Cognitive Correlates of Cerebral Vasoreactivity on Transcranial Doppler in Older Adults

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Background: This study was performed to explore the possible contributions of cerebral hemodynamic changes to the cognitive impairment in patients with Alzheimer’s disease (AD). Methods: A total of 194 participants were included: 52 controls, 75 patients with mild cognitive impairment (MCI), and 67 patients with AD. Demographic characteristics, vascular risks, mini-mental state examination (MMSE), and clinical dementia rating (CDR) were assessed, and magnetic resonance imaging of the brain was performed to evaluate white matter hyperintensities (WMHs). Using transcranial Doppler (TCD) ultrasonography, cerebrovascular reactivity (CVR) was evaluated with a breath-holding test, in addition to the mean blood flow velocity (MFV), pulsatility index (PI), and resistance index (RI) of the middle cerebral artery. Results: After adjusting for covariates such as age, education, WMH severity, and vascular risks, TCD parameters such as MFV, PI, and RI did not differ between the 3 groups. However, CVR was significantly reduced in the AD group (45.33 ± 11.49%), compared with the other groups (56.36 ± 14.65%, controls; 53.84 ± 15.47%, MCI group; \( P < .001 \)). Multiple regression analyses also showed that CVR was associated with MMSE scores. CVR differed according to the CDR scores (\( P < .001 \)). Conclusions: Our finding may be suggestive of an underlying microangiopathic mechanism in AD patients. Furthermore, there was an association between the impaired function of cerebral microvessels and cognitive impairment. Further research is needed to fully establish whether altered cerebral hemodynamics may be considered an independent factor in predicting cognitive decline or an effect of pathologic processes involved in AD. Key Words: Transcranial Doppler—cerebral vasoreactivity—Alzheimer’s disease—old adults.

Changes in cerebrovascular structure and functions contribute to cognitive impairment in aging and dementia. In addition to vascular dementia, several epidemiologic and imaging studies have provided evidence supporting the vascular pathogenesis of Alzheimer’s disease (AD), which is considered as a pure neurodegenerative dementia. These studies have suggested that vascular risk factors directly reduce cerebral perfusion to a critical level of dysfunction, enhancing neuronal death in AD. Chronic cerebral hypoperfusion could affect the brain cellular health and the development of neurodegenerative pathologies.

Transcranial Doppler (TCD) ultrasonography is a noninvasive and inexpensive technique for evaluating cerebral hemodynamics. It is widely accepted that examination of blood flow velocity in the intracranial arteries...
and its changes during different challenge tests (eg, CO₂ and acetazolamide), evaluated by TCD ultrasonography, provide a good assessment of the status of cerebral blood flow. TCD methods are used to assess functional cerebrovascular contributions to cognitive impairment in dementia and aging and may help in the differentiation of dementia from normal aging. Decreased mean flow velocity (MFV), increased pulsatility index (PI), and decreased cerebrovascular reactivity (CVR) in the middle cerebral artery have been reported in AD patients. Another study has suggested that CVR is a significant predictor of cognitive decline in AD patients.

However, there are few reports on patients with mild cognitive impairment (MCI). To our knowledge, to date, no study has assessed all TCD parameters such as MFV, PI, resistance index (RI), and CVR in subjects with normal cognition, those with MCI, and those with AD. Moreover, the differences in these parameters according to dementia severity, evaluated using the clinical dementia rating (CDR) scale, are still unclear.

To compare hemodynamic changes related to cerebral blood flow and vascular resistance in older adults with a wide spectrum of cognitive impairments, we assessed MFV, PI, RI, and CVR by using TCD ultrasonography in older adults with very mild-to-severe AD, those with MCI, and aged controls, and the relationship between these parameters and cognitive impairment or dementia severity was evaluated.

