Cardiovascular Disease Risk Is Associated With Middle Cerebral Artery Blood Flow Velocity in Older Adults

Sophy J. Perdomo, PhD;[1] Jaimie Ward, MS;[1] Yumei Liu, MD, PhD;[1] Eric D. Vidoni, PT, PhD;[2] Jason F. Sisante, PhD;[1,3] Kiersten Kirkendoll, DPT;[1] Jeffrey M. Burns, MD;[2] Sandra A. Billinger, PT, PhD[1]

[1]Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, Kansas City, KS
[2]University of Kansas Alzheimer's Disease Center, University of Kansas Medical Center, Fairway, KS
[3]Department of Physical Medicine and Rehabilitation, University of Kansas Medical Center, Kansas City, KS

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Purpose: The aim of this study was to evaluate the relationship of cardiovascular disease (CVD) on middle cerebral blood flow velocity (MCAv) at rest and during exercise. A secondary aim was to explore the relationship between MCAv and (1) the presence of white matter lesions (WMLs) and (2) cognitive function. **Methods:** We recruited individuals who were cognitively normal older adults. Cardiovascular disease risk was assessed by the Pooled Cohort atherosclerotic CVD (ASCVD) risk score. Transcranial Doppler ultrasound measured middle cerebral artery at rest and during a bout of moderate-intensity exercise. We quantified WMLs from magnetic resonance imaging and cognitive function outcomes included executive function, language, processing speed, and attention. **Results:** Seventy-two participants 70.1 $\pm$ 4.7 years of age completed the study protocol. Atherosclerotic cardiovascular disease risk score was significantly associated with resting and exercise MCAv ($P < .01$) but not associated with WMLs ($P > .468$). We observed a significant association between resting and exercise MCAv and language processing ($P = .010$) but not other cognitive domains. **Conclusions:** In cognitively normal older adults, higher ASCVD risk score was associated with blunted resting and exercise MCAv and with lower language processing performance. These results highlight the need for CVD risk management to maintain optimal brain health. **(Cardiopulm Phys Ther J. 2019;00:1–9)** *Key Words: ultrasound imaging, brain health, aging*

INTRODUCTION AND PURPOSE

Cardiovascular disease (CVD) risk factors play a major role in late-life cognitive function, as well as the occurrence of stroke, vascular dementia, and Alzheimer disease (AD).[1,2] Impaired cerebrovascular regulation may be the foundational link between CVD risk and poor brain health.[3–8] Furthermore, higher CVD risk in 142 middle-aged and older adults was a significant predictor for lower brain blood flow velocity in both the carotid and middle cerebral arteries (MCAs).[4] Cardiovascular disease risk and

aortic stiffness can negatively affect cerebral blood flow in healthy, cognitively normal adults.[9] However, over time, impaired cerebral blood flow regulation may lead to repeated ischemic injury, such as white matter lesions (WMLs),[10] stroke, and even AD.[11] Therefore, health care professionals on the front lines of care should assess CVD risk to maximize optimal brain health.

Understanding middle cerebral blood flow velocity (MCAv) at rest and during an acute exercise challenge may provide valuable information for individuals at risk for cerebral pathology or suboptimal brain aging. Our previous work was the first to show a blunted cerebrovascular response during exercise in individuals with elevated beta-amyloid, a known risk factor for AD[12] when compared with those who were nonelevated. With further examination between groups, we reported that participants with elevated beta-amyloid also had greater CVD risk. The already present elevated beta-amyloid potentially obscured our ability to identify the unique contributions of CVD risk to brain health. Therefore, to better understand the relationship between CVD risk on MCAv, we designed this study to focus on individuals characterized as nonelevated for the presence of beta-amyloid and without cognitive impairment. The current study evaluated the association of CVD risk (defined as the atherosclerotic CVD [ASCVD] risk score)[13] on MCAv at rest and during a single bout of moderate-intensity exercise.

We hypothesized that individuals with higher ASCVD risk would have blunted MCAv at rest and during exercise. A second study objective was to explore the relationship between MCAv and (1) WML and (2) cognitive function. We hypothesized that blunted MCAv at rest and during exercise would be associated with higher WML and reduced cognitive function.

