Pilot Study to Characterize Middle Cerebral Artery Dynamic Response to an Acute Bout of Moderate Intensity Exercise at 3- and 6-Months Poststroke

Sandra A. Billinger, PhD; Alicen A. Whitaker, DPT; Allegra Morton, BS; Carolyn S. Kaufman, BS; Sophy J. Perdomo, PhD; Jaimie L. Ward, MS; Sarah M. Eickmeyer, MD; Stephen X. Bai, MD; Luke Ledbetter, MD; Michael G. Abraham, MD

BACKGROUND: The primary aim of this study was to characterize the middle cerebral artery blood velocity (MCAv) dynamic response to an acute bout of exercise in humans at 3- and 6-months poststroke. As a secondary objective, we grouped individuals according to the MCAv dynamic response to the exercise bout as responder or nonresponder. We tested whether physical activity, aerobic fitness, and exercise mean arterial blood pressure differed between groups.

METHODS AND RESULTS: Transcranial Doppler ultrasound measured MCAv during a 90-second baseline followed by a 6-minute moderate intensity exercise bout. Heart rate, mean arterial blood pressure, and end-tidal CO2 were additional variables of interest. The MCAv dynamic response variables included the following: baseline, time delay, amplitude, and time constant. Linear mixed model revealed no significant differences in our selected outcomes between 3- and 6-months poststroke. Individuals characterized as responders demonstrated a faster time delay, higher amplitude, and reported higher levels of physical activity and aerobic fitness when compared with the nonresponders. No between-group differences were identified for baseline, time constant, or exercise mean arterial blood pressure. In the nonresponders, we observed an immediate rise in MCAv following exercise onset followed by an immediate decline to near baseline values, while the responders showed an exponential rise until steady state was reached.

CONCLUSIONS: The MCAv dynamic response profile has the potential to provide valuable information during an acute exercise bout following stroke. Individuals with a greater MCAv response to the exercise stimulus reported statin use and regular participation in exercise.

Key Words: blood flow ▪ brain ▪ exercise ▪ stroke ▪ vascular function

Impaired cerebrovascular hemodynamic response during exercise has been reported in individuals within 1 year poststroke.1 We previously demonstrated individuals with middle cerebral artery (MCA) stroke showed no significant differences in resting MCA blood velocity (MCAv) when compared with age- and sex-matched peers.2 However, the MCAv dynamic response during exercise was significantly lower for those poststroke. Despite the impaired cerebrovascular response to exercise, a 6-month aerobic exercise treadmill training program in chronic stroke survivors conferred benefit on cerebrovascular reserve for those randomized to the intervention when compared with controls.3 This evidence, albeit limited, suggests potential impairment in cerebrovascular control mechanisms following stroke.
The primary objective of this study was to characterize the MCAv dynamic response to a moderate intensity acute exercise bout at rest and during an acute bout of exercise.

Participants

Methods

Participants

The primary objective of the study was to characterize the MCAv and dynamic response profile at 3- and 6-months poststroke. Since no prior data are available for a power analysis, we chose to enroll 20 participants. To account for a 25% to 30% dropout rate, we overenrolled by 6 for a sample size of 26 participants.

We identified individuals poststroke during the acute or inpatient rehabilitation stay at the University of Kansas Health System. Inclusion criteria were (1) unilateral ischemic stroke, (2) stenosis in the common and internal carotid artery including intracranial stenosis of <70%.,3,5 A radiologist (L.L.) made this interpretation using ultrasound imaging or angiogram in the electronic medical record, (3) 35 to 95 years of age, (4) physician approval for exercise participation, (5) able to walk >10 m without physical assistance, and (6) able to travel to the university for the experimental protocol. Exclusion criteria were (1) unable to consent, (2) inability to perform continuous reciprocal stepping with their lower extremities on the seated recumbent stepper (T5XR NuStep, Inc., Ann Arbor, MI), (3) diagnosis of other neurologic disease, and (4) use of supplemental oxygen.

We accessed the electronic medical record (S.X.B.) after consent and following the 3-month visit for information such as lesion location, stroke cause and stroke treatment (tissue plasminogen activator, thrombectomy). Lesion size was calculated (S.X.B.) using a clinical scan either the day of admission or the following day using established methods.6,7

Experimental Procedure

Study visits occurred in a laboratory setting at 3- and 6-months poststroke. Participants were asked to abstain from caffeine for a minimum of 6 hours, a meal for 2 hours, and vigorous exercise at least 12 hours before the study visit.4,8 The University of Kansas Medical Center Human Subjects Committee approved all experimental procedures. Institutionally approved written informed consent was obtained from each individual before study participation.

Familiarization

The laboratory room in which the experimental protocol took place was dimly lit, quiet, and maintained a constant temperature between 22°C and 24°C.8 All external stimuli were kept to a minimum. Participants completed the familiarization session as previously described.2,4,8 Briefly, participants practiced using the recumbent stepper while the target work rate was determined. Participants were familiarized with the nasal cannula and instructed to breathe only through their
nose. This ensured that we obtained accurate measures for end-tidal carbon dioxide ($P_{ETCO_2}$). Following familiarization, we obtained height, weight, and completed remaining study documents for demographics, modified Rankin scale, the Montreal Cognitive Assessment, and self-reported physical activity for the nonexercise estimated $VO_2$ maximum.9

**Protocol Set-Up**

Individuals were instrumented with the following equipment: (1) transcranial Doppler ultrasound (Multigon Industries Inc., Yonkers, NY), an adjustable headband, and 2-MHz transcranial Doppler ultrasound probes for acquisition of MCAv (cm×s⁻¹). The transcranial Doppler ultrasound sonographer was blinded to the side of stroke and entered the room only after the participant was set up to find the MCAv signal; (2) A 5-lead ECG (Cardiocard, Nasiff Associates, Central Square, NY) recorded heart rate (HR); (3) beat-to-beat MAP was obtained from the left middle finger (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands); and (4) nasal cannula and capnograph (BCI Capnocheck Sleep 9004 Smiths Medical, Dublin, OH). We monitored $P_{ETCO_2}$ to ensure participants did not hyperventilate,8 resulting in lower $P_{ETCO_2}$ and cerebral artery vasoconstriction.

