Original Article

Effects of Nilvadipine on Cerebral Blood Flow in Patients With Alzheimer Disease

A Randomized Trial

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Abstract—Cerebrovascular changes, including reduced cerebral blood flow (CBF), occur early in the development of Alzheimer disease and may accelerate disease progression. This randomized, double-blind, placebo-controlled study investigated how 6 months of treatment with the calcium antagonist nilvadipine would affect CBF in patients with mild-to-moderate Alzheimer disease. CBF was measured with magnetic resonance arterial spin labeling in whole-brain gray matter and in a priori defined regions of interest including the hippocampus. Fifty-eight patients were randomly assigned (29 in each group), of whom 22 in both groups had no magnetic resonance exclusion criteria and were medication compliant over 6 months. Mean age was 72.8±6.2 years, mean mini-mental state examination was 20.4±3.4. Nilvadipine treatment lowered systolic blood pressure (Δ=−11.5 [95% CI, −19.7 to −3.2] mm Hg; P<0.01), while whole-brain gray-matter CBF remained stable (Δ=5.4 [95% CI, −6.4 to 17.2] mL/100 g per minute; P=0.36). CBF in the hippocampus increased (left: Δ=24.4 [95% CI, 4.3–44.5] mL/100 g per minute; P=0.02; right: Δ=20.1 [95% CI, −0.6 to 40.8] mL/100 g per minute; P=0.06). There was no significant change in CBF in the posterior cingulate cortex (Δ=5.2 [95% CI, −16.5 to 27.0] mL/100 g per minute; P=0.63) or other regions of interest. In conclusion, nilvadipine reduced blood pressure and increased CBF in the hippocampus, whereas other regions showed stable or small nonsignificant increases in CBF. These findings not only indicate preserved cerebral autoregulation in Alzheimer disease but also point toward beneficial cerebrovascular effects of antihypertensive treatment.

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Key Words: Alzheimer disease ■ blood pressure ■ disease progression ■ hippocampus ■ nilvadipine

In Alzheimer disease (AD), pathophysiological changes occur years to decades before the first onset of clinical symptoms.[1] These changes not only encompass the well-known accumulation of aggregated amyloid-β and τ but also cerebrovascular changes.[2] Early cerebrovascular pathology in AD includes structural changes to the cerebrovascular bed and amyloid deposition in vascular walls, which together may compromise cerebral blood flow (CBF).[3–5]

A reduction in CBF has been established as an early marker of AD, predicting disease progression[6] and correlating with cognitive impairment.[7] For example, reduced CBF in the posterior cingulate cortex (PCC) measured using magnetic resonance imaging (MRI) arterial spin labeling (ASL) in cognitively healthy participants predicted subsequent cognitive decline.[8] Whether these early changes in CBF are truly a manifestation of cerebrovascular pathology, or whether they are simply a consequence of reduced metabolic demand leading to reduced CBF, has been the topic of debate for decades.[9]

There are several indications that reduced CBF in AD is a manifestation of cerebrovascular dysfunction that is causally related to the AD process. For example, vascular pathology has been demonstrated in AD transgenic mouse models.[10] Similarly, in human familial AD, white matter hyperintensities and cerebral microbleeds are increased in asymptomatic mutation carriers compared with noncarriers.[11]

For sporadic, late-onset AD, cerebrovascular pathology forms a plausible mechanism to explain how midlife hypertension—the major risk factor for cerebrovascular disease—confers

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an increased risk of late-life AD.[12,13] This line of thought, wherein hypertension leads to cerebrovascular dysfunction, which in turn induces or aggravates neuronal dysfunction and AD pathology, is supported by ample preclinical research[14,15] and a recent clinical study.[16]

Restoring CBF through vascular (eg, antihypertensive) treatment could, therefore, become a new and feasible therapeutic target aimed at slowing down the progressive cognitive and functional decline in AD. In experiments from our own group in an AD mouse model, hypertension in middle-aged animals led to reductions in CBF.[17] In that same model, antihypertensive treatment with the angiotensin receptor blocker eprosartan augmented CBF, specifically in the hippocampus.[18]