METHODS

Participants

Participants were recruited from a registry of individuals at the University of Kansas Alzheimer's Disease Center (KU ADC). Inclusion criteria were (1) 65 to 90 years of age; (2) cognitively normal/nondemented based on neuropsychological testing and a clinical dementia rating = 0; and (3) completion of [18F] florbetapir positron emission tomography scan within 6 months of our experimental procedures. Exclusion criteria included (1) Diagnostic and Statistical Manual of Mental Disorders-IV defined drug or alcohol abuse within the previous 2 years; (2) clinically significant depression or anxiety; (3) insulin-dependent diabetes; (4) myocardial infarction or symptoms of coronary artery disease within the previous 2 years; (5) acute decompensated congestive heart failure or class IV heart failure; (6) major orthopedic disability; and (7) inability to exercise due to pain or physician restrictions. For this study, we excluded individuals who were characterized as having elevated beta-amyloid status as previously reported.[12]

Written informed consent was obtained for all participants before any data collection. Approval for this study was granted by the Institutional Review Board at the University of Kansas Medical Center.

Correspondence: Sandra A. Billinger, PT, PhD, Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, 3901 Rainbow Boulevard, MS 2002, Kansas City, KS 66160 (sbillinger@kumc.edu).

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Experimental Procedure

All participants began study procedures between 7:30 and 9:00 AM. Participants abstained from caffeine for 12 hours, physical activity for 24 hours, and a large meal for 2 hours.[12,14] Participants were asked to refrain from taking their morning medications until after the procedure. After consent, health questionnaires including assessment of CVD risk factors were completed followed by the experimental protocol to assess cerebrovascular regulation.

Cardiovascular Disease Risk

We calculated ASCVD risk using the Pooled Cohort Equation provided by the American Heart Association and the American College of Cardiology Guideline on the Assessment of Cardiovascular Risk.[13] The ASCVD risk score was calculated using the Pooled Cohort equation that incorporates sex, age, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (SBP), as well as smoking, diabetes, and hypertension treatment status.[13] Supine SBP was assessed after 20 minutes of rest. Cholesterol values were obtained during the clinic visit to the KU ADC between 1-2 months before the transcranial Doppler (TCD) measures.

Middle Cerebral Artery Blood Flow Velocity

The laboratory room for the experimental session was dimly lit, the temperature was maintained between 22 and 24°C, and external stimuli were kept to a minimum during testing.[15–17] Unpublished data from an existing data set (n = 70) in our laboratory demonstrated that the mean intratrial coefficient of variation during the resting condition was 7.7% for MCAv ($MCAv_{mean}$), 6.7% for mean arterial pressure (MAP), and 8.6% for end-tidal carbon dioxide ($P_{ET}CO_2$), and during the exercise condition, $MCAv_{mean}$ was 10.0%, 7.9% for MAP, and 8.0% for $P_{ET}CO_2$.

All participants sat quietly on the exercise device for 15 minutes during the experimental protocol set up. The study team member (Y.L. and S.J.P.) performing the TCD ultrasound scan was blinded to any information related to

medical history, cardiovascular risk status, and any imaging data related to amyloid or WMLs. The MCA was measured using TCD ultrasound. The headset with a 2-MHz robotic probe (RobotoC2MD; Multigon Industries, Yonkers, NY) was placed on the temporal window and fixed in place. The left MCA was the primary vessel of interest. If a signal was not obtainable, then the right MCA was used.[12,15] Once the optimal signal was identified, the imaging process began for mean MCAv ($MCAv_{mean}$) at rest and during exercise. Mean arterial pressure was measured using a finger plethysmograph (Finometer Pro; Finapres Medical Systems, Amsterdam, The Netherlands), which was placed on the middle finger of the left hand. A nasal cannula was placed in the participants' nares and adjusted as needed to ensure optimal $P_{ET}CO_2$ reading. (BCI Capnocheck 9004) We monitored $P_{ET}CO_2$ during exercise to ensure participants were not hyperventilating, which is known to induce cerebral vasoconstriction and lower cerebral blood flow.[18] Heart rate (HR) was measured using a 5-lead electrocardiogram. Mean arterial pressure, $P_{ET}CO_2$, and $MCAv_{mean}$ were averaged across each condition (rest and exercise).

For the seated rest condition, participants sat quietly on a recumbent stepper (NuStep, T5XR). Baseline data for all variables were recorded for 8 minutes. After the rest condition, participants performed a single bout of exercise at moderate intensity using the recumbent stepper. Moderate intensity was defined as 40% to 60% of age-predicted HR reserve.[19] Participants were instructed to maintain a step rate of approximately 90 steps per minute.[20] All participants began the exercise at 40 W. The resistance was then increased until the target HR range was reached. Once participants were in steady state for one continuous minute, the 8-minute exercise session began. Data were sampled at 500 Hz using an analog to digital data acquisition board (National Instruments) and custom script written for MATLAB (v2015; Mathworks, Natick, MA).

