Send Orders for Reprints to reprints@benthamscience.net

Current Alzheimer Research, **2014**, *11*, **11-17**

Impaired Cerebral Autoregulation and Vasomotor Reactivity in Sporadic Alzheimer's Disease

Aisha S.S. Meel-van den Abeelen, Joep Lagro, Arenda H.E.A. van Beek and Jurgen A.H.R. Claassen*

Radboud University Medical Center, Department of Geriatric Medicine and Radboud Alzheimer Center, Donders Institute for Brain, Cognition and Behaviour, The Netherlands

Abstract: *Background* Understanding the relationship between vascular disease and Alzheimer's disease (AD) will enhance our insight into this disease and pave the way for novel therapeutic research. Cerebrovascular dysfunction, expressed as impaired cerebral autoregulation and cerebral vasomotor reactivity, has been observed in transgenic mouse models for AD. Translation to human AD is limited and conflicting however. *Objective* To investigate if impaired cerebral autoregulation and cerebral vasomotor reactivity, found in animal models for AD, are present in human sporadic AD. *Methods* In 12 patients with mild to moderate AD (75 SD 4 yr) and 24 controls matched for age and history of hypertension, all without diabetes, we measured blood pressure (Finapres) and cerebral blood flow-velocity (transcranial Doppler). Cerebral autoregulation was assessed during changes in blood pressure induced by single and repeated sit-stand maneuvers. Cerebral vasomotor reactivity was assessed during hyperventilation and inhalation of 5 % carbon dioxide. *Results* During single sit-stands, controls had a 4% (SD 8) decrease in cerebrovascular resistance during a reduction in blood pressure, and an 8 % (SD 11) increase during a rise in blood pressure, indicating normal cerebral autoregulation. These changes were not seen in AD ($p=0.04$). During repeated sit-stands, blood pressure fluctuated by 20 % of baseline. This led to larger fluctuations in cerebral blood flow in AD (27 (6) %) than in controls (22 (6) %, $p < 0.05$). Cerebral vasomotor reactivity to hypercapnia was reduced in AD (42.7 % increase in CBFV, versus 79.5 % in controls, $p = 0.03$). *Conclusion* Observations of impaired cerebrovascular function (impaired autoregulation and vasoreactivity) in transgenic mouse models for AD were confirmed in patients with sporadic AD.

Keywords: Cerebral circulation, cerebral amyloid angiopathy, transcranial doppler, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD), the leading cause of dementia, is a progressive neurodegenerative disorder. Worldwide, AD is highly prevalent and places a huge burden on patients and caregivers [1, 2]. While the number of AD patients grows, there remains limited understanding of this disease and its underlying causes. This is reflected in the lack of an effective curative treatment for AD.

A large body of recent evidence suggests a strong link between AD and vascular disorders and vascular risk factors [3-6]. The exact relationship however between these factors and AD remains poorly understood. Better understanding of how vascular factors relate to AD may therefore enhance our insight into this disease and pave the way for novel therapeutic research.

Research into the vascular pathophysiology of AD can be categorized in two hypothesized 'causal directions', one direction wherein vascular disease leads to (or promotes) Alzheimer pathology, and another, opposite, direction wherein Alzheimer pathology causes vascular disease. These two 'directions' are likely to interact, as is exemplified by cerebral autoregulation.

Cerebral autoregulation (CA) is the mechanism that aims to maintain a stable cerebral blood flow in the event of a change in blood pressure (BP) [7, 8]. Evidence that AD is associated with severe impairment in CA was first observed by Niwa *et al.* (2002) [9]. In this study, mice carrying a human AD mutation were unable to preserve cerebral blood flow when their BP was lowered. This evidence was corroborated by studies showing *in vitro* impairment in cerebrovascular function and structure in models for AD [9, 10]. Although this is an example of the vascular hypothesis direction wherein AD leads to vascular disease, the possible consequences of this impairment in CA serve to illustrate the complex interaction between the two directions: the impairment in CA (due to vascular changes brought about by AD) increases the risk of cerebrovascular insufficiency (e.g. ischemia, hypoperfusion) which in turn may contribute to the progression of AD [11].

In addition to an impairment in CA, evidence also suggests that cerebral vasomotor reactivity (CVMR) is affected in AD. CVMR is a mechanism that reflects the uniquely strong response of cerebral blood vessels to changes in arterial carbon dioxide concentration [12]. Two different mouse models for AD demonstrated cerebral microvascular impairment in vasomotor reactivity to hypercapnia [10, 13].

*Address correspondence to this author at the Radboud University Medical Center, Department of Geriatric Medicine, 925, PO Box 9101, 6500 HB, Nijmegen, The Netherlands; Tel: +31 24 3616772; Fax: +31 24 3617408; E-mail: jurgen.claassen@radboudumc.nl

1875-5828/14 $58.00+.00

Whether these animal model findings of impaired CA and CVMR can be translated to human AD remains uncertain [11]. The aim of this study was to assess CA and CVMR in patients with AD and age-matched controls, with the hypothesis that CA and CVMR both show impaired vasodilatatory responses in human AD, comparable to observations in AD animal models.