Raw data acquisition occurred through an analog-to-digital unit (NI-USB-6212, National Instruments) and custom-written software operating in MATLAB (v2014a, The Mathworks Inc., Natick, MA).

**Exercise Protocol**

We used moderate-intensity exercise (45%–55% of the participant’s HR reserve) for the acute exercise bout. We determined the HR range from 1 of 2 equations: (1) age-predicted (220–age) HR maximum or (2) 164–0.72×age for participants using β-blocker medication.10

The baseline recording lasted 90 seconds followed by 6 minutes of moderate intensity exercise. Following the 6-minute exercise bout, the participant engaged in an active cool down for 2 minutes followed by rest until HR, MCAv, and MAP returned to baseline values. Participants performed a second exercise bout and data points were averaged to optimize signal-to-noise ratio.8 All variables were sampled at 500 Hz and then interpolated to 2.0 Hz. Three-second averages were calculated and then smoothed using a 9-second sliding window average. We used R version 3.2.4 (R Core Team, Vienna, Austria)11 with the “nlm” function package to model the dynamic response profile. To ensure data quality, data with R-to-R intervals >5 Hz or changes in peak blood velocity >10 cm/s in a single cardiac cycle were considered artifact and censored. If acquisitions had >15% of data points censored, they were discarded.

**MCAv and Dynamic Response Profile**

Kinetics were modeled for MCAv over the entire exercise bout with a mono-exponential model:

$$MCA_v(t) = BL \times (t \leq TD) + (BL + Amp \times (1 - e^{-\frac{(t-TD)/\tau}{\tau}})) \times (t > TD)$$

where $MCA_v(t)$ is the MCAv at any point in time, BL is baseline before exercise onset, Amp is the peak amplitude of the response above resting BL, TD is the time delay preceding the exponential increase in MCAv, and $\tau$ is the time constant or time-to-63% of the peak amplitude. The cerebrovascular response (CVR) is the difference between the BL and mean MCAv sampled during steady-state exercise between 3 and 4.5 minutes.

For this study, individuals whose MCAv increased in a close-to-exponential pattern being well-fit by a delay+exponential function were labeled as responders. Individuals whose data revealed poor model fit (excessive TD value >100 s, or Amp value <2 cm×s⁻¹ or exercise MCAv values below resting baseline) or a nonexponential response were labeled as nonresponders.

**Six-Minute Walk Test**

Participants were given a 20-minute rest following the exercise session. HR and blood pressure were taken to ensure the participant sufficiently recovered from the exercise bout and values returned to resting. The 6-minute walk test was performed in a hallway with no distractions or foot traffic according to guidelines outlined by the American Thoracic Society.12

**Statistical Analysis**

Data supporting the results of this study are available upon request to the corresponding author. Data are presented as mean±SD unless stated otherwise. To account for the missing data across study visits, we used a linear mixed model to test for differences between 3- and 6-months poststroke. Time was used as a categorical variable and entered into the model as a fixed effect. To test for between-group differences (responders versus nonresponders), we performed 1-way ANOVA or Mann–Whitney $U$ test as appropriate following visual inspection of probability plots and Shapiro–Wilk tests. Fisher exact tests were used for categorical data. Differences were considered significant when $P<0.05$.

**RESULTS**

**Participant Characteristics**

Twenty-seven participants gave consent to participate in the study. One person gave consent twice because this individual experienced 2 separate
stroke events. The first stroke was in the left MCA and then the right MCA stroke occurred a year later. The 3- and 6-month data for this person have been published as a case report.13 Data from the second stroke (right MCA) was not included in the present article because this was a unique case. Participants (n=26) were 69% men, 63.0±14.0 years of age, and 96.3±12.6 days poststroke. Sixty-nine percent identified as White, 0% as Hispanic, 31% as Black, 4% as Native American, and 4% as Asian. Multiple race categories were selected. Resting systolic blood pressure was 138.5±18.3 mm Hg and diastolic blood pressure was 80.4±11.2 mm Hg. Individuals were characterized as overweight with a body mass index of 29.8±5.5 kg×(m²)−1. Estimated $\dot{V}O_2$ maximum was 23.2±8.9 mL×kg⁻¹×min⁻¹. Right and left stenosis was ≤50% for bilateral common and internal carotid arteries in all participants. No serious adverse events occurred during any study visit.

Eighteen participants (72.2% men) returned for the 6-month visit. Participants were 65.7±14.1 years of age and 188.4±14.1 days poststroke. There were 83.3% identified as White, 0% as Hispanic, 22.2% as Black, and 5.6% as Native American. Multiple race categories were selected. Reasons for loss to follow-up included the following: unable to contact (n=2); participant’s son had a stroke (n=1); hospitalized (n=1); visit scheduled but did not attend study visit (n=2); no transportation (n=1); and participant died (n=1).

**MCAv Dynamic Response Across Time**

**Three-Month Visit**

Of the 26 participants, 4 individuals were excluded from analysis because of the following: a valid MCAv signal was not acquired (n=3) and poor MCAv signal acquisition during exercise (n=1). Data are presented for 22 participants.

