30} = 8.73, P = .001$; diastolic: $F_{2,30} = 7.16, P = .003$) and stiffness (β-stiffness: $F_{2,30} = 9.19, P = .001$; Ep: $F_{2,30} = 12.08, P < .001$) (Figure S2B and Table 2). Carotid systolic diameter decreased at both 2 and 30 minutes after exercise and was smaller than the control condition at 2 minutes post ($P < .05$). Carotid β-stiffness and Ep increased from baseline to 2 minutes after exercise and were greater than the control condition, with β-stiffness remaining elevated compared with baseline at 30 minutes after exercise ($P < .05$).

A condition × time interaction was observed for MCA conductance ($F_{2,30} = 5.11, P = .012$). The MCA conductance decreased from baseline to 2 minutes after exercise and was different from the control condition ($P < .05$). The MCA PI increased (time effect: $F_{1,4,21.3} = 4.2, P = .04$) and mean velocity (time effect: $F_{1,4,20.6} = 3.92, P = .05$) and diastolic velocity (time effect: $F_{1,4,20.4} = 3.94, P = .05$) decreased at 30 minutes post compared with 2 minutes post in both conditions (Figure S2C and D). No significant main effects were detected for MCA systolic velocity.

### Cognitive Performance

No condition × time interactions were detected. Congruent reaction time in both conditions decreased from baseline to both postmeasurement periods (time effect: $F_{2,30} = 22.05, P < .001$), whereas incongruent reaction time only decreased from baseline to 2 minutes post (time effect: $F_{2,30} = 6.52, P = .004$) (Table 2). No significant main effects were detected for interference reaction time or flancker congruent or incongruent hit rates.

### Discussion

This study sought to examine the effects of acute aerobic exercise on cerebrovascular hemodynamics and cognitive function in individuals with MS. The present data suggest that in individuals with relapsing-remitting MS, acute exercise results in 1) increases in carotid artery...
### Table 2. Hemodynamics and cognitive performance at rest and after control and exercise conditions

| Variable                          | Control condition | Exercise condition | P value (effect size, $\eta^2$) |
|-----------------------------------|-------------------|--------------------|---------------------------------|
|                                   | Baseline          | 2 min post         | 30 min post                     | Condition effect | Time effect | C×T    |
| **Systemic**                      |                   |                    |                                 |                 |             |        |
| SP, mm Hg                         | 115 ± 13          | 116 ± 15           | 118 ± 16<sup>a</sup>           | .08 (0.19)      | <.01 (0.03) | <.01 (0.37) |
| DP, mm Hg                         | 69 ± 11           | 71 ± 11            | 73 ± 12                         | .91 (0.01)      | .01 (0.26)<sup>d</sup> | .13 (0.13) |
| Mean pressure, mm Hg              | 84 ± 11           | 86 ± 12            | 88 ± 13<sup>d</sup>            | .32 (0.07)      | <.01 (0.34) | .02 (0.24) |
| Heart rate, beats per min         | 64 ± 9            | 64 ± 10            | 63 ± 8                          | .08 (0.19)      | <.01 (0.03) | <.01 (0.37) |
| PET-CO$_2$, %                     | 4.24 ± 0.42       | 4.13 ± 0.61        | 3.96 ± 0.69                     | .77 (0.01)      | .15 (0.13)  | .52 (0.05) |
| **Carotid**                       |                   |                    |                                 |                 |             |        |
| SP, mm Hg                         | 106 ± 13          | 107 ± 15           | 110 ± 16<sup>a</sup>           | .09 (0.18)      | .06 (0.17)  | .01 (0.26) |
| Systolic diameter, mm             | 6.86 ± 0.61       | 6.94 ± 0.66        | 6.91 ± 0.72                     | .27 (0.08)      | .16 (0.12)  | <.01 (0.37) |
| Diastolic diameter, mm            | 6.39 ± 0.57       | 6.48 ± 0.61        | 6.45 ± 0.67                     | .56 (0.02)      | .50 (0.04)  | <.01 (0.32) |
| Ep, kPa                            | 68.6 ± 16.6       | 67.5 ± 18.3        | 68.9 ± 18.3                     | .02 (0.30)      | .03 (0.21)  | <.01 (0.45) |
| **Middle cerebral**               |                   |                    |                                 |                 |             |        |
| Systolic velocity, cm/s           | 92 ± 15           | 91 ± 14            | 91 ± 15                         | .43 (0.04)      | .33 (0.07)  | .67 (0.03) |
| Diastolic velocity, cm/s          | 38 ± 10           | 37 ± 9             | 38 ± 9                          | .10 (0.17)      | .05 (0.21)<sup>bd</sup> | .37 (0.06) |
| Vm/MP, cm/s per mm Hg             | 0.70 ± 0.12       | 0.68 ± 0.12        | 0.69 ± 0.12                     | .06 (0.21)      | .01 (0.32)  | .01 (0.25) |
| **Congruent flanker**             |                   |                    |                                 |                 |             |        |
| Reaction time, ms                 | 572 ± 72          | 544 ± 65           | 550 ± 79                        | .94 (0.01)      | <.01 (0.59)<sup>bd</sup> | .63 (0.03) |
| Accuracy, %<sup>e</sup>           | 93.8 ± 8.0        | 95.7 ± 5.6         | 95.3 ± 4.2                      | .03             | .34         | .42     |
| **Incongruent flanker**           |                   |                    |                                 |                 |             |        |
| Reaction time, ms                 | 616 ± 77          | 580 ± 76           | 612 ± 93                        | .42 (0.04)      | <.01 (0.30)<sup>e</sup> | .17 (0.11) |
| Accuracy, %<sup>e</sup>           | 75.6 ± 28.8       | 77.3 ± 29.2        | 77.6 ± 29.3                     | .52             | .35         | .75     |
| **Flanker interference**          |                   |                    |                                 |                 |             |        |
| Reaction time, ms                 | 43 ± 64           | 35 ± 59            | 62 ± 47                         | .19             | .16         | .43     |

