Age-related decline in peripheral vascular health predicts cognitive impairment

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Received: 11 March 2019 / Accepted: 1 April 2019 / Published online: 27 April 2019
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Abstract Preclinical studies demonstrate that generalized endothelial cell dysfunction and microvascular impairment are potentially reversible causes of age-related vascular cognitive impairment and dementia (VCID). The present study was designed to test the hypothesis that severity of age-related macro- and microvascular

dysfunction measured in the peripheral circulation is an independent predictor of cognitive performance in older adults. In this study, we enrolled 63 healthy individuals into young (< 45 years old) and aged (> 65 years old) groups. We used principal component analysis (PCA) to construct a comprehensive peripheral vascular health

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Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11357-019-00063-5>) contains supplementary material, which is available to authorized users.

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index (VHI) encompassing peripheral microvascular reactivity, arterial endothelial function, and vascular stiffness, as a marker of aging-induced generalized vascular dysfunction. Peripheral macrovascular and microvascular endothelial function were assessed using flow-mediated dilation (FMD) and laser speckle contrast imaging tests. Pulse waveform analysis was used to evaluate the augmentation index (AIx), a measure of arterial stiffness. Cognitive function was measured using a panel of CANTAB cognitive tests, and PCA was then applied to generate a cognitive impairment index (CII) for each participant. Aged subjects exhibited significantly impaired macrovascular endothelial function (FMD, $5.6 \pm 0.7\%$ vs. $8.3 \pm 0.6\%$ in young, $p = 0.0061$), increased arterial stiffness (AIx $29.3 \pm 1.8\%$ vs $4.5 \pm 2.6\%$ in young, $p < 0.0001$), and microvascular dysfunction (2.8 ± 0.2 vs 3.4 ± 0.1 -fold change of perfusion in young, $p = 0.032$). VHI showed a significant negative correlation with age ($r = -0.54$, $p < 0.0001$) and CII significantly correlated with age ($r = 0.79$, $p < 0.0001$). VHI significantly correlated with the CII ($r = -0.46$, $p = 0.0003$). A decline in peripheral vascular health may reflect generalized vascular dysfunction and predict cognitive impairment in older adults.

Keywords Aging · Endothelial function · Microvascular dysfunction · Cognitive impairment · VCID

Introduction

As life span increases in the Western world, age-related cognitive decline has become a growing public health issue (Gorelick et al. 2011; Lobo et al. 2000). Recent studies highlighted the importance of vascular contributions to cognitive impairment and dementia (VCID) by establishing a strong link between impaired cerebrovascular health and cognitive decline. Several lines of evidence support the concept that age-related cerebromicrovascular impairment and endothelial dysfunction play a causal role in the pathogenesis of VCID (Gorelick et al. 2011; Tarantini et al. 2017; Toth et al. 2017) and, possibly, Alzheimer's disease (AD) (Iadecola and Gottesman 2018). First, clinical studies indicate that dysregulation of cerebral blood flow is related to cognitive decline in older adults (Toth et al. 2017). Second, restoration of cerebral microvascular function and blood flow regulation by dietary or pharmacological interventions in animal models of aging results in a significant improvement of cognitive

function (Tarantini et al. 2018). Further, cardiovascular risk factors that promote accelerated vascular aging, including hypertension, diabetes mellitus, and obesity, are known to promote VCID, at least in part, by inducing cerebromicrovascular impairment and endothelial dysfunction (Gorelick et al. 2011; Tucsek et al. 2014). These findings suggest that cerebromicrovascular and endothelial dysfunctions are potentially reversible causes for cognitive decline in older adults.

Although several techniques are available to assess cerebral blood flow in human subjects (e.g., functional MRI) to identify patients at risk for VCID among community-dwelling older individuals, the cost and availability of these techniques require development of new screening approaches for an outpatient clinic. In addition, development of novel methods to assess vascular health may provide a tool to characterize efficiency of interventions for prevention of VCID in larger population-based studies.