White Matter Lesions

The NeuroImaging Core of the XX ADC performed data acquisition for the magnetic resonance imaging (MRI) according to the Alzheimer's Disease Neuroimaging Initiative, which is a multisite longitudinal study of aging and dementia. Our neuroimaging facility uses a Siemens 3.0 Tesla scanner high-resolution T1 weighted and T2 for anatomical assessment (MP-RAGE; 1*1*1.2 mm voxels; TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FOV 256 mm, 9° flip angle). Lesions were segmented by the lesion growth algorithm[21] as recommended and implemented in the LST toolbox version 2.0.15 (www.statisticalmodelling.de/lst.html) for SPM12. The algorithm first segments the MP-RAGE T1 images into the 3 main tissue classes (cerebrospinal fluid, gray matter, and white matter). This information is then combined with the coregistered FLAIR (0.9*0.9*5-mm voxels; TR: 9000 ms, TE = 91 ms, TI = 2500 ms, FOV 240 mm, 150° flip angle) intensities to calculate lesion belief maps. By thresholding these maps with a prechosen initial threshold (k = 0.13), an initial binary lesion map is obtained and subsequently grown according to hyperintensities in the FLAIR image to produce a lesion probability map. The optimal initial lesion threshold was identified as the consensus of 3 raters visually inspecting lesion probability maps in 2 independent data sets (n = 5 age-matched older adults, n = 5 individuals with multiple sclerosis). Total volume of WML was quantified.

Cognitive Function Evaluation

Participants were evaluated for dementia at the XX ADC using the National Alzheimer's Coordinating Center's Uniform Data Set (UDS) neuropsychological test battery scale used by the US ADC network.[22,23] This allows for collaboration, standardized data collection, and longitudinal studies across the ADC network.[24–26] We calculated cognitive domain scores for executive function, language, processing speed, and attention normalized to a cognitively normal sample of older adults as previously reported.[27] During the study, the National Alzheimer's Coordinating Center modified their battery of tests, and this resulted in the inability to maintain uniform testing across all participants, particularly in the memory domain. Consequently, we used only the tests common to both batteries, and the summed free recall of the Free and Cued Selective Reminding Test[28] for memory domain of all participants which our site had been additionally administering to all participants. We normalized this memory domain to a similar population.[29]

Statistical Analysis

Data were assessed for normality using Shapiro–Wilk, and appropriate statistical analyses were conducted. To examine differences between individuals having a low ASCVD risk (ASCVD score $<7.5\%$) and those having an elevated ASCVD risk (ASCVD score $\geq 7.5\%$),[13] Welch t test, Wilcoxon rank-sum test, or test of proportions were performed. To evaluate the influence of ASCVD risk on resting and exercise $MCAv_{mean}$, linear regressions were used.

Age is an important covariate of $MCAv_{mean}$. However, age was not adjusted for in these initial linear regression models due to its large contribution to the ASCVD risk score.[13] We did perform a subanalysis to evaluate these linear regression models adjusting for age. Furthermore, race was not included in the analysis of the ASCVD risk score subcomponents secondary to the entire study sample identifying as white, non-Hispanic. To examine the relationship between $MCAv_{mean}$ and WML, both simple linear regressions and linear regression models adjusting for ASCVD risk were used. In addition, linear regressions adjusted for age, sex, and education were used to evaluate the relationship between $MCAv_{mean}$ and cognitive

function. All data analyses were performed in Stata 15 (StataCorp; LLC, College Station, TX).

RESULTS

Participant Characteristics

Eighty-five participants enrolled in this study, and 72 participants had complete data sets for the primary analysis. Reasons for incomplete data sets and not being included in the analyses were missing cholesterol values (n = 9) and either an unobtainable MCAv signal or artifact during exercise (n = 4). Resting and exercise MCAv data for participants (n = 20) in this study has also been previously published.[11] Participants were educated, white non-Hispanic (100%) women (69%) with a mean age of 70.0 years (SD = 4.7) (Table 1). All participants identified as being physically inactive[30] and had varying levels of WMLs (M = 2.72, SD = 3.04). Nine participants were taking beta-blockers and 8 reported taking calcium-channel blockers. All participants reached the target HR range using the appropriate estimated HR equations. Participants had no history of cerebrovascular disease by clinical presentation and MRI.[1]

Relationship of Cardiovascular Disease Risk on Middle Cerebral Blood Flow Velocity