At present, translational evidence in human AD is lacking, as research into cerebrovascular interventions in clinical AD is scarce.[19] Specifically, there is limited, if any, evidence on how blood pressure (BP) lowering treatment will affect cerebral perfusion in older people at risk of AD or with established AD. Gaining this knowledge has become even more relevant since the Systolic Blood Pressure Intervention Trial Memory and cognition IN Decreased hypertension (SPRINT MIND) study reported potential cognitive benefits of intensive BP-lowering treatment.[20]

In the present work, we asked how BP lowering with antihypertensive medication would affect CBF in patients with Alzheimer clinical syndrome in a mild-to-moderate dementia stage. This was a preplanned substudy within a larger randomized controlled trial with nilvadipine—a dihydropyridine calcium antagonist that is in use as an antihypertensive agent.

This study had 2 main aims. We recently demonstrated that patients with AD have preserved dynamic cerebral autoregulation,[21] implying that a reduction in BP through antihypertensive treatment would not jeopardize CBF, contrary to common assumption. Therefore, the first aim was to demonstrate the effects of BP lowering using antihypertensive treatment on global CBF. The second aim was to investigate whether the observation in an animal model of improved hippocampal CBF with BP lowering[18] could be translated to clinical research.

Materials and Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. This was a preplanned substudy of the NILVAD trial (Nilvadipine in AD) (NCT02017340; EudraCT No. 2012-002764-27), which was a multicenter, randomized, double-blind, placebo-controlled study (RCT) of nilvadipine versus placebo in patients with AD.[22] See Methods in the online-only Data Supplement for details on trial design, participants, and data collection.

MRI and Hemodynamic Measurements

All data collection for this substudy took place at Radboudumc. Starting 1 week before the study visits, participants recorded their BP every morning and evening, after 5 minutes of relaxation, using a home BP measurement monitor (Microlife Watch BP Home). Starting from the evening before the visit, participants refrained from caffeine and alcohol. During the visit, MRI imaging and hemodynamic measurements were performed, and blood samples were drawn for hematocrit estimation.

MRI Protocol

All imaging was performed on a 3T Trio MRI (Siemens, Germany).

For registration purposes and segmentation of gray matter and brain structures, a 3-dimensional magnetization-prepared rapid gradient-echo T1-weighted sequence was performed using the following parameters: repetition time (TR)/echo time, 2300/4.71 ms; matrix, 256×256; 192 slices; voxel size, 1×1×1 mm. Additional structural sequences included a fluid-attenuated inversion recovery (TR/echo time, 12 000/121 ms; matrix, 250×250; 48 slices; 0.7×0.7×3 mm), used for calculating white matter lesion volume, and susceptibility-weighted imaging (TR/TE, 27/20 ms; matrix, 250×250; 144 slices; 1×1×1 mm) for assessment of microbleeds.

We used a multi-inversion time-pulsed ASL sequence with flow alternating inversion recovery labeling combined with a 3D-GRASE readout.[23] The parameters of the ASL sequence were as follows: 10 inversion times (start, 500 ms; end, 2750 ms; increment, 250 ms), 2 averages per inversion time, and bolus length of 1400 ms. The 3D-GRASE readout parameters were as follows: TR/TE, 4000/13.26 ms; matrix, 64×48; 30 slices; 3.4×3.4×4 mm; flip angle, 100°; turbo factor, 23; echo planar imaging factor, 12; partial Fourier (with zero filling in z direction), 6/8; bandwidth, 2298 Hz/pixel. In addition, a calibration image (without labeling) with TR of 100 ms was acquired. Reproducibility of this method has been reported elsewhere.[24] Additional details on data processing and analysis are provided in the section Methods in the online-only Data Supplement.

Ultrasound Hemodynamic Measurements

CBF was additionally assessed during 5 minutes of sitting and 5 minutes of standing, with transcranial Doppler ultrasonography using 2 MHz probes (Multi-Dop; Compumedics DWL, Germany), recording CBF velocity in the middle cerebral arteries, captured continuously at 200 Hz (MP150; Biopac Systems).

Data Analysis

MRI Measurements

Cerebral Blood Flow

ASL-MRI data were postprocessed using FSL software (version v5.0.9; FMRIB, United Kingdom).[25] See Methods in the online-only Data Supplement for a detailed description.

