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# The effects of a 7-day water aerobics exercise intervention on the cerebral hyperemic response to a cognitive task in individuals with Multiple Sclerosis

*Manuscript Type: Original Research*

Brandon S. Pollock[1], Jennifer Petersen[2], Dayana Calvo[2], Hayden Gerhart[3], Keith Burns[1], John McDaniel[2], Mary B. Spitznagel[2], Angela L. Ridgel[2]

[1]*Walsh University, North Canton, OH*
[2]*Kent State University, Kent, OH*
[3]*Indiana University of Pennsylvania, Indiana PA*

**Introduction**: Widespread cerebral hypometabolism occurs in multiple sclerosis (MS) which can result in cognitive dysfunction. The purpose of this study was to determine the effects of a 7-day water aerobics exercise intervention on the cerebral hyperemic response to a cognitive task in individuals with MS.
**Methods**: Thirty-one individuals diagnosed with MS were assigned to an exercise group (N = 17) or a control group (N = 14). For 7 days, the control group maintained normal activity, while the exercise group participated in water aerobic exercise. Oxygenated hemoglobin ($O_2Hb$) was measured using near-infrared spectroscopy at rest and during a cognitive task prior to and after the 7 day period.
**Results**: For the exercise group, there was no significant difference between $O_2Hb$ from rest to cognition at pre-testing ($t(16) = -1.91$, $p = 0.07$), however $O_2Hb$ significantly increased from rest during cognition at post-testing ($t(16) = -2.30$, $p = 0.04$). For the control group, $O_2Hb$ significantly increased from rest during cognition at pre-testing ($t(13) = -2.51$, $p = 0.03$), but did not at post-testing ($t(13) = -1.6$, $p = 0.13$).
**Conclusions**: Water aerobics exercise could be a useful therapy for improving the cerebral perfusion in individuals with MS.

***Key Words***: Multiple Sclerosis, Cognition, Perfusion, Exercise

Corresponding author: Brandon Pollock, bpollock@walsh.edu

## Introduction

Cerebral blood flow and perfusion are often impaired in individuals with multiple sclerosis (MS)[1-3]. Cerebral hypoperfusion in MS is associated with cognitive dysfunction, lesion formation, axon degeneration, and fatigue[4]. Therefore, restoring cerebral blood flow and oxygen metabolism may offer a therapeutic target for those with MS. In addition to the well-known health benefits of exercise, considerable evidence indicates that exercise improves many symptoms of MS[5-10]. Furthermore, greater physical activity in individuals with MS is related to increased energy, social functioning, mental and physical health[11]. Exercise increases cerebral blood flow and oxygen metabolism[12], and has also been suggested to have a prophylactic influence on cerebral impairments occurring in MS[13]. For example, exercise has been shown to demonstrate moderate-to-large increases in prefrontal cortex oxygenated hemoglobin ($O_2Hb$), deoxygenated hemoglobin (HHb), and total hemoglobin (tHb)[12]. Higher levels of fitness have also been associated with preserved gray matter volume in individuals with MS[13].

However, many individuals with MS experience exercise related thermoregulatory disturbances and are sensitive to increases in body temperature[14]. This heat sensitivity is a result of nerve demyelination, a consequence of the disease, and it is highly correlated with fatigue, pain, and decreased concentration[15]. Because heat conductance occurs 25 times faster in the water than in the air, individuals with MS tolerate water aerobics exercise with a lower occurrence of adverse effects[16,17]. However, no studies have yet determined the effects of water aerobic exercise on the cerebral hyperemic response to a cognitive task in individuals with MS. Therefore, the purpose of this study was to determine the effects of a 7-day water aerobics exercise intervention on the cerebral hyperemic response to a cognitive function test in individuals with MS. It was hypothesized that the cerebral hyperemic response to a cognitive function test would improve in individuals with MS following 7 consecutive days of water aerobics exercise.

## Methods

### *Participants*

Thirty-one individuals diagnosed with MS were recruited. Inclusion criteria included neurologist diagnosis of MS, English-speaking, with age over 18 years. Exclusion criteria included current MS symptom exacerbation, females who were pregnant or trying to get pregnant, history of non-MS related neurological disorder or injury, past or current history of severe psychiatric illness, alcohol or drug abuse, learning disorder or developmental disability, or sensory function precluding cognitive testing.