**Six-Month Visit**

Of the 18 individuals who returned, we excluded 3 participants from analysis. Reasons for exclusion included an invalid resting MCAv signal because of equipment/technical issues (n=2) and poor MCAv signal acquisition during exercise, which resulted in >15% of data points censored (n=1). Statistical analyses were conducted on 15 participants.

The MCAv baseline and kinetic measures during moderate intensity exercise showed no differences over time for either MCA (Table 1). We found no differences between race ($P=0.09$) or sex ($P=0.21$) for all MCAv data and hemodynamic data (blood pressure, HR, and $P_{ETCO_2}$) at rest and during exercise at either 3- or 6-month visits, which is possibly because of insufficient power in the small sample size.

**Responders and Nonresponders (3 Months Poststroke)**

**MCAv Dynamic Response**

Table 2 presents demographics for each group. We observed 12 participants whose MCAv increased in a close-to-exponential pattern being well-fit by a delay-exponential function (responders). The remaining 10 individuals (nonresponders) demonstrated poor model fit and nonexponential response (n=9) or MCAv was below baseline (n=1) after exercise onset on the ipsilesional side. On the contralesional side, MCAv decreased below baseline after exercise onset for the same individual (n=1) and we observed a nonexponential response.
Billinger et al  MCAv Response Poststroke

in the other participants (n=9). No between-group differences were reported for age, body mass index, 6-minute walk test, or the Montreal Cognitive Assessment. The responders were more likely to report taking a statin medication, had greater physical activity levels, and had higher estimated $\dot{V}O_2$ maximum values ($P<0.05$).

The Figure shows the baseline and MCAv response after the onset of moderate intensity exercise for

| Table 2. Characteristics of Responders and Nonresponders at 3 Months Poststroke |
|---------------------------------------------------------------|
| **Responders (n=12)** | **Nonresponders (n=10)** | **F-test** | **P Value** |
| Age, y | 59.4 (51.5 to 67.4) | 67.3 (55.8 to 78.8) | 1.7 | 0.21 |
| Sex, % (n) | 58% (7) | 70% (7) | 0.68 |
| Race or ethnicity*, % (n) | | | | |
| White | 83% (10) | 50% (5) | 0.17 |
| Black | 17% (2) | 50% (5) | 0.17 |
| Native American | 0% (0) | 10% (1) | 0.46 |
| Hispanic/Latino | 0% (0) | 0% (0) | ... |
| Asian | 0% (0) | 10% (0) | 0.46 |
| Time poststroke to 3-mo visit, d | 94.8 (89.5 to 100.0) | 99.5 (86.6 to 112.4) | 0.7 | 0.42 |
| BMI, kg×(m$^2$)$^{-1}$ | 31.2 (27.3 to 35.2) | 28.2 (24.7 to 31.8) | 1.5 | 0.24 |
| Lesion size, cm$^3$ | 70.6 (−4.2 to 145.5) | 20.7 (−23.2 to 64.5) | 1.7 | 0.22 |
| Estimated $\dot{V}O_2$ maximum, mL×kg$^{-1}$×min$^{-1}$ | 26.6 (20.9 to 32.3) | 18.3 (12.8 to 24.0) | 5.2 | 0.03 |
| Physical activity score | 2.8 (1.9 to 3.6) | 1.6 (1.1 to 2.1) | 6.4 | 0.02 |
| MoCA | 22.0 (18.3 to 25.7) | 23.8 (21.4 to 26.2) | 0.8 | 0.39 |
| mRS | 2.1 (1.5 to 2.5) | 2.2 (1.5 to 2.9) | 0.3 | 0.62 |
| 6-minute walk test, m | 338.4 (257.1 to 419.8) | 264.6 (165.5 to 363.6) | 1.7 | 0.21 |
| Stroke cause | | | | |
| Cryptogenic | 33% (4) | 60% (6) | 0.12 |
| Intracranial atherosclerotic disease | 17% (2) | 0% (0) | 0.07 |
| Cardioembolic | 33% (4) | 30% (3) | 1.00 |
| Thrombotic | 17% (2) | 10% (1) | 0.80 |
| Stroke location | | | | |
| Middle cerebral artery | 75% (9) | 50% (5) | 0.74 |
| Posterior cerebral artery | 0% (0) | 10% (1) | 0.52 |
| Lacunar | 17% (2) | 20% (2) | 1.00 |
| Pontine | 8% (1) | 10% (1) | 1.00 |
| Thalamic | 0% (0) | 10% (1) | 0.52 |
| Thrombectomy (n) | 33% (4) | 10% (1) | 0.32 |
| tPA and thrombectomy (n) | 17% (2) | 10% (1) | 1.00 |
| tPA (n) | 25% (3) | 60% (6) | 0.19 |
| Medications (n) | | | | |
| β-Blocker | 67% (8) | 70% (7) | 1.00 |
| Calcium channel blocker | 42% (5) | 20% (2) | 0.38 |
| ACE inhibitor | 33% (4) | 0% (0) | 0.10 |
| Angiotensin II receptor blocker | 25% (3) | 20% (2) | 1.00 |
| Statins | 92% (11) | 60% (6) | 0.03 |
| Diuretics | 8% (1) | 10% (1) | 1.00 |
| Blood thinners | 58% (7) | 40% (4) | 0.67 |
| Aspirin | 33% (4) | 50% (5) | 0.67 |
| Insulin | 8% (1) | 40% (4) | 0.14 |
| Metformin | 8% (1) | 20% (2) | 0.57 |
| Antidepressants | 33% (4) | 40% (4) | 1.00 |

Data are presented as mean (95% CI). ACE indicates angiotensin-converting enzyme; BMI, body mass index; MoCA, Montreal Cognitive Assessment; mRS, Modified Rankin Scale; tPA, tissue plasminogen activator; and $\dot{V}O_2$, oxygen uptake.