Note: Data are given as mean ± SD unless otherwise indicated.

Abbreviations: C×T, condition × time effect; DP, diastolic pressure; Ep, elastic modulus; PET-CO$_2$, partial pressure of end-tidal carbon dioxide; SP, systolic pressure; Vm/MP, mean velocity/mean pressure (conductance).

<sup>a</sup>P < .05, 2 minutes post versus 30 minutes post.
<sup>b</sup>P < .05, baseline versus 2 minutes post.
<sup>c</sup>P < .05, exercise versus control.
<sup>d</sup>P < .05, baseline versus 30 minutes post.
<sup>e</sup>Nonparametric analyses, effect size $\eta^2$ not calculated.
stiffness, 2) reductions in conductance and unaltered pulsatility and mean velocity in the MCA, and 3) no differential effects on cognitive performance compared with the control condition. Taken together, transient increases in arterial stiffness immediately after an acute bout of aerobic exercise do not seem to acutely alter cerebral hemodynamic pulsatility or executive function in adults with MS.

Individuals with MS experienced transient increases in carotid artery stiffness immediately after acute exercise that returned to baseline levels by 30 minutes after exercise. This is in-line with a growing body of literature indicating that acute aerobic exercise elicits complex effects on arterial stiffness that vary by arterial segment (central vs peripheral) and timing after exercise. Markers of central artery stiffness (such as the carotid) may not be as sensitive as peripheral artery stiffness to the acute effects of aerobic exercise, and artery stiffness seems to increase immediately after aerobic exercise before returning to baseline values in individuals without MS. This acute change in large artery stiffness may be partially modulated by acute changes in mean pressure and heart rate, both of which were elevated immediately after exercise compared with the control condition. As such, individuals with MS seem to exhibit similar acute increases in carotid artery stiffness and blood pressure after aerobic exercise as adults without MS.

