Cerebral Circulation - Cognition and Behavior 2 (2021) 100024

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

Longitudinal changes in the control mechanisms for blood pressure and cerebral blood flow in Alzheimer's disease: Secondary results of a randomized controlled trial

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ARTICLE INFO

Keywords:
Autonomic function
Orthostatic hypotension
Cerebral perfusion
Blood pressure
Hypertension
Cerebral autoregulation

ABSTRACT

Objective: Dynamic cerebral autoregulation (dCA) and baroreflex sensitivity (BRS) are key mechanisms involved in the homeostasis of blood pressure (BP) and cerebral blood flow. We assessed changes in these mechanisms in Alzheimer's disease (AD) during a 1.5 year follow-up.

Methods: In this secondary analysis of a randomized controlled trial we measured beat-to-beat BP, heart rate, and cerebral blood flow velocity at baseline, 0.5 and 1.5 years, during: rest (spontaneous oscillations), repeated sit-stand maneuvers (induced oscillations), an orthostatic challenge, and hypo- and hypercapnia. dCA was estimated using transfer function analysis and the autoregulatory index on spontaneous and induced oscillations. BRS was estimated by calculating the heart rate response to BP changes during induced oscillations. Linear mixed models were used to assess changes over time.

Results: 56 patients were included (mean age:73 ± 6 years, 57% female). BRS did not change over time. dCA parameters showed small changes after 0.5 years, suggestive of a reduction in efficiency (e.g. higher gain [linear mixed effect model: B = 0.09, SE = 0.03, $P = 0.008$] and lower phase [B = -9.7, SE= 3.2, $P = 0.004$] in the very low frequency domain, and lower autoregulatory index during induced oscillations [B = -0.69, SE = 0.26, $P = 0.010$]). These changes did not show further progression after 1.5 years of follow-up.

Discussion: In this sample of patients with dementia due to AD we found no evidence that dCA or BRS become impaired during AD progression. This paves the way for further studies that investigate the safety and benefits of antihypertensive treatment in patients with AD.

1. Introduction

Vascular disease is an important contributor to cognitive impairment and dementia, not only vascular dementia, but also Alzheimer's disease (AD) [1–6]. For example, in the vast majority of patients clinically diagnosed with Alzheimer's dementia, the underlying neuropathology shows a mix of AD and cerebrovascular pathology [7, 8]. In addition to its contribution to the dementia per se, vascular disease also frequently co-exists in patients with dementia in the form of comorbidity. For example, in typical samples of patients with AD aged around 75 years, approximately 40 % have hypertension, and 15% have diabetes [5, 9]. Vice versa, many patients who are referred for treatment of vascular disease have cognitive impairment or dementia as comorbidity [10].

In clinical practice, an important unsolved question is whether patients with dementia are more sensitive to adverse effect of vascular treatment, for example blood pressure (BP) lowering treatment [10]. Three mechanisms have been quoted to underly such an increased an risk. First, involvement of autonomic centers in the brainstem or insula by Alzheimer pathology could impair baroreflex function, which could then increase the risk of orthostatic hypotension [11, 12]. Second, cerebrovascular disease in Alzheimer's disease, i.e. the combination of cerebral amyloid angiopathy, small vessel disease, and atherosclerosis, could impair cerebral autoregulation, leading to cerebral hypoperfusion when BP is reduced [13–15]. Third, cerebrovascular involvement in AD

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https://doi.org/10.1016/j.cccb.2021.100024
Received 9 May 2021; Received in revised form 1 July 2021; Accepted 5 July 2021
Available online 10 July 2021

may reduce cerebral vasomotor reactivity to carbon dioxide (CVMR) [16].

However, cross-sectional studies on baroreflex function and on cerebral autoregulation in dementia and cognitive impairment have shown conflicting results [9, 11, 13–15, 17]. To address this knowledge gap, this study investigated baroreflex sensitivity (BRS), dynamic cerebral autoregulation (dCA), and cerebral vasomotor reactivity (CVMR) to carbon dioxide (CO_2) in patients with dementia due to AD. We assessed longitudinal changes over a period of 1.5 years to address effects of AD progression with advancing pathology. In addition, we tested the response of these regulatory mechanisms to mild BP lowering treatment with the calcium-channel blocker nilvadipine.

2. Material and methods

2.1. Study design

Data for this study were derived from the cerebral blood flow (CBF) substudy of the Nilvad trial (EudraCT No. 2012-00276427, NCT02017240), a European multicenter, randomized, double-blind, placebo-controlled trial to investigate the efficacy of 1.5 year use of nilvadipine on cognitive decline in 511 patient with mild-to-moderate AD. A complete description of the trial has been published previously [18]. The study found that nilvadipine had no effect on disease progression [19]. The CBF-substudy included participants from 2 centers in the Netherlands (Radboud university medical center, Nijmegen and Rijnstate, Arnhem) and primarily focused on the effect of the intervention on global and regional CBF [20]. Ethical approval was provided by the medical ethics committee (CMO Arnhem-Nijmegen, No. 2012–508). Written informed consent was obtained from every patient and a relevant caregiver. The study was carried out according to the Declaration of Helsinki.

2.2. Participants

Participants were recruited from the memory clinics of the participating centers. Patients were eligible if they had a diagnosis of probable AD, based on the 2011 criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association [21]. Using the more recent 2018 National Institute on Aging - Alzheimer's Association Research Framework, these patients would be characterized as Alzheimer's Clinical Syndrome [22]. Additional inclusion criteria were age $\geq$ 50 years, Mini-Mental State Examination score between 12–26 [23], in-office systolic BP between 100–159 mmHg, and diastolic BP between 65–99 mmHg. Exclusion criteria were use of a calcium-channel blocker, beta-blocker or alpha-blocker, dementia due to other causes, and the presence of a medical condition that would preclude participation (including chronic heart failure, unstable angina pectoris, or recent history of acute myocardial infarction). Patients using a cholinesterase inhibitor were eligible if they were on a stable dose for 3 months prior to screening. A complete list of in- and exclusion criteria is provided in the trial protocol [18].