There is a strong clinical and experimental evidence that aging and pathophysiological conditions that accelerate vascular aging (e.g., hypertension, diabetes mellitus, and obesity) promote generalized endothelial dysfunction and cause similar functional and phenotypic changes in the peripheral vasculature and cerebral circulation (Ungvari et al. 2018). This concept is also supported by extensive pre-clinical studies that showed beneficial effects of several approaches, including pharmacological and dietary interventions, on cerebromicrovascular reactivity and cerebral blood flow, as well as in peripheral arteries and arterioles (Pearson et al. 2008; Tarantini et al. 2018; Toth et al. 2014). The evolution of the concept of generalized endothelial cell dysfunction and microvascular impairment in aging provided the framework for studies to develop surrogate markers based on functional assessment of peripheral vascular beds to identify patients at risk for VCID.

Present study was designed to test the hypothesis that severity of age-related macro- and microvascular dysfunction measured in the peripheral circulation is an independent predictor of cognitive performance in older adults. In this study, we used a principal component analysis (PCA)-based approach to construct a comprehensive peripheral vascular health index encompassing peripheral microvascular reactivity, arterial endothelial function, and vascular stiffness, as a marker of aging-induced generalized vascular dysfunction. We chose vascular parameters, the direct, and reproducible

measurements of which can be easily performed on geriatric patients in an outpatient setting. The association between age-related decline in the peripheral vascular health index and decreased cognitive performance was established.

Methods

All procedures performed in the present study were approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center. Eligible patients were enrolled in this study upon familiarizing with and signing the informed consent form.

Patient selection

For this cross-sectional study, we recruited healthy individuals of 21 to 92 years of age. Clinical characteristics of study participants are presented in Table 1. Exclusion criteria consisted of untreated hypertension, untreated diabetes, active cancer, recent or active cardiovascular disease (heart failure, myocardial infarction, angina, stroke), presence of peripheral artery disease,

active infection, medication that can interfere with normal cognitive function, and for postmenopausal women, hormone replacement therapy. Habits (such as smoking) and any other major medical condition were noted.

Cognitive testing

Subjects were asked to arrive after a light breakfast and to avoid caffeine consumption in the morning of examinations. To assess different cognitive domains, a selection of tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition) was used. The CANTAB Connect Research tool is a validated and reliable tool that allows early detection of signs of age-related cognitive impairment (Rabbitt and Lowe 2000; Wild et al. 2008). Testing started with a Motor Screening Task to determine the presence of any sensorimotor deficit. Data from further tests were evaluated only from patients who passed this test. Testing was continued with a battery of tests optimized to detect age-related cognitive decline: reaction time, sustained attention, visual memory, short-term recognition, visual matching, and spatial working memory. Subjects were left alone in a quiet environment during the test with the

Table 1 Baseline characteristics of study participants

	< 45 years old	> 65 years old	<i>p</i> (<i>t</i> test or χ^2 test, where applicable)
<i>N</i>	31	29	
Age (years)	35 ± 6.76	78 ± 6.26	
Gender			0.07
Males	20	12	
Females	11	17	
BMI (kg/m ²)	26 ± 4.38	26.9 ± 6.25	0.48
Blood pressure (mmHg)			
Systolic	117.81 ± 10.1	125.16 ± 12.39	0.02
Diastolic	76.41 ± 7.28	78.12 ± 7.47	0.39
Ethnicity			0.33
Caucasian	28	28	
African-American	3	1	
Comorbidity			0.25
Diabetes	1	1	
Hypertension	3	12	
Highest level of education			0.0006
High school degree or lower	0%	11.11%	
College degree or higher	100%	88.88%	

touchscreen device running the application (10.5" iOS tablet).