Materials and Methods

Participants

This was a single-center observational study approved by the Institutional Review Board of The Catholic University of Korea, Bucheon St. Mary’s Hospital. All participants provided informed consent. Between May 2011 and December 2012, we consecutively enrolled patients who visited the hospital’s Department of Neurology clinic. A total of 194 participants were recruited, comprising 52 controls, 75 MCI patients, and 67 AD patients. Healthy older adults who requested a medical evaluation for a routine assessment of possible cerebrovascular diseases, owing to concerns related to stroke or positive vascular risk factors, were included as controls. The control participants had no cognitive complaints, and their scores on the Korean version of the mini-mental state examination (K-MMSE) were more than −1.0 standard deviations (SDs) compared with age- and education-matched norms, and their CDR scores were zero. Patients with MCI fulfilled the clinical diagnostic criteria for MCI. All MCI patients had subjective complaints of memory loss, objective impairment in memory (−1.5 SD on a neuropsychological test of memory [Seoul verbal learning test]), and no significant functional decline. Criteria of the National Institute of Neurological and Communicative Disorders and the Stroke and the Alzheimer’s Disease and Related Disorders Association were used to diagnose probable AD. AD patients with CDR scores of 2 or 3 were excluded because they could not cooperate with breath holding, which was performed for TCD assessment of vasoreactivity.

All participants underwent physical and neurologic examinations, blood tests (ie, complete blood count, blood chemistry, vitamin B12/folate, and syphilis serology), thyroid function tests, assessment of global cognitive functioning with the K-MMSE, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain, and TCD measurements. The height and weight of the subjects were measured, and body mass index (BMI) was calculated. Participants’ history of vascular risk factors (ie, hypertension, diabetes, hyperlipidemia, ischemic heart disease, stroke, and smoking) was recorded. Participants were excluded from the study if they showed large territorial infarcts or multiple lacunes on MRI, were younger than 55 years of age, had a history of diseases (other than MCI or AD) that may cause cognitive disorders, or had major psychiatric disease. Participants with a diagnosis of delirium were excluded and those unable to be assessed because of conditions such as blindness and/or deafness. Individuals with a history of alcoholism or other substance abuse or dependence within the past 10 years were also excluded. Carotid artery stenosis was defined according to the North American Symptomatic Carotid Endarterectomy Trial method, and patients with carotid artery stenosis of greater than 50% lumen diameter reduction were excluded. MRA was performed in all patients to exclude the presence of intracranial artery stenosis that might interfere with the hemodynamic status.

MRI Assessment

All participants underwent 3.0-T brain MRI (Intera; Philips Medical Systems, Best, The Netherlands), including fluid-attenuated inversion recovery imaging and T1/T2-weighted imaging. The slice thickness was 5 mm without an interslice gap. The three-dimensional time-of-flight method was used as the imaging protocol of MRA. Periventricular white matter hyperintensities (WMHs) (PVHs) and deep WMHs (DWHs) were separately evaluated according to the method proposed by the Clinical Research for Dementia of South Korea study. The severity of DWHs was graded according to their largest diameter, as follows: D1 (<10 mm), D2 (≥10 and <25 mm), and D3 (≥25 mm). PVHs were rated as PI if the cap and band were less than 5 mm, P2 if the cap or band was 5 mm or greater and less than 10 mm, and P3 if the cap or band was 10 mm or greater. By...
modifying the previous criteria,\textsuperscript{31} we added grade 0 (absence; D0 or P0) to the individual classifications of PVHs and DWHs, and the severity of total WMHs was reclassified as follows: none (grade 0), minimal (grade 1), moderate (grade 2), and severe (grade 3).\textsuperscript{32}

TCD Measurements

TCD basal examination was performed using a 2-MHz Doppler probe (Viasys Healthcare, Model Sonara) through the temporal bone window, by a sonographer who was blinded to the clinical diagnosis. The participants were placed in the supine position, and the TCD probe was fixed on the temporal window. The proximal segments of the middle cerebral artery at depths of 55-65 mm were examined on each side, and the MFV was evaluated. In addition, PI and RI were calculated. PI was calculated by subtracting the end-diastolic velocity from the peak systolic velocity and then dividing by the MFV. Thus, the PI is analogous to pulse pressure and is recognized as a measure of distal flow resistance and vascular wall rigidity. The RI is a measure of peripheral flow resistance and is calculated by subtracting the end-diastolic velocity from the peak systolic velocity and then dividing by the peak systolic velocity.

After baseline assessments, CVR was evaluated using a breath-holding (BH) test. Participants were requested to hold their breath for at least 30 seconds to reach a maximal increase in flow velocity, and the MFV during the BH task (hypercapnic condition) was recorded. All TCD data were recorded for offline analysis. Measurements were repeated under basal conditions, at the maximum increase in flow velocity during hypercapnia. CVR was calculated as a percentage of baseline MFV and absolute changes by subtracting the baseline values from the maximum MFV during the BH task, as follows:

\[ \text{CVR} = \left( \frac{\text{MFV}_{\text{BH}} - \text{MFV}_{\text{rest}}}{\text{MFV}_{\text{rest}}} \right) \times 100 \]

where MFV\(_{\text{BH}}\) is the maximum MFV during the BH task, and MFV\(_{\text{rest}}\) is the resting (baseline) MFV in the middle cerebral artery.