2.3. Intervention

Participants were randomized (1:1) to a daily dose of 8 mg of nilvadipine or placebo. It was previously shown that properties of 8 mg of nilvadipine are comparable to 5 mg of amlodipine [24]. In the Nilvad trial, the intervention resulted in a reduction of BP of 7.5/3.0 mmHg compared to placebo [25]. Blinding and randomization steps are described in detail in the trial protocol [18]. The intervention was distributed every 3 months and compliance was monitored by collecting and counting the used treatment packs and leftover capsules. All participants had an informal caregiver that ensured daily medication intake.

2.4. Hemodynamic measurements

At baseline, after 0.5 and 1.5 years, hemodynamic measurements were performed in the laboratory of the Radboudumc. Starting from the evening before the measurements, participants refrained from caffeine and alcohol. Heart rate (HR) was recording with a 3-lead electrocardiogram system (Biopac Systems Inc, Goleta, CA, USA). Continuous arterial BP was measured in the index or middle finger of the non-dominant hand using volume clamp-photoplethysmography (Finapres Medical Systems, Amsterdam, the Netherlands). An arm sling was used to keep the hand at heart level. CBF velocity (CBFV) in the middle cerebral arteries was measured using transcranial Doppler (TCD) ultrasonography. Two 2-MHz probes (Multi-Dop, Compumedics DWL, Singen, Germany) were placed over the temporal window and fixed with a customized headband (Spencer Technologies, Seattle, WA, USA). Exhaled CO_2 was monitored with a nasal cannula using capnography (BIOPAC Systems, Goleta, CA). All signals were recorded at 200 Hz using the data acquisition system AcqKnowledge (MP150, BIOPAC Systems, Goleta, CA).

The measurement protocol was similar to the one described previously [9]. First, a 5 min rest measurement was performed. Rest measurements were done under three conditions: supine, seated, and standing. Because supine and standing measurements provided similar results to seated measurements, here we only report the results of the 5 min seated rest. Next, a 5 min repeated sit-to-stand procedure (alternating 10s sitting and 10s standing) was performed. Then, an orthostatic challenge was performed to assess BP and CBFV drop and recovery after standing up, consisting of 3 repetitions of 2 min sitting and 1 min standing. Finally, CVMR was assessed by inducing hypocapnia by hyperventilating at a frequency of 0.5 Hz (1 s breathing in, 1 s breathing out) for 30s, followed by a 5 min resting period and hypercapnia by inhalation of a gas mixture with increasing concentrations of CO_2 (30 s 3%, 30 s 4%, 3 min 5%).

2.5. Data processing and analysis

All scripts have previously been described in detail [9]. Data were pre-processed and analyzed using custom-written Matlab scripts (version 2014b, the MathWorks Inc., Natick, MA, USA). Beat-to-beat data was transformed to mean arterial pressure (MAP) and mean CBFV (MCBFV). dCA was estimated during 5 min of rest and during 5 min of repeated sit-to-stand, by determining the autoregulatory index (ARI, arbitrary units), a value between 0 (absence of dCA) and 9 (excellent dCA), and by performing a transfer function analysis (TFA) between MAP and CBFV, using the CARNet Matlab script version 1, 2016 (www.car-net.org/content/resources/tools) [26]. TFA results in parameters of gain, phase and coherence. Gain (cm/s/mmHg) represent the degree of damping by dCA of the BP oscillations (lower gain indicates better dCA). Phase (degrees) represents the shift in time between CBFV and BP oscillations, due to the faster recovery of CBFV compared to BP (higher phase indicates better dCA). Coherence (arbitrary units), a value between 0 and 1, can be used as a quality check of the signals, as it indicates the amount of output variance explained by the input. During rest, gain, phase and coherence were averaged over the very low frequency (0.02–0.07 Hz) and low frequency (0.07–0.2 Hz) bands, where dCA is most active. During the sit-to-stand procedure, TFA parameters were averages at the sit-to-stand frequency band of 0.05 Hz (0.04–0.06 Hz), which contain the strong oscillations in BP and CBFV induced by the maneuver. Measurements with coherence < 0.3 were excluded.

BRS (ms/mmHg) was estimated using the inter-beat (RR) interval and SBP signals recorded during the repeated sit-to-stand maneuvers, by calculating directional cardiac BRS for BP increases and decreases [27]. The slope between RR-interval and SBP was calculated for each segment of SBP increase or decrease. The median of all segments resulted in BRS_{up} and BRS_{down}. In addition, TFA between SBP and RR-interval was performed and the gain over the frequency band 0.07-0.14 Hz was used

to estimate BRS (higher gain indicates better BRS).

From the orthostatic challenge, we extracted BP, HR and CBFV during rest, the initial response upon standing and recovery values, similar to previously published normative data [28]. Rest values were defined as the average of 30 s before standing up. The initial response was defined as the difference between rest and the nadir reached within the first 40 s after standing. Recovery was defined as the difference between rest and the average value after 50–60 s of standing. Outcomes were calculated as percentage from rest and results of the three repetitions were averaged [29].

For CVMR, we first calculated the cerebrovascular conductance index (CVCi, MCBFV/MAP) to account for confounding effects of CO_2 on BP [30]. Subsequently, CVMR (%) was calculated as the difference between maximal CVCi during hypercapnia and minimal CVCi during hypocapnia, divided by the mean CVCi during normocapnia.