Evaluating differences between individuals having a low ASCVD risk (ASCVD score <7.5%) and those having an elevated ASCVD risk (ASCVD score ≥7.5%) revealed between-group differences. Participants with an elevated CVD risk had significantly lower resting and exercise $MCAv_{mean}$. We report a significant difference in resting

TABLE 1

Participant Characteristics

Demographics	Overall (n = 72)	Elevated ASCVD Risk (n = 54)	Low ASCVD Risk (n = 18)	*P*
Age (y)	70.0 (4.7)	71.3 (4.7)	66.3 (1.5)	<0.0001
Female (%)	69	59.3	100	0.001
White non-Hispanic (%)	100	100	100	—
Education (y)	16.8 (2.5)	16.5 (2.4)	17.7 (2.3)	0.076
BMI (kg/m^2)	26.7 (4.4)	27.4 (4.6)	24.8 (2.8)	0.015
Cardiovascular disease risk characteristics				
ASCVD score	15.0 (9.0)	18.2 (8.2)	5.5 (1.2)	<0.0001
Systolic blood pressure (mm Hg)	131.0 (15.0)	134.4 (14.2)	120.6 (13.1)	0.001
Total cholesterol (mmol/L)	190.2 (35.3)	185.9 (35.2)	203.3 (33.3)	0.066
HDL cholesterol (mmol/L)	60.0 (18.1)	58.2 (17.7)	65.4 (19.0)	0.123
Blood pressure treatment %	31.0	40.7	0	0.001
Diabetes %	3.0	3.7	0	0.408
Smoking status %	1.4	1.9	0	0.561
Resting and exercise parameters				
Resting $MCAv_{mean}$ (cm/s)	47.1 (11.1)	44.8 (11.0)	53.9 (8.3)	0.001
Exercise $MCAv_{mean}$ (cm/s)	53.4 (12.6)	50.4 (11.5)	62.1 (11.9)	0.001
Resting mean arterial pressure (mm Hg)	73.5 (12.6)	74.1 (10.4)	71.8 (17.8)	0.129
Exercise mean arterial pressure (mm Hg)	106.3 (20.9)	105.6 (18.8)	108.1 (26.8)	0.792
Resting CO_2 (mm Hg)	33.9 (5.2)	33.4 (5.2)	35.4 (5.1)	0.071
Exercise CO_2 (mm Hg)	37.9 (4.5)	37.5 (4.3)	39.1 (4.8)	0.183
Cognitive domains				
Processing speed	0.012 (0.397)	−0.015 (0.421)	0.092 (0.312)	0.257
Executive function	−0.172 (0.816)	−0.103 (0.886)	−0.377 (0.523)	0.156
Language processing	0.265 (0.705)	0.243 (0.725)	0.331 (0.653)	0.634
Attention	−0.214 (0.828)	−0.253 (0.795)	−0.097 (0.934)	0.558
Memory	0.592 (0.924)	0.546 (0.964)	0.728 (0.802)	0.435

Data are presented as mean (SD). Atherosclerotic cardiovascular disease (ASCVD) score indicates atherosclerotic cardiovascular disease. Cognitive domain scores are normalized.

BMI, body mass index; MCAv, middle cerebral blood flow velocity.

$MCAv_{mean}$ between those with a low ASCVD risk (M = 53.95 cm/s, SD = 8.27) and those with an elevated ASCVD risk (M = 44.79 cm/s, SD = 11.00); t (40.8) = 3.72, $P = .001$. Similarly, exercise $MCAv_{mean}$ was significantly different between individuals characterized as low ASCVD risk (M = 62.12 cm/s, SD = 11.93) and those with an elevated ASCVD risk (M = 50.43 cm/s, SD = 11.53); t (29.6) = 3.63, $P = .001$. Resting and exercise MAP and $P_{ET}CO_2$ were not different (Table 1).

Resting $MCAv_{mean}$ significantly decreased on average by 0.43 cm/s ($r^2 = 0.124$, $P = .002$) for every unit increase in ASCVD score (Fig. 1). Exercise $MCAv_{mean}$ significantly decreased on average by 0.55 cm/s ($r^2 = 0.153$, $P = .001$) for every unit increase in ASCVD score (Fig. 1). In the subanalysis, adjusting these models for age revealed resting $MCAv_{mean}$ decreased on average by 0.47 cm/s ($r^2 = 0.124$, $P = .046$) for every unit increase in ASCVD score while exercise $MCAv_{mean}$ decreased by 0.58 cm/s ($r^2 = 0.153$, $P = .027$) for every unit increase in ASCVD score.

