Cerebrovascular hemodynamics, gait, and falls in an elderly population

MOBILIZE Boston Study

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ABSTRACT

Objective: To determine whether alterations in cerebral blood flow regulation are associated with slow gait speed and falls in community-dwelling elderly individuals.

Methods: The study sample consisted of 419 individuals from the MOBILIZE Boston Study (MBS) who had transcranial Doppler ultrasound measures of cerebral blood flow velocity. The MBS is a prospective cohort study of a unique set of risk factors for falls in seniors in the Boston area. We measured beat-to-beat blood flow velocity in the middle cerebral artery in response to 1) changes in end-tidal CO₂ (cerebral vasoreactivity) and 2) blood pressure changes during a sit-to-stand protocol (cerebral autoregulation). Gait speed was measured during a 4-meter walk. Falls were tracked by monthly calendars, and demographic and clinical characteristics were assessed at baseline.

Results: A multivariate linear regression analysis showed that cerebral vasoreactivity was cross-sectionally related to gait speed ($p = 0.039$). Individuals in the lowest quintile of vasoreactivity had lower gait speeds as compared to those in the highest quintile ($p = 0.047$). In a negative binomial regression analysis adjusted for relevant covariates, the relationship between cerebral vasoreactivity and fall rate did not reach significance. However, when comparing individuals in the lowest to highest quintile of cerebral vasoreactivity, those in the lowest quintile had a higher fall rate ($p = 0.029$).

Conclusions: Impaired cerebral blood flow regulation, as measured by cerebral vasoreactivity to CO₂, is associated with slow gait speed and may lead to the development of falls in elderly people.

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GLOSSARY

ACEI = angiotensin converting enzyme inhibitors; **ADL** = activities of daily living; **ABP** = arterial pressure monitoring; **BFV** = blood flow velocity; **CES-D** = Center for Epidemiologic Studies Depression Scale; **CVR** = cerebrovascular resistance; **HR** = heart rate; **HVLT-R** = Hopkins Verbal Learning Test-Revised; **L-NMMA** = L-NG-monomethyl arginine; **MBS** = MOBILIZE Boston Study; **MCA** = middle cerebral artery; **SPPB** = Short Physical Performance Battery; **VR** = vasoreactivity; **WMSA** = signal abnormalities in cerebral white matter.

Slowing of gait speed is common in elderly people and associated with the development of falls and loss of independence.¹ At 60 years of age, 85% of people have a normal gait; however, by the age of 85 years or older, the percent with normal gait has dropped to 18%.² Abnormalities in gait are associated with falls, which occur annually in nearly 30% of community-dwelling elderly people over age 65.³ For such a common abnormality in older age there is relatively limited information about mechanisms underlying acquired abnormalities in gait and their progression to falls and functional decline.

A myriad of diseases, drugs, and environmental hazards have been identified as potential causes of falls in elderly people. Among these, signal abnormalities in cerebral white matter (WMSA), which are also strongly associated with cerebrovascular disease, are among the stron-

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gest risk factors for slowing of gait, falls, and functional decline in the elderly.^{4,5} Recent studies of cerebral blood flow regulation have shown that cerebral CO₂ vasoreactivity (VR), a nitric oxide mediated vasodilatory response to CO₂ in cerebral arterioles, is also impaired in WMSA.^{6,7} CO₂ vasoreactivity measures the small vessel arteriolar response to changes in arterial carbon dioxide in the brain, which is thought to be mediated by the endothelial lining of these vessels. This notion is supported by studies which have shown that 1) CO₂ VR is impaired in individuals with hypertension and diabetes who are known to have impaired endothelial function, 2) administration of nitric oxide donors improves CO₂ VR in individuals with impaired endothelial function, and 3) blockade of nitric oxide synthase by continued infusion of L-NG-monomethyl arginine (L-NMMA) inhibits CO₂ VR.⁸⁻¹¹

While studies have shown that WMSA are associated with slow gait speed, falls, and alterations in cerebral blood flow regulation, the relationship between cerebrovascular hemodynamics and the slowing of gait speed and falls rates has not been studied. Our study was designed to specifically examine this relationship. We studied the relationship between cerebrovascular function, slowing of gait speed, and fall rates in a representative community-dwelling population of older adults participating in the MOBILIZE Boston Study (MBS) who were followed prospectively for falls.¹² To quantify cerebrovascular function, we measured the cerebral blood flow response to changes in 1) CO₂ (cerebral VR) and 2) blood pressure (cerebral autoregulation). We hypothesized that slowing of gait speed and falls are associated with impaired cerebral VR and autoregulation.