Arterial endothelial function assessment using flow-mediated dilation

Flow-mediated dilation (FMD) measurements were obtained according to the American College of Cardiology guidelines. Before each measurement, blood pressure was measured and study participants rested for 20 min in a supine position. Endothelial function in brachial artery was measured with a flow-mediated dilation approach using an Acuson Sequoia 256 Doppler Ultrasound system equipped with 8-MHz linear sonography probe (Acuson 8L5). In brief, a sphygmomanometer cuff was placed below the antecubital fossa on the forearm of right arm, and automatic inflator (Hokanson E20 Rapid Cuff Inflator) was used to immediately inflate and maintain the cuff pressure at 50 mmHg above current systolic blood pressure for 5 min. After the release of cuff occlusion, vascular responses were recorded for 3 min. Flow-mediated dilation was measured as the percent change of brachial artery diameter after the 5-min occlusion to baseline diameter of brachial artery. Data were analyzed using edge-detecting and wall-tracking Brachial Analyzer for Research (Medical Imaging Applications LLC) software.

Microvascular function assessment using laser speckle contrast imaging

After assessment of macrovascular endothelial function, microvascular endothelial function was evaluated on the contralateral arm (Csipo et al. 2018). In brief, a sphygmomanometer cuff was placed above the left antecubital fossa, and, after recording of 60 s of stable baseline perfusion, occlusion was performed by inflating arterial cuff to 50 mmHg above current systolic blood pressure for 5 min. After the release of cuff occlusion, vascular responses were recorded for 3 min using a Perimed PSI System (Perimed, Järfälla, Sweden). Skin temperature was measured with a non-contact thermometer (Thermoworks TW2) from less than 10 mm at the back of the hand, the first and last phalanx of middle finger. Recordings were evaluated off-line, and baseline perfusion, maximal post-occlusive perfusion, and acute reperfusion was measured. Acute reperfusion is the rapid change in perfusion, and the slope is calculated between the occluded phase and the time point 4 s after releasing cuff occlusion.

Arterial stiffness assessment

Arterial stiffness was assessed by pulse wave analysis on the same day. Peripheral artery pressure waveform signals were recorded from the radial artery and arterial stiffness was evaluated by measuring aortic augmentation indices using SphygmoCor software (AtCor Medical, SphygmoCorCVMS) (Butlin and Qasem 2017). The recordings with operator index > 90 was used for data analysis.

Data analysis

All measurements of FMD, microvascular endothelial function, and arterial stiffness were conducted by operators blinded to a study design. All statistical tests were performed in GraphPad Prism 6.0 (GraphPad Software, La Jolla, CA, USA). The relationships between FMD, laser speckle contrast imaging (LSCI), and arterial stiffness measurements were assessed using Pearson's correlation coefficients. When comparing young vs aged groups, parameters were first tested with a D'Agostino-Pearson normality test and then compared by *t* test or nonparametric Mann-Whitney *U* test appropriately. A *p* value < 0.05 was considered significant.

Principal component analysis (PCA) was used for dimension reduction of vascular and cognitive data. The first principal component (PC1) is the best synthetic indicator of the range of variability of the variables considered. Using this approach, the biological information dispersed over the multiple measurements was combined and condensed in a single variable. Using PC1, vascular measures were reduced in a vascular health index (VHI), whereas cognitive measures were reduced into a complex cognitive impairment index. All PCA calculations were performed with the PAST3 software (Hammer et al. 2001). Loadings for each PCA-generated index can be found in the Supplemental Material (Supplemental Figs. 1 and 2).

Results

Participants

Table 1 shows the baseline characteristics of young (< 45 years old) and aged (> 65 years old) study participants. Three study participants were middle-aged (46 to 64 years

old) and were excluded from the group comparisons, but included in the correlation analysis.

Owing to the selection method, there were no significant differences between the two groups in sex, ethnicity, BMI, and comorbidities (hypertension and diabetes, Table 1). The aged population showed higher systolic blood pressure values, however still in the normal range. Diastolic blood pressure was not different between the groups. Majority of participants had a college degree or higher.

Aging is associated with arterial endothelial dysfunction and increased arterial stiffness

To determine the effects of aging on arterial endothelial function, we have implemented a commonly accepted protocol to measure FMD in response to short-term occlusion of the forearm arteries (Benjamin et al. 2004). We found that aged individuals in our cohort showed significantly impaired FMD responses ($p = 0.0061$) compared to young controls (Fig. 1a), extending previous findings (Benjamin et al. 2004).