Evaluating the subcomponents of the ASCVD score showed that age influenced resting $MCAv_{mean}$. For every additional year, resting $MCAv_{mean}$ decreased by 0.64 cm/s ($r^2 = 0.072$, $P = .022$) and exercise $MCAv_{mean}$ decreased by 0.81 cm/s on average ($r^2 = 0.091$, $P = .010$). Males had a significantly lower resting $MCAv_{mean}$ by 5.70 cm/s compared with females ($r^2 = 0.571$, $P = .043$). Individuals with diabetes exhibited a lower resting $MCAv_{mean}$ by 17.79 cm/s ($r^2 = 0.071$, $P = .024$), and exercise $MCAv_{mean}$ was blunted by 17.46 cm/s ($r^2 = 0.052$, $P = .053$) on average compared to those without diabetes. No other ASCVD risk subcomponent was associated with $MCAv_{mean}$ (Table 2).

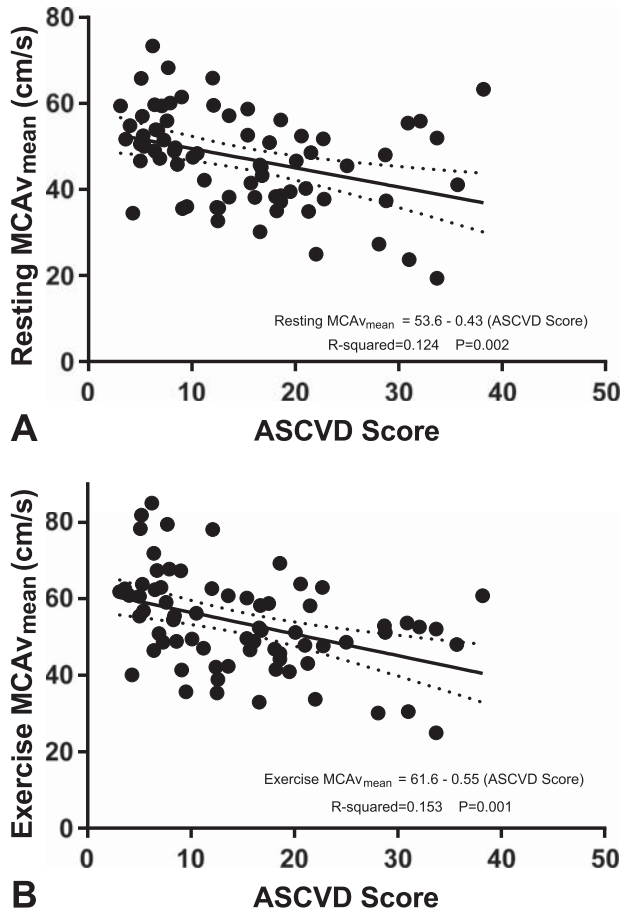

Fig. 1. Associations between ASCVD risk score and $MCAv_{mean}$; (A) resting $MCAv_{mean}$ and (B) exercise $MCAv_{mean}$. *P* values, R^2 values, and regression equations are from simple linear regression models evaluating the influence of CVD risk on cerebrovascular regulation. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease.

Middle Cerebral Blood Flow Velocity and Atherosclerotic Cardiovascular Disease Score with White Matter Lesions

Neither resting $MCAv_{mean}$ ($\beta = -0.03$ cm/s, $r^2 = 0.008$, $P = .468$) nor exercise $MCAv_{mean}$ ($\beta = -0.02$ cm/s, $r^2 = 0.004$, $P = .595$) were associated with WML (n = 66). Models adjusting for ASCVD risk score did not alter associations between resting or exercise $MCAv_{mean}$ and WML. These adjusted models revealed that ASCVD risk score was significantly associated with WMLs. Further investigation demonstrated for every unit increase in ASCVD risk score, WML increased by 0.10 mL ($r^2 = 0.082$, $P = .020$). This relationship was maintained after a sensitivity analysis removing outliers.

Middle Cerebral Blood Flow Velocity and Cognitive Function

Adjusting models for age, education, and sex revealed that language processing was significantly associated with

TABLE 2

β Coefficients for Cardiovascular Disease Risk and MCAv Characteristics

	Resting $MCAv_{mean}$	Exercise $MCAv_{mean}$
ASCVD score	−0.43 ($P = .002$)[b]	−0.55 ($P = .001$)[b]
Age	−0.64 ($P = .022$)[a]	−0.81 ($P = .010$)[a]
Sex	−5.70 ($P = .043$)[a]	−4.82 ($P = .136$)
Total cholesterol	0.04 ($P = .284$)	0.05 ($P = .262$)
HDL cholesterol	0.10 ($P = .159$)	0.12 ($P = .133$)
Systolic blood pressure	−0.08 ($P = .370$)	−0.16 ($P = .106$)
Blood pressure treatment	−0.89 ($P = .756$)	−2.52 ($P = .437$)
Diabetes	−17.79 ($P = .024$)[a]	−17.46 ($P = .053$)
Smoking	−11.70 ($P = .297$)	−12.17 ($P = .342$)

β Coefficients are from individual simple linear regressions of MCAv values with ACSVD score and its subcomponents. Atherosclerotic cardiovascular disease (ASCVD) score indicates atherosclerotic cardiovascular disease.