2.6. Other variables

At baseline and after 1.5 years, severity of dementia, cognitive functioning, and daily functioning were assessed using the Clinical Dementia Rating (CDR) scale, the 12-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Disability Assessment for Dementia, respectively [31–33]. Information on medical history, medication use and smoking (current, yes/no) was collected as baseline and throughout the study.

Home BP measurements at baseline were used to identify participants with hypertension, using definitions from the European Society of Hypertension (i.e. mean systolic BP $\geq$ 135 mmHg and/or mean diastolic BP $\geq$ 85 mmHg). Home BP measurements were performed by the participants (aided by their caregiver) every morning and evening for 7 days, after 5 min of rest, using a memory-equipped, validated home BP monitor (WatchBP Home, Microlife, Switzerland). Mean systolic and diastolic BP were calculated if at least 12 measurements were available, after excluding measurements of the first day.

2.7. Statistical analysis

For our primary aim, we performed a mixed model analysis to assess the effect of time on the hemodynamic outcomes, with additional fixed effects for age, sex and intervention group. A sensitivity analysis, limited to patients that completed all 3 visits, was performed. For our secondary aim, we excluded data of patients that discontinued the intervention (compliance < 80% between baseline and 0.5 years, or between baseline and 1.5 years). A similar mixed model was performed, with the addition of the interaction term between time and intervention group, to assess the effect of the intervention. We used two-tailed testing with an alpha of 0.05. Effects were reported as unstandardized *B* coefficients with 95% confidence intervals. Characteristics were reported as mean ± SD or percentage (n). Mixed models were performed using the lme4 package in *R* version 3.6.2 (*R* Foundation for Statistical Computing, Vienna, Austria) and descriptive statistics were performed with IBPM SPSS Statistics 25.0 (SPSS, Inc, Chicago, IL).

3. Results

3.1. Characteristics

Between June 2013 and March 2015, 58 participants were included in the study (Fig. 1). Two participants were excluded because it was not possible to continuously measure their BP due to Raynaud's phenomenon (n=1) and irregular heartbeats (n = 1), leaving 56 participants available for analysis. There was no loss to follow-up. However, complete datasets could not be obtained in all participants, because of the lack of aTCD window, inability of the participants to complete the procedure or signals not meeting the quality criteria set for the analysis. Participants were randomized into 29 patients receiving nilvadipine and 27 receiving placebo. Characteristics are presented in Table 1. Participants had a mean age of 73±6 years, and 57% were female. 48% (n = 27) of the participants had hypertension at baseline, of which 41% were receiving antihypertensive treatment at baseline.

3.1.1. Progression of AD

Baseline ADAS-cog was 31.9 ± 10.2 points. The mean increase after 1.5 years was 8.1 ± 8.5 points, indicating deteriorating cognitive function. Baseline DAD was 32.2 ± 7.0 points and decreased by 10.6 ± 9.5 points after 1.5 years, indicating worsening daily functioning. At

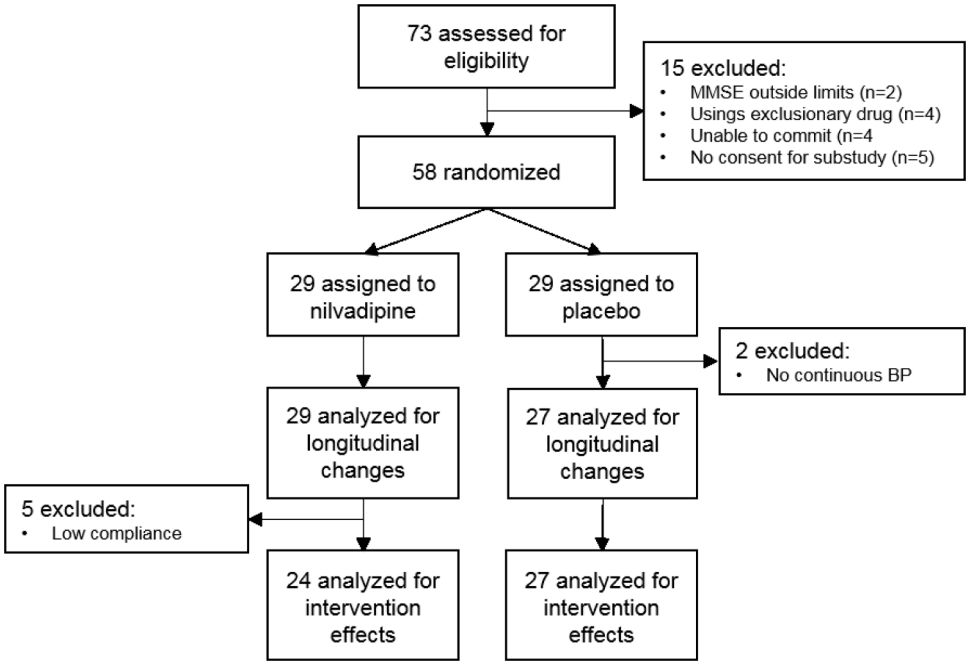

Fig. 1. CONSORT-based flow diagram.
Abbreviations: MMSE, mini-mental state examination; BP, blood pressure

Table 1
Baseline characteristics of the study population.