### *Protocol*

All procedures were approved by the Institutional Review Board of Kent State University and participants provided written consent. Physician confirmation of diagnosis and approval for exercise was obtained for all participants. First, participants visited the laboratory where they completed the Multiple Sclerosis Functional Composite (MSFC) to determine their level of disability. In brief, the MSFC contains a test of walking speed, arm dexterity, and cognitive function, and is expressed as a single score on a continuous scale[18]. Participants were then quasi-randomly assigned to either an exercise group (N = 17) or non-exercise group (N = 14), and familiarized with the N-back test (1-Back, 2-Back, Brain Workshop version 4.8.4)[19]. Participants rested in the seated position for 8 minutes while study investigators continuously measured cerebral hyperemia using near-infrared spectroscopy (NIRS, specifications listed below). Oxygenated hemoglobin, HHb, and tHb were averaged over the last minute of rest to calculate resting $O_2Hb$, HHb, and tHb. Following baseline assessment, participants performed the N-back. With regards to the intervention, the exercise group performed 7 consecutive days of hour-long aquatic exercise under the supervision of a certified exercise physiologist and certified water aerobics instructor, while those assigned to non-exercise maintained their current lifestyle. Both groups returned to the laboratory for post-testing within 48 hours following these 7 days.

### *NIRS Measurements*

Near-infrared spectroscopy (OxymonMkIII, Artinis Medical Systems, Netherlands) was used to measure concentration changes of oxygenated hemoglobin ($O_2Hb$), deoxygenated hemoglobin (HHb) and total hemoglobin (tHb). The NIRS probe was placed on the midline of the right pre-frontal cortex of participants, 1 cm above the supraorbital ridge[20], and an ACE bandage was wrapped around the participant's forehead as well as the NIRS probe to block ambient light. Data were acquired at a sampling frequency of 10 Hz and for analysis down sampled to obtain 1 data point every 5 seconds. During data collection $O_2Hb$, HHb, and tHb concentration changes were displayed in real time.

*N-back Test*

The N-back test was used as a tool for stimulating cerebral hyperemia (1-Back and 2-Back, Brain Workshop version 4.8.4)[19]. Participants first performed the 1-back, then the 2-back, each lasting approximately 3 minutes. The average $O_2Hb$, HHb, and tHb throughout the last minute of the 1-back were averaged with the average $O_2Hb$, HHb, and tHb throughout the last minute of the 2-back, respectively, to calculate $O_2Hb$, HHb, and tHb during cognition. The N-back was used as a cerebral hyperemic stimulus for the purposes of this study, therefore test performance scores were not recorded.

*Exercise Protocol*

Water aerobics exercise took place between 8:00-9:00 AM at the university recreation center. The water temperature of the pool was 84º. Exercise began with a 5 minute warm-up consisting of walking and stretching in the water. The warm up was followed by 40 minutes of water aerobics exercise, consisting of eight 4 minute intervals, with each interval separated by a 1 minute rest period. Intervals 1 and 5 focused on upper body strength training using the resistance of the water to complete shoulder lateral raises, chest flyes, bicep curls, and triceps extensions. Intervals 2, 4, 6, and 8 consisted of structured walking at different speeds (up to jogging) with intermittent changes in direction. Intervals 3 and 7 concentrated on lower body movements, such as hip abduction and adduction and hip flexion and extension, as well as some slightly more complex movements to mimic speed skating, making a figure 8 and performing jumping jacks. Exercise concluded with a 5 minute cool-down consisting of walking and stretching in the water.

*Statistical Analysis*

A one-way ANOVA was used to compare differences between age, education, duration of disease, and level of disability between the control and exercise groups. For both groups, paired samples t-tests were used to determine significant differences between $O_2Hb$, HHb and tHb from rest to cognition before and after the intervention (IBM SPSS Statistics 24). Statistical significance was set at $p \leq 0.05$.