MATERIALS AND METHODS

Study Population

We studied 12 patients with mild to moderate AD (age 75 ± 4 yr) and 24 controls matched for age and –because hypertension is a common comorbidity in AD - also for history of hypertension. None of the AD patients or controls had diabetes, however. All subjects were carefully screened by a geriatrician including a medical history, physical examination, and electrocardiogram to exclude acute medical conditions or cardiovascular diseases other than hypertension. Patients with AD were diagnosed as probable AD by a multidisciplinary memory clinic team using the NINCDS-ADRDA criteria [14, 15] based on clinical evaluation and additional diagnostic tests, such as MRI-scan of the brain (which was consistent with mild global atrophy combined with hippocampal atrophy and no or minimal cerebrovascular disease), neuropsychological testing (which showed a predominant disorder in episodic memory) and cerebrospinal fluid analysis (available in n= 4, showing a biomarker profile consistent with AD). Informed consent was obtained from patients and their proxy [16], and from controls, before they entered the study. The study was approved by the medical ethical committee.

Data Acquisition

BP was measured continuously and noninvasively in the middle finger of the right hand using Finapres (Finapres Medical Systems, the Netherlands). The hand and arm were supported securely and comfortably with a sling, providing a stable position of the hand and arm at heart level throughout the whole measurement. It has been shown that BP measured indirectly in a finger by photoplethysmography is reliable in assessing changes in BP that correlate well with auscultatory BP measurements in the upper arm [17].

Cerebral blood flow velocity (CBFV) was obtained in the middle cerebral arteries (MCA) by transcranial Doppler ultrasonography. The left and right MCA were insonated by placing a 2-MHz Doppler probe (Multi-Dop, Compumedics DWL, Germany) over the temporal window. The MCA were identified according to their signal depth, velocity, and wave characteristics [18]. If only one signal was available due to one-sided temporal window failure, we included this available signal for analysis. The probes were locked at a constant angle and position during data collection with a customized headband (Spencer technologies, Seattle, Wa.).

End-tidal CO_2 ($etCO_2$) was monitored with a nasal cannula using capnography (BIOPAC Systems, Goleta, Ca.).

Experimental Procedure

All experiments were performed in the morning, at least 2 h after a light breakfast and 12 h after the last caffeinated beverage or alcohol, in a quiet, environmentally controlled laboratory with an ambient temperature of 22°C. After at least 10 min of rest in sitting position, a baseline measurement of 5 min was recorded during spontaneous respiration.

To assess CA, subjects were asked to perform a single sit-to-stand protocol. Subjects sat in a straight-backed chair and were asked to stand up. The protocol consisted of three trials of 2-min sitting followed by standing for 1 min. After this, repeated sit-stand maneuvers were performed [19]. Patients were coached into performing these maneuvers at a frequency of 0.05 Hz (10s sitting, 10s standing) for 5 min. During all maneuvers, subjects were instructed to keep normal breathing and to avoid performing a Valsalva maneuver. Adherence to this was confirmed by inspecting the CO_2 waveforms and $etCO_2$ registrations.

To estimate CVMR a previously described protocol was used [20], consisting of a 30 s period of coached hyperventilation, followed by 2 minutes of spontaneous breathing. Next, subjects were asked to inhale a gas mixture containing 7% CO_2, 21% O_2, and 72% N_2 through a tightly fitting mouthpiece until a stable plateau of CBFV had been reached. With this protocol a wide range of changes in $etCO_2$ can be obtained.

Data Processing

All data were simultaneously recorded at 200 Hz. Post processing was performed using custom-written MATLAB scripts. Real time beat-to-beat mean values of BP and CBFV were calculated as waveform integration of the BP and CBFV signal within each cardiac cycle.

The CVMR protocol evaluated changes in CBFV, BP, and calculated cerebrovascular conductance index (CVCI), during the transitions from hypocapnia (induced by hyperventilation) to normocapnia and from normocapnia to hypercapnia (induced by 7% CO2 inhalation).

Because changes in CO_2 cause changes in BP, which in turn may directly affect CBFV, CVCI, expressed as CBFV changes divided by BP changes, was used to minimize the confounding effects of differences in BP response during CVMR testing between subjects on CVMR estimation [21].

For CA, to evaluate the beat-to-beat dynamics of BP and CBFV responses to acute posture changes in the single sit-stand protocol, we calculated the differences between the sitting value (averaged over a period of 20 s) and the value at the nadir of BP (average of 5 values surrounding the nadir) for BP and CBFV.

The repeated sit-stand maneuvers were evaluated by calculating the differences between the maximal sitting value (average of 5 values surrounding the top) and the value at the nadir of BP after standing (average of 5 values surrounding the nadir) for BP and CBFV for each sit-to-stand maneuver.

