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Transcranial Doppler and lower extremity function in older adults:

Einstein Aging Study

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Abstract

Objective—To determine whether transcranial Doppler ultrasound (TCD) measures of mean blood flow velocity (MBFV) in the major cerebral arteries are associated with measures of lower extremity function in community-dwelling older adults.

Design—Cross-sectional study

Setting—Community Sample

Participants—Participants were 200 non-demented adults, age 70 and over, participating in the Einstein Aging Study (EAS).

Measurements—All participants completed TCD assessments and tests of lower extremity function at an annual clinic visit. Average MBFV for the anterior circulation (the left and right anterior (ACA) and middle (MCA) cerebral arteries), and posterior circulation, (both vertebral arteries (VA) and basilar artery (BA)) were acquired using a standardized TCD protocol. Lower extremity function was characterized by gait speed (cm/s) measured using an instrumented

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Ali Ezzati: data analysis, interpretation of data, manuscript preparation, and intellectual contributions to content

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walkway, balance assessed by unipedal stance time (UPST, in seconds), and lower extremity strength by timed repeated chair rise (seconds).

Results—Participants had an average age of 79.5 and 54% were women. Multiple regression models adjusted for age, sex, race, education, and medical comorbidities showed that decreased MBFVs in the MCA were associated with slower gait speed and chair rise time but not with UPST. Ordinal regression models showed that decreased MBFVs in the VA and BA was associated with worse performance on the UPST.

Conclusion—Decreased MBFVs in the anterior and posterior cerebral circulation were associated with worse lower extremity function and balance in older adults. This result might be indicative of the importance of age-related changes in cerebral hemodynamics in function of brain regions involved in specific aspects of physical performance.

Search terms

Transcranial Doppler; gait and balance; older adults

INTRODUCTION

Mobility is a major determinant of independence in older adults. Aging is associated with a decline in physical performance, which manifests as slowing of gait and poor balance [1, 2]. Mobility disability, defined by slow gait velocity measured during normal walking, predicts onset of adverse health events [3]. Elderly persons with mobility disability are less likely to remain in the community, have increased hospitalization rates and increased morbidity and mortality [3–5]. Prior work has demonstrated that peripheral arterial disease and history of clinical coronary artery disease and stroke are associated with subsequent decline in lower extremity motor function and with development of mobility disability [6–9]. Therefore it is important to identify risk factors leading to lower extremity functional decline and develop effective screening tools to identify and guide interventions. To date, most studies have focused on the peripheral effects of vascular factors on muscle strength, and cardiac fitness. Fewer studies have examined the extent to which central cerebrovascular status and function affect mobility.

Changes in cerebrovascular structure and function may contribute to lower extremity function in older adults, possibly through alterations in the brain regions involved in locomotion including the cerebellum, frontal, and prefrontal cortices. [10, 11]. Transcranial Doppler ultrasound (TCD) is an inexpensive, rapid, noninvasive technique for evaluating cerebrovascular hemodynamics, [12] and can be used easily in healthy population as well in patients who are unable to undergo more advanced imaging techniques (i.e. MRI or PET scan). TCD parameters such as mean blood flow velocity (MBFV) and their variation during different challenge tests are valid markers of cerebral circulatory changes. These measures are associated with structural brain changes as reflected by its association with increased burden of white matter hyperintensities (WMH) and decreased cortical thickness [13–15].

In this study, we sought to determine the relationship between cerebral blood flow in the anterior and posterior circulation, and lower extremity function as measured by gait speed,

balance and strength in a community sample of healthy older adults. We hypothesized that decreased MBFVs in vessels supplying premotor and motor cortex as well as subcortical motor tracts (i.e. anterior circulation: the ACA and MCA) are associated with slow gait, while decrease MBFVs in vessels supplying blood flow to cerebellum and brain stem (i.e. posterior circulation: the VA and the BA) have stronger association with measures of balance.

METHODS

Study Population

The Einstein Aging Study is a community based longitudinal study of cognitive aging in adults aged 70 years and older. Study design and methods have been described in detail previously [16]. Participants enrolled in the EAS met the following eligibility requirements: age ≥ 70 years, Bronx residents, non-demented, non-institutionalized, English-speaking and able to walk without personal assistance. Participants who met diagnostic criteria for dementia at enrollment were excluded from this analysis. Dementia diagnosis assigned at consensus case conference was based on the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). [17] Other exclusion criteria were severe visual or auditory impairments, active psychiatric symptomatology, and non-ambulatory status.