[a]$P < .05$.

[b]$P < .01$.

BP, blood pressure; MCAv, middle cerebral blood flow velocity; SBP, systolic blood pressure.

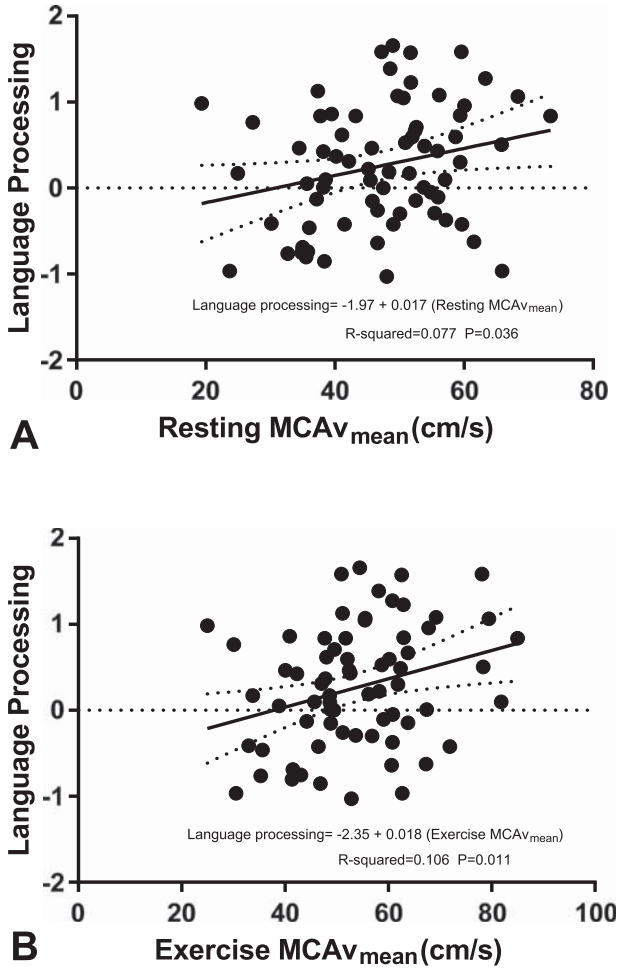

Fig. 2. Associations between $MCAv_{mean}$ and language processing (normed z-scores); (A) resting $MCAv_{mean}$ and (B) exercise $MCAv_{mean}$. *P* values, R^2 values, and regression equations are from linear regression models evaluating the relationship of cerebrovascular regulation and language processing adjusting for age, education, and sex.

both resting and exercise $MCAv_{mean}$. Language processing significantly increased by 0.02 for every cm/s increase in resting $MCAv_{mean}$ ($r^2 = 0.077$, $P = .036$) (Fig. 2) and by 0.02 for every cm/s increase in exercise $MCAv_{mean}$ ($r^2 = 0.106$, $P = .011$) (Fig. 2).

Adjusting models for age, education, and sex revealed that executive function was not significantly associated with resting $MCAv_{mean}$ ($\beta = -0.004$ cm/s, $r^2 = 0.042$, $P = .727$) or exercise $MCAv_{mean}$ ($\beta = -0.009$ cm/s, $r^2 = 0.058$, $P = .264$). Adjusting models for age, education, and sex revealed that memory was not associated with resting $MCAv_{mean}$ ($\beta = 0.01$ cm/s, $r^2 = 0.098$, $P = .243$) or exercise $MCAv_{mean}$ ($\beta = 0.02$ cm/s, $r^2 = 0.116$, $P = .100$). Adjusting models for age, education, and sex revealed that processing speed was not associated with resting $MCAv_{mean}$ ($\beta = -0.004$ cm/s, $r^2 = 0.069$, $P = .351$) or exercise $MCAv_{mean}$ ($\beta = 0.0008$ cm/s, $r^2 = 0.057$, $P = .835$). Similarly, attention was not associated with resting $MCAv_{mean}$ ($\beta = 0.01$ cm/s, $r^2 = 0.056$, $P = .492$) or exercise $MCAv_{mean}$ ($\beta = 0.01$ cm/s, $r^2 = 0.069$, $P = .229$).