*One individual selected multiple race categories.
Billinger et al.  MCAv Response Poststroke

Responders and nonresponders. Data from the MCAv kinetics analysis are presented in Table 3. During seated rest before exercise onset, baseline ipsilesional and contralesional MCAv data were not significantly different between groups. After exercise onset, the ipsilesional MCAv amplitude was significantly reduced in the nonresponders. This finding is expected based on group assignment (responder/nonresponder). For the 5 participants with poor model fit, we observed a significantly slower TD response for the nonresponders on the ipsilesional side while the \( \tau \) was not different. Only 1 person in the nonresponder group had data for analysis that fit the model, although a negative amplitude (below baseline). The remaining participants (n=9) showed a nonexponential response. We report a significantly higher ipsilesional CVR for the responders (6.18±4.28 cm×s\(^{-1}\)) when compared with the nonresponders (0.48±2.07 cm×s\(^{-1}\); \( F(1,22) =26.93, P<0.001 \)). Similarly, we report between-group differences in the contralesional CVR (responders: 9.04±5.18 cm×s\(^{-1}\) versus nonresponders: 0.20±3.05 cm×s\(^{-1}\); \( F(1,22) =18.43, P<0.001 \)).

Baseline and Exercise Response in MAP, \( P_{ETCO_2} \) and HR

The baseline and exercise-induced responses (Δ) in MAP, \( P_{ETCO_2} \), and HR are shown in Table 3. The baseline and steady-state exercise for MAP, \( P_{ETCO_2} \), and HR were not significantly different. We found between-group differences for ΔMAP and ΔHR (\( P<0.025 \)) but not Δ\( P_{ETCO_2} \) (\( P=0.22 \)).

Responders and Nonresponders (6 Months Poststroke)

All individuals characterized as a responder at the 3-month visit remained so at the 6-month visit. Three individuals initially characterized as a nonresponder met the criteria for responder. Of these 3 individuals, 2 increased their physical activity score from a 2 (low-intensity walking for 10 minutes or less) to a 5 (vigorous activity). The other individual remained in the category of 2 for both visits. Three individuals changed medications related to blood pressure, anticoagulation, or antiplatelet therapy, which may have influenced MCAv response or other hemodynamic measures at rest or during exercise. In the responder group, 1 person discontinued clopidogrel. In the nonresponder group, lisinopril was added to the medication list while another person reported discontinued use of lisinopril, furosemide, and clopidogrel.

There were no group differences between responders (n=10) and nonresponders (n=5) for age (\( P=0.06 \)), time poststroke (6-month visit, \( P=0.47 \)), body mass index (\( P=0.58 \)), Montreal Cognitive Assessment score (\( P=0.54 \)), Modified Rankin Scale (\( P=0.40 \)), or self-reported physical activity score (\( P=0.10 \)). We report significant differences for the nonexercise estimate for \( \dot{VO}_2 \) maximum (\( P<0.01 \)), and 6-minute walk test (\( P=0.02 \)).

Figure. Ipsilesional and contralesional MCAv response to moderate intensity exercise at 3 months poststroke.

MCAv indicates middle cerebral artery blood velocity.
**MCAv Dynamic Response**

Responders worked at a higher workload \((P=0.04)\) with no significant differences in the rate of perceived exertion \((P=0.96)\). Baseline MCAv was not different between groups for the ipsilesional \((P=0.58)\) and contralesional \((P=0.87)\) side. On the ipsilesional side, the nonresponders showed a significantly slower TD \((P=0.04)\) and lower amplitude \((P=0.04)\) while \(\tau\) was not different \((P=0.93)\). For the contralesional side, no between-group significant differences were found for any MCAv dynamic response variables. We report a significantly higher ipsilesional CVR for the responders \((7.19\pm4.40 \text{ cm}\times\text{s}^{-1})\) when compared with the nonresponders \((1.30\pm2.99 \text{ cm}\times\text{s}^{-1})\), \(F_{(1,15)}=7.18, P=0.02\). Similarly, we report between-group differences in the contralesional CVR \((P=0.03)\) for responders: \(8.39\pm4.65 \text{ cm}\times\text{s}^{-1}\) versus nonresponders: \(2.78\pm2.05 \text{ cm}\times\text{s}^{-1}\), \(F_{(1,15)}=6.39, P=0.03\).

For participants who had baseline and CVR values at both 3- and 6-month study visits, we compared the change over time for individuals characterized as responders \((n=7)\) and nonresponders \((n=5)\) at the initial 3-month study visit. For the ipsilesional side, baseline MCAv declined by \(2.47\pm5.16 \text{ cm}\times\text{s}^{-1}\) for the responders while the nonresponders showed a \(5.26\pm9.52 \text{ cm}\times\text{s}^{-1}\) reduction. During the exercise bout, CVR change was \(0.29\pm3.63 \text{ cm}\times\text{s}^{-1}\) for the responders while the nonresponders showed a \(2.66\pm1.55 \text{ cm}\times\text{s}^{-1}\) increase in CVR from 3 to 6 months. For the contralesional side, the change in baseline MCAv was \(−2.81\pm3.49 \text{ cm}\times\text{s}^{-1}\) \((\text{responders})\) and \(−3.01\pm8.90 \text{ cm}\times\text{s}^{-1}\), CVR values mirrored the MCAv for both responders \((0.90\pm1.60 \text{ cm}\times\text{s}^{-1})\) and nonresponders \((1.16\pm2.05 \text{ cm}\times\text{s}^{-1})\) on the ipsilesional side. No values were significantly different \((P>0.12)\), likely because of the small number of participants in each group.