Cognitive and Neurological Measures

Korean Version of the Mini-Mental State Examination

The K-MMSE is the Korean modification and translation of the MMSE.\textsuperscript{33} The MMSE is a frequently used instrument to assess global cognitive functioning and to identify individuals with cognitive impairment. Consistent with the MMSE, the K-MMSE scores range from 0 to 30, with lower scores indicating greater cognitive impairment.

Clinical Dementia Rating

The CDR scale is a 5-point rating scale used to indicate the presence and level of severity of AD.\textsuperscript{25,24} CDR scores are based on the measures of cognitive and functional performance of patients in 6 domains, that is, memory, orientation, community affairs, judgment and problem solving, personal care, and home and hobbies, as assessed using a structured interview. Each of these domains is rated on the following 5-point scale, with the exception of personal care, which is rated on a 4-point scale (with no .5 rating): 0 (no impairment), .5 (questionable impairment), 1 (mild impairment), 2 (moderate impairment), and 3 (severe impairment). Scores from each of these domains are combined using an algorithm to create a composite CDR score. This composite, or global, CDR score can be classified as follows: 0 (no dementia), .5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), or 3 (severe dementia). The CDR scale is also used to provide a sum of boxes score, which is calculated by adding each of the 6 domain scores, with the scores ranging from 0 to 18 (higher scores indicate greater impairment).

Statistical Analyses

Preliminary analyses were performed to examine the differences in demographic characteristics and medical history between the 3 groups (ie, control, AD, and MCI) by using analysis of variance and chi-square analyses, as appropriate. Group differences in cognitive and neurologic measures, WMH severity levels, and TCD parameters were further examined using analysis of covariance and chi-square test, after adjusting for age and years of education. Adjustment for severity of WMHs was also made for comparisons of TCD parameters. The Scheffé method was used for multiple comparisons among the 3 groups. Correlation analyses were performed to examine the associations of MFV, PI, RI, and CVR with age, years of education, K-MMSE scores, WMH severity, and number of vascular risk factors, and then, repeatedly after controlling for age. Multiple regression analyses for the dependent variables of each TCD parameter were performed with independent variables of age, K-MMSE scores, WMH severity, and the number of vascular risk factors including hypertension, diabetes, dyslipidemia, ischemic heart disease, smoking, and stroke history. A probability value of \( P < .05 \) was considered statistically significant, and all tests were 2-tailed. The data were analyzed using SPSS 15.0 (SPSS, Chicago, IL).

Results

Characteristics of the Participants

A total of 194 participants were included in this study. Most of the participants were female (71.649%, \( n = 139 \) participants). The mean ages of the participants significantly differed between the 3 groups, with the AD group being the oldest. The AD patients had significantly fewer years of education than did the MCI patients and controls.
Even after adjusting for age and years of education, the K-MMSE, CDR, and WMH scores significantly differed between the 3 groups. There were no group differences in BMI or vascular risk factors. TCD parameters differed between the 3 groups: MFV was 51.60 \pm 13.01 cm/second in the control group, 49.05 \pm 13.28 cm/second in the MCI group, and 45.13 \pm 13.65 cm/second in the AD group (P = .029); PI was 1.18 \pm .44 in the control group, 1.38 \pm .53 in the MCI group, and 1.51 \pm .66 in the AD group (P = .007); RI was .65 \pm .11 in the control group, .68 \pm .10 in the MCI group, and .71 \pm .10 in the AD group (P = .007); and CVR was 56.36 \pm 14.65% in the control group, 53.84 \pm 15.47% in the MCI group, and 45.33 \pm 11.49% in the AD group (P < .001). However, after adjusting for age, education, and WMH severity, only CVR significantly differed between the 3 groups. Tables 1 and 2 present the means, SDs, and analysis of variance, analysis of covariance, and chi-square results.