This way only the amplitude relationship between changes in BP and CBFV was taken into account, the phase shift between BP and CBFV was disregarded. In addition to these absolute values, we also expressed these changes as percentage of baseline. The average of the trials for a group was then computed.

Finally, we determined the transfer function analysis (TFA) from the spontaneous oscillations in the baseline measurement as a measure for CA using the method described by Zhang *et al.* (1998) and reviewed in [8]. The time series of mean BP and CBFV were first subdivided into 950-point segments with 50% overlap for spectral estimation. This process resulted in five segments of data for the segment periodogram average. Fast Fourier transforms were implemented with each Hanning-windowed segment and averaged to quantify the transfer function. For quantification of CA the positive phase shift and the gain between BP and CBFV were quantified as means of the following frequency bands: very low frequency (VLF): 0.02-0.07Hz; low frequency (LF): 0.07-0.15Hz.

The TFA is based on the high-pass filter model of cerebral autoregulation, wherein BP oscillations at lower frequencies are buffered better than higher frequencies, leading to lower gain (better damping) in these lower frequencies. Also, a characteristic of this model is that the counteractive actions of autoregulation lead to a phase shift between CBF and BP in these lower frequencies [8].

Statistical Analysis

Results are presented as the means ± standard deviations (SD) or percentages unless otherwise stated. Differences in variables between patients and controls were evaluated with the independent student t-test for continuous variables and the chi-squared (χ^2) statistic for proportions. The results were considered to be significant for p-values < 0.05.

RESULTS

Subject Characteristics

Demographic and baseline data for the 12 AD patients and the 24 controls are summarized in (Table **1**). AD and controls were well matched for age and history of hypertension, however there was more use of anti-hypertensive medication in AD (p=0.01), and BP was somewhat higher at baseline (although only significant for diastolic BP, p=0.03). Previous studies [22-24] have shown higher cerebrovascular resistance in AD. This trend was observed here but did not reach significance likely due to the small sample and high intra-individual variability.

Cerebral Vasomotor Reactivity

One healthy control could not perform the CVMR procedure adequately and was excluded from this analysis. (Table **2**) summarizes the hemodynamic results for CVMR.

AD patients and controls had similar $etCO_2$ values for baseline and for the minimum and maximum $etCO_2$ levels reached during hyperventilation and CO_2 breathing (p>0.05, Table **2**). Changes in BP were also similar in both groups during normocapnia, hyperventilation and CO_2 breathing. Changes in CBFV did not differ during baseline or hyperventilation, however during 7 % CO_2 breathing CBFV increased less in AD (p<0.01). This difference in the CBFV response over the full range from hypocapnia to hypercapnia between AD and controls is also shown in (Fig. **1**). CVMR was decreased in AD for hypercapnia (42.7 % increase in CBFV, versus 79.5 % in controls, p = 0.03) but not for hypocapnia (30.0 % decrease in CBFV, versus 32.4 % in controls, p = 0.2). Over the full range of etCO2, the CVMR was also clearly reduced in AD (controls 111.6%, AD 73.2%, p<0.01).

Expressed as a ratio of CBFV changes over changes in $etCO_2$, CVMR was also lower in AD compared to controls (1.09 ±0.39 vs. 1.44±0.43 $cm.s^{-1}.mmHg^{-1}$, p = 0.02).

Table 1. Baseline Characteristics

	AD Patients (n = 12)	Controls (n = 24)
Age (years)	74 (4)	76 (4)
Sex (male/female)	9/3	18/6
MMSE (0-30)	22 (5) †	29 (1)
CAMCOG (0-104)	69 (13)	NA
CDR (0-3)	0.9 (0.2)	0
Hypertension (n(%))	6 (50)	9 (38)
SBP (mmHg)	140 (33)	127 (19)
DBP (mmHg)	69 (13) †	58 (9)
BP (mmHg)	105 (24)	100 (11)
CBFV (cm/s)	45 (15)	50 (11)
CV resistance (mmHg*s/cm)	2.6 (1)	2.1 (0.6)
Medication use		
• Beta blocker	4/12	3/24
• ACE inhibitor	2/12	0/24
• ARB	0/12	0/24
• Calcium channel blocker	1/12	0/24
• Thiazide diuretics	3/12 †	0/24

All values are mean (SD). AD= Alzheimer's disease patients. MMSE= Mini Mental State Examination. CAMCOG = Cambridge cognitive examination, higher scores are better, cut-off scores are age and education-dependent but usually lie between 77-84). CDR: clinical dementia rating scale, 0 = normal, 0.5 = mild cognitive impairment, 1 = mild dementia, 2 = moderate and 3 = severe dementia. BP = mean arterial blood pressure, SBP= systolic and DBP = diastolic blood pressure. CBFV= mean cerebral blood flow velocity, CV resistance = cerebrovascular resistance (CBFV/BP). †significantly different (p<0.05) from control.