Increases in carotid artery stiffness would be expected to impair its ability to reduce transmission of pulsatile energy into the brain. We noted a time effect for MCA PI, with delayed reductions at 30 minutes compared with 2 minutes. This effect seems to be largely driven by a modest increase in MCA pulsatility at 2 minutes after exercise, although this did not reach statistical significance. Although MCA pulsatility increased by approximately 8% immediately after exercise, the average value (~1.04) was lower than those seen in other populations vulnerable to cognitive impairment (hypertension, ~1.20). Thus, despite increases in carotid artery stiffness, the absolute effects on MCA pulsatility in individuals with MS were modest and not significant. One possibility is that increases in hemodynamic pulsatility transmitted through a stiffened carotid artery may be adequately buffered by compensatory shifts in cerebrospinal fluid, venous outflow, or the lymphatics/glymphatics system, as described by the Monro-Kellie doctrine. Although further work is necessary to identify the exact mechanism, these data suggest that individuals with MS exhibit some level of cerebrovascular “resilience” against transient increases in cerebral pulsatile transmission in acute exercise settings.

Conductance of the MCA decreased immediately after exercise compared with the control condition. This reduction in conductance may reflect intact cerebral autoregulation, whereby intracranial and extracranial (ie, carotid) vasoconstriction prevents excessive pressure-driven increases in cerebral blood flow that would be expected to occur in the absence of any autoregulatory change in diameter. Indeed, we observed no substantial increases in MCA mean velocity (a proxy of blood flow) after exercise. Reductions in MCA conductance via cerebral vasoconstriction may contribute to modest increases in MCA pulsatility at 2 minutes after exercise, particularly combined with elevated heart rate. In contrast, postexercise cerebrovascular vasoconstriction may also help attenuate the transmission of pulsatile hemodynamics downstream by increasing pressure from wave reflections that damp pulsatile blood velocity. Thus, reductions in conductance may be one mechanism responsible for protecting the brain from excessive hemodynamic pulsatility after acute exercise in individuals with MS; however, further cerebrovascular studies are necessary to confirm this hypothesis.

Contrary to the present hypothesis, changes in flanker accuracy were similar between the exercise and control conditions. Moreover, the cost of interfering stimuli on executive control (interference reaction time) was unaltered after exercise. Thus, cognitive performance does not seem to be affected by transient increases in carotid artery stiffness after exercise, perhaps owing to intact cerebral defenses against excessive pulsatility in individuals with MS. This is similar to healthy young adults, in whom increases in pulsatile pressure and artery stiffness after acute resistance exercise do not detrimentally affect cognitive performance. It is possible that negative effects of acute increases in pulsatility on cognitive function are evident only among aged individuals who exhibit age-related impairments in cerebrovascular defenses against pulsatility. Individuals with MS seem to exhibit similar resiliency as healthy adults without MS against the potential negative effects of acute increases in artery stiffness and cerebral pulsatility on cognitive performance.

We noted reductions in reaction time in both the exercise and control conditions, suggesting that the exercise stimulus did not have a significant effect on reaction time despite the statistically powerful within-subject repeated-measures design. Reductions in reaction time in both conditions may be indicative of a practice effect inherent in within-day testing designs that attenuated the ability to identify the direct effects of exercise on reaction time. These practice effects would likely have equal effects in both trials given the randomized,
counterbalanced order. Thus, the lack of a direct exercise effect on reaction time suggests that the exercise stimulus may not have been sufficient to elicit beneficial changes. Longer duration, greater intensity, or different exercise modalities could have a more favorable effect on the brain; however, recent data suggest that the 20-minute bout of aerobic exercise used herein has been proved to be effective in MS previously.\textsuperscript{32,33} Discrepancies with the present findings may reflect differences in task familiarization procedures or baseline cognitive function in this sample of individuals with MS. The participants had lower mean ± SD Symbol Digit Modalities Test scores (51 ± 15) compared with previous work by Sandroff et al (63 ± 10 and 60 ± 8).\textsuperscript{32,33} Future work is necessary to examine the potential modifying effect of baseline characteristics and cognitive function on acute exercise responses.

