Influence of Galantamine on Vasomotor Reactivity in Alzheimer’s Disease and Vascular Dementia Due to Cerebral Microangiopathy

Karl-Jürgen Bär, MD; Michael Karl Boettger, MD; Nicole Seidler; Hans Joachim Mentzel, MD; Christoph Terborg, MD; Heinrich Sauer, MD

Background and Purpose—Recent reports suggest that vascular factors play a crucial role in the development and progression of Alzheimer’s disease. We aimed to assess vasomotor reactivity in patients with Alzheimer’s disease and vascular dementia due to microangiopathy using transcranial Doppler sonography and near-infrared spectroscopy during a CO₂ exposition task.

Methods—The normalized CO₂ reactivity assessed at the middle cerebral artery and the oxygenated and deoxygenated hemoglobin of the frontal cortex were obtained. To investigate the impact of cholinergic deficiency known for Alzheimer’s disease on vasomotor reactivity, both groups were reinvestigated during treatment with the acetylcholine esterase inhibitor galantamine.

Results—Transcranial Doppler analysis revealed significantly reduced normalized CO₂ reactivity for Alzheimer’s disease and vascular dementia. Vasomotor reactivity assessed by near-infrared spectroscopy was decreased in patients with vascular dementia, but not in Alzheimer’s disease. Galantamine treatment showed a beneficial effect, normalizing these parameters close to age-matched control levels.

Conclusions—Our results suggest that Alzheimer’s disease is associated with a lack of vasomotor reactivity, which might be associated with disturbed autoregulation indicating a potential risk for a decreased protection of brain tissue against blood pressure changes. Additionally, a diminished increase of cortical oxygenated hemoglobin during the CO₂ test was apparent in patients with vascular dementia. Galantamine treatment influenced vascular reactivity in the CO₂ test, thus providing evidence for the cholinergic deficiency, thereby adding to vascular dysregulation in Alzheimer’s disease, but also indicating an important role of cholinergic system dysfunction for vascular dementia. (Stroke. 2007;38:000-000.)

Key Words: autonomic nervous system • Alzheimer’s disease • dementia • near-infrared spectroscopy • transcranial Doppler sonography

The pathology of Alzheimer’s disease (AD) has long been predominantly associated with deposition of amyloid and neurofibrillary tangles as well as basal forebrain cholinergic deficits and extensive neuronal loss in the cortex and hippocampus.

Although Alois Alzheimer initially described the affection of cerebral vessels as part of the histological picture of the disease,¹ vascular pathology still remains a clinical exclusion criterion for physicians.² Recently, more and more evidence has accumulated supporting the idea that neurovascular dysfunction substantially contributes to cognitive decline and neurodegeneration in AD, thus altering the traditional neurocentric view.³ A neurovascular hypothesis for the pathogenesis of AD has been proposed⁴ suggesting manifold pathogenic cascades, including dysregulation of cerebral blood flow (CBF), hypoperfusion,⁵ faulty clearance of amyloid-β peptides,⁶ and aberrant angiogenesis.⁷ Neurovascular mechanisms particularly gained attention when epidemiological studies indicated similar risk factors for the development of vascular dementia and AD, including diabetes, hypertension, hypercholesterolemia, hyperhomocysteinemia, and the apolipoprotein-E genotype.³,⁸ These data are supported by histopathological and functional changes of large and small cerebral vessels in AD.⁹

Physiologically, the adaptation of global and regional CBF to changes in posture, arterial pressure, or an alternating demand of oxygen and glucose is realized by a wide variety of mechanisms integrated into a highly differentiated regulatory system. For example, metabolic and ionic factors such as [K⁺] and [H⁺] mediate the major part of local coupling between neuronal activity or metabolism and CBF by inducing vaso constriction or dilatation of cerebral arteries and
arterioles in specific brain regions. More globally, cerebral autoregulation adjusts CBF for a wide range of systemic blood pressure.10 CBF can further be increased or decreased by perivascular factors (eg, acetylcholine released by parasympathetic nerves or norepinephrine released by sympathetic nerves, respectively), which are, besides other sources, released by vascular nerves.11 Interestingly, hypoperfusion has recently been shown to affect cholinergic neurons, thus linking both pathophysiological factors.12

We hypothesized that CO2-induced vasodilation as a measure for vasomotor reactivity (VMR) is severely impaired in AD due to the lack of cholinergic innervation in AD.13 Furthermore, we aimed to compare VMR of patients with AD to VMR changes caused by microangiopathy in patients with vascular dementia (VaD) as previously shown for cerebral microangiopathy by our group.14 We further hypothesized that the plant alkaloid galantamine, which is routinely used for the treatment of AD,15 improves VMR due to the increased cholinergic neurotransmission caused by its acetylcholine esterase inhibitor (AChE inhibitor) activity and its potentiating effect on nicotinic acetylcholine receptors.16 This hypothesis is supported by a recent report that another AChE inhibitor, donepezil, can restore disturbed dynamic cerebrovascular regulation in AD.17