DISCUSSION

The present investigation resulted in several novel findings. First, older adults characterized as nondemented and "healthy brain aging" (no cerebrovascular disease such as stroke and nonelevated for beta-amyloid) with higher ASCVD risk had blunted resting and exercise $MCAv_{mean}$ than those with lower ASCVD risk. Second, resting and exercise $MCAv_{mean}$ were not associated with WML. However, WML volume was associated with ASCVD risk, such that individuals with a higher ASCVD risk had a higher WML. Third, higher resting and exercise $MCAv_{mean}$ were associated with language processing skills but not with other measures of cognition. These results extend the current evidence and highlight those with higher CVD risk have reduced MCAv during exercise, which may be an indicator of cerebrovascular health.[3,31–35]

Cardiovascular Disease Risk and Middle Cerebral Blood Flow Velocity

$MCAv_{mean}$ during rest provides valuable information for establishing a baseline. However, the addition of exercise $MCAv_{mean}$ provides a much more comprehensive evaluation of MCAv response to a physical demand. Exercise is a physiological challenge to the cerebrovasculature due to increases in cardiac output, MAP, and sympathetic nervous system activity.[36,37] Thus, evaluating the response of $MCAv_{mean}$ to exercise provides a unique assessment of cerebrovascular control[12] and perhaps could be used to characterize the risk and progression of poor brain health.

Furthermore, there is evidence to suggest that lower resting cerebral blood flow velocity is associated with similar measures of CV risk. The Framingham general cardiovascular risk profile was related to lower resting $MCAv_{mean}$ in 160 healthy adults with a mean age of 59 ($n = 160$).[4] Similarly, another study reported that a higher Framingham risk score was associated with lower resting cerebral blood flow using MRI techniques in large data set ($n = 576$) of adults with a mean age of 46 years.[3] This study extends the current scientific knowledge by adding an exercise challenge to the MCAv assessment. Similar to rest, we report higher ASCVD score resulted in a lower exercise $MCAv_{mean}$, further supporting the importance of maintaining cardiovascular health. In addition, when comparing individuals having a low ASCVD risk (ASCVD score $<7.5\%$) and those having an elevated ASCVD risk (ASCVD score $\geq 7.5\%$), we found that those with an elevated risk had significantly lower resting and exercise $MCAv_{mean}$. Overall, the results of this study provide support that CVD risk influences $MCAv_{mean}$. We provide evidence that rest and exercise $MCAv_{mean}$ are blunted in those with elevated ASCVD risk and the importance of monitoring CVD risk for optimal brain health.

In addition to the ASCVD risk score, this study assessed the ASCVD subcomponents to ascertain whether specific components were driving the relationship between

the ASCVD score and resting and exercise $MCAv_{mean}$. The findings of this study revealed that age, sex, and diabetes were associated with either resting or exercise $MCAv_{mean}$. These results are consistent with studies reporting that individuals who are older, male, and diabetic have suboptimal cerebrovascular health.[38–41] Given the current emphasis on cerebrovascular health and chronic disease, we provide support for the perspective that individuals with diabetes may be at risk for cerebrovascular dysfunction. Although only 2 participants had a diagnosis of diabetes, we found these individuals had a significantly lower resting (−17.8 cm/s) and exercise $MCAv_{mean}$ (−17.5 cm/s) compared to those without diabetes. Several mechanisms could explain our findings in these 2 participants. Diabetes is associated with increased blood viscosity that impairs blood flow, thereby reducing cerebral blood flow.[42–44] Hyperglycemia results in a loss of vessel elasticity, which has been linked to reduced cerebral blood flow.[45–47] In addition, diabetes has a high prevalence of hypertension,[48] which is known to result in both structural and functional cerebrovascular alterations, such as hypertrophy and remodeling of the cerebrovasculature, increases in resistance, impaired functional hyperemia (neurovascular decoupling), and reductions in cerebral blood flow.[49] Targeting therapeutic and lifestyle interventions to reduce ASCVD risk, especially those at greatest risk for diabetes, are likely to be very important given the association between diabetes and dementia.[50] Thus, further research in this area is warranted to elucidate the mechanisms contributing to reduced resting and exercise $MCAv_{mean}$ in people with diabetes.