METHODS The study sample consisted of 419 individuals from the MBS, which is a prospective cohort study of a unique set of risk factors for falls in community-dwelling seniors living in the Boston area. The design and methodology for this study have been previously described in detail.^{12,13} In brief, 765 persons aged 70 and older were enrolled using door-to-door population-based recruitment. To be included, individuals had to be >70 years (or age >65 if living with a spouse of a participant), able to understand and communicate in English, able to walk 20 feet without personal assistance (walking aids permitted), and expected to be in the area for 2 years. Exclusion criteria included

terminal disease, severe vision or hearing deficits, and Mini-Mental State Examination score <18).

Baseline assessment included a home interview and a detailed clinic examination. Falls were tracked for 24 months by having participants return fall calendar postcards to the research center at the end of each month. Subjects recorded the actual date of falls on the calendars. Those who failed to return the postcards were contacted by telephone. Reports of falls were followed up with a telephone interview to assess the circumstances and consequences of each fall. On any given month, approximately one third of the participants had to be contacted by phone. This included calls to remind the participants to mail the calendars by the 15th of each month and calls to complete missing information on the previously received calendars. Fewer than 1% of calendars were missing each month.¹⁴

The specific measures relevant to our study included cerebral hemodynamics, medical history, fall history, activities of daily living (ADL),¹⁵ cognition, medications, and depression. The clinic examination included blood pressure, the Short Physical Performance Battery (SPPB),¹⁶ and laboratory tests (i.e., hemoglobin A1C, lipid panel). The time to walk 4 meters is a component of the SPPB, which was used to assess gait speed.

Standard protocol approvals, registrations, and patient consents. The MBS was approved by the Institutional Review Board of Hebrew SeniorLife and all subjects provided written informed consent.

Transcranial Doppler ultrasound. Instrumentation. Subjects reported to the Cerebrovascular Laboratory at the Hebrew SeniorLife Institute for Aging Research and were instrumented for heart rate (HR, ECG) and beat-to-beat arterial pressure monitoring (ABP, Finapres, Ohmeda Monitoring Systems, Englewood, CO).¹⁷ End-tidal CO₂ was measured using a Vacumed CO₂ Analyzer (Ventura, CA) attached to a nasal cannula.

TCD ultrasonography (MultiDop X4, DWL-Transcranial Doppler Systems Inc., Sterling, VA) was used to measure middle cerebral artery (MCA) mean blood flow velocity (BFV) at rest and in response to 1) changes in end-tidal CO₂ and 2) blood pressure during a sit-to-stand protocol, as previously described.¹⁷ The MCA signal was identified according to standard criteria¹⁸ and recorded at a depth of 50 to 60 mm using a Mueller-Moll probe fixation device. The envelope of the velocity waveform, derived from a fast-Fourier analysis of the Doppler frequency signal, was digitized at 500 Hz, displayed simultaneously with the ABP, ECG, and end-tidal CO₂ signals, and stored for later off-line analysis. Previous studies, using a variety of techniques (¹³³Xe, SPECT, MRI) and stimuli, have validated transcranial Doppler measures of relative changes in cerebral flow velocity as representative of changes in cerebral blood flow.¹⁹⁻²⁵

CO₂ vasoreactivity protocol. BFV in the MCA was measured continuously while subjects inspired a gas mixture of 8% CO₂, 21% O₂, and balance nitrogen for 2 minutes and then mildly hyperventilated to an end-tidal CO₂ of approximately 25 mm Hg for 2 minutes. MCA BFV was plotted against end tidal CO₂ while breathing room air, 8% CO₂, or hyperventilating. Cerebral VR was measured as the slope of this relationship and expressed as change in cerebral blood flow per mm Hg change in end-tidal CO₂.