**Baseline and Exercise Response in MAP, \(P_{\text{ET}}\text{CO}_2\), and HR**

No between-group differences were found for resting and exercise hemodynamic responses, \(\Delta\text{MAP}, \Delta\text{HR},\) or \(\Delta P_{\text{ET}}\text{CO}_2\).

**DISCUSSION**

Aerobic exercise, identical to the intensity used in this study, is recommended for overall health post-stroke.\(^{14}\) Cerebral blood flow increases because of cortical activation and increased oxygen demand during physical exercise. Impairments in the ability to
increase cerebral blood flow (cerebrovascular dysfunction) during demand may contribute to neural dysfunction. Therefore, this study provides important and relevant information regarding the cerebrovascular response to a single bout of moderate intensity exercise in people living with stroke. The main primary findings of the current investigation are as follows: (1) MCAv kinetic response was stable from 3 to 6 months poststroke for bilateral MCAs, and (2) MCAv kinetic response (amplitude and TD) significantly differed for those with higher estimated \( \dot{V}O_2 \) maximum, suggesting that engaging in regular physical activity benefits cerebrovascular health. This finding was consistent for the ipsilesional and contralesional side at 3 and 6 months.

**MCAv Dynamic Response Across Time**

The primary objective of this study was to characterize the MCAv response in humans at 3- and 6-months poststroke. To our knowledge, this longitudinal cerebrovascular assessment at rest and in response to exercise had not been previously conducted. We hypothesized that the MCAv dynamic response profile would improve from 3 to 6 months poststroke. This rationale was developed from published work highlighting improved longitudinal changes in aerobic fitness at 1, 3, and 6 months poststroke and aerobic fitness positively influences peripheral vascular health measures in individuals poststroke. Our hypothesis that MCAv dynamic response would improve with time was not supported by our findings. We have reported high reproducibility within older adults for resting and exercise MCAv and bilateral reproducibility for the MCAv kinetic measures. Therefore, measurement error from our sophonographers (S.P., C.K.) was unlikely. Because of the small sample size, we may have insufficient power to detect differences in MCAv.

**MCAv Dynamic and Hemodynamic Responses 3 Months Poststroke**

Research has demonstrated that once exercise begins, neural activation in the brain increases the metabolic requirements above normal resting values in order to maintain proper function and this demand is met with increased cerebral blood flow. Our laboratory and others have shown that moderate intensity continuous exercise produces the greatest increase in MCAv compared with low and high intensity (above anaerobic threshold) continuous exercise. Therefore, we expected the MCAv dynamic response to increase following exercise onset in people with stroke. In this study, we report that not all participants demonstrated an exponential increase in MCAv in response to moderate intensity exercise.

In fact, almost half (10 of the 22) of the individuals enrolled showed a nonexponential MCAv response (nonresponders) following exercise onset. This could be indicative of slowed vasomotor control within the cerebrovasculature as both sides showed slower MCAv kinetics (increased TD) or nonexponential MCAv increase. CVR is the change in MCAv from rest to steady-state exercise and allows us to compare all participants. For the responders, both the ipsilesional and contralesional CVR showed a significantly higher value when compared with the nonresponders at the 3- and 6-month study visits. When considering potential factors, the data in Table 2 show no between-group differences for age, sex, race or ethnicity, time of study visit, or the calculated lesion size from the electronic medical record. We found that responders had greater statin use, self-reported physical activity levels, and estimated \( \dot{V}O_2 \) maximum values. One previous study grouped healthy young adults based on self-reported physical activity levels into low and high fitness. Those in the high fitness group demonstrated a greater change in MCAv in response to rebreathing-induced hypercapnia while no resting MCAv differences were found. This finding, combined with the present study, underscores the value in considering dynamic challenges such as exercise. Furthermore, others have reported that physically active individuals with higher \( \dot{V}O_2 \) maximum values exhibit better cerebral hemodynamics than sedentary individuals. Although the evidence reporting the dynamic cerebrovascular response to exercise after stroke is limited, the present study suggests that engagement in physical activity and exercise poststroke may confer some benefit to overall cerebrovascular health. This finding is important because overall brain health is directly related to both cardiovascular and cerebrovascular health.

We acknowledge that individuals in the responder group also reported a significantly higher use of statin medications. In fact, 3 months of statin treatment after stroke improved cerebrovascular reactivity compared with the control group, while no differences in resting cerebral blood flow were reported.

We acknowledge that we cannot definitively state a cause-and-effect relationship between MCAv dynamic response and physical activity or statin use with this current study design. Future work should consider all vascular risk factors and their role in the MCAv response to exercise. The Figure highlights a significantly blunted CVR and altered kinetics profile in a subset of people poststroke (nonresponders) who may greatly benefit from physical exercise participation to improve cerebrovascular health. This benefit may be derived through the engagement of muscular contraction and cortical activation (motor and sensorimotor areas) during...
physical exercise, which facilitates increased cerebral metabolism and neurovascular coupling to optimally increase cerebral blood flow.\textsuperscript{21} The potential exists that the nonresponders demonstrate reduced regional perfusion pressure whereby resistance is low, which results in an impaired or diminished cerebrovascular response to exercise.\textsuperscript{1} Although the response was diminished across the 6-minute exercise session, it was not completely absent in all nonresponders. Our study was not designed to test whether being a responder is physiologically superior to that of a nonresponder, and we should consider whether a diminished exercise response may be a protective mechanism following stroke. Therefore, future studies should integrate other imaging modalities such as arterial spin labeling and functional magnetic resonance imaging with dynamic MCAv response to better understand the cerebrovascular response to stimuli poststroke. Furthermore, future work should test whether aerobic exercise interventions can increase the MCAv kinetic response profile and other cerebrovascular outcomes after stroke while accounting for statin use.