### Table 1. Clinical characteristics of control, MCI, and AD participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (N = 52)</th>
<th>MCI (N = 75)</th>
<th>AD (N = 67)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.2 \pm 6.5</td>
<td>69.4 \pm 8.2</td>
<td>74.6 \pm 6.2</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.2 \pm 1.5</td>
<td>23.7 \pm 3.0</td>
<td>17.2 \pm 4.5</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Education (y)</td>
<td>10.5 \pm 4.0</td>
<td>7.7 \pm 4.5</td>
<td>5.0 \pm 4.4</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>CDR</td>
<td>.00 \pm .00 (0~0)</td>
<td>.50 \pm .00 (5~5)</td>
<td>.72 \pm .25 (5~1)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>CDR-SOB</td>
<td>.10 \pm .20 (0~5)</td>
<td>1.55 \pm .68 (5~3.0)</td>
<td>4.23 \pm 1.47 (1.5~8)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>BMI</td>
<td>23.2 \pm 2.8</td>
<td>23.6 \pm 2.9</td>
<td>23.1 \pm 3.2</td>
<td>.587</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; BMI, body mass index; CDR, clinical dementia rating; DM, diabetes mellitus; DWMH, deep white matter hyperintensities; F, female; HTN, hypertension; IHD, ischemic heart disease; M, male; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PVH, periventricular hyperintensities; SOB, sum of boxes; WMHs, white matter hyperintensities.

Values are presented as mean \pm standard deviation (range) or number (percentage).

Statistical analysis was performed by using analysis of covariance and chi-square test, adjusted for age and education years.

*P < .05 for Scheffe post hoc analysis between control and AD.
†P < .05 for Scheffe post hoc analysis between MCI and AD.
‡P < .05 for Scheffe post hoc analysis between control and MCI.

### Table 2. TCD parameters in control, MCI, and AD participants

<table>
<thead>
<tr>
<th>TCD variables</th>
<th>Control (N = 52)</th>
<th>MCI (N = 75)</th>
<th>AD (N = 67)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFV (cm/s)</td>
<td>51.60 \pm 13.01</td>
<td>49.05 \pm 13.28</td>
<td>45.13 \pm 13.65</td>
<td>.349*</td>
</tr>
<tr>
<td>PI</td>
<td>1.18 \pm .44</td>
<td>1.38 \pm .53</td>
<td>1.51 \pm .66</td>
<td>.174*</td>
</tr>
<tr>
<td>RI</td>
<td>.65 \pm .11</td>
<td>.68 \pm .10</td>
<td>.71 \pm .10</td>
<td>.270*</td>
</tr>
<tr>
<td>CVR (%)</td>
<td>56.36 \pm 14.65</td>
<td>53.84 \pm 15.47</td>
<td>45.33 \pm 11.49</td>
<td>.022*</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; CVR, cerebrovascular reactivity; MCI, mild cognitive impairment; MFV, mean flow velocity; PI, pulsatility index; RI, resistance index; TCD, transcranial Doppler.

Values are presented as mean \pm standard deviation.

Statistical analysis was performed by using analysis of variance and analysis of covariance, adjusted for age, education years, and white matter hyperintensities on magnetic resonance imaging.

*P < .05 for Scheffe post hoc analysis between control and AD.
†P < .05 for Scheffe post hoc analysis between MCI and AD.
Associations of TCD Parameters with K-MMSE Scores and Vascular Risks

Age correlated with MFV ($r = -.271, P < .001$), PI ($r = .277, P < .001$), RI ($r = .377, P < .001$), and CVR ($r = -.128, P = .051$). Partial correlation analyses after adjusting for age showed that CVR was associated with years of education ($r = .206, P = .002$) and WMH severity ($r = -.115, P = .085$). K-MMSE scores correlated with PI ($r = -.192, P = .004$), RI ($r = -.184, P = .005$), and CVR ($r = .263, P < .001$).

Table 3 shows multiple regression models evaluating the associations of MFV and CVR with age, education years, K-MMSE score, WMH severity, and the number of vascular risk factors ($N = 189$).