We sought to examine whether exercise-induced changes in arterial stiffness and cerebral blood flow might contribute to the transient improvements in cognitive function often reported for approximately 30 minutes after exercise.\textsuperscript{23} This study did not include a control group, and we are unable to directly compare the responses observed herein with a sample of adults without MS. Using the available literature, however, the observations suggest that the acute cerebrovascular responses to aerobic exercise in individuals with MS are largely similar to observations in middle-aged adults.\textsuperscript{47} Thus, individuals with MS do not seem to have abnormal cerebrovascular responses to exercise, although further research with direct comparison within the study design is necessary. Regarding cognitive function, some data indicate that individuals with MS exhibit beneficial effects of acute exercise\textsuperscript{32,33} on cognitive function, similar to observations in healthy adults.\textsuperscript{33} The present data did not show a significant effect of exercise on executive function in adults with MS. Based on the effects observed herein, whereas only 18 participants would be necessary to detect interaction effects for cerebral hemodynamics (MCA PI and mean velocity), samples ranging from approximately 55 to more than 200 participants would be necessary to detect interaction effects for executive function after exercise (approximate required numbers for 0.80 power: reaction time, ~55; accuracy, ~86 to >200; interference, 56 to >200). As such, the exercise bout used in this study did not seem to elicit robust changes in cognitive function despite success in previous literature.\textsuperscript{32,33} Future studies should investigate 1) exercise bouts of greater intensity or longer duration to identify the optimal dose of exercise to modulate cognitive function in this population and 2) whether upper/lower body motor dexterity mediates the effect of acute exercise on cognitive function in individuals with MS.

Herein, cerebrovascular hemodynamics were assessed in the seated position, which may contribute to slightly longer carotid stiffness values\textsuperscript{52} compared with the supine position used in most studies. This may alter the mean values but does not influence our ability to detect the effect of exercise compared with a time control on carotid stiffness. This study assessed individuals with relapsing-remitting MS who still had adequate mobility to facilitate exercise. Results may differ in progressive MS or those in the later stages of disease progression. Participants were tested in the medicated state owing to 1) safety concerns with abstaining from MS-related medications and 2) this representing the most ecologically valid approach to document the effects of aerobic exercise on cerebrovascular and cognitive function. Future studies should investigate the effects of acute exercise and exercise training on improving cardiac function in relation to cognitive function because the aging brain becomes more reliant on cardiac output\textsuperscript{55} and this dependence may have greater consequence in individuals with MS.\textsuperscript{54}

Compared with a control condition, acute aerobic exercise elicited transient increases in blood pressure and carotid artery stiffness and decreases in MCA conductance in individuals with MS. The decrease in MCA conductance may have prevented penetration of pulsatile hemodynamics because MCA pulsatility did not statistically significantly increase after exercise. Exercise had similar effects on cognitive performance compared with the control condition, and processing speed increased after both conditions. There is promising evidence that exercise can play an important role in slowing cognitive decline in individuals with MS, but further work is necessary to identify the role of changes in cerebrovascular hemodynamics in mediating these effects.

**PRACTICE POINTS**

- Acute increases in blood pressure and carotid artery stiffness and decreases in cerebral conductance do not alter executive function after acute aerobic exercise in adults with MS.
- Further research is necessary to fully understand the effects and implications of exercise on brain health in MS.

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References

1. Chen AY, Chongsawat AO, Leadholm KL. Multiple sclerosis: frequency, cost, and economic burden in the United States. J Clin Neurosci. 2017;45:180-186.

2. Niki K, Sugawara M, Chang D, et al. A new noninvasive measurement of cerebral blood flow contributes to cognitive aging (from the Framingham Heart Study). J Appl Physiol. 2012;112:297-324.

3. Sandroff BM, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

4. Sandroff BM, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

5. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

6. Tarumi T, Gonzales MM, Fallow B, et al. Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. J Hypertens. 2013;31:2400-2409.

7. Sandroff BM, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

8. Jefferys WR, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

9. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

10. 足袋を履いてのリラクゼーション：効果についての検討．Nihon Kagaku Shikkan Gakkai Zasshi. 2018;56:153-160.

11. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

12. Sandroff BM, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

13. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

14. Sandroff BM, DeBlois JP, Schuff N, et al. Arterial stiffness: insights from Framingham and Iceland. Eur J Vasc Endovasc Surg. 2018;56:153-160.

15. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

16. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.

17. McCombe TD, Craner DE, Sage MD, et al. Impact of a single bout of aerobic exercise on regional brain perfusion and reaction time performance in healthy young adults. PLoS One. 2014;9:e85163.