For evaluation of arterial stiffness, we have utilized an established method of assessment of central arterial pressure waves and performed pulse waveform analysis (Butlin and Qasem 2017). When heart rate-corrected augmentation indices of young and aged participants were compared, we found that aged individuals exhibited significantly ($p < 0.0001$) increased arterial stiffness as compared to younger controls (Fig. 1b).

Aging is associated with microvascular dysfunction

For assessment of microvascular endothelial function, a similar to FMD protocol was used to measure reactive hyperemia in skin and nail beds of the upper extremity in response to temporary occlusion of brachial artery using a novel method of LSCI (Fig. 2a, b). While this method has been previously used in healthy volunteers aged 20–62 years old (Khalil et al. 2015) and demonstrated promising results and good correlation to pulse-wave velocity and macrovascular endothelial function measurements, the method has not been utilized in a truly geriatric population. We found that older individuals had significantly impaired microvascular function, as indicated by the decreased maximal perfusion ($p = 0.032$, Fig. 2c) and lower rate of acute reperfusion ($p = 0.015$, Fig. 2d) upon the release of arterial occlusion when compared to young group. We observed a moderate positive and significant correlation between microvascular endothelial function and arterial

Fig. 1 Aging is associated with macrovascular dysfunction and increased arterial stiffness. **a** Flow-mediated dilation, measured in the brachial artery in response to a short-term occlusion of the forearm arteries, was significantly impaired in aged individuals > 65 years old vs. young subjects < 45 years old, $n = 27$ vs. $n = 27$, $p = 0.0061$. **b** Augmentation index, as a measure of vascular arterial stiffness, was evaluated using pulse waveform analysis and showed significantly increased stiffness in older adults ($n = 27$) vs. young subjects ($n = 31$), $p < 0.0001$

FMD ($r = 0.32$, $p = 0.026$, Fig. 2e). This finding is consistent with the concept that reactive hyperemia upon the release of arterial occlusion is partially mediated by endothelium-dependent microvascular mechanisms. Acute reperfusion rate also showed a moderate negative and significant correlation with the augmentation index ($r = -0.37$, $p = 0.0072$, Fig. 2f), consistent with the modulatory role of vascular stiffness in the response and that LSCI may serve as a useful tool and as a secondary measure to confirm findings of the arterial stiffness.

Age-related decline in peripheral vascular health index predicts cognitive impairment

We used a PCA-based approach to generate a comprehensive vascular health index as a surrogate marker of

Fig. 2 Aging is associated with microvascular dysfunction. **a** A representative image of Laser Speckle Contrast Imaging (LSCI) obtained during assessment of microvascular endothelial function in the skin and nailbeds of the young individual (27 years old, male). Microvascular endothelial function was assessed after a short-term occlusion of brachial vessels using a standard arterial pressure cuff inflated to a subject's systolic blood pressure + 50 mmHg. **b** A representative image of the skin perfusion in the young (27 years old, black line) and aged (68 years old, red line) individual during baseline, occlusion, and post-occlusion after the release of arterial cuff pressure. **c** Microvascular endothelial function, measured using LSCI as a ratio of maximal to baseline skin perfusion, was significantly impaired in older adults (> 65 years old, $n = 26$) vs young subjects (< 45 years old, $n = 28$), $p = 0.032$. **d** Acute reperfusion, the measure of rapid change in the perfusion that is calculated from a slope between arterial occlusion and the first 4 s after the release of arterial cuff, represents stiffness of the arterial microvasculature in the hand. Acute reperfusion was significantly lower in aged ($n = 22$) vs young subjects ($n = 27$), $p = 0.015$. **e** We observed a positive moderate ($r = 0.32$) and significant ($p = 0.026$) correlation between microvascular endothelial function and macrovascular endothelial function measured by flow-mediated dilation. **f** We observed a negative moderate ($r = -0.37$) and significant ($p = 0.0072$) correlation between arterial stiffness measured using LSCI approach and augmentation index measured using pulse waveform analysis