The baseline values and steady-state hemodynamic responses were not significantly different, while \( \Delta \text{MAP} \) and \( \Delta \text{HR} \) differed between the groups. We acknowledge that these differences may be largely driven by higher workloads in the responder group, which likely influenced the MCAv amplitude response. One individual (responder) exercised at 110 W. He was an avid cyclist before his stroke and had begun to exercise at his study visit. Our study did not include information on prestroke exercise status. The potential exists that prestroke exercise status may have an effect on the ipsilesional and contral-lesional MCAv response to exercise and warrants further investigation. We report no between-group differences for baseline, steady state, or \( \Delta \text{P}_\text{ETCO}_2 \).

We are confident that the lower MCAv amplitude in the nonresponders is not the result of hyperventilation. We closely monitor \( \text{P}_\text{ETCO}_2 \) during the exercise bout to ensure our participants stay within the prescribed HR range without hyperventilation.\textsuperscript{8}

The literature is well-established that MAP increases with age\textsuperscript{30} and after stroke,\textsuperscript{14} which provides unique opportunities to study exercise-induced changes in MAP and HR. The cerebrovasculature and the associated neuroprotective mechanisms have the ability to autoregulate and buffer the sudden acute increases in MAP associated across various exercise intensities.\textsuperscript{15} As observed in the Figure, the nonresponders show a rapid rise in the MCAv response to exercise followed by an immediate decline with values remaining near baseline. One proposed hypothesis for this unexpected response may be an impairment in the cerebrovascular control mechanisms following stroke\textsuperscript{8} or altered neural integration of afferent input from the exercising lower extremities.\textsuperscript{4,31} Despite the proposed increased neural activation typical with the transition from rest to exercise and demand for energy, MCAv did not exponentially increase in those characterized as nonresponders.

Our data are timely given the increased interest and concern for the role of high-intensity interval training on cerebrovascular response, especially for those with neurological conditions such as stroke.\textsuperscript{15,32,33} A published clinical practice guideline for physical therapy suggests that higher locomotor intensities benefit walking speed and endurance in chronic stroke.\textsuperscript{34} However, the lack of data regarding high-intensity exercise and cerebrovascular response (reviewed in 15,33) and a recent publication studying the cerebrovascular response to a 30-sec-ond bout of high-intensity exercise\textsuperscript{32} suggest that caution should be taken when implementing this type of protocol, because the evidence for safety with the brain and the delicate cerebrovasculature has not been broadly tested. The current knowledge of cerebrovascular control during an acute exercise bout, especially following stroke, is still in its infancy and warrants further investigation.

**MCAv Dynamic and Hemodynamic Responses 6 Months Poststroke**

In the chronic phase of stroke recovery, the responders exercised at higher workloads. The only between-group differences for TD and amplitude on the ipsilesional side remained. All other MCAv kinetic variables and hemodynamic responses were not different. The reduced sample size warrants caution when interpreting the findings. A noteworthy observation was that 2 of the 3 newly characterized responders had increased their self-reported physical activity. Whether the increase in physical activity was the primary driver of the higher MCAv amplitude responses remains an important query for future work.

Several limitations in the study design should be considered. First, using transcranial Doppler ultrasound, the assumption of constant MCA diameter is important in order for the MCAv to be used as a direct proxy for cerebral blood flow.\textsuperscript{8} Second, maximal exercise testing was not performed to determine maximal HR for the exercise intensity dose. We acknowledge that the exercise intensity could be under- or overdosed. However, as evidenced by the increase in \( \text{P}_\text{ETCO}_2 \) during exercise, it is unlikely that individuals exercised above anaerobic levels. Third, before exercise onset, we observed a rise in baseline MCAv that was not observed in our prior work with healthy...
participants or older adults. We propose this may be an anticipatory response to our verbal instructions 15 s before exercise onset. Finally, we included people with posterior circulation stroke. We acknowledge that the MCAv response to exercise may not be related or reflective of what occurs in the posterior circulation at 3- or 6-months poststroke.

CONCLUSIONS

The cerebrovascular response to acute exercise remained unchanged between 3- and 6-months poststroke. Physical activity participation and statin use may positively influence the MCAv dynamic response during exercise poststroke. Further exploration into the cerebrovascular control mechanisms or other stroke-specific characteristics that may result in a diminished response (nonresponders) to exercise and various intensities is needed. The MCAv kinetic response may better inform future exercise trials designed to benefit overall brain health.

ARTICLE INFORMATION

Received June 1, 2020; accepted December 9, 2020.

Affiliations

From the Department of Physical Therapy and Rehabilitation Science (S.A.B., A.A.W., M.M., C.S.K., J.P.J., J.L.W.), Department of Physical Medicine and Rehabilitation (S.A.B., S.M.E., S.X.B.), Department of Neurology (S.A.B., M.G.A.), Department of Molecular and Integrative Physiology (S.A.B., C.S.K.) and Department of Diagnostic Radiology (L.L.), University of Kansas Medical Center, Kansas City, KS; Department of Radiological Sciences, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA (L.L.); Department of Interventional Radiology, University of Kansas Medical Center, Kansas City, KS (M.G.A.); and Department of Medicine, University of Pittsburgh, PA (S.J.P.).