Atherosclerotic Cardiovascular Disease Risk, Cerebrovascular Regulation, and White Matter Lesions

Current evidence suggests that lower cerebral blood flow and blunted cerebrovascular regulation are associated with WMLs.[38,51,52] However, our results with $MCAv_{mean}$ did not support the hypothesis that these measures would be associated with higher WMLs. This discrepancy may be due to differences in methodology. In this study, we assessed resting and exercise $MCAv_{mean}$ and not cerebrovascular regulation. Previous studies used MRI and acetazolamide administration to measure cerebral blood flow response. These different methods could lead to different results, and thus, further research is needed. We believe that exercise provides a unique physiologic challenge to the human system and provides insight into the interconnection between cerebrovascular health and dysfunction.[12] Exercise has great ecological validity as it is clinically prescribed and is recommended that health care providers assess and promote physical activity.[53] Although not a primary aim of the study, higher ASCVD score was associated with a higher WML. This is consistent with previous work demonstrating that CVD risk factors are positively associated with WML[39,54] and underscore the importance to minimize CVD risk factors across the lifespan.

Middle Cerebral Blood Flow Velocity and Cognitive Function

Reduced cerebral blood flow is associated with cognitive decline and an increased risk for stroke and AD.[55] Our results partly support the association between reduced $MCAv_{mean}$ with cognitive function. We found resting and exercise $MCAv_{mean}$ to be associated with reduced language processing. Previous work has reported cerebrovascular regulation to be associated with overall cognitive function and other cognitive domains.[12,56,57] These differences may, in part, be due to cognitive assessments, participant demographics, or our methodology as we did not directly assess cerebrovascular regulation. Our participants were well-characterized cognitively normal older adults and at lower risk of developing AD as evidenced by nonelevated beta-amyloid levels, which likely affected the relationship between resting and exercise $MCAv_{mean}$ and cognition. The cohort underwent standardized cognitive evaluation using the UDS neuropsychological test battery and the CDR, providing a rich, standardized cognitive profile and reducing the risk of contamination of our sample by prodromal dementia.[22,23] This allowed us to explore the specific contribution of CVD risk factors to resting and exercise $MCAv_{mean}$ and cognitive function.

Study participants self-identified as white, non-Hispanics which limits the interpretation of results to individuals from other racial and ethnic backgrounds who may be at higher risk for CVD and have differing cardiac risk factors. In addition, study participants were mostly female, which could have affected our results, given the known sex differences in MCAv.[58] As in our previous work, we have acknowledged TCD is an indirect measure of cerebral blood flow and does not account for changes in vessel diameter.[59] Although it has been reported that vessel diameter does not change,[60] this has not been unequivocally established.[61,62] Moreover, cholesterol values were collected during clinic visit and not drawn at the same visit as the MCAv experimental protocol, which could alter the ASCVD score. Finally, it would have been preferable to maintain a complete and consistent cognitive battery throughout the study. However, as noted in this manuscript, norming was performed either through a published UDS normative calculator or, in the case of the Free and Cued Selective Reminding Test, to a separate age, sex, and education-appropriate population of individuals from our previous work.[29] Finally, we must acknowledge the r-square values are small, which suggest that the variables are not accounting for much of the explained variability. Future research should explore other potential variables that may influence brain health.

Considerations for Clinical Practice

The findings presented here highlight the importance of maintaining heart health for brain health. This topic is timely because we observe increased life expectancy and

the occurrence of noncommunicable diseases are projected to rise.[63] A timely publication by the American Heart Association, Defining Optimal Brain Health in Adults, strongly recommends humans minimize CVD risk factor across the lifespan to maintain both cardiovascular and brain health.[1] As physical therapists, we should regularly evaluate our patients' CVD risk using several metrics (blood pressure, diet, body weight, and exercise) and educate patients on CVD risk management that are optimal for heart and brain health. These findings add to a growing body of evidence that the ASCVD score has potential clinical utility to assess CVD risk either through the downloadable applications or adapting the "medical record using patient data and published equations."[13] However, further characterization about the relationship between resting and exercise $MCAv_{mean}$ and ASCVD score, including longitudinal studies are necessary.

CONCLUSIONS

Individuals with elevated ASCVD risk present with blunted resting and exercise $MCAv_{mean}$ compared to those with lower ASCVD risk. We report that specific subcomponents of ASCVD risk was associated with blunted resting and exercise $MCAv_{mean}$. Finally, resting and exercise $MCAv_{mean}$ was associated with reduced language processing. Although these results suggest CVD risk management may be important for optimal brain health, more research is needed to examine other factors that may influence CVD health.

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