To test our hypotheses, we measured CO2-induced VMR by means of transcranial Doppler sonography (TCD) and near-infrared spectroscopy (NIRS) in patients with AD and VaD and compared it with values obtained from age-matched control subjects as well as young control subjects to relate our findings to the influence of aging. For patients with AD and those with VaD, a second assessment was performed during treatment with galantamine.

**Methods**

**Patients**

Patients were recruited from routine hospital admissions or the outpatient clinic, diagnosed in a specialized dementia center, and followed up in our memory clinic. Therefore, a standardized diagnostic procedure containing clinical examination, cranial MRI scanning, electroencephalography, and cerebrospinal fluid investigation for tau and β-42/40 ratio was performed. The diagnosis of dementia was established after performing a neuropsychological test series including the Mini-Mental State Examination,18 the Wechsler Memory Test19 and the Nürnberg Altersinventar.20 Severity of dementia was staged according to the Clinical Dementia Rating.21 Extracranial and TCD examinations were performed to exclude significant carotid or vertebral stenosis. As exclusion criteria, signs of combined vascular and tau pathology, hemodynamically relevant obstructions of extracranial vessels, window failure in TCD examination, and previous acetylcholine inhibitor treatment were defined. Data from patients who did not attend follow-up investigations were not included in the analysis. According to NINCDS-ADRDA2 and NINDS-AIREN criteria,22 two patient groups were formed containing patients with probable AD and patients with possible VaD, respectively. For VaD, only patients with MRI signs of microangiopathy were included, whereas signs of macroangiopathy were defined as exclusion criteria. For details, see Tables 1 and 2.

**Control Subjects**

Control subjects matched with respect to age and sex, recruited from a local community center, as well as young control subjects consisting of hospital employees and medical students were included. All control subjects showed normal results in clinical, neurological, and neuropsychological examinations.

**Informed Consent**

All participants or their legal guardians were informed about the nature and the aim of the study and were only included after giving written informed consent to a protocol approved by the Ethics Committee of the Friedrich-Schiller-University, Jena. All investigations performed were in accordance with the Declaration of Helsinki (1975).

**Testing Protocol**

All examinations mentioned subsequently were performed directly after inclusion in the study in all participants. In addition, patients were investigated a second time after galantamine treatment, consisting of 8 mg/d for 2 weeks and 16 mg/d for another 3 weeks. The latter dose was chosen because it has been shown to improve global ratings in probable or possible AD.18

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**Table 1. Demographic Data of Participants**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AD</th>
<th>VaD</th>
<th>Controls Old</th>
<th>Controls Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.9±11.9</td>
<td>69.4±8.0</td>
<td>64.7±10.0</td>
<td>24.9±2.3</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>4.08±2.01</td>
<td>5.12±1.63</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>12</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140–160 mm Hg</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>&gt;160 mm Hg</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
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<td>Medication</td>
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<td></td>
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<td></td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>3</td>
<td>11</td>
<td>2</td>
<td>0</td>
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<td>CoA-reductase inhibitors</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
Data Acquisition and Preprocessing

Blood Pressure
Mean arterial blood pressure (MAP) was continuously measured using a noninvasive, beat-to-beat finger blood pressure monitor (TNO Biomedical Instrumentation, Amsterdam, The Netherlands).

Transcranial Doppler
Cerebral blood flow velocity was recorded simultaneously from both middle cerebral arteries (MCA) using a TCD device (X4; DWL Medizintechnik, Sipplingen, Germany) as previously described. In brief, probes were placed at both temporal bone windows. Doppler signals obtained from the M1 segment of MCA were identified and measured at a depth of 45 to 55 mm. From these signals, time-averaged MCA blood flow velocity was calculated and continuously monitored.

Near-Infrared Spectroscopy
Near-infrared spectroscopy (NIRO 500; Hamamatsu Photonics) was used to detect changes in concentrations of oxygenated hemoglobin (O2Hb), deoxygenated hemoglobin (HHb), and total hemoglobin (cHb) during normocapnia and hypercapnia. The transmitting probe was placed on the left side of the forehead 2 cm lateral to the midline and 3 to 4 cm above the supraorbital ridge, and the receiving probe was fixed 5 cm lateral to the previous. To discriminate between extra- and intracranial oxygenation, cutaneous blood flow was monitored using laser Doppler flowmetry (MFB3; Moor Instruments) as described previously. From these data, the difference of flux between baseline and CO2 exposure was determined and compared in a paired t test.