Parameter	Total	Nilvadipine	Placebo
n	56	29	27
Age, years	73.2 ± 6.1	73.3 ± 6.9	73.1 ± 5.3
Female, %	57.1 (32)	55.2 (16)	59.3 (16)
MMSE score (range: 0–30)	20.5 ± 3.4	20.1 ± 3.5	21.0 ± 3.4
ADAS-cog score (range:0–80)	31.9 ± 10.2	33.1 ± 11.3	30.7 ± 8.9
Clinical Dementia Rating, % - 0.5	35.7 (20)	34.5 (10)	37.0 (10)
- 1	48.2 (27)	48.3 (14)	48.1 (13)
- 2	1.61 (9)	17.2 (5)	16.1 (9)
DAD score (range: 0–40)	32.2 ± 7.0	31.3 ± 7.4	33.1 ± 6.5
Use of acetylcholinesterase inhibitor, %	82.1 (46)	82.8 (24)	81.5 (22)
Use of memantine, %	10.7 (6)	13.8 (4)	7.4 (2)
Diabetes, %	5.4 (3)	10.3 (3)	0 (0)
History of CVD, %	16.1 (9)	6.9 (2)	25.9 (7)
Use of AHT, %	28.6 (16)	31.0 (9)	25.9 (7)
Systolic BP, mmHg	137.0 ± 18.6	138.2 ± 20.2	135.7 ± 17.3
Diastolic BP, mmHg	77.2 ± 10.1	79.2 ± 10.8	75.3 ± 9.1
Hypertension, %	48.2 (27)	51.7 (15)	44.4 (12)

Values are mean ± standard deviation or % (n). ADAS-cog: higher score indicates worse performance. MMSE and DAD: higher score indicates better performance. Hypertension is defined as mean systolic BP ≥ 135 mmHg and/or mean diastolic BP ≥ 85 mmHg using home BP measurements.
Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; AHT, antihypertensive treatment; BP, blood pressure; CVD, cardiovascular disease; DAD, Disability Assessment for Dementia; MMSE, Mini-Mental State Examination.

baseline, 16% ($n = 9$) were classified with CDR 2 and none with CDR 3. After 1.5 years, this changed to 33 ($n = 19$) and 16 ($n = 9$), for CDR 2 and CDR 3, respectively.

3.2. Longitudinal changes in hemodynamics

An overview of all hemodynamic parameters at baseline and follow-up is presented in Table 2.

3.2.1. Blood pressure and baroreflex function

After 0.5 years, BP was reduced in the whole group (Fig. 2). For Finapres recorded BP, reductions in MAP were most evident during the repeated sit-stand procedures (B = -9.2, SE = 3.2, $P = 0.005$), and less so during the rest measurement (B = -6.2, SE = 3.1, $P = 0.051$). For home BP measurements, both systolic BP (B = -3.4, SE = 1.4, $P = 0.020$) and diastolic BP (B = -1.7, SE = 0.7, $P = 0.017$) were lower at 0.5 years of follow-up compared to baseline. No differences were observed after 1.5 years. Baroreflex sensitivity did not change over time (supplementary Figs. 1,2).

3.2.2. Cerebral blood flow, CVMR, and autoregulation

No changes over time were observed for MCBFV during rest or during repeated sit-stand (Fig. 2). CVMR did not change over time (supplementary Figs. 1,2). The assessment of dCA measured using spontaneous oscillations (seated rest) showed an increase in gain (B = 0.09, SE = 0.03, $P = 0.008$), normalized gain (B = 0.25, SE= 0.08, $P = 0.003$), and a reduction in phase (B = -9.7, SE = 3.2, $P = 0.004$), all in the VLF domain, after 0.5 years of follow-up. The direction of all these changes suggests a reduction in dCA in the VLF domain, where autoregulation is normally most active and efficient (Fig. 3). After 1.5 years, only phase remained significantly different from baseline (B = - 11.1, SE= 3.3, $P = 0.001$). No clear changes over time were observed for autoregulation parameters in the LF domain, except for a reduction in phase at 0.5 years (B = -4.9, SE = 2.8, $P = 0.086$). The ARI also suggested a small reduction over time at 0.5 years, although this was not statistically significant (B = -0.55, SE = 0.29, $P = 0.058$) (Fig. 4). TFA of the induced oscillations in the VLF domain (0.05 Hz), using the repeated sit-stand procedure, showed no changes in gain or phase parameters over time (Fig. 3). In contrast, the ARI derived from these measurements did show a significant reduction at 0.5 years (B = -0.69, SE = 0.26, $P = 0.010$) and 1.5 years (B = -0.57, SE = 0.27, $P = 0.046$) (Fig. 4). In summary, dCA parameters showed small changes after 0.5 years, suggestive of a reduction in autoregulation efficiency, but these changes did not show further progression after 1.5 years of follow-up.

3.2.3. Orthostatic challenge

The orthostatic challenge revealed no differences over time in the initial changes in hemodynamics upon standing and in the recovery after 1 min, with the exception of a reduced initial increase in HR, observed after 1.5 years (B = -3.11, SE = 1.13, $P = 0.007$) (Supplementary Fig. 3).

3.2.4. Sensitivity analysis

The sensitivity analysis limited to complete cases included $n = 23$ for dCA at rest, $n = 19$ for dCA during repeated sit-stand, $n = 33$ for BRS, $n = 10$ for CVMR, and $n = 43$ for the orthostatic challenge. This analysis gave similar results, except that the change in gain for the VLF domain, and the change in ARI during repeated sit-stand were no longer statistically significant (Supplementary Table 1).

3.3. Effects of the blood pressure lowering intervention

Five participants from the intervention group (nilvadipine) were excluded from this analysis because they discontinued the intervention ($n = 2$ between baseline and 0.5 years, $n = 3$ between 0.5 years and 1.5 years). Hemodynamic parameters by treatment group (nilvadipine vs placebo) are shown in Figs. 2–4 and in Supplementaryl Figs. 1–3. Results from the regression models are shown in Supplementary Table 2.