Standing protocol. The active sit-to-stand procedure, which produces immediate orthostatic hypotension without altering the spatial relation between the Doppler probe and the insonated

vessels, was developed in our laboratory and previously described in detail.²⁶ Data were collected continuously during the final 1 minute of sitting and 1 minute of standing. Cerebrovascular resistance (CVR) was calculated as the ratio of mean arterial pressure to mean blood flow velocity (appendix e-1 on the *Neurology*® Web site at www.neurology.org).

Assessment of cognition, gait, and balance and muscle strength. Verbal memory was assessed using the Hopkins Verbal Learning Test–Revised (HVLT-R).^{27,28} Executive function was assessed using the Trailmaking Test (parts A and B).^{29,30} SPPB was used to measure lower extremity mobility performance.^{1,16} Leg strength and muscle power were measured using a double leg press (Keiser Pneumatic Leg Press, Fresno, CA) (see appendix e-1).

Statistical analysis. Means, standard deviations, frequencies, and percentages were calculated to characterize the study sample. The sample was also stratified by whether a subject had an adequate window to obtain TCD measurements. Two-sample *t* tests and χ^2 tests were performed to determine if key variables differed by TCD status.

Negative binomial regression was used to model the association between cerebrovascular hemodynamic measures and fall rates while adjusting for relevant covariates and using time at risk as an offset. Negative binomial regression models are a generalization of the Poisson regression model.³¹ The Poisson distribution assumes that the mean equals the variance. This assumption typically does not hold as the variance is often much higher than the mean. Although overdispersion does not bias the coefficients, it does result in underestimates of standard errors and overesti-

mates of χ^2 statistics, thus increasing type I errors. Because of this concern, we used negative binomial regression models to account for overdispersion.

Multivariate linear regression was used to analyze the association between vasoreactivity and various continuous outcomes including gait speed, executive function (Trail Making Tests A and B), memory function (Hopkins Verbal Learning Test),²⁷ and depression (Center for Epidemiologic Studies Depression Scale) (CES-D).³² In all models, quintiles of cerebrovascular hemodynamic variables were created and indicator (dummy) variables were constructed.

RESULTS Subject characteristics. Table 1 summarizes the demographic and clinical characteristics of the MBS cohort. Subjects with a TCD window were significantly taller, healthier, and more likely to be male and Caucasian compared to those without a TCD window. Those with a TCD window had a significantly lower burden of vascular risk factors and performed much better in SPPB, ADL, and Mini-Mental State Examination assessments. There was no significant difference in the number of falls between those with and without a TCD window.

Cerebrovascular hemodynamics of the study population. Table 2 summarizes the cerebrovascular hemodynamics of individuals with a TCD window during the sit-to-stand and VR protocols. The mean BFV and VR measures were similar to previously reported values for this age group.²⁶ Standing was associated with a hypotensive stimulus and corresponding declines in BFV and CVR. As previously shown,³³ hypocapnia and hypercapnia were also associated with changes in blood pressure similar to those seen during the sit-to-stand protocol. The magnitudes of the blood pressure changes were not significantly different between the VR and the sit-to-stand protocols.

Cerebral vasoreactivity, gait speed, cognition, depression, and motor function. We first examined the relationship between VR and gait speed using a multivariate linear regression analysis, and adjusted for age, gender, race, diabetes, stroke, hypertension, hyperlipidemia, and height (table 3). Higher cerebral VR was associated with faster gait speed after adjusting for these covariates ($p = 0.039$). In order to explore nonlinear associations, we also examined the associations between gait speed and quintiles of VR. Individuals who were in the lowest quintile of cerebral VR had a lower gait speed (slowest walkers) compared to those in the highest quintile of VR who had the highest gait speed (fastest walkers) ($p = 0.047$).