Reactivity Test
The CO2 task, which causes cerebral vasodilation due to hypercapnia, was used to assess vasomotor reactivity. For baseline recordings, subjects could be obtained. When the subjects were offered room air through a breathing mask. When the difference between oxygenated and deoxygenated hemoglobin concentration (Hbdiff) was calculated to enhance signal-to-noise ratio and CR-Hbdiff was used as an additional reactivity index.

Cerebrospinal Fluid
Cerebrospinal fluid samples were obtained from every patient. Tau concentrations were measured in duplicate using an enzyme-linked immunosorbent assay (Innotest h-tau antigen; Innogenetics, Ghent, Belgium). Aβ40 and 42 levels were assessed using the Amyloid Aβ40 or Aβ42 ELISA High Sensitivity Kit (The Genetics Company, Zurich, Switzerland).

Statistical Analyses
Analyses were performed using SPSS. After confirming normal distribution of obtained data using Kolmogorov-Smirnov test, a multivariate analysis of variance using the between-subject factor GROUP (AD, VaD, control old, control young) and a Bonferroni-corrected multivariate post hoc analysis were applied for calculating differences between neuropsychological impairment, NCR-DMAP, and NIRS parameters.

Results
Group Allocation and Sample Size
Taking into account the NINDS-AIREN and NINCDS-ADRDA criteria, together with results from MRI evaluation, cerebrospinal fluid tau determination (>300 pg/mL for AD) and clinical signs of microangiopathy, a total of 17 patients in the AD group and 17 patients in the VaD group completed this study. Furthermore, data from 20 young and old control subjects could be obtained.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AD</th>
<th>VaD</th>
<th>Controls Old</th>
<th>Controls Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>23.9±4.0</td>
<td>21.12±5.33</td>
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<td>NA</td>
</tr>
<tr>
<td>CDR</td>
<td>2.19±0.68</td>
<td>1.94±0.79</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Erkinjunti scale</td>
<td>2.18±2.07</td>
<td>5.65±2.32</td>
<td>1.18±1.41</td>
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</tr>
<tr>
<td>tau, pg/mL</td>
<td>624.7±105.3</td>
<td>233.5±91.8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>beta 42/40 ratio</td>
<td>0.98±0.35</td>
<td>1.59±0.39</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.48±1.36</td>
<td>5.18±1.43</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BP baseline, mm Hg</td>
<td>132.1±11.9</td>
<td>141.8±9.7</td>
<td>136.9±11.6</td>
<td>122.4±7.6</td>
</tr>
<tr>
<td>BP follow-up, mm Hg</td>
<td>127.3±14.1</td>
<td>146.2±8.9</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

All data presented as mean±SD. MMSE indicates Mini-Mental State Examination; BP, blood pressure; NA, not available.
Vasomotor Reactivity

The multivariate analysis of variance revealed a significant main effect of GROUP for the normalized CO₂-induced vasomotor reactivity normalized to mean arterial blood pressure change (NCR-ΔMAP; F[3,70]=7.175; P<0.0001), for oxygenated hemoglobin (CR-O₂Hb; F[3,70]=21.38; P<0.0001), for deoxygenated hemoglobin (CR-HHb; F[3,70]=3.91; P<0.012), and for the difference between oxygenated and deoxygenated hemoglobin (CR-Hbdiff; F[3,70]=11.19; P<0.0001).

For differences between groups, we performed Bonferroni-corrected post hoc analyses. These revealed significant differences for NCR-ΔMAP when comparing old control subjects with patients with AD (Figure 1A, P<0.01) or with patients with VaD (Figure 1A, P<0.03). No differences were observed between young and old control subjects and between patients with AD and those with VaD. Although significant differences for CR-O₂Hb were observed when patients with VaD were compared with old (Figure 2A, P<0.0006) and young control subjects (Figure 2A, P<0.0001), the same parameter obtained from AD only differed significantly from young control subjects (Figure 2A, P<0.0001)

Furthermore, a significant distinction between patients with VaD and aged (P<0.0002) as well as young control subjects (P<0.0001) was obvious for CR-Hbdiff as well as for the comparison between patients with AD and young control subjects (P<0.014). CR-HHb, CR-cHb, and Δflux did not significantly differ between groups.