Participants completed baseline and annual follow-up assessments at the study clinic. Between May 2012 and May 2015, EAS clinic visits included both TCD and physical performance assessments. A total of 243 participants completed both in the same annual exam. Among these participants, 200 (82%) had adequate acoustic bone windows to insonate all major cerebrovascular vessels including the right and left ACA, right and left MCA, right and left VA and the BA (Supplementary Figure 1). Inability to insonate some vessels may result from aging and variations in anatomy, and our yield is consistent with prior work [18].

The EAS study was approved by institutional review board of Albert Einstein College of Medicine.

Gait and balance assessment

We selected three established performance based tests that provide assessments of various aspects of lower extremity function in aging[19]. Given the role of gait speed as a universal screening measure of health and function in older patients as well as its role as a robust predictor of multiple adverse geriatric outcomes, we focused on gait speed (cm/s) in this analysis. [20] A computerized walkway mat (457.2×90.2×0.6 cm) with embedded pressure sensors (GAITRite, CIR systems, USA) was used for quantitative gait studies. Subjects were asked to walk on the mat at their “normal pace” for two trials in a well-lit hallway while wearing comfortable footwear. Start and stop points were marked by white lines on the floor placed 3 feet from the mat edge to account for initial acceleration and terminal deceleration. The mean of the two trials was automatically computed by the computer software. The participants did not use any walking aids while walking on the walkway. Our group has

previously reported the high reliability of the GAITRite system, and specifically gait speed measurements in older adults [21].

Unipedal stance time (UPST), a sensitive balance test, which has been reported to predict falls in older adults, was recorded as the time participants balanced on one foot (self-selected) without support (maximum 30 seconds) [22, 23]. Participants who could not complete the UPST test, were assigned a time of zero seconds. In addition, time taken to get up from a chair five times unassisted (chair rise time in seconds) was used as a test of balance and lower extremity strength [24]. Chair rise is a composite measure of lower extremity performance with previous studies indicating that both lower extremity strength as well as balance contributes to chair rise performance in middle aged and older adults [25, 26]. The measures included are all components of the of the Short Physical Performance battery, a validated measure of function that has been reported to predict mobility and disability in older adults [19, 27].

Transcranial Doppler ultrasound

Using a standardized bi-lateral scanning protocol [28], a complete TCD examination was performed on each individual by a single experienced sonographer using single-gate non-imaging transcranial Doppler sonography (Neurovision TOCM system with 2-MHz transducers; Multigon Industries, Inc, Yonkers, NY) and a fixation device. Temporal bone windows were used to interrogate the anterior, middle, and posterior cerebral arteries. The foraminal window was used to interrogate the vertebral arteries and the basilar artery. Individual Doppler spectra and cerebral blood flow velocities (cm/sec) were recorded and saved for each arterial segment. MBFVs were analyzed at the central TCD laboratory Core by an experienced neurosonologists as previously described [29].

Other covariates

During each study visit, participants also completed a full medical and neurological evaluation by study clinicians, as well as demographic and medical history assessments. Hypertension was defined as a self-reported history of hypertension or systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or both, or use of antihypertensive medications. Participants were also asked whether a physician had ever told them they had diabetes, arthritis, stroke, myocardial infarction, heart failure, or coronary artery bypass surgery or other revascularization procedures for a coronary artery. History of heart disease was defined as self-reported history of myocardial infarction, heart failure, or coronary artery disease.

Statistical Analysis

Baseline characteristics of this analysis sample and the overall EAS cohort were compared with descriptive statistics. Characteristics of participants in the analysis sample were compared with those who were excluded using independent t-tests and χ^2 analysis.