3.3.1. Blood pressure and baroreflex function

Home BP did not differ significantly between groups. However, MAP from Finapres during rest was lower for the intervention compared to placebo after 1.5 years (B = -13.3, SE = 6.6, $P = 0.046$. After 0.5 years, MAP measured with Finapres during the repeated sit-stand maneuvers was also lower for the intervention (B = -17.3, SE = 5.9, $P = 0.005$). For baroreflex sensitivity, the BRS_{up} increased in the intervention group compared to placebo after 1.5 years, indicating better baroreflex function ($B = 2.35$, SE = 1.04, $P = 0.027$).

3.3.2. Cerebral blood flow, CVMR, and autoregulation

Mean CBFV at rest or during repeated sit-stands did not differ between groups. Overall, there was limited evidence for any effect of the intervention (nilvadipine) on dCA and CVMR. After 1.5 years, phase in the VLF domain decreased in the intervention group compared to placebo (B = -14.3, SE= 6.7, $P = 0.037$), but without concomitant changes in gain, while in the LF domain only gain increased in the intervention group compared to placebo ($B = 0.15$, SE= 0.07, $P = 0.040$), without concomitant changes in phase. No other differences were observed.

3.3.3. Orthostatic challenge

The orthostatic challenge showed a slightly larger initial drop in MAP ($B = 4.33$, SE = 1.91, $P = 0.026$) and lower initial increase in HR (B = -5.39, SE = 2.11, $P = 0.012$) for the intervention group after 0.5 years (Supplementary Table 2). In addition, the 1 min recovery of MCBFV was somewhat lower for the intervention compared to placebo, (B = -5.08, SE = 1.91, $P = 0.010$). Note that the beta (B) corresponds to the % differences between groups in MAP, HR and CBF.

4. Discussion

In a longitudinal study in patients with dementia due to Alzheimer's disease, we investigated three key mechanisms involved in the homeostasis of BP and CBF: baroreflex function, dynamic cerebral autoregulation, and cerebral vasomotor reactivity. The main aim of the

Table 2
Hemodynamic parameters at baseline and follow-up.

Parameter	Baseline		After 0.5 years			After 1.5 years		
	mean	SD	mean	SD	*P*	mean	SD	*P*
Dynamic cerebral autoregulation (spontaneous oscillations)								
n for analysis	39		36			33		
MAP, mmHg	83.1	18.3	77.7	13.0	0.051	80.3	19.1	0.372
MCBFV, cm/s	39.1	8.8	39.4	8.9	0.973	37.8	7.4	0.144
Autoregulatory index	4.69	1.69	4.18	1.92	0.058	4.46	1.55	0.325
$Gain_{VLF}$, cm/s/mmHg	0.46	0.16	**0.55**	**0.21**	**0.008**	0.50	0.16	0.304
$Gain_{norm\text{-}VLF}$, cm/s/mmHg	1.17	0.36	**1.41**	**0.39**	**0.003**	1.32	0.34	0.073
$Phase_{VLF}$, degrees	55.19	23.43	**46.59**	**22.15**	**0.004**	**45.1**	**18.7**	**0.001**
$Gain_{LF}$, cm/s/mmHg	0.64	0.18	0.65	0.18	0.859	0.64	0.17	0.710
$Gain_{norm\text{-}LF}$, cm/s/mmHg	1.67	0.55	1.67	0.41	0.989	1.69	0.41	0.852
$Phase_{LF}$, degrees	37.2	18.4	**30.4**	**16.4**	**0.003**	33.0	13.7	0.086
Dynamic cerebral autoregulation (0.05 Hz induced oscillations)								
n for analysis	34		33			27		
MAP, mmHg	93.5	16.0	**82.9**	**16.6**	**0.005**	87.7	17.8	0.140
MCBFV, cm/s	39.6	7.4	40.9	6.9	0.358	39.1	6.0	0.251
Autoregulatory index	4.72	1.26	**4.09**	**1.27**	**0.010**	**4.10**	**1.28**	**0.046**
Gain, cm/s/mmHg	0.61	0.18	0.66	0.13	0.164	0.62	0.17	0.794
$Gain_{norm}$, cm/s/mmHg	1.50	0.40	1.61	0.32	0.279	1.61	0.49	0.222
Phase, degrees	46.7	13.6	47.5	14.0	0.608	45.4	12.6	0.863
Baroreflex sensitivity								
n for analysis	45		41			33		
SBP, mmHg	151.3	28.5	145.3	23.8	0.103	143.5	28.6	0.163
RR-interval, s	0.84	0.12	0.84	0.14	0.922	0.85	0.14	0.725
Gain, ms/mmHg	3.25	1.65	3.08	1.47	0.264	3.46	2.06	0.999
BRS_{up}, ms/mmHg	4.24	2.78	4.16	2.68	0.875	5.11	4.16	0.180
BRS_{down}, ms/mmHg	3.55	2.38	3.68	3.28	0.961	3.58	2.02	0.766
Cerebral vasomotor reactivity to CO_2								
n for analysis	32		27			23		
CVMR, %	0.45	0.15	0.43	0.20	0.670	0.41	0.21	0.393
Orthostatic change and recovery								
n for analysis[a]	55 (33)		50 (31)			47 (28)		
MAP initial change, %	84.6	7.6	84.4	7.7	0.818	84.8	9.8	0.945
HR initial change, %	121.1	8.2	120.1	9.8	0.316	**118.3**	**7.8**	**0.007**
MCBFV initial change, %	88.2	6.4	89.6	5.1	0.387	89.0	7.5	0.532
MAP recovery, %	97.9	7.4	97.4	8.1	0.363	98.0	9.6	0.975
HR recovery, %	112.3	6.8	112.4	7.9	0.967	113.3	7.4	0.381
MCBFV recovery, %	97.1	5.3	98.2	5.8	0.397	97.5	4.5	0.760