Influence of Galantamine Treatment

For treatment with galantamine of patients with AD and those with VaD, the mixed 2-way analysis of variance showed a significant overall effect of all parameters (NCR-ΔMAP, CR-O₂Hb, CR-HHb, CR-cHb, and CR-Hbdiff) for the within-subjects factor TIME (before and after galantamine; F[1,28]=10.89; P<0.001), for the between-subjects factor GROUP (AD and VaD; F[1,28]=3.6; P<0.012), and for TIME × GROUP interaction (F[1,28]=3.2; P<0.02).

The two-way analysis of variance revealed a significant effect of the factor TIME for the parameters NCR-ΔMAP (F[1,32]=18.7; P<0.001) and CR-O₂Hb (F[1,32]=7.45; P<0.01) applying Greenhouse-Geisser correction (Figures 1B and 2B). No TIME × GROUP interaction was observed. Paired t tests revealed a significant effect of treatment for NCR-ΔMAP in patients with AD (P<0.006) and patients with VaD (P<0.007), whereas significant differences for CR-O₂Hb (P<0.01) were obvious in patients with VaD only (Figures 2A and 2B). Parameters not displayed in figures are depicted in Table 3.

Correlations

NCR-ΔMAP and CR-O₂Hb significantly correlated in all participants (r=0.344, P<0.003; Figure 1C).

In patients with AD or VaD, CR-O₂Hb correlated with the extent of neuropsychological impairment as assessed using the Mini-Mental State Examination (r=0.59, P<0.0002, Figure 2C). After galantamine treatment, we further found a positive correlation between NCR-ΔMAP and CR-O₂Hb (r=0.356, P<0.03) for both diseases.

Additionally, a significant correlation was found in patients with AD, but not in patients with VaD, between β-42/40 ratio and CR-O₂Hb (P<0.003) as well as between β-42/40 ratio and CR-Hbdiff (P<0.02) before as well as after medication.
Blood Pressure

For baseline mean arterial blood pressure in all groups, see Table 2. Blood pressure usually rose during CO2 tests (mean of all patient groups: 8.4±7.3 mm Hg). Yet, there were no significant differences compared with baseline and between patient groups. Similarly, no significant difference was obvious in control subjects (9.5±8.2 mm Hg).

Discussion

Recent clinical studies pointed to a decrease of CBF and glucose utilization in AD,27,28 For instance, studies applying single photon emission computed tomography revealed a globally reduced blood flow and, in particular, a focal reduction of CBF in the bilateral posterior parietotemporal cortex in patients with AD.29

We present evidence in humans that CO2-induced VMR in the MCA is severely impaired in AD, thus confirming our primary hypothesis. In fact, VMR during CO2-induced hyperemia is reduced to a similar degree in probable AD and possible VaD. To date, some clinical studies in patients with AD using TCD showed a decrease in MCA blood flow velocity.17,30 However, reduced CBF might result from diminished cerebral oxygen demand and thus resemble a reduced cerebral metabolism in severely atrophied brains.31 This might especially be important because sustained orthostatic hypotension has been described in AD.32 We have chosen the CO2-induced hyperemia test, which leads to vasodilation most likely due to pH changes, activation of vasoactive neuronal pathways, and the involvement of vasoactive substances such as nitric oxide or adenosine33 to investigate cerebral vasoregulation in patients with AD.

From our results, we can assume that the fine tuning of brain perfusion and arterial pressure is impaired in patients with AD or VaD. The lack of these protective mechanisms either by extravascular or vascular factors (eg, cerebral amyloid angiopathy) might influence disease progression, especially because brain perfusion impairment is one of the earliest AD signs. Therefore, further investigations establishing the degree of VMR disturbance at different disease stages in patients with AD are of major importance.

Despite VMR of the MCA being severely impaired in both patients with AD and those with VaD, the actual oxygenated hemoglobin in the frontal cortex (CR-O2Hb) as obtained by NIRS is decreased in patients with VaD only, thus corroborating previous results of patients with microangiopathy.14 These findings are well in line with positron emission tomography studies showing preserved responsiveness to CO2 in AD but severe impairment in VaD.34 The main focus of VaD pathology as represented in the typical clinical picture is located in subcortical brain regions. However, our results suggest impairment in cortical regions as demonstrated previously.35 In future studies, a direct comparison and correlation between positron emission tomography and Doppler examinations might be beneficial to elucidate how changes in local blood flow might influence perfusion and metabolism in the related brain area.