Cerebral Autoregulation: Cerebral Blood Flow Responses to Single Step Changes in Blood Pressure

The hemodynamic changes for the single sit-stand maneuvers are summarized in (Table **3**). The posture change from sit to stand evoked transient reductions in BP and CBFV, but did not result in a difference between AD and control in either the maximum reduction in BP, the maximum reduction in CBFV, or the time to nadir.

However, normal CA, in an attempt to restore CBF to baseline following a reduction in BP, will cause a reduction in cerebrovascular resistance. Despite similar proportions of

changes in BP and CBFV, this expected normal reduction in cerebrovascular resistance was observed in controls but not in AD (difference: -0.06 mmHg*s/cm, p=0.04, see Table **3**). The posture change from standing back to sitting led to similar increases in BP. Also here, the expected increase in cerebrovascular resistance when CA attempts to buffer this increase in BP was not observed in AD. As a result, the proportional increase in CBFV for a similar increase in BP was larger in AD (p=0.02; Table **3**, Fig. **2**). Together, these results show impaired responses in cerebrovascular resistance in AD, indicating diminished CA.

Table 2. Cerebral Vasomotor Reactivity Results

Hypocapnia (Hyperventilation)	**AD Patients (n = 12)**	**Controls (n = 23)**
BP (mmHg)	94 (33)	93 (15)
CBFV (cm/s)	32(12)	32 (9)
CVCI (cm/s/mmHg)	0.32 (0.1)	0.35 (0.1)
$etCO_2$ (mmHg)	19 (6)	19 (6)
Normocapnia	**AD Patients (n = 12)**	**Controls (n = 23)**
BP (mmHg)	118 (25)	111 (15)
CBFV (cm/s)	44 (16)	48 (11)
CVCI (cm/s/mmHg)	0.38 (0.1)	0.44 (0.1)
$etCO_2$ (mmHg)	30 (5)	31 (5)
Hypercapnia (CO_2 Breathing)	**AD Patients (n = 12)**	**Controls (n = 23)**
BP (mmHg)	139 (33)	138 (21)
CBFV (cm/s)	62 (22) †	83 (19)
CVCI (cm/s/mmHg)	0.46 (0.2) †	0.60 (0.1)
$etCO_2$ (mmHg)	48 (9)	51 (6)

All values are mean (SD). See legend table **1**. CVCI= cardiovascular conductance index (BP/CBFV), $etCO_2$ =end-tidal CO_2. † significantly different ($p<0.05$) from control.

Cerebral Autoregulation: Cerebral Blood Flow Responses to Repeated Changes in Blood Pressure

Average BP and CBFV over time during the repeated sit-stand procedure are shown in (Fig. **3**). Three AD patients were not able to perform the repeated sit-stand procedure, due to reduced motion and balance control, and impaired physical fitness, and were excluded from this analysis. The maximum hemodynamic changes caused by the repeated sit-stands are reported in (Table **4**). The repeated sit-stand maneuvers caused similarly large perturbations in absolute and relative (percentage) changes in BP ($p > 0.3$) in AD and controls. However, the relative changes in CBFV were higher in AD (27 ± 6 %) than in controls (22 ± 6 %) ($p = 0.03$), suggesting less effective damping by cerebral autoregulation.

Cerebral Autoregulation: Transfer Function Analysis

A comparison between AD and controls based on the parameters derived from TFA (phase and gain in the very low, and low frequency ranges of spontaneous oscillations in BP and CBFV) revealed no differences..Very low frequency: phase AD 0.88±0.3 rad, phase controls 0.76±0.3 rad, $p > 0.05$; gain AD 0.39±0.2 $cm.s^{-1}.mmHg^{-1}$, gain controls 0.47±0.1 $cm.s^{-1}.mmHg^{-1}$ $p > 0.05$. Low frequency: phase AD 0.76±0.3 rad, controls 0.73±0.3 rad, $p > 0.05$; gain AD 0.64±0.4 $cm.s^{-1}.mmHg^{-1}$, controls 0.63±0.2 $cm.s^{-1}.mmHg^{-1}$, $p > 0.05$.

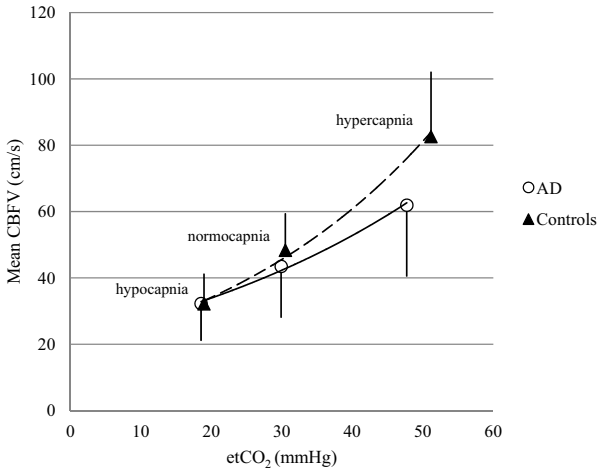

Fig. (1). Mean cerebral blood flow-velocity (CBFV) changes induced by hyperventilation (hypocapnia) and CO_2 breathing (hypercapnia) in AD patients and healthy controls. Solid line: AD. Dashed line: controls.