Acknowledgments

We would like to thank Emily Nardo for assistance with data collection and Madison Henry for assistance with data organization.

Sources of Funding

Dr Billinger was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K01HD067318). Dr Whitaker and Ms. Morton received support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (T32HD057850). Ms. Morton received a Student Scholarship in Cerebrovascular Disease and Stroke from the American Heart Association. Dr Perdomo received partial support from the University of Kansas Alzheimer’s Disease Center (P30OA035982), University of Kansas Medical Center Biomedical Research Training Program and the National Institute on Aging Diversity Supplement to R01AG058162. REDCap at KU Medical Center is supported by the Clinical and Translational Science Award (UL1TR000001) from the National Center for Research Resources and National Center for Advancing Translational Science (NCATS) was a grant awarded to the University of Kansas Medical Center for Frontiers: The Heartland Institute for Clinical and Translational Research. The National Center for Advancing Translational Science awarded to the University of Kansas Frontiers the Clinical and Translational Science Institute (UL1TR002366). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Disclosures

Dr Billinger reports a patent pending (18KU028M-02). Dr Abraham reports consulting for Stryker Neurovascular and Penumbra Inc. outside the submitted work. The remaining authors have no disclosures to report.

REFERENCES

1. Robertson AD, Atwi S, Kostoglou K, Verhoef N, Oh PI, Mitsis GD, Marzolini S, MacIntosh BJ. Cerebrovascular pulsatility during rest and exercise reflects hemodynamic impairment in stroke and cerebral small vessel disease. Ultrasound Med Biol. 2019;45:3116–3127. DOI: 10.1016/j.ultrasmedbio.2019.08.019.

2. Kempf KS, Whitaker AA, Lui Y, Witte E, Perdomo SJ, Ward JL, Eickmeyer S, Ledbetter L, Abraham M, Billinger SA. The effect of stroke on middle cerebral artery blood flow velocity dynamics during exercise. J Neurol Phys Ther. 2019;43:212–219. DOI: 10.1097/NPT.0000000000000289.

3. Ivey FM, Ryan AS, Hafer-Macko CE, Macko RF. Improved cerebral vasomotor reactivity after exercise training in hemiparetic stroke survivors. Stroke. 2011;42:1994–2000. DOI: 10.1161/STROKEAHA.110.607879.

4. Ward JL, Craigh JC, Liu Y, Vidoni ED, Maleisky R, Poole DC, Billinger SA. Effect of healthy aging and sex on middle cerebral artery blood velocity dynamics during moderate intensity exercise. Am J Physiol Heart Circ Physiol. 2018;315:H492–H501. DOI: 10.1152/ajpheart.0129.2018.

5. Guo ZN, Liu J, Xing Y, Yan S, Lv C, Jin H, Yang Y. Dynamic cerebral autoregulation is heterogeneous in different subtypes of acute ischemic stroke. PLoS One. 2014;9:e93213. DOI: 10.1371/journal.pone.0093213.

6. Newman GC. Clarification of abc/2 rule for ICH volume. Stroke. 2007;38:862.

7. Majersik JJ, Cols JW, Gollelde J, Rost NS, Chan Y-F, Guroi ME, Lindgren AG, Woo D, Fernandez-Cadenas I, Chen DT, et al. Recommendations from the International Stroke Genetics Consortium, part 1: standardized phenotypic data collection. Stroke. 2015;46:279–284. DOI: 10.1161/STROKEAHA.114.006839.

8. Billinger SA, Craig JC, Kwapiszeski SJ, Sisante J-F, Vidoni ED, Maletsky R, Poole DC. Dynamics of middle cerebral artery blood flow velocity during moderate intensity exercise. J Appl Physiol. 2017;122:1125–1133. DOI: 10.1152/japphyphys.00995.2016.

9. Jurca R, Jackson AS, LaMonte MJ, Morrow JR, Blair SN, Wareham NJ, Haskell WL, van Mechelen W, Church TS, Jakicic JM, et al. Assessing cardiorespiratory fitness without performing exercise testing. Am J Prev Med. 2005;29:185–193. DOI: 10.1016/j.amepre.2005.06.004.

10. Brawner CA, Ehrman JK, Schairer CA, Cao JJ, Keyes SJ. Predicting maximum heart rate among patients with coronary heart disease receiving beta-adrenergic blockade therapy. Am Heart J. 2004;148:910–914.

11. RCoreTeam. A Language and Environment for Statistical Computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2013.

12. Crape RO, Casaburi R, Coates AL, Enright PL, McLintyre NR, McKay RT, Johnson D, Wanger JS, Zeballos RJ. ATS statement: guidelines for six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–117.

13. Kaufman CS, Bai SX, Ward JL, Eickmeyer SM, Billinger SA. Middle cerebral artery blood velocity dynamic response profile during exercise is attenuated following multiple ischemic strokes: a case report. Physiol Rep. 2019;7:e14268. DOI: 10.14814/phy2.14268.

14. Billinger SA, Arena R, Bernhard J, Eng JJ, Franklin BA, Johnson CM, Mackay-Lyons M, Macko RF, Mead GE, Roth EJ, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2532–2553. DOI: 10.1161/STR.0000000000000222.

15. Lucas SJ, Cotter JD, Brassard P, Bailey DM. High-intensity interval exercise and cerebrovascular health: curiosity, cause, and consequence. J Cereb Blood Flow Metab. 2015;35:902–911. DOI: 10.1038/jcbfm.2015.49.