We hypothesized that the cholinergic deficiency known for AD might account for the changes in VMR, especially because a beneficial effect of the AChE inhibitor donepezil

Figure 2. NIRS. Differences for CR-O2Hb between control subjects (old: control subjects matched with respect to age and sex, n=20; young: control subjects from a different age population, n=17) and patients with AD disease (n=17) and VaD (n=17) are depicted as box plots (A). Into NCR, no significant difference was obvious between old control subjects and AD, but between control subjects and VaD. The effect of galantamine treatment is depicted in (B) showing an increase of oxygenated hemoglobin in VaD to the level of patients with AD, but no significant change in AD itself. NIRS parameters showed significant correlations to Mini-Mental State Examination scores (C) for both patients with AD (empty squares) and patients with VaD (filled circles) as well as when including both in the analysis as shown here. Boxes in (A) and (B) indicate data between the 25th and 75th percentile with the horizontal bar reflecting the median (■=mean; ○=1st and 99th percentile; —=minimum and maximum of data; *P<0.05; **P<0.01; ***P<0.001).
on dynamic cerebrovascular regulation has recently been shown.\textsuperscript{17} To test our hypothesis, we reassessed our patients after the application of galantamine, a substance also known for its AChE inhibitor properties. Using this experimental approach, we could indeed demonstrate a clear influence of this substance on VMR of the MCA in both patients with AD and those with VaD. These findings indicate a profound effect of cholinergic drugs on VMR. Underlying this cholinergic hypothesis are reported findings of an alteration of cerebrovascular reactivity to acetylcholine and bradykinin from the endothelium and a disturbed cerebral autoregulation in an animal model of AD, which is characterized by an overexpression of amyloid precursor protein.\textsuperscript{36}

Interestingly, an increased CR-O\textsubscript{2}Hb on galantamine treatment was obvious only in patients with VaD as assessed using CO\textsubscript{2} exposure. This might indicate that in addition to acetylcholine-associated dysregulation at the MCA level, cholinergic deficiency in cerebral microvessels might further resemble an important factor for VaD. Recent studies revealed that the cholinergic system is indeed affected in VaD due to widespread disconnection of cholinergic innervation of the cortex.\textsuperscript{12} As an additional underlying cause, low pH due to poor perfusion is being discussed to cause cholinergic neurons to degenerate.\textsuperscript{37}

Another finding of this study is the correlation between β-42/40 ratio and CR-HHb and CR-Hb\textsubscript{diff}, although CR-O\textsubscript{2}Hb was not significantly decreased in patients with AD. This correlation might be of relevance, because Aβ1 to 40 has been shown to reduce functional hyperemia in mouse neocortex during somatosensory activation,\textsuperscript{38} thus indicating an association of low 1 to 40 amyloid with VMR or even neurovascular coupling. However, we cannot exclude that this correlation mirrors disease progression rather than an interaction between β amyloid and VMR.

In our study, we investigated young control subjects in addition to control subjects matched with respect to age to describe the effect of aging. Interestingly, in the absence of cognitive deficits, only NIRS parameters worsen slightly with age, possibly due to atherosclerotic changes and altered endothelial function (see also the distribution of values in Figure 1C), thus being well in line with previously reported data.\textsuperscript{38}

### Limitations

In the vasomotor reactivity test used in our study, an increase of 1% in end-tidal CO\textsubscript{2} was used to induce vasodilation. In this attempt, a steady state between expiratory air and pulmonary blood CO\textsubscript{2} concentrations can be assumed within less than 1 second assuming normal diffusing capacity of the lungs.\textsuperscript{39} Determining arterial blood gases instead of end-expiratory concentrations resembling a more precise method was avoided in our study to exclude possible arousal and interference in our cognitively impaired patients.

Furthermore, patients at the age of developing dementia are usually on regular medication, and some compounds might alter VMR, thus confounding the results of our study. We have tried to match the control group in this respect. However, larger study populations are needed to corroborate our findings and to estimate the influence of this confounding factor. To exclude a confounding of results by a previous intake of AChE inhibitors, patients who had a respective history were excluded from the study.

### Summary

In conclusion, our results suggest that AD is associated with a lack of VMR in the MCA, which might be associated with disturbed autoregulation indicating a potential risk for a decreased protection of brain tissue against blood pressure changes. Additionally, we showed for patients with VaD a diminished increase of cortical CR-O\textsubscript{2}Hb during the CO\textsubscript{2} test. Furthermore, we could show the AChE inhibitor galantamine to influence vascular reactivity in the CO\textsubscript{2} test, thus providing evidence for the cholinergic deficiency adding to vascular dysregulation in Alzheimer’s dementia, but also indicating an important role of cholinergic system dysfunction for VaD. Hence, given future studies confirm the effects seen here during long-term treatment, this might add to the importance of vascular pathology in AD as well as to cholinergic deficiency as an important factor for VaD and may thus indicate an additional mechanism in attenuating disease progression for both AD and VaD.

### Acknowledgments

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Disclosures

None.

References


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