DISCUSSION

The main finding of this study is that patients with AD demonstrated impairments in CA and CVMR that were similar to observations of cerebrovascular dysfunction in transgenic mouse models for AD. AD patients had a blunted vasodilatatory response to hypercapnia (impaired CVMR) as well as insufficient vasodilatatory and vasoconstrictor responses to decreases and increases in BP (impaired CA).

Preclinical research suggests that Alzheimer pathology affects vascular function [9-11, 13, 25]. This research involved mouse models for Alzheimer disease (AD) and *in vitro* observation of animal and human vascular cells, such as endothelial cells. Post-mortem studies confirm that there are cerebrovascular changes, related to amyloid pathology, in human AD, including degenerated string capillaries and reduced markers linked to vasoconstriction and vasodilatation [26]. Together, this work implies that adaptive cerebrovascular responses may be impaired in AD, such as the cerebral vasodilatatory response to hypotension (cerebral autoregulation), or to increased neuronal demand for oxygen (neurovascular coupling), see [11, 25] for review. Such impaired responses would represent an increased risk of insufficient blood supply to the brain in a patient with AD and could accelerate cognitive decline. It is therefore essential to understand if these impaired cerebrovascular responses are observed not only in animal or *in vitro* human models, but also in humans known to have AD.

Such translational evidence was limited thus far, however. To date, five studies had investigated CA in human AD [23, 24, 27-29], for review see [11], but found no evidence

Table 3. Sit-Stand Maneuver

	Single Sit-to-Stand		Single Stand-to-Sit	
	AD Patients (n = 12)	**Controls (n = 24)**	**AD Patients (n = 12)**	**Controls (n = 24)**
Absolute change				
BP (mmHg)	-18 (5)	-20 (6)	15 (5)	13 (6)
CBFV (cm/s)	-9 (6)	-8 (2)	7 (4) †	4 (3)
CV-Resistance (mmHg*s/cm)	0.06 (0.3) †	-0.1 (0.1)	-0.02 (0.2)	0.10 (0.2)
Percentage change				
BP (%)	-18 (7)	-21 (7)	21 (11)	21 (10)
CBFV (%)	-18(8)	-17 (5)	24 (15) †	13 (9)
CV-Resistance (%)	3 (7)	-4 (8)	-0.8 (9)†	8 (11)
tBP nadir (s)	11 (6)	11 (3)	5 (0.8)	6 (2)

All values are mean (SD). See legend table 1. tBP nadir = time from standing up to the nadir of blood pressure. For stand-to-sit, this was the time from sitting down to the maximum increase in blood pressure. † = significantly different ($p<0.05$) from control.

for impairment of CA. Four of these studies investigated dynamic CA (the CBF response to fluctuating changes in blood pressure), using transcranial Doppler to measure CBF [23, 24, 27, 28]. All three used transfer function analysis (TFA) to assess CA [7, 8]. This method may be less sensitive to detect more subtle impairment in CA in small samples. This is supported by the fact that also in the present study TFA did not reveal a difference in autoregulation between AD patients and healthy controls. TFA combines responses to BP increases and decreases, and does not consider each direction separately. The suggestion that TFA may be less sensitive is further supported by the fact that two of the studies that used TFA also investigated changes in cortical oxygenation and found that frontal cortical oxygenation changes in response to BP changes were stronger in AD, suggesting microvascular impairment, despite normal findings on TFA [27, 28].

The fifth study investigated static CA (the CBF response to a steady-state reduction in BP, comparable to the experiment Niwa *et al.* [9] performed in mice) using PET to measure CBF [29]. No differences were observed between AD and controls, however, the response to increases in BP was not tested and a calcium-channel blocker was used to lower BP, and this may have supported CA by promoting cerebral vasodilatation [11].

Regarding CVMR, two previous studies have investigated CVMR in AD, and confirmed our observation of impaired CVMR [22, 30].

Our study adds to these seven earlier studies by combining CA and CVMR assessment in the same patients. In addition, the method we used to measure CA was more straightforward and therefore perhaps more sensitive to changes than transfer function analysis. CA operates by adapting cerebrovascular resistance to changes in BP [8]. We investigated these changes in cerebrovascular resistance during reductions and increases in BP induced by changes in posture, thus avoiding pharmacological interventions to change BP. We show that these changes in cerebrovascular resistance were reduced in AD, suggesting impaired ability to dilate and constrict. In addition, we challenged CA by inducing repeated increases and decreases in BP, and this led to larger fluctuations in CBF in AD. Again, this suggests that CA is less able to dampen these changes because vasodilatation and constriction are impaired.