For the MBFV measures, we used the average value of the mean right and left ACAs, MCAs, and VAs in the analyses. Henceforth, the terms ACA, MCA and VA refer to these average values. Multivariate linear regression models were used to examine the association

of gait speed and chair rise time with MBFV of blood vessels supplying motor cortex (ACA and MCA) and blood vessels supplying blood flow to cerebellum and brain stem structures (BA and VA), while adjusting for demographic variables including age, sex, education, and ethnicity, and also clinical covariates including history of hypertension, diabetes, and heart disease as defined above. Quartiles of UPST were generated from the overall distribution within the study sample. Proportional odds models were used to evaluate the association between UPST quartiles and MBFV of each vessel, and the OR reflects the OR for being in the next higher quartile of UPST associated with a 1 cm/sec increase in MBFV. The proportional odds assumption of ordinal regression was met.

All statistical analyses were conducted by using Stata software, version 12 (StataCorp LP, College Station, Texas)

RESULTS

Demographics and sample characteristics

Participants in the analysis sample had an average age of 79.5 and 54% were women. Participants included in the analysis sample were significantly younger, and more likely to be male compared with excluded participants. Prevalence of vascular risk factors was similar for those included and those excluded from the analyses (Table 1).

Table 2 summarizes the lower extremity function tests and TCD characteristics of the participants. Mean test performance indicates that the study group was relatively healthy. The MBFVs were comparable to previously reported values for similar age groups [30]. Also gait speed, chair rise time, and Unipedal stand time was similar to values previously reported for the larger EAS sample [31] as well as other samples of older adults [32].

Transcranial Doppler MBFV and locomotor function

Lower MBFVs in the MCA were associated with slower gait speed after adjusting for covariates (β=0.18, p= 0.007). There was no significant association between MBFVs of other major vessels and gait speed.

Regression models relating MBFV to repeated chair rise time showed an inverse relation between MBFVs in MCA and chair rise time; higher MBFVs were associated with shorter repeated chair rise time (β=−0.17, p= 0.021), which indicates better balance and lower extremity strength. There was no significant association between MBFVs of other major vessels and repeated chair rise time.

Finally, we examined the association between MBFVs and quartiles of UPST using ordinal regression models. These models indicated that participants with higher MBFVs in VA and in BA had longer UPST (OR= 1.05, p=0.022 and OR= 1.07, p=0.019 respectively), while there was no significant association between MBFVs in ACA and in MCA with UPST.

DISCUSSION

In this study we aimed to better understand the association between lower extremity function and the status of cerebrovascular health hemodynamics as assessed by TCD measures of MBFV in the anterior and posterior cerebral circulation in an aging populations. Data from population based studies of healthy older adults linking motor function and cerebral vascular status or function have been limited. Our results indicate that lower blood flow velocity in MCA is associated with slower gait and slower chair rise time in community dwelling older adults. Decreased blood flow in the posterior cerebral circulation was associated with shorter UPST, an indicator of worse balance and fall risk. Our results emphasize the importance of cerebral hemodynamics in maintaining lower extremity function.

The MCA carries more than 80% of the blood supply to the cerebral cortex [32], and together with the ACA, as part of anterior circulation, they provide the entire blood supply to premotor and motor cortex [33]. Motor regions specifically supplied by the MCA include lateral part of frontal, whole parietal, as well as deeper structure like basal ganglia and internal capsule[34]. Prior transcranial Doppler studies have shown that cerebral vasoreactivity in the MCA adversely affects gait speed and is associated with higher rates of falls in an aging population [35, 36]. Our data shows similar results - an association between low blood flow velocities in the MCA and worse gait speed and chair rise performance. This effect might be partially due to the fact that walking and sit to stand performance depend on the motor and sensory functions that are controlled by the brain areas supplied by the MCA [33].

Our results indicate that MCA-MBFV is associated with gait speed and ACA-MBFV marginally with both gait speed and chair rise time, partially confirming our hypothesis. The ACA supplies most midline portions of the frontal lobes, superior medial parietal lobes, and also deeper structures such as the anterior limb of the internal capsule, part of the caudate nucleus, and the anterior part of the Globus pallidus, which are structures involved in motor control and higher control of gait and balance [34]. Larger studies are needed to confirm our observations.