generalized vascular dysfunction (Berni et al. 2011). Vascular health index was comprised of a number of vascular parameters obtained from assessment of peripheral microvascular reactivity, arterial endothelial function, and vascular stiffness. In this analysis, we found that principal component 1 (PC1) was a biggest contributor to the observed change in vascular reactivity, function, and stiffness (eigenvalue of 2.46, Supplemental Fig. 1A). Supplemental Fig. 1B shows the factor loadings (the correlation coefficients between the PC1 scores and original variables), indicating that physiological parameters from all vascular measurements are triggered by the same major physiological phenomenon (i.e., “vascular health” that is affected by aging). The positive correlation of FMD and microvascular perfusion parameters with PC1 indicates that high component scores correspond to an improved vascular function. Consistently with this interpretation, the augmentation index displays negative correlation with the PC1. We used PC1 as a cumulative score (“vascular health index”) that makes it possible to correlate age-related changes in vascular health to cognitive outcome measures without any ambiguity linked to the multiplicity of tests. The vascular health index (PC1) showed moderate

negative and significant correlation with age ($r = -0.54$, $p < 0.0001$, Fig. 3b).

The CANTAB cognitive panel had an output of 13 major outcome measures that were relevant in an aging population, 12 of which showed significantly worse performance in the aged population compared to young (Table 2). Cognitive impairment was measured by reducing these major outcome measures with the same method described for the creation of the vascular health index. The first component of the PCA that separated the population (Fig. 3c) was used as a cumulative score (cognitive impairment index). The loadings and composition of PC1 are shown in Supplemental Fig. 2. The cognitive impairment index showed a strong positive correlation with age ($r = 0.79$, $p < 0.0001$, Fig. 3d), demonstrating an age-related decline in higher brain function in our cohort.

The vascular health index showed a significant negative correlation with the cognitive impairment index ($r = -0.46$, $p = 0.0003$, Fig. 4), demonstrating that deterioration of vascular health predicts cognitive impairment in older adults.

Discussion

Present study provides evidence that age-related decline in peripheral vascular health predicts cognitive dysfunction in older adults. Our results extend findings of previous investigations demonstrating that in otherwise healthy individuals, aging itself is a critical risk factor for vascular impairment, including arterial endothelial dysfunction, microvascular impairment, and increased arterial stiffness (Butlin and Qasem 2017; Kim et al. 2015, Kim et al. 2014). There is strong clinical and preclinical evidence that vascular impairment is a generalized phenomenon in aging (Ungvari et al. 2018). Because age-related cerebrovascular impairment is causally linked to the pathogenesis of VCID, we propose that assessment of peripheral vascular health could be used to identify patients at risk of VCID. Further, a comprehensive peripheral vascular health index encompassing peripheral microvascular reactivity, arterial endothelial function, and vascular stiffness may be used as a surrogate marker of aging-induced generalized vascular dysfunction in studies on the pathogenesis and prevention of VCID.

The mechanisms by which functional and phenotypic alterations of the cerebral microvasculature promote the

Fig. 3 Development of surrogate markers for vascular and cognitive health in aging population. To construct a comprehensive peripheral vascular health and cognitive impairment indices, encompassing peripheral microvascular reactivity, arterial endothelial function, vascular stiffness, and measures obtained from CANTAB research panel respectively, we used a PCA-based

approach. **a, b** The vascular health index (PC1) showed moderate negative ($r = -0.54$) and significant ($p < 0.0001$) correlation with age. **c, d** Cognitive impairment index showed a strong positive ($r = 0.79$) and significant ($p < 0.0001$) correlation with age, indicating an age-related decline in higher brain function in our cohort

pathogenesis of VCID are likely multifaceted (Toth et al. 2017). There is a strong evidence from clinical and pre-clinical studies that age-related endothelial dysfunction significantly impairs regulation of cerebral blood flow, which promotes cognitive dysfunction (Toth et al. 2017). In the brain, endothelium-mediated vasodilation plays a key role in neurovascular coupling (also known as functional hyperemia) (Tarantini et al. 2017; Toth et al. 2015b). Neurovascular coupling responses are critical for moment-to-moment adjustment of nutrient and oxygen delivery to match the increased requirements of activated neurons. There is a strong evidence that selective disruption of endothelium-mediated neurovascular coupling responses (e.g., by pharmacological inhibition of NO synthesis or genetic