**Table 3. Multivariate linear regression models evaluating the association of TCD values such as MFV and CVR with age, education years, K-MMSE score, WMH severity, and the number of vascular risk factors ($N = 189$)**

<table>
<thead>
<tr>
<th>Dependent</th>
<th>Independent</th>
<th>$\beta$</th>
<th>SE</th>
<th>$P$ value</th>
<th>$r^2$</th>
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</thead>
<tbody>
<tr>
<td>MFV</td>
<td>Intercept</td>
<td>76.355</td>
<td>11.497</td>
<td>&lt;.001</td>
<td>.076</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>-42</td>
<td>.135</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>-395</td>
<td>.237</td>
<td>.096</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K-MMSE</td>
<td>.245</td>
<td>.206</td>
<td>.237</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WMHs</td>
<td>-39</td>
<td>1.313</td>
<td>.767</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of vascular risk factors</td>
<td>-554</td>
<td>.825</td>
<td>.502</td>
<td></td>
</tr>
<tr>
<td>CVR</td>
<td>Intercept</td>
<td>.338</td>
<td>.122</td>
<td>.006</td>
<td>.093</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>.001</td>
<td>.001</td>
<td>.544</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>.002</td>
<td>.003</td>
<td>.336</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K-MMSE</td>
<td>.005</td>
<td>.002</td>
<td>.017</td>
<td></td>
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<tr>
<td></td>
<td>WMHs</td>
<td>-.017</td>
<td>.014</td>
<td>.222</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of vascular risk factors</td>
<td>-.004</td>
<td>.009</td>
<td>.658</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CVR, cerebrovascular reactivity; K-MMSE, Korean version of mini-mental state examination; MFV, mean flow velocity; SE, standard error; TCD, transcranial Doppler; WMHs, white matter hyperintensities. Vascular risk factors were included among hypertension, diabetes, dyslipidemia, ischemic heart disease, smoking, and previous stroke. MFV was dependent on age, and CVR was dependent on the K-MMSE scores.

Furthermore, CVR was lower in the AD patients than in the controls and MCI patients, independently of age (and WMHs on MRI). TCD parameters such as MFV, PI, RI, and CVR were correlated with age, and notably, general cognition evaluated by the MMSE was associated with PI, RI, and CVR, independently of age and vascular risks. CVR was lower in patients with very mild or mild AD than in the controls and MCI patients.

**Discussion**

In the present study, AD patients had a lower MFV, higher PI and RI, and lower CVR than the controls. Furthermore, CVR was lower in the AD patients than in the controls and MCI patients, independently of age (and WMHs on MRI). TCD parameters such as MFV, PI, RI, and CVR were correlated with age, and notably, general cognition evaluated by the MMSE was associated with PI, RI, and CVR, independently of age and vascular risks. CVR was lower in patients with very mild or mild AD than in the controls and MCI patients.

**Figure 1.** CVR values according to CDR scores. Statistical analysis was performed by using analysis of covariance, adjusted for age, education years, and white matter hyperintensities on magnetic resonance imaging with Sheffe’s post hoc analysis. The CVR scores were 56.36 ± 14.65% (n = 52) in the control group, 53.84 ± 15.47% (n = 75) in the MCI group, 46.57 ± 11.26% (n = 38) in the AD group with a CDR of .5, and 43.79 ± 11.79% (n = 29) in the AD group with a CDR of 1, and CVR differed significantly after adjusting for age, education, and WMH severity ($P = .019$). Multiple comparisons showed that CVR was higher in the controls and MCI patients than in the AD patients with a CDR of .5 or 1.

Abbreviations: AD, Alzheimer’s disease; CDR, clinical dementia rating; CVR, cerebrovascular reactivity; MCI, mild cognitive impairment.
Most TCD studies have reported lower MFVs in demented patients, such as those with AD.\textsuperscript{18-20} However, 2 studies including MCI patients reported no significant differences between the MCI and control groups.\textsuperscript{35,36} PI was also calculated and was found to be increased in AD patients.\textsuperscript{18-20} There were no significant differences in PI between the MCI patients and the controls.\textsuperscript{35} Various methods have been used for evaluating CVR, and the breath-holding index (BHI) is commonly used to assess the effects of hypercapnia.\textsuperscript{18,23,37,38} Some studies reported that the BHI was lower in AD patients than in healthy controls,\textsuperscript{18,38} which is similar to the results reported by Lee et al\textsuperscript{39} who used a closed-circuit rebreathing method. Interestingly, lower CVR in nondemented patients was found to be associated with preceding cognitive decline.\textsuperscript{14} Silverstrini et al\textsuperscript{37} reported that a lower BHI was associated with a more rapid cognitive decline in AD patients. However, Anzola et al\textsuperscript{36} reported no differences in the cardiovascular response to hypercapnia between the MCI and control groups.