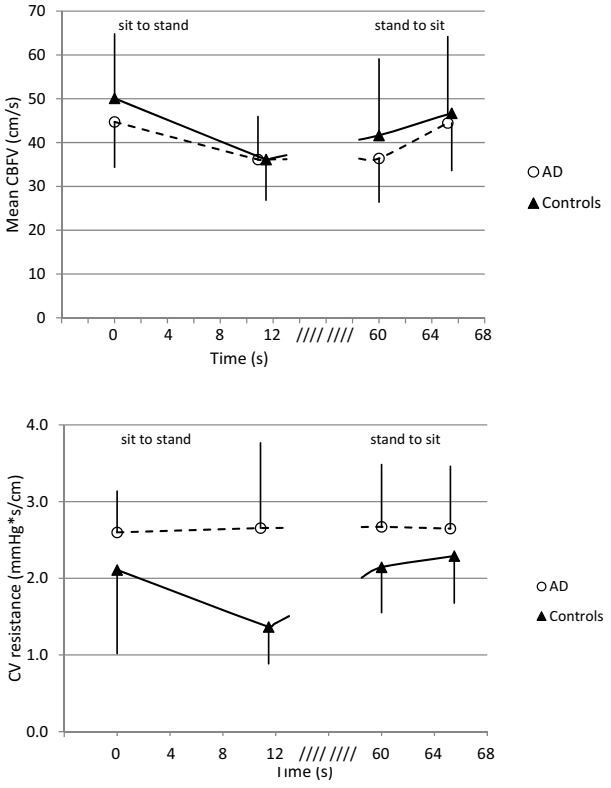

Fig. (2). Mean cerebral blood flow-velocity (CBFV) changes (top) and cerebrovascular resistance index (bottom) induced by single sit-stand and stand-sit maneuver in AD patients and healthy controls. Sit-stand: standing up after 2 min sitting. Stand-sit: return to sitting after 1 min standing. Solid line: controls. Dashed line: AD.

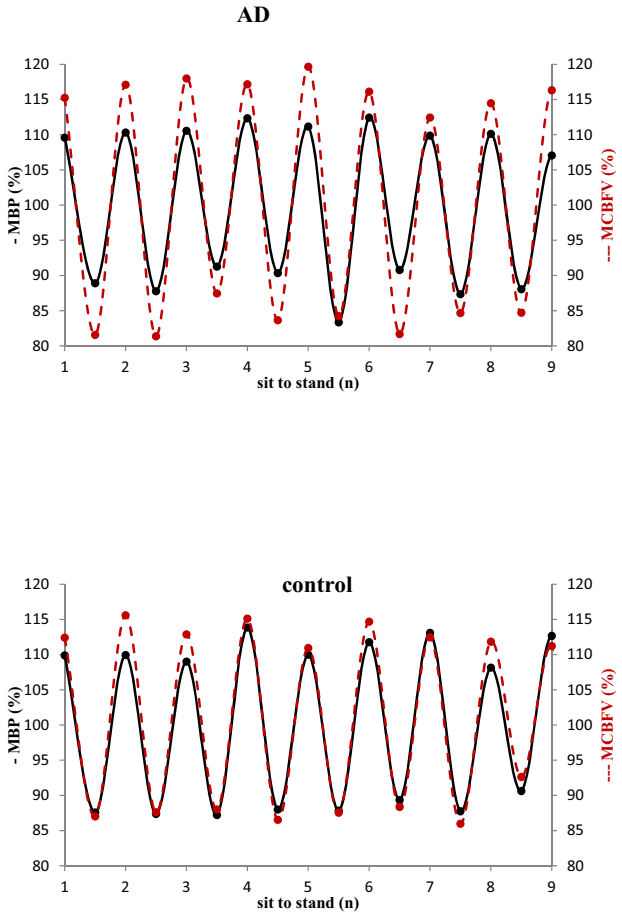

Fig. (3). Average percent changes in mean arterial blood pressure (BP, black lines) and cerebral blood flow-velocity (CBFV, red dashed lines) for the repeated sit- stand procedure for controls (top graph) and AD (bottom graph). 8 consecutive repetitions of 10 s standing followed by 10 s sitting are shown. X-axis represents the number of sit-stands. Note that this graphical representation only shows differences in amplitude, the temporal relationship between BP and CBFV, including any phase shift cannot be determined in this way.

Table 4. Maximal Changes Caused by Repeated Sit-stand Procedure

	AD Patients (n = 9)	Controls (n = 24)
Absolute change		
BP (mmHg)	20 (4)	21 (6)
CBFV (cm/s)	11 (4)	11 (5)
Percentage change		
BP (%)	20 (4)	21 (4)
CBFV (%)	27 (6)†	22 (6)

All values are mean (SD). See legend table 1. †significantly different ($p<0.05$) from the control group.

While CA assesses vasodilatation and constriction in response to changes in BP, CVRM assesses these responses to changes in CO_2. AD patients had reduced vasodilatation to hypercapnia, but vasoconstriction to hypocapnia was not affected. In summary, AD patients had impaired vasodilatation and constriction responses to changes in BP, and impaired vasodilatation responses to hypercapnia.