To better understand potential mediators of the relationship between cerebral VR and gait speed or falls, we next examined the relationship between VR and 2 other clinical measures, depression and cognition. We specifically chose these 2 measures because

Table 1 Clinical characteristics of the MOBILIZE Boston Study (MBS) cohort and the subsets with and without transcranial Doppler studies (TCD)^a

	Total MBS (n = 765)	MBS with TCD (n = 419)	MBS without TCD (n = 346)	p Value
Age, y, mean (SD)	78.1 (5.4)	77.9 (5.4)	78.4 (5.5)	0.21
Women, n (%)	489 (63.9)	233 (55.6)	256 (74.0)	0.0001
Caucasian, n (%)	596 (78.0)	365 (87.1)	231 (67.0)	0.0001
Diabetes mellitus, n (%)	141 (18.7)	62 (15.0)	79 (23.2)	0.004
CAD, n (%)	11.0 (3.3)	10.7 (2.8)	11.5 (3.7)	0.002
Hypertension, n (%)	598 (79.1)	313 (75.2)	285 (83.8)	0.004
Hyperlipidemia, n (%)	359 (46.9)	192 (45.8)	167 (48.3)	0.50
Stroke, n (%)	76 (10.0)	36 (8.6)	40 (11.6)	0.15
Gait time, s, mean (SD)	5.1 (1.8)	4.8 (1.5)	5.5 (2.0)	0.0001
Fall rate, mean (SD)	1.4 (2.4)	1.5 (2.8)	1.2 (1.8)	0.17
Height, cm, mean (SD)	163.6 (9.8)	164.8 (10.0)	162.1 (9.5)	0.0002
Mobility, SPPB, mean (SD)	9.3 (2.5)	9.8 (2.2)	8.7 (2.7)	0.0001
ADL, mean (SD)	0.3 (0.6)	0.2 (0.5)	0.4 (0.7)	0.0001
MMSE, n (%)				
25–30	627 (82)	364 (87)	263 (76)	0.0001
18–24	138 (18)	55 (13)	83 (24)	0.0001

Abbreviations: ADL = activities of daily living; CAD = coronary artery disease; MMSE = Mini-Mental State Examination; SPPB = Short Physical Performance Battery.

^a Fall rate is the number of falls per person per year. *p* Values compare those with and without TCD. The N in each column heading refers to the total possible number of subjects in that group. In this cohort, 3.4% were 65–70 years old and 95.5% were >70 years old (1 subject <65). The gait speeds of subjects aged 65–70 did not differ from those aged 70 or more years: 0.93 (0.86–1.01) m/s vs 0.86 (0.84–0.88) m/s, $p = 0.13$.

Table 2 Cerebrovascular hemodynamics during sit-to-stand and vasoreactivity^a

Measure	Sitting	Standing	
Sit-to-stand protocol (n = 334)			
MAP, mm Hg	69.05 ± 13.12	50.16 ± 13.99	
MFV, cm/s	41.86 ± 10.12	34.00 ± 9.89	
CVR, mm Hg × s/cm	1.76 ± 0.61	1.61 ± 0.68	
Heart rate, bpm	65.47 ± 10.01	78.11 ± 12.57	
Measure	Room air	Hypercapnia	Hypocapnia
CO ₂ breathing protocol (n = 419)			
End-tidal CO ₂ , mm Hg	33.47 ± 3.89	54.06 ± 4.00	24.57 ± 4.17
MAP, mm Hg	73.34 ± 13.30	85.18 ± 27.29	60.17 ± 16.26
MFV, cm/s	40.90 ± 10.13	66.02 ± 16.86	31.78 ± 8.90

Abbreviations: CVR = cerebrovascular resistance; MAP = mean arterial blood pressure; MFV = mean flow velocity; VR = vasoreactivity.

^a All values are mean ± SD.

they have been clinically associated with age-related slowing of gait speed and falls, and radiographically linked with WMSA. We found no significant relationship between cerebral VR and depression (CES-D), memory (HVLT), or executive function (Trails A and B) (results not shown).