Reported P-value corresponds to the effect of time, resulting from linear mixed models with random intercept and slope per patient and adjusted for age, sex and intervention group. Spontaneous oscillations: measurement of cerebral autoregulation during seated rest. Induced oscillations: measurements of autoregulation during repeated sit-stand maneuvers to induce oscillations at 0.05 Hz (VLF).
Abbreviations: CVMR, cerebral vasomotor reactivity; HR, heart rate; LF, low frequency; MAP, mean arterial pressure; MCBFV, mean cerebral blood flow velocity; NORM, normalized; RR, inter beat interval; SBP, systolic blood pressure; VLF, very low frequency.
[a] Number between brackets indicates the n for analysis of MCBFV.

present study was to see if these mechanisms were affected by the further progression of AD, over a follow-up period of 1.5 years. In addition, we investigated the effects of a BP lowering challenge to these mechanisms, i.e. antihypertensive treatment, using a RCT design of nilvadipine versus placebo. The main findings of this study are that dCA, while normal at baseline compared to controls [9], was marginally reduced after 0.5 years of follow-up, however without crossing the threshold of impairment, while BRS remained normal. CVMR, which was already reduced at baseline [9] showed no further reduction over time. Further, adding BP lowering treatment with nilvadipine did not affect either dCA, BRS, or CVMR, and did not lead to cerebral hypoperfusion or orthostatic hypotension.

4.1. Longitudinal changes in hemodynamics

Impairment of these key mechanisms, dCA, baroreflex function, and CVMR, in AD has frequently been suggested in the literature, but never demonstrated beyond doubt, except for CVMR [16]. We have previously shown that baroreflex function and dCA were comparable to age-matched controls in patients with MCI and dementia due to AD [9]. The same group of dementia patients was used in the current study, and we now expand these previous findings by showing the effects of disease progression on these mechanisms. Progression of AD over a period of 1.5 years involves further spreading of amyloid but mainly tau pathology, leading to parenchymal neurodegeneration. In theory, it was possible that at baseline, the impact of pathology on autonomic function was too small to lead to significant differences between patients and controls, but that further progression would have unmasked these autonomic changes and have led to impairment in baroreflex function and dCA [1]. In addition, progression of AD is thought to involve also cerebrovascular pathology, including cerebral amyloid angiopathy [4, 6]. This progression could then unmask impairments in dCA, and lead to worsening of the impairment in CVMR.

We only observed a small but consistent reduction in parameters that estimate the efficiency of dCA [26]. There was a small reduction in VLF phase, coupled with a small increase in VLF gain, and an almost significant reduction in ARI when we studied autoregulation using spontaneous oscillations under resting conditions. When we induced stronger oscillations in the VLF, there also was a reduction in ARI, although phase and gain (in VLF) no longer showed changes. The magnitude of these changes was small, and values remained within the (lower) limits of normal. It is therefore possible that, only with very advanced Alzheimer pathology, autoregulation becomes impaired. However, these changes were only noted after 0.5 years of follow-up and did not progress over the next year.

Progression of AD was not associated with an impairment in baroreflex function. Autonomic dysfunction in AD has been suggested in small studies, e.g. [34], and recently in a larger study [35]. The latter study