This is an important translational finding [9, 10, 13]. Criticism of transgenic animal models for AD is that they are not representative for the majority of AD patients who have sporadic AD (i.e. who do not have genetic mutations leading to AD). Our observation of similar cerebrovascular dysfunction in human sporadic AD and transgenic mouse models leads to the following considerations. First, it can be argued that the observation of impaired CA and CVMR in our patients are caused not by AD but by comorbid vascular disorders that may be more prevalent in AD. Indeed, even though we tried to match for hypertension, as in many other studies AD patients had higher BP. However, the animal models find similar cerebrovascular dysfunction, in the absence of confounding human vascular comorbidity. This comparison supports the interpretation that the observed changes in CA and CVMR are related to AD. Second, the animal models link impaired CA and CVMR to cerebral amyloid angiopathy, reflecting vascular deposition of amyloid-beta [9, 13]. The impairment in CVMR in AD was similar to that observed in patients with cerebral amyloid angiopathy [30] and compares to the impairment of CVMR in the transgenic models. Third, the impairments in CA and CVMR are in line with post-mortem observations in AD that found cerebrovascular changes that were suggested to cause impairments in dilatation and constriction [26]. Taken together, this evidence suggests that the cerebrovascular impairments observed in animal models for AD are also observed in sporadic AD, and may both be explained by vascular effects of amyloid-beta.

Limitations of this study are the small sample size. However, despite this small sample, the differences in CA and CVRM were already obvious. Second, the diagnosis of AD remains a clinical one. No pathological confirmation of the underlying disease was available. Still, previous studies have shown that a clinical diagnosis is only inaccurate in about 11% of mild cases when compared to pathological diagnosis [31]. AD was diagnosed by a multidisciplinary memory clinic team consisting of several geriatricians, neuropsychologists, occupational therapists and speech therapists. Lewy body dementia and vascular dementia were excluded based on diagnostic criteria for these conditions, using information obtained by means of history, clinical examination, laboratory tests and MRI.

Finally, the clinical implications of the observed impairments in CA and CVRM are unclear. The impairment in CA is clear but subtle, and did not lead to severe hypoperfusion, and may not lead to cerebral ischemia. Indeed, we recently found no increased susceptibility to white matter lesions in AD [32]. It is not unthinkable however that chronic mild hypoperfusion contributes to brain atrophy in AD. Impaired CVMR may affect neurovascular coupling, which may contribute to cognitive dysfunction [25].

CONCLUSION

AD patients have impaired cerebral autoregulation, leading to reduced ability to stabilize CBF during changes in BP,

as well as impaired CVRM, which leads to much smaller increases in CBF with hypercapnia. These findings are similar to observations in transgenic animal models for AD, where impaired CA and CVMR are thought to be induced by amyloid pathology, especially perivascular amyloid depositions. These translational findings support the vascular hypothesis for AD, specifically the direction where AD causes vascular dysfunction.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This study was supported by grants from ISAO (Internationale Stichting Alzheimer Onderzoek) and the Netherlands Heart Foundation) to dr. Claassen.

REFERENCES

[1] Burns A. The burden of Alzheimer's disease. Int J Neuropsychopharmacol 3(7): 31-8 (2000).

[2] Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, *et al.* Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol 7(9): 812-26 (2008)

[3] Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, *et al.* Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc 53(7):1101-7 (2005).

[4] Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. JAMA 277(10): 813-7 (1997).

[5] White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, *et al.* Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann NY Acad Sci 977: 9-23 (2002).

[6] Iwamoto T, Kanetaka H, Takasak M, Takazawa K. Hemodynamic changes in Alzheimer's and Binswanger's diseases as evaluated by second-derivative finger photoplethysmography. Geriatr Gerontol Int 3: 243-9 (2003).

[7] Panerai RB. Assessment of cerebral pressure autoregulation in humans--a review of measurement methods. Physiol Meas 19(3): 305-38 (1998).

[8] van Beek AH, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. J Cereb Blood Flow Metab 28(6): 1071-85 (2008).

[9] Niwa K, Kazama K, Younkin L, Younkin SG, Carlson GA, Iadecola C. Cerebrovascular autoregulation is profoundly impaired in mice overexpressing amyloid precursor protein. Am J Physiol Heart Circ Physiol 283(1): H315-23 (2002).

[10] Dorr A, Sahota B, Chinta LV, Brown ME, Lai AY, Ma K, *et al.* Amyloid-beta-dependent compromise of microvascular structure and function in a model of Alzheimer's disease. Brain 135(Pt 10): 3039-50 (2012).

[11] Claassen JA, Zhang R. Cerebral autoregulation in Alzheimer's disease. J Cereb Blood Flow Metab 31(7): 1572-7 (2011).

[12] Kety SS, Schmidt CF. The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men. J Clin Invest 27(4): 484-92 (1948).