The same analysis was then applied to explore the relationship between VR and motor function assessed by SPPB and leg muscle strength. We found no significant relationship between cerebral VR and these measures of motor function (results not shown).

Cerebral vasoreactivity and falls. Given the significant relationship between VR and gait speed, we next examined the relationship between cerebrovascular hemodynamics and the annual rate of falls using a negative binomial regression model (table 4). The relationship between rate of falling and cerebral VR

Table 3 Relationship between vasoreactivity and gait speed^a

	Estimate	95% Confidence limits
Vasoreactivity (unadjusted analysis with vasoreactivity as a continuous measure)	0.0487	−0.0063 to 1.1038
Vasoreactivity (adjusted analysis with vasoreactivity as a continuous measure)	0.0552	0.0027 to 0.1076
Vasoreactivity (adjusted analysis)		
Quintile 1	—	—
Quintile 2	0.0402	−0.0254 to 0.1057
Quintile 3	0.0063	−0.0593 to 0.0719
Quintile 4	0.0522	−0.0138 to 0.1183
Quintile 5	0.0818	0.0139 to 0.1496

^aAdjusted for age, gender, race (white-ref.), diabetes, height, stroke, hypertension, and hyperlipidemia. Quintile 1 is the referent quintile.

Table 4 Relationship between vasoreactivity and fall rate^a

	Rate ratio	95% Confidence limits
Vasoreactivity (unadjusted analysis)	1.43	0.99 to 2.07
Vasoreactivity (adjusted analysis)	1.47	0.99 to 2.18
Vasoreactivity (adjusted analysis)		
Quintile 1	1.70	1.06 to 2.73
Quintile 2	1.13	−0.37 to 0.62
Quintile 3	1.41	0.89 to 2.24
Quintile 4	1.25	0.77 to 2.02
Quintile 5	—	—

^aAdjusted for age, gender, race (white-ref.), diabetes, stroke, hypertension, and hyperlipidemia. Quintile 5 is the referent quintile.

did not reach significance with or without adjustment for covariates ($p = 0.057$). We also examined the associations between fall rate and quintiles of VR. Individuals in the lowest quintile of vasoreactivity had a fall rate that was 1.7 (95% confidence interval 1.06–2.73) times higher than those in the highest quintile with and without adjustment for covariables ($p = 0.029$ for the adjusted analysis, table 4).

The figure shows the rate of falls in each quintile of VR. Those in the lower quintiles of VR had a higher annual rate of falls than those in the highest quintile ($p = 0.06$ for overall trend).

Unlike cerebral VR, cerebral autoregulation, measured during the sit-to-stand procedure, was not significantly associated with gait speed or the rate of falling. BFV and CVR during sitting and standing, as well as their percent change from sitting to standing, did not have a significant association with the annual rate of falls (results not shown).

DISCUSSION Slowing of gait speed and falls in older people are often due to complex and multifactorial pathophysiologies. The primary goal of our study was to better understand their association with cerebrovascular hemodynamics by examining the relationship between cerebral blood flow regulation, slow gait speed, and the development of falls. Data from population-based studies linking cerebrovascular hemodynamics to slowing of gait speed and the development of falls have not been previously published.

Our data indicate that cerebral vasoreactivity to CO₂, a measure of cerebral endothelial function,^{8–11} is associated with slower gait speed and marginally with falls. It appears that those in the lowest quintile of VR may have a higher rate of falls compared to those in the highest quintile of VR. Given that low

Figure Falls and vasoreactivity

The relationship between the rate of falls and the quintiles of vasoreactivity adjusted for age, gender, race (white-ref.), diabetes, stroke, hypertension, and hyperlipidemia. Quintile 5 is the highest and the referent quintile.

cerebral VR is also associated with WMSA,^{6,7} the relationship between impairments in VR and mobility may be mediated by WMSA. However, in the absence of imaging data, this possibility is speculative.