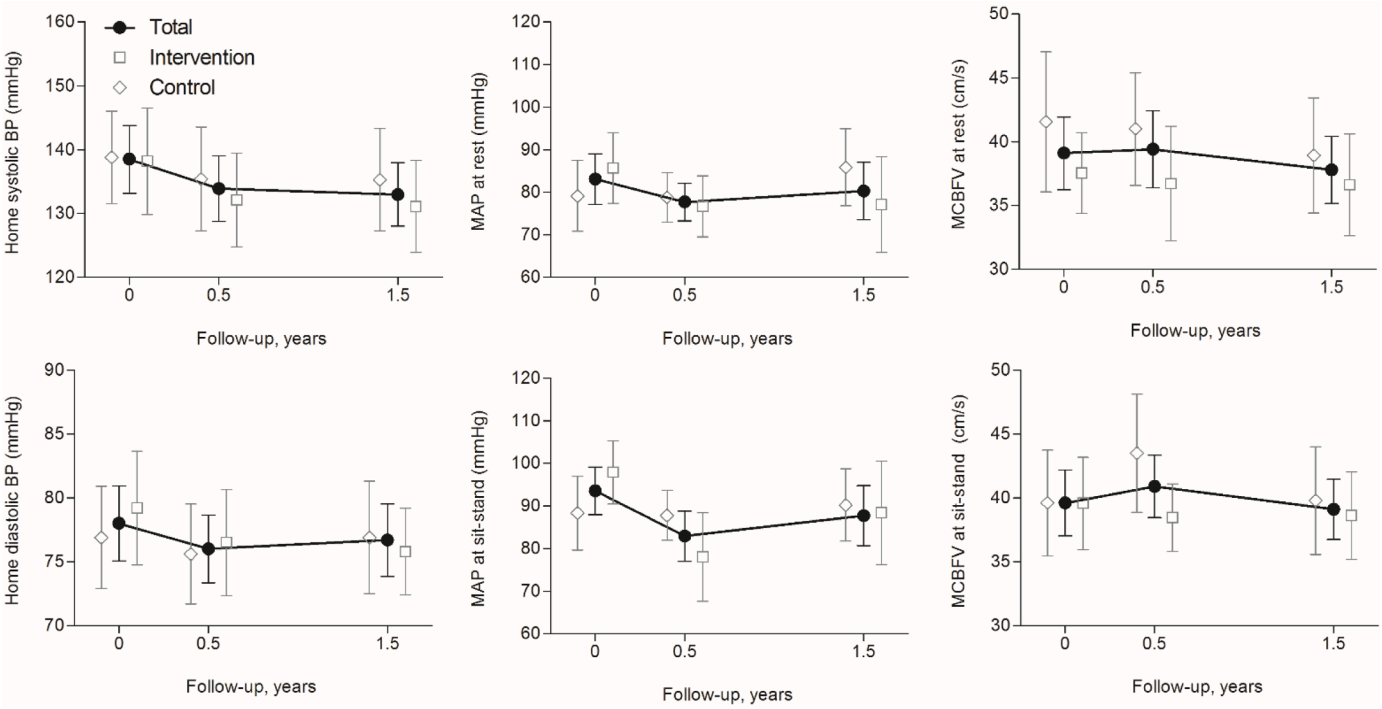

Fig. 2. Longitudinal changes in blood pressure and cerebral blood flow velocity.
Changes over time are shown for the total group (black, solid circles), and for the intervention (grey, open squares) and placebo (grey, open diamonds) group separately.
Abbreviations: BP, blood pressure; MAP, mean arterial pressure; MCBFV, mean cerebral blood flow velocity.

found differences in heart rate variability in patients with amnestic mild cognitive impairment (suspected early stage Alzheimer's disease), suggestive of autonomic dysfunction. However, no differences in BP response to standing were noted, and baroreflex function was not measured. A possible explanation for these discrepant findings is that AD affects sympathetic and/or parasympathetic activity [36], which leads to changes in heart rate variability, without affecting baroreflex function, and therefore without causing orthostatic hypotension.

4.2. *Effects of nilvadipine on autoregulation, baroreflex, and CVMR*

Further evidence for an absence of baroreflex failure in AD is that treatment with nilvadipine did not lead to orthostatic hypotension, or reduction in baroreflex function. In theory, the effects of this calcium-channel blocker on heart rate and vascular tone could unmask baroreflex failure. While we did see effects on heart rate (i.e. a reduction in the initial heart rate response following standing), and on vascular tone (i.e. a larger reduction in BP immediately after standing), BRS was not reduced, but rather increased, and there was no increase in orthostatic hypotension. This observation is confirmed by the larger Nilvad trial, wherein we showed that there was no increased prevalence of OH in patients with AD, and no increase in OH following nilvadipine [25].

Nilvadipine had no consistent effect on autoregulation parameters, and, while it lowered BP as expected, it had no effect on CBF. During an orthostatic challenge, the recovery of CBF after one minute was marginally lower for nilvadipine (96.5%) than for placebo (99.5%), while BP also appeared lower at one minute, although this did not reach statistical significance. This small reduction in CBF also argues against failure of autoregulation.

4.3. *Strengths and limitations*

Strengths of our study include the longitudinal design, which allowed us to study the effects of 1.5 years of disease progression. In addition, where many studies of CBF use supine measurements, we added seated and standing measurements, which have better external validity as patients spend most of their time upright. Finally, by adding an intervention with an antihypertensive agent, we included a challenge for the systems we aimed to probe, to help unmask impairments. Limitations are that we were unable to investigate strong challenges to these systems, for example the effect of intensive BP lowering, as in the SPRINT trial [37]. For ethical reasons, we first wanted to investigate the effects of a moderate challenge by adding a single, low dose, agent. The Nilvad trial was performed according to high methodological standards, but the data presented in this paper are secondary data and analyses should be considered exploratory. Finally, we had no biomarker (cerebrospinal fluid or PET-amyloid) confirmation of Alzheimer pathology for our patients. All patients met criteria for 'Alzheimer's clinical syndrome' [22], and are representative for patients clinically diagnosed with Alzheimer dementia in a memory clinic, with cerebrovascular comorbidity [9].

4.4. *Conclusion*

We found no evidence that dynamic cerebral autoregulation or baroreflex function become impaired during progression of Alzheimer's disease. Baroreflex function showed no changes over time, whereas autoregulation only showed changes in the first 6 months of follow-up, however without a clinically relevant impairment, and no further decline in the subsequent 12 months. Further, these patients did not demonstrate increased vulnerability to starting an antihypertensive agent. This paves the way for further studies that investigate the safety and benefits of antihypertensive treatment in patients with Alzheimer's disease.