## Results

*Participant Demographics*

Thirty-one individuals diagnosed with MS completed the study. Seventeen individuals were allocated to the exercise group, and fourteen to the non-exercise group. A one-way ANOVA revealed no significant differences in age ($F(1,29) = 0.002$, $p = 0.97$) education ($F(1,29) = 2.08$, $p = 0.16$), duration of disease ($F(1,29) = 0.29$, $p = 0.59$), and level of disability ($F(1,24) = 0.06$, $p = 0.81$) between the groups (Table 1).

*Oxygenated Hemoglobin*

Paired samples t-tests revealed that for the exercise group, there was no significant difference in $O_2Hb$ from rest to cognition at pre-testing ($t(16) = -1.91$, $p = 0.07$), but $O_2Hb$ significantly increased during cognition from rest at post-testing ($t(16) = -2.30$, $p = 0.04$). For the control group, $O_2Hb$ significantly increased during cognition from rest at pre-testing ($t(13) = -2.51$, $p = 0.03$), but there was no significant difference in $O_2Hb$ from rest to cognition at post-testing ($t(13) = -1.6$, $p = 0.13$) (Table 2).

*Deoxygenated Hemoglobin*
Paired samples t-tests revealed that for the exercise group, there were no significant differences in HHb from rest and cognition at pre-testing ($t(16) = 2.09$, $p = 0.05$) and post-testing ($t(16) = 0.96$, $p = 0.35$). For the control group, there were also no significant differences in HHb from rest and cognition at pre-testing ($t(13) = 0.26$, $p = 0.80$) and post-testing ($t(13) = 0.92$, $p = 0.38$) (Table 2).

*Total Hemoglobin*
Paired samples t-tests revealed that for the exercise group, there were no significant difference in tHb between rest and cognition at pre-testing ($t(16) = -1.12$, $p = 0.28$) and post-testing ($t(16) = -1.66$, $p = 0.12$). For the control group, tHb were significantly greater during cognition than rest at pre-testing ($t(13) = -2.38$, $p = 0.03$), but there was no significant difference in tHb from rest to cognition at post-testing ($t(13) = -1.03$, $p = 0.13$) (Table 2).

**Table 1.** Summary of participant and group characteristics.

| **Variable** | Total Sample (N = 31) (Mean ± SD) | Exercise (N = 17) (Mean ± SD) | Control (N = 14) (Mean ± SD) | Sig. |
|---|---|---|---|---|
| **Type of MS:** | | | | |
| Relapsing Remitting | 26 | 15 | 11 | |
| Secondary Progressive | 2 | 0 | 2 | |
| Primary Progressive | 2 | 1 | 1 | |
| Primary Relapsing | 1 | 1 | 0 | |
| **Race:** | | | | |
| Caucasian | 25 | 14 | 11 | |
| Hispanic/Latino | 1 | 0 | 1 | |
| African American | 5 | 3 | 2 | |
| Gender (female, male) | (28,3) | (15,2) | (13,1) | |
| Age (years) | 48.77 ± 2.49 | 48.71 ± 9.58 | 48.86 ± 9.91 | $p = 0.97$ |
| Education (total years) | 15.02 ± 2.11 | 14.44 ± 2.11 | 15.71 ± 2.81 | $p = 0.16$ |
| Diagnosis (years since) | 11.42 ± 8.50 | 12.18 ± 9.71 | 10.50 ± 7.01 | $p = 0.59$ |
| MSFC (a.u.) | -0.06 ± 0.53 | -0.09 ± 0.57 | -0.04 ± 0.51 | $p = 0.81$ |

Note: Multiple Sclerosis Functional Composite (MSFC)

**Table 2.** Differences in O2Hb, HHb, and tHb from rest to cognition for each group pre-intervention and post-intervention.

| **Variable** | Exercise (N = 17) (Mean ± SD) | | Control (N = 14) (Mean ± SD) | |
|---|---|---|---|---|
| | Pre-test | Post-test | Pre-test | Post-test |
| Δ $O_2Hb$ | 1.07 ± 2.30 | 1.12 ± 2.05* | 1.62 ± 2.42* | 0.96 ± 2.24 |

| | | | | |
|---|---|---|---|---|
| Δ HHb | -0.45 ± 0.89 | -0.19 ± 0.82 | 1.30 ± 1.42 | -0.22 ± 0.91 |
| Δ tHb | 0.62 ± 2.29 | 0.93 ± 2.32 | -0.11± 0.69 | 0.74 ± 2.69* |

*Significant increase from rest to cognition.