Unlike cerebral VR, measures of pressure regulation (cerebral autoregulation) were not related to falls or slow gait speed. Given that age-related WMSA accumulate in the deep watershed border zones, it was our expectation that impaired pressure autoregulation would be associated with slow gait speed and predictive of falls. Our group,²⁶ as well as others,³⁴⁻³⁶ have previously demonstrated that in a number of other clinical entities, including aging, hypertension, stroke, and carotid stenosis, there is a dissociation between cerebral VR and measures of cerebral pressure autoregulation. In other words, these clinical conditions are all associated with intact cerebral autoregulation, but impaired cerebral VR. One explanation for this dissociation may be that our current measures of autoregulation are not sensitive enough to detect subtle changes. It is also possible that impaired autoregulation occurs after the development of endothelial dysfunction, and with time this association may emerge. The presence and magnitude of WMSA could help us to understand better the dissociation between cerebral vasoreactivity and autoregulation, but our cohort did not have MRI.

Based on recent data which show that individuals with weaker quadriceps muscle strength had greater gait variability and an enhanced effect of WMSA volume on falls,⁵ we also examined the relationship between cerebral VR and motor function, as measured by SPPB and leg muscle strength. We did not find any association between cerebral VR and these measures of motor function. Our findings suggest that with the exception of gait speed, these other mea-

asures of motor function do not appear to be related to cerebral VR. Interestingly, while those individuals in the lowest quintiles of vasoreactivity had lower gait speed and higher fall rates compared to those in the highest quintile, the results were not as clear in middle quintiles, especially in quintile 2. One possible explanation for these findings may be the nonlinear relationship between these variables.

Our study provides novel evidence that impaired cerebral vasoreactivity, as a measure of endothelial function, is associated with slow gait speed and the development of falls in elderly people without dementia. Given that a number of measures such as statins, angiotensin converting enzyme inhibitors (ACEI), and daily exercise can improve endothelial function, as well as promote endothelial repair mechanisms,³⁷ our findings suggest a novel strategy for the prevention of falls in elderly people. The potential value of cardiovascular risk reduction for the prevention of falls is underscored by recent findings that blood pressure lowering with ACEI leads to regression of WMSA.³⁸

There are several limitations to our study. First, the absence of imaging data limits our ability to draw conclusions about the role of WMSA or other structural lesions in our findings. Despite ample data linking WMSA to gait disorders and falls, and WMSA to impaired cerebral VR, there are no direct data on the relationship among all 3 factors. Future imaging studies in our cohort will provide the necessary data to directly examine these relationships. Second, the individuals in the cohort who had a TCD window were generally healthier than those who did not have a window, limiting the generalizability of our findings. While a TCD window is absent in about 35% of the elderly population, no prior studies have com-

pared the clinical characteristics of those with and without a TCD window. Overall, it seems that those who had a window were more likely to be healthy white males. Traditionally, hyperostosis of the skull has been identified as the main obstacle to transtemporal insonation of the basal cerebral arteries. How the differences between those with and without a TCD window relate to hyperostosis or whether there are entirely different mechanisms at play that result in failure of transtemporal insonation is unknown. Third, it is important to note that a number of prior studies have established that the traditional measure of cerebral VR (MFV changes in response to changes in end-tidal CO₂) is a complex measure which may also reflect the effects of simultaneous changes in MAP. Fourth, we must also emphasize that this is a cross-sectional study of VR and gait speed. With the future availability of longitudinal data and MRIs from our cohort, we may find that WMSA are the cause of both impaired VR and slow gait. Until we have these data, the causal pathway remains unknown. Finally, it is important to note that while our discussion has been limited to endothelial function and NO reactivity, there may be a host of other factors that could be responsible for the change in VR.

Despite these limitations, our findings are novel and advance our understanding of the relationship between cerebral vasoreactivity, slow gait, and falls. They also should motivate future studies to better define the role of WMSA in the relationship between impaired cerebral VR and falls. These studies will have significant therapeutic implications. Identification of early markers of cerebrovascular dysfunction that are predictive of falls will be an important step toward prevention of these devastating events in elderly people.

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DISCLOSURE

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