depletion of eNOS) results in cognitive impairment in experimental animals (Tarantini et al. 2015; Tarantini et al. 2017). Functional microvascular contributions to vascular cognitive impairment also include disruption of the blood-brain barrier (Toth et al. 2017) and consequential increases in neuroinflammation due to activation of microglia in response to plasma constituents entering the brain from the leaky capillaries. Importantly, a critical mechanism, which exacerbates age-related disruption of the blood-brain barrier, is increased penetration of pulsatile pressure waves into the cerebral microcirculation due to, in part, increased stiffness of aged peripheral arteries (Garcia-Polite et al. 2017; Gorelick et al. 2011; Pase et al. 2016; Thorin-Trescases et al. 2018; Toth et al. 2013). The same vascular alterations promote

Table 2 Cognitive performance of study participants. Cognitive performance of study participants was assessed via CANTAB research panel, including five tests (*DMS* delayed matching to sample, *PAL* paired associates learning, *RTI* reaction time, *RVP* rapid visual information processing, *SWM* spatial working memory). The cognitive assessment provided 13 major outcome measures, which were used to compare the performance of the young and aged groups

	< 45 years old	> 65 years old	<i>p</i>
DMSMLAD	3254 ± 154.84	4259 ± 265.45	0.0021
DMSPC	92 ± 1.42	82 ± 1.74	0.0001
PALFAMS28	16 ± 0.61	9 ± 0.72	< 0.0001
PALTEA28	8 ± 1.85	27 ± 2.83	< 0.0001
RTIFMDMT	269 ± 12.39	340 ± 19.34	0.0035
RTIFMDRT	363 ± 7.53	377 ± 8.65	0.2231
RVPA	0.926 ± 0.0076	0.858 ± 0.0132	< 0.0001
RVPMDL	423 ± 10.42	546 ± 28.56	< 0.0001
SWMBE4	0.31 ± 0.15	1.37 ± 0.28	0.0016
SWMBE468	5.12 ± 1.5	18.96 ± 1.47	< 0.0001
SWMBE6	1.19 ± 0.43	5 ± 0.57	< 0.0001
SWMBE8	3.62 ± 1.04	12.59 ± 0.97	< 0.0001
SWMS	5.7 ± 0.57	9.41 ± 0.36	< 0.0001

DMSMLAD DMS mean correct latency (all delays); *DMSPC* DMS percent correct; *PALFAMS28* PAL First Attempt Memory Score; *PALTEA28* PAL total errors; *RTIFMDMT* RTI median five-choice movement time; *RTIFMDRT* RTI median five-choice reaction time; *RVPA* *RVPA'* (A prime), signal detection measure of subject sensitivity to target sequence; *RVPMDL* RVP median response latency; *SWMBE4* SWM between error (four boxes); *SWMBE468* SWM between errors; *SWMBE6* SWM between error (six boxes); *SWMBE8* SWM between error (eight boxes); *SWMS* SWM strategy

the development of cerebral microhemorrhages in the aged brain (Ungvari et al. 2017), which also contribute to cognitive decline.

The cellular and molecular mechanisms of vascular aging that underlie the functional and structural alterations of both peripheral and cerebral arteries are complex. Among the mechanisms that contribute to endothelial dysfunction in aging, a large body of evidence suggests that age-related oxidative stress, exacerbated by circulating IGF-1 deficiency and inflammation, decreases the bioavailability of NO and promotes endothelial dysfunction both in peripheral arteries and cerebral circulation in aged laboratory animals and in older adults (Pearson et al. 2008; Tarantini et al. 2018; Toth et al. 2015a, Toth et al. 2014; Ungvari et al. 2018). Accordingly, treatments that attenuate oxidative stress,