Ours is the first study to investigate all TCD parameters such as MFV, PI, RI, and CVR in a wide range of participants such as normal controls, MCI patients, and AD patients. In this study, MFV was primarily associated with age, and CVR was associated with cognition, independently of age and other covariates. After adjusting for age and other vascular risks, CVR, but not MFV, was lower in AD patients. This suggests that pathologic changes in AD are more closely related with CVR than with the flow velocity itself, independently of age and other vascular risk factors. CVR was associated with cognition, as assessed with the MMSE, in older adults including those with normal cognition, MCI patients, and AD patients, and was lower in AD patients than in subjects with normal cognition and those with MCI. A reduced CVR is known to be correlated with microangiopathy severity, which increases vascular resistance.\textsuperscript{40,41} CVR is known to be influenced by atherosclerosis through disturbances in the integrity and function of the arterial wall, and in this study, a reduction in CVR in response to hypercapnia was indicative of cerebral small-vessel pathology\textsuperscript{14,40} because subjects with cerebral artery stenosis were excluded from the present study.

Abnormalities in TCD measurements in dementia patients could reflect a number of pathologic processes such as cerebral amyloid angiopathy,\textsuperscript{38,42} arteriolar sclerosis, or endothelial dysfunction, particularly within the microvascular system.\textsuperscript{43} Decreases in the responsiveness of the cerebrovascular system during cognitive tasks may also be a function of the surrounding neurons and astrocytes. These alterations of cerebral blood flow may be a cause or consequence of age- and dementia-related neuropathology such as cerebral atrophy. For example, it could simply mean that reduced blood flow velocities represent the reduced metabolism of an atrophied brain. Alternatively, reduced blood flow velocities, and thus, reduced blood flow, may directly lead to cellular dysfunction and death in vulnerable areas such as the hippocampus.\textsuperscript{14,44} Ruitenberg et al\textsuperscript{14} found that there was a negative association between the resting mean velocity and hippocampal and/or amygdala volume and that cerebrovascular disease did not mediate this relationship. This suggests that cerebral blood flow velocity may be directly associated with brain structure volumes. These observations are additionally supported by the presence of lacunar infarcts and strokes that worsen the clinical features of AD,\textsuperscript{45-47} further suggesting that deficiencies in cerebral blood flow are directly associated with neuronal and synaptic damage. In addition, many aging individuals show an increase in cerebral arterial, arteriolar, and capillary resistance because of the deposition of fibrillar amyloid-β peptides in the vascular walls. The luminal diameter is reduced, and endothelial cells, pericytes, and smooth muscle cells are destroyed by this cerebrovascular amyloidosis. These alterations affect the blood–brain barrier, vascular contractility, and vascular integrity, thereby resulting in stenosis as well as vascular fragility–promoting cerebral hemorrhages and neuronal injury.\textsuperscript{46,49}

One limitation of the TCD method is related to the structure of the temporal window. The temporal window, where the TCD ultrasound probe is placed, thickens with age, making recording more difficult. A population-based study reported that 25% of the participants were lost because an adequate TCD signal could not be obtained, especially in older women.\textsuperscript{14,50} These failure rates should be considered when planning TCD-based studies. However, this technique is well tolerated and portable, does not require participants to remain still, and allows metal implants to remain in place, unlike expensive and high-spatial resolution cerebral blood flow imaging techniques such as positron emission tomography and single-photon emission computed tomography. Furthermore, TCD equipment is widely used in clinical and research facilities worldwide. Another limitation is that we did not consider medications such as antihypertensive drugs, statins, and antiplatelet agents, which could affect microvascular alterations. Finally, it is unclear whether the decreased microvascular changes reflect the diminished demand caused by advanced neurodegeneration or whether cerebral small-vessel disease precedes and contributes to dementia and neurodegeneration. Long-term follow-up of patients with normal cognition and those with MCI could strengthen the results and confirm the hypothesis.

Dementia seemed to be associated with increased vessel resistance and a reduced cerebrovascular response to increased/decreased environmental CO\textsubscript{2} on TCD evaluation. Blood flow velocities seem to decrease with age in late life. These TCD findings correspond with known
structural vascular changes.\textsuperscript{15,51} We believe that the TCD technique can substantially contribute to the understanding of the underlying cerebrovascular contributions to age-related cognitive impairment and dementia. Furthermore, this technique may be used for developing novel therapeutic strategies for evaluating CVR and is reliable for differentiating between dementia subtypes or predicting the clinical progression of cognitive decline.\textsuperscript{14,23,37}

References


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