**Discussion**
This study examined the effects of seven days of water aerobic exercise on the cerebral hyperemic response to a cognitive function test in individuals with MS. It was hypothesized that this response would improve from pre-testing to post-testing for the exercise group, but not for the control group. Prior to the exercise intervention, $O_2Hb$ did not increase during the cognitive stimulus, however following the week of exercise $O_2Hb$ did increase from rest to cognition. In contrast, the control group demonstrated significant increases in $O_2Hb$ and tHb from rest to cognition during their initial test, but not during their follow up test.

Neural activation is coupled with increased regional cerebral blood flow, and it is widely accepted that the degree of increase in regional cerebral blood flow exceeds that of the increase in regional cerebral oxygen metabolic rate[21]. Therefore the cerebral hyperemic response to cognitive activation is thought to be increased oxygenated and total hemoglobin[22,23], where the change in total hemoglobin reflects the change in blood volume and is correlated with the change in blood flow[24]. Following exercise, this response improved for the exercise group (increased $\Delta O_2Hb$ and ΔtHb) and worsened for the control group (decreased $\Delta O_2Hb$). This suggests an improved cerebral hyperemic response to the cognitive function test occurred in the exercise group following the intervention, and a reduced cerebral hyperemic response to the cognitive function test occurred in the control group. These results agree with previous studies suggesting that exercise increases prefrontal cortex $O_2Hb$ and tHb in healthy individuals[12], and others suggesting that exercise may improve neurogenesis and cerebral impairments in MS[13,25].

For both groups, no significant differences were observed in HHb from rest to cognition at pre-testing and post-testing. This was interesting, because normal cerebral hyperemic response to cognitive activation is thought to be decreased HHb[23,26]. However, the magnitude of this response has been shown to be reduced in the elderly compared to the young[23], and it is possible that an absence of decreased HHb during brain activation in our participants with MS may be a result of aging[23], reduced cortical microvascular oxygenation[27], or intracranial venous congestion associated with chronic cerebrospinal venous insufficiency[28]. It is also possible that because $O_2Hb$ concentration exceeds metabolic demand upon neuronal activation, $O_2Hb$ affords a better NIRS signal than HHb, and it is therefore more sensitive at detecting differences in activation[29]. These interpretations are speculative, as the best method for differentially interpreting changes in $O_2Hb$ relative to changes in HHb is currently unclear[29].

Cerebral perfusion is often impaired in individuals with MS[1-3], and many individuals with MS experience thermoregulatory disturbances and are sensitive to exercise induced increases in body temperature[14]. In the present study, 7 days of water aerobic exercise increased the cerebral hyperemic response to a cognitive function test in individuals with MS, suggesting that just seven consecutive days of water aerobics exercise may improve cerebral perfusion in those with MS, and supporting literature indicating that individuals with MS tolerate water aerobics exercise well[16,17].

*Limitations and Conclusions*

A limitation to this study is that accuracy of cognitive test performance was not formally assessed. This was because the cognitive test was only used as a stimulus for eliciting a cerebral hyperemic response. Although a researcher remained with participants throughout to ensure that they were attending to and putting forth effort, we cannot determine degree of effort or ensure that it was equal across participants in an objective, standardized manner. A second limitation is the quasi-randomization of groups; however, the groups did not differ in age, education, duration of disease, and level of disability. Lastly, our NIRS system includes only one optode, which allowed us to measure cerebral perfusion in only one location. Overall, water aerobics exercise could be a useful therapy for improving the cerebral hyperemic response to cognition in individuals with MS.

**Media-Friendly Summary**

Individuals with multiple sclerosis (MS) may experience abnormal brain blood flow which can result in impaired thinking ability. This study showed that seven days of water aerobics exercise may improve brain blood flow in individuals with MS.

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