16. Mackay-Lyons MJ, Makrides L. Longitudinal changes in exercise capacity after stroke. Arch Phys Med Rehabil. 2004;85:1608–1612.

17. Billinger SA, Mattlage AE, Ashenden AL, Lentz AA, Harter G, Rippe MA. Aerobic exercise in subacute stroke improves cardiovascular health and physical performance. J Neurol Phys Ther. 2012;36:159–165. DOI: 10.1097/NPT.0b013e318274d492.

18. Perdomo SJ, Ward J, Liu Y, Vidoni ED, Sisante JF, Kirkendoll K, Burns JM, Billinger SA. Cardiovascular disease risk is associated with middle cerebral blood flow velocity in older adults. Cardiopulm Phys Ther J. 2020;31:38–46. DOI: 10.1097/CPT.0000000000000110.

19. Gonzalez-Afonso J, Dalsgaard MK, Osada T, Vollensties D, Dawson EA, Yokoyama CC, Secher NH. Brain and central haemodynamics and oxygenation during maximal exercise in humans. J Physiol. 2004;557:331–342. DOI: 10.1113/jphysiol.2004.060574.
20. Jorgensen LG, Perko M, Hanel B, Schroeder TV, Secher NH. Middle cerebral artery flow velocity and blood flow during exercise and muscle ischemia in humans. J Appl Physiol (1985). 1992;72:1123–1132. DOI: 10.1152/jappl.1992.72.3.1123.

21. Linkis P, Jorgensen LG, Olesen HL, Madsen PL, Lassen NA, Secher NH. Dynamic exercise enhances regional cerebral artery mean flow velocity. J Appl Physiol. 1995;78:12–16. DOI: 10.1152/jappl.1995.78.1.12.

22. Moraine JJ, Lamotte M, Berre J, Niset G, Leduc A, Naeije R. Relationship of middle cerebral artery blood flow velocity to intensity during dynamic exercise in normal subjects. Eur J Appl Physiol Occup Physiol. 1993;67:35–38. DOI: 10.1007/BF00377701.

23. Witte E, Liu Y, Ward JL, Kempf KS, Whittaker A, Vidoni ED, Craig JC, Poole DC, Billinger SA. Exercise intensity and middle cerebral artery dynamics in humans. Respir Physiol Neurobiol. 2019;262:32–39. DOI: 10.1016/j.resp.2019.01.013.

24. Ide K, Horn A, Secher NH. Cerebral metabolic response to submaximal exercise. J Appl Physiol. 1999;87:1604–1608. DOI: 10.1152/jappl.1999.87.5.1604.

25. Hwang J, Kim K, Brothers RM, Castelli DM, Gonzalez-Lima F. Association between aerobic fitness and cerebrovascular function with neurocognitive functions in healthy, young adults. Exp Brain Res. 2018;236:1421–1430. DOI: 10.1007/s00221-018-5230-6.

26. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, Thomas KN, Williams MJ, Atkinson G. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol. 2008;586:4005–4010. DOI: 10.1113/jphysiol.2008.158279.

27. Bailey DM, Marley CJ, Brugniaux JV, Hodson D, New KJ, Ogoh S, Ainslie PN. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. Stroke. 2013;44:3235–3238. DOI: 10.1161/STROKEAHA.113.002589.

28. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, Bae H-J, Bauman MA, Dichgans M, Duncan PW, et al. Defining optimal brain health in adults: a presidential advisory from the American Heart Association/American Stroke Association. Stroke. 2017;48:e284–e303. DOI: 10.1161/STR.0000000000000148.

29. Pretnar-Oblak J, Sabovic M, Sebestjen M, Pogacnik T, Zaletel M. Influence of atorvastatin treatment on l-arginine cerebrovascular reactivity and flow-mediated dilatation in patients with lacunar infarctions. Stroke. 2006;37:2540–2545.

30. Hart EC, Joyner MJ, Wallin BG, Charkoudian N. Sex, ageing and resting blood pressure: gaining insights from the integrated balance of neural and haemodynamic factors. J Physiol. 2012;590:2069–2079. DOI: 10.1113/jphysiol.2011.224642.

31. Sato K, Sadamoto T, Ueda-Sasahara C, Shibuya K, Shimizu-Okuyama S, Osada T, Kamo M, Saito M, Kagaya A. Central command and the increase in middle cerebral artery blood flow velocity during static arm exercise in women. Exp Physiol. 2009;94:1132–1138. DOI: 10.1113/expphysiol.2009.048595.

32. Labrecque L, Drapeau A, Rahimaly K, Imhoff S, Billaut F, Brassard P. Comparable blood velocity changes in middle and posterior cerebral arteries during and following acute high-intensity exercise in young fit women. Physiol Rep. 2020;8:e14430. DOI: 10.14814/physrep.2.14430.

33. Calverley TA, Ogoh S, Marley CJ, Steggall M, Marchi N, Brassard P, Lucas SJE, Cotter JD, Roig M, Ainslie PN, et al. HiITing the brain with exercise; mechanisms, consequences and practical recommendations. J Physiol. 2020;598:2513–2530. DOI: 10.1113/JP275021.

34. Hornby TG, Reisman DS, Ward IG, Scheets PL, Miller A, Haddad D, Fox EJ, Fritz NE, Hawkins K, Henderson CE, et al. Clinical practice guideline to improve locomotor function following chronic stroke, incomplete spinal cord injury, and brain injury. J Neurol Phys Ther. 2020;44:49–100. DOI: 10.1097/NPT.0000000000000303.