Funding sources

This work was supported by the Dutch Alzheimer Society (Grant

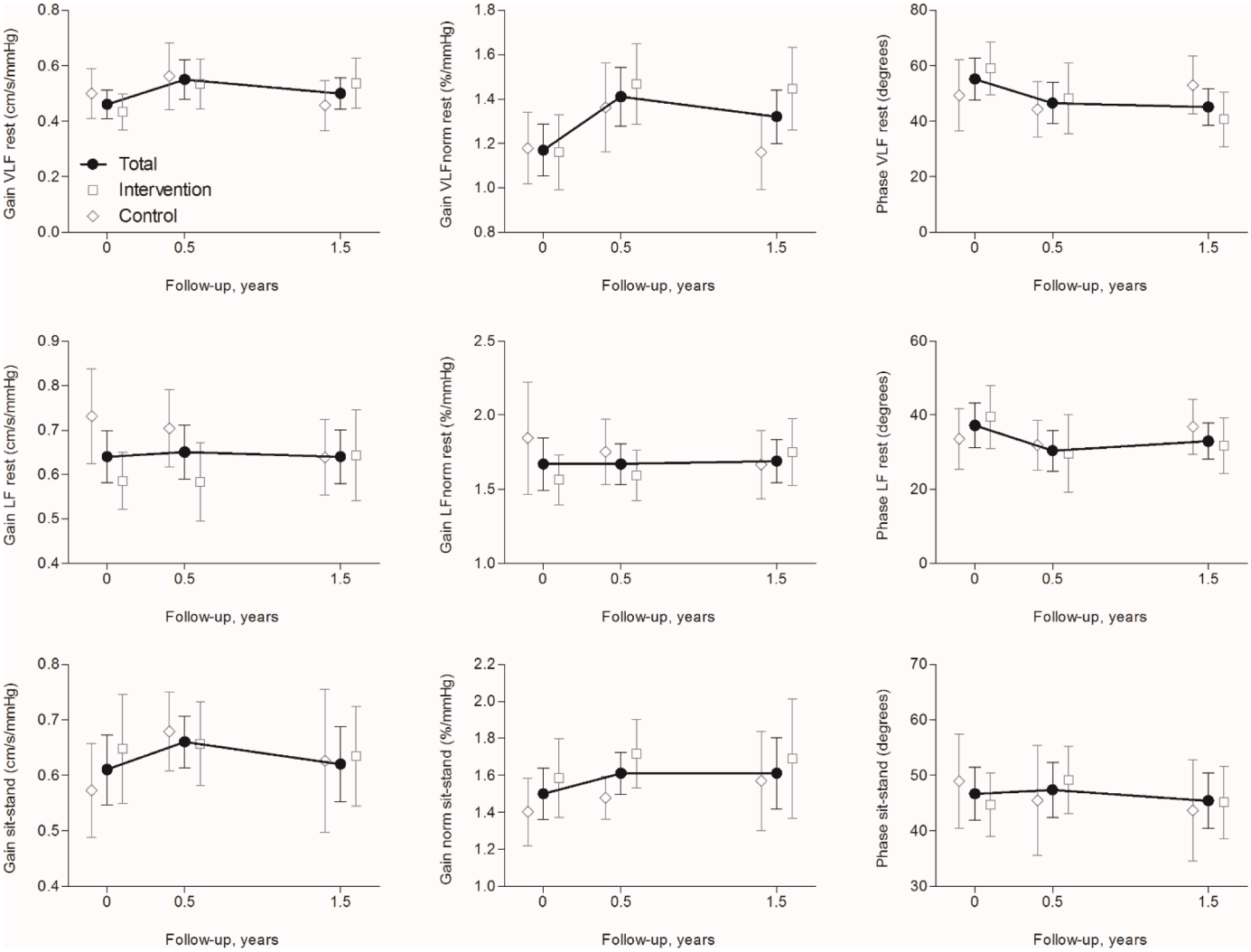

Fig. 3. Longitudinal changes in parameters of transfer function analysis for cerebral autoregulation.
Transfer function analysis of dynamic cerebral autoregulation during spontaneous oscillations (seated rest) and during induced oscillations (sit-stand maneuvers at 0.05 Hz). Changes over time are shown for the total group (black, filled circles), and for the intervention (grey, open squares) and placebo (grey, open diamonds) group separately.
Abbreviations: LF, low frequency; norm, normalized; VLF, very low frequency.

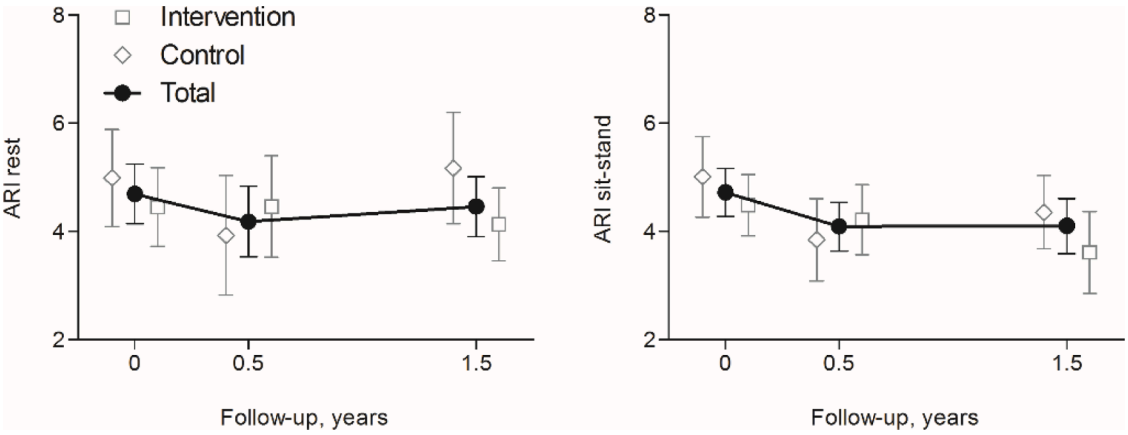

Fig. 4. Longitudinal changes in the autoregulatory index.
Autoregulatory index of dynamic cerebral autoregulation during spontaneous oscillations (seated rest) and during induced oscillations (sit-stand maneuvers at 0.05 Hz). Changes over time are shown for the total group (black, filled circles), and for the intervention (grey, open squares) and placebo (grey, open diamonds) group separately.
Abbreviations: ARI, autoregulatory index.

WE.09-2015-03) and the Alzheimer's Drug Discovery Foundation (Grant 20121210). The Nilvad study was funded by the European Commission Framework 7 Program Health Theme collaborative project (Grant 279093, awarded to BL, Principal Investigator).

Acknowledgments

We are grateful to all participants and their caregivers for their time and effort. We would like to thank all involved study personnel in Radboudumc for their assistance with recruitment and data collection.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2021.100024.

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