Our results also showed a significant association between higher blood flow velocities in the VA and BA and longer UPST. UPST is a sensitive test for quantifying static balance ability [23] and is associated with other important factors in older adults such as gait performance [37], frailty [38] and fall rates [39]. Very few studies have examined the relationship between changes in task-related brain activation and mobility performance or lower extremity function. To our knowledge, there is no study directly identifying all brain regions essential for performing unipedal stance test. However, based on the fact that unipedal stance requires a combination of strength, sensation, speed, and balance in various truncal and lower extremity muscle groups, it is expected that a complex sensorimotor network involving primary and supplementary motor areas, deep brain structure (i.e. corticospinal tract), as well as cerebellum and other brainstem structures affect performance on this test. The basilar artery and the vertebral arteries are major vessels of the posterior circulation and provide the blood supply to cerebellum and other brainstem structures, which are particularly important in regulation of balance [33]. Our results may suggest that decreased

blood flow in the posterior circulation indicate pathological changes in the brain regions supplied by these vessels, which in turn affect control of static balance.

Age related pathologies are associated with several alterations across the entire cerebrovascular system, which in turn can adversely affect cerebral blood flow [29, 40, 41]. Arterioles in the deep white matter regions become tortuous and with increasing vascular tortuosity, cerebral blood flow becomes perfusion-dependent, leaving these deep white matter regions vulnerable to chronic hypoperfusion [42]. These changes result in small vessel disease characterized by narrowing or even occlusion of the arterial lumen resulting in chronic ischemia and/or structural changes in the deep brain white matter regions. Vessels in the cerebral gray matter also undergo similar structural changes with the cerebral arterioles, decline in capillary density, thickening and fibrosis in and around the basement membrane of these vessels cerebral blood flow is affected by all these aging associated changes. Several studies have shown that lower cerebral blood flow is associated with increased WMH and decreased cortical thickness in different parts of brain [13–15], which might in manifest in functional decline in older adults including deterioration of locomotor function [43].

In this study we provided novel evidence that decreased cerebral blood flow is associated with impaired physical performance as evidenced by measures of gait and balance. Further, the results show specificity, with physical functions related to blood flow in the vessels serving the brain regions which control those functions. The strength of this study includes use of validated diagnostic tests and procedures, and the use of data from the EAS, which is a longitudinal study of a systematically recruited, ethnically and educationally diverse community-based elderly cohort. Despite this, a few limitations should be noted. The cross-sectional design of this study, precludes concluding a direct causal relation between tested measures. Furthermore, we did not assess the cardiac output status, limiting our ability to analyze potential influences on intracerebral hemodynamics. However, our results did not change after adjusting for hypertension and history of heart disease, including heart failure, and diabetes, which may minimize the effect of cardiac output and systemic atherosclerosis on brain hemodynamics. Additionally, we did not study the potential effect of other medications (i.e. statins or antidepressants) or other possible confounders like smoking and alcohol use in this study. Among the covariates that were controlled in this study, arthritis, peripheral arterial disease and diabetes may affect gait and balance through peripheral factors, however other peripheral factors such as direct measures of muscle strength were not measured in this study.

Although there is a high correlation between MBFV and cerebral blood flow, the two measures are not synonymous. In prior studies in younger adults with minimal or no vascular disease, TCD measurements of mean blood flow velocity was shown to be a valid tool for determination of the CBF autoregulation, and the changes in CBF reliably evaluated by TCD [44]. Nevertheless, in persons with significant intracranial pathology this association might vary significantly [45]. In arterial stenosis, the flow velocity at that site is increased as a function of the cross-sectional luminal area, while the flow is also dependent on other parameters such as arterial elasticity and sheer stress. Given that our study population is healthy older adults and none have significant intracranial stenosis, the correlation between MBFV and cerebral blood flow is expected to be high. TCD measure of

cerebral blood flow velocity is therefore a reasonable approximation of segmental cerebral blood flow in our study, although we cannot make a definite conclusion whether the observed association between MBFV and lower extremity function tests would translate to an association between CBF and lower extremity function. Further studies with direct measures for CBF and dynamic changes of MBFV while performing tests are required to better understand the role of regional CBF for specific motor tasks.

In conclusion, our study emphasize the importance of cerebral blood flow for locomotor function. Considering that a number of different interventions including life style modification, daily exercise, medications like statins, angiotensin converting enzyme inhibitors, and anti-platelets can improve or protect endothelial function of the cerebral arteries and therefore maintain healthy brain hemodynamics, our findings may suggest potential strategies for prevention of decline in locomotor function in the elderly. Future longitudinal studies with multimodal imaging technics are warranted to investigate the causal relationship between cerebral blood flow and perfusion with locomotor function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Impact statement

We certify that this work is novel.