Fig. 4 Age-related decline in peripheral vascular health index predicts cognitive impairment. The vascular health index showed a significant negative ($r = -0.46$) and significant ($p = 0.0003$) correlation with the cognitive impairment index, indicating that deterioration of vascular health predicts cognitive impairment in older adults

including mitochondria-targeted antioxidants (Gioscia-Ryan et al. 2014; Tarantini et al. 2018) and dietary antioxidative compounds (Pearson et al. 2008; Toth et al. 2014), significantly improve endothelial function in both vascular beds. There is increasing evidence that in rodent models of aging, cerebrovascular protection conferred by these treatments is paralleled by a significant improvement in cognitive function (Oomen et al. 2009; Tarantini et al. 2018).

There are also important lessons learned in terms of key methodological considerations and strategies for assessment of microvascular function and cognitive performance in older individuals. Microcirculatory endothelial function has garnered much attention over the past years, primarily due to recognition of the importance of microvasculature in pathophysiology of cardiovascular, cerebrovascular, and metabolic diseases, as well as due to understanding that majority of endothelium lies within the microcirculation. Nevertheless, there are no standard methodologies to assess microvascular dysfunction (Houben et al. 2017; Muris et al. 2012) and to integrate analysis of microvascular and macrovascular dysfunction in the same subjects (Kim et al. 2015, Kim et al. 2014). The LSCI methodology is highly effective in quantifying microvascular blood flow (Barcelos et al. 2017; Boas and Dunn 2010; Briers et al. 2013; de M Matheus et al. 2017). The LSCI-based microvascular reactivity assay can be easily and quickly performed together with the FMD and arterial stiffness/pulse-wave velocity measurements in an outpatient setting

(Khalil et al. 2015). CANTAB-based evaluation of cognitive function is frequently used in research studies as well as in clinical practice, and the results correlate well with traditional neuropsychological test measures (Smith et al. 2013). Producing a single composite vascular health index and a cognitive impairment index based on a diverse set of individual indicators has advantages, including simplicity of correlation and interpretation of data.

The present study has few limitations. First, this study is cross-sectional in nature, and therefore, it is challenging to establish direct cause and effect relationship. Hence, further large-scale longitudinal studies in this area are needed. Second, further validation studies are warranted to correlate results of peripheral vascular measurements with changes in cerebral blood flow and cerebral vascular reactivity in the same subjects. Third, the present study was conducted on subjects relatively free of other important co-morbidities that can affect vascular function and, thereby, cognition. Future studies on larger cohorts of geriatric patients with comorbid conditions will test the predictive power of peripheral vascular health assessment to identify patients at risk for VCID. We believe that it is a strength of our approach that potential cardiovascular risk factors of VCID (e.g., obesity, diabetes) impair brain function through altering the function of cerebral microvessels. Thus, assessing general effects of cardiovascular risk factors on (micro)vascular function using our approach may likely predict their effect on cerebrovascular regulation and, consequently, on brain function as well.

In conclusion, severity of age-related macro- and micro-vascular dysfunction in the peripheral circulation is an independent predictor of cognitive performance in older adults.

Funding information This work was supported by grants from the American Heart Association (ST, ZU, and AC), the Oklahoma Center for the Advancement of Science and Technology (to AC, AY, ZU), the National Center for Complementary and Alternative Medicine (R01-AT006526 to ZU), the National Institute on Aging (R01-AG055395, R01-AG047879; R01-AG038747), the National Institute of Neurological Disorders and Stroke (NINDS; R01-NS100782, R01-NS056218), the Oklahoma Shared Clinical and Translational Resources (OSCTR) program funded by the National Institute of General Medical Sciences (U54GM104938, to AY), the Presbyterian Health Foundation (to ZU, AC, AY), and the EU-funded Hungarian grant EFOP-3.6.1-16-2016-00008. The authors was supported by the NIA/NIH-funded Geroscience Training Program in Oklahoma (T32AG052363) and the Cellular and Molecular GeroScience CoBRE (1P20GM125528, sub#5337).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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