[13] Han BH, Zhou ML, Abousaleh F, Brendza RP, Dietrich HH, Koenigsknecht-Talboo J, *et al.* Cerebrovascular dysfunction in amyloid precursor protein transgenic mice: contribution of soluble and insoluble amyloid-beta peptide, partial restoration via gamma-secretase inhibition. J Neurosci 28(50): 13542-50 (2008).

[14] Blacker D, Albert MS, Bassett SS, Go RC, Harrell LE, Folstein MF. Reliability and validity of NINCDS-ADRDA criteria for Alzheimer's disease. The National Institute of Mental Health Genetics Initiative. Arch Neurol 51(12): 1198-204 (1994).

[15] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34(7): 939-44 (1984).

[16] Meulenbroek O, Vernooij-Dassen M, Kessels R, Graff M, Sjogren M, Schalk B, *et al.* Informed consent in demetnia research. Legislation, theoretical concepts and how to assess capacity to consent. Eur Geriatr Med 1(1): 58-63 (2010).

[17] Imholz BP, Wieling W, Langewouters GJ, van Montfrans GA. Continuous finger arterial pressure: utility in the cardiovascular laboratory. Clin Auton Res 1991; 1(1): 43-53 (1999).

[18] Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurol Surg 57(6): 769-74 (1982).

[19] van Beek AH, Olde Rikkert MG, Pasman JW, Hopman MT, Claassen JA. Dynamic cerebral autoregulation in the old using a repeated sit-stand maneuver. Ultrasound Med Biol 36(2): 192-201 (2010).

[20] van Beek AH, de Wit HM, Olde Rikkert MG, Claassen JA. Incorrect performance of the breath hold method in the old underestimates cerebrovascular reactivity and goes unnoticed without concomitant blood pressure and end-tidal CO(2) registration. J Neuroimaging 21(4): 340-7 (2011).

[21] Claassen JA, Zhang R, Fu Q, Witkowski S, Levine BD. Transcranial Doppler estimation of cerebral blood flow and cerebrovascular conductance during modified rebreathing. J Appl Physiol 102(3): 870-7 (2007).

[22] Bar KJ, Boettger MK, Seidler N, Mentzel HJ, Terborg C, Sauer H. Influence of galantamine on vasomotor reactivity in Alzheimer's disease and vascular dementia due to cerebral microangiopathy. Stroke 38(12): 3186-92 (2007).

[23] Claassen JA, Diaz-Arrastia R, Martin-Cook K, Levine BD, Zhang R. Altered cerebral hemodynamics in early Alzheimer disease: a pilot study using transcranial Doppler. J Alzheimers Dis 17(3): 621-9 (2009).

[24] Gommer ED, Martens EG, Aalten P, Shijaku E, Verhey FR, Mess WH, *et al.* Dynamic cerebral autoregulation in subjects with Alzheimer's disease, mild cognitive impairment, and controls: evidence for increased peripheral vascular resistance with possible predictive value. J Alzheimers Dis 30(4): 805-13 (2012).

[25] Zlokovic BV. Neurodegeneration and the neurovascular unit. Nat Med 16(12): 1370-1 (2010).

[26] Hunter JM, Kwan J, Malek-Ahmadi M, Maarouf CL, Kokjohn TA, Belden C, *et al.* Morphological and pathological evolution of the brain microcirculation in aging and Alzheimer's disease. PLoS One 7(5): e36893 (2012).

[27] van Beek AH, Lagro J, Olde-Rikkert MG, Zhang R, Claassen JA. Oscillations in cerebral blood flow and cortical oxygenation in Alzheimer's disease. Neurobiol Aging 33(2): 428 e21-31 (2012).

[28] van Beek AH, Sijbesma JC, Jansen RW, Rikkert MG, Claassen JA. Cortical oxygen supply during postural hypotension is further decreased in Alzheimer's disease, but unrelated to cholinesterase-inhibitor use. J Alzheimers Dis 21(2): 519-26 (2012).

[29] Zazulia AR, Videen TO, Morris JC, Powers WJ. Autoregulation of cerebral blood flow to changes in arterial pressure in mild Alzheimer's disease. J Cereb Blood Flow Metab 30(11): 1883-9 (2010).

[30] Menendez-Gonzalez M, Garcia-Garcia J, Calleja S, Rojo J, Ribacoba R. Vasomotor Reactivity Is Similarly Impaired in Patients with Alzheimer's Disease and Patients with Amyloid Hemorrhage. J Neuroimag 21(2): e83-e5 (2011).

[31] Salmon DP, Thomas RG, Pay MM, Booth A, Hofstetter CR, Thal LJ, *et al.* Alzheimer's disease can be accurately diagnosed in very mildly impaired individuals. Neurology 59(7): 1022-8 (2002).

[32] Spies P, Verbeek M, Sjörgen M, de Leeuw F, Claassen J. Alzheimer biomarkers and clinical Alzheimer disease were not associated with increased cerebrovascular disease in a memory clinic population. Curr Alzheimer Res 11(1): 40-47(2013).

Received: November 04, 2012 Revised: April 08, 2013 Accepted: November 11, 2013