This study shows an association between specific lower extremity functions and mean arterial velocity based on Transcranial Doppler measurement for the first time.

Table 1

Sample characteristics

	Total EAS N=538	EAS with TCD and GAIT N=200	EAS without TCD and GAIT N=338	p-value
Age, y, mean (SD)	80.8(6.1)	79.5(5.7)	81.5(6.1)	<0.001
Sex, Women, n (%)	352(65.4)	108(54)	244(72.2)	<0.001
Race, White, n (%)	302(56.1)	119(59.5)	183(54.1)	0.459
Education, y, mean (SD)	14.6(3.3)	14.8(3.4)	14.5(3.2)	0.206
Hypertension, n (%)	372(69.1)	136(68.0)	236(69.8)	0.658
Diabetes, n (%)	116(21.6)	38(19.0)	78(23.1)	0.266
Stroke, n (%)	26(4.8)	6(3.0)	20(5.9)	0.127
Heart disease[1], n (%)	75(13.9)	28(14.0)	47(13.9)	0.976
Arthritis[2], n (%)	372(69.1)	132(66.0)	240(71.0)	0.224

[1]Includes participants with history of any of myocardial infarction, heart failure, or coronary artery disease,

[2]history of osteoarthritis or rheumatoid arthritis

Table 2

Lower extremity function and transcranial Doppler characteristics of study sample

Measure	Study sample, N=200
Gait speed, cm/s, mean (SD)	94.4 (20.1)
Chair rise time, sec, mean (SD)	14.5 (3.7)
Unipedal stance time, sec, median (range)	5.3 (0–30)
ACA-MBFV[1], cm/s, mean (SD)	31.3(6.5)
MCA-MBFV, cm/s, mean (SD)	34.1(7.1)
PCA-MBFV, cm/s, mean (SD)	28.2(4.2)
BA-MBFV, cm/s, mean (SD)	22.3(7.1)
VA-MBFV, cm/s, mean (SD)	19.9(4.4)

MBFV=mean flow velocity, ACA=anterior cerebral artery, MCA=middle cerebral artery, PCA= posterior cerebral artery, BA=Basilar artery, VA=vertebral artery

[1]Average MBFV of right and left vessel is reported for ACA, MCA, PCA, and VA.

[2]Anterior circulation MBFV is the average MBFV for right and left ACA and MCA.

Table 3

Linear regression models showing relationship between gait speed, chair rise time and mean blood flow velocity by TCD.

Mean Blood Flow Velocity (MBFV),(cm/sec)	Gait speed[1]		Chair rise time[1]	
	Beta	**P-value**	**Beta**	**P-value**
ACA	0.10	0.126	−0.12	0.116
MCA	**0.18**	**0.007**	**−0.17**	**0.021**
BA	0.02	0.826	−0.05	0.502
VA	0.05	0.453	−0.06	0.466

MBFV=mean flow velocity, ACA=average of left and right anterior cerebral arteries, MCA=average of right and left middle cerebral arteries, BA=Basilar artery, VA=average of right and left vertebral arteries. Significant results are bolded in the table.

[1]Adjusted for age, sex, race, education, diabetes, hypertension, stroke, heart disease, and arthritis.

Table 4

Results of proportional odds models showing relationship between quartile of unipedal stance time and mean blood flow velocity by TCD.

Mean Blood Flow Velocity (MBFV),(cm/sec)	**OR for being in the next higher quartile of Unipedal stance time[1]**		
	Odds ratio	**95% confidence interval**	**P value**
ACA-MBFV	1.03	0.98–1.07	0.209
MCA-MBFV	1.03	0.99–1.06	0.118
BA-MBFV	**1.05**	**1.01–1.10**	**0.022**
VA-MBFV	**1.07**	**1.01–1.14**	**0.019**

MBFV=mean flow velocity, ACA=anterior cerebral artery, MCA=middle cerebral artery, BA=Basilar artery, VA=vertebral artery. Significant results are bolded in the table.

[1]Adjusted for age, sex, race (white-ref.), education, diabetes, hypertension, stroke, heart disease, and arthritis.