Atrophy

Brain volumetric changes were estimated from the T1 images using the SIENAX and SIENA functions of FSL (default settings), respectively. Hippocampal volume and hippocampal atrophy were estimated for each T1 using the longitudinal Freesurfer automated subcortical processing stream.

Structural (Vascular) Lesions

White matter lesions were segmented on the fluid-attenuated inversion recovery images by the lesion prediction algorithm[26] using LST (version 2.0.15 for SPM12), with the T1 as reference images, where $P > 0.5$ was used as threshold for lesion identification. Susceptibility-weighted images at baseline and at month 6 were rated independently for microbleeds by 2 authors (D.L.K.d.J. and J.A.H.R.C.) using the microbleed assessment rating scale.[27] Infarcts were routinely assessed by trained radiologists.

Doppler Hemodynamic Measurements

All data were preprocessed using semiautomated custom-written Matlab scripts (version 2014b; MathWorks, Inc), which resulted in beat-to-beat mean CBF velocity. After visual inspection for poor CBF velocity signal quality, the remaining datasets were included for further analysis.[21,28] For the sitting and standing position, the 5-minute averages of mean CBF velocity were calculated.[21]

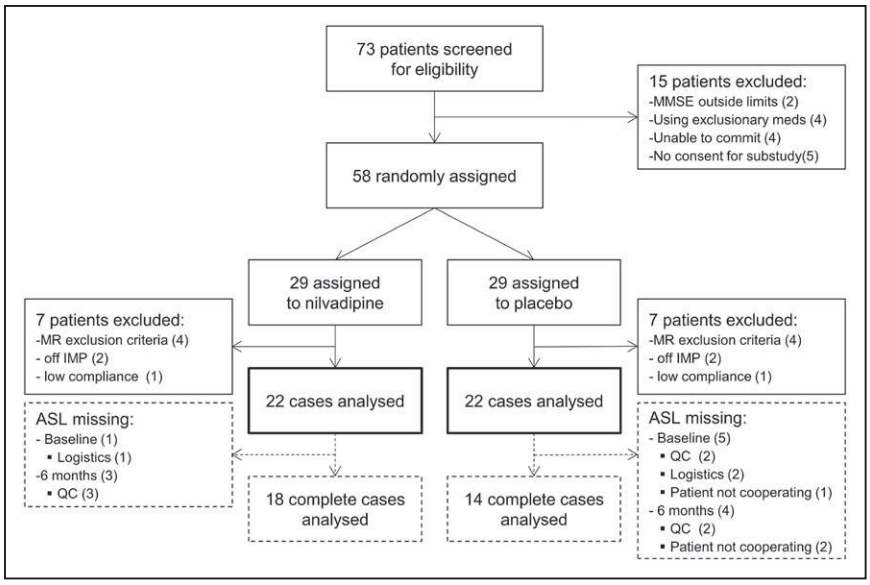

Figure 1. CONSORT guideline–based flowchart. ASL indicates arterial spin labeling; IMP, investigational medicinal product (study medication); MMSE, mini-mental state examination; MR, magnetic resonance; and QC, quality control.

Statistical Analysis

All statistical analyses were performed on the per-protocol population based on complete cases using SPSS (version 22.0.0.1; IBM). See Methods in the online-only Data Supplement for a detailed description of statistical analysis, primary and secondary variables, and sample size calculation.

Results

Participants

Of the 73 patients screened for eligibility between June 1, 2013, and March 31, 2015, 63 were included in the main NILVAD trial and, therefore, eligible for participation in this substudy, of which 58 gave consent. These patients were randomized into 29 patients receiving nilvadipine and 29 receiving placebo. At 6 months, there were no dropouts. However, 7 participants in each group were not included for further analysis for this substudy because of MRI exclusion criteria (n=8), noncompliance (n=4), or discontinuation of the study medication (n=2), causing these participants to fail the predefined criteria for the per-protocol analysis. The enrollment, the allocation process, and reasons for exclusion of analysis are presented in Figure 1.

Baseline characteristics are listed in Table 1 (and complete-case characteristics in Table S1 in the online-only Data Supplement); participants had an age (mean±SD) of 72.8±6.2 years and mini-mental state examination of 20.4±3.4. There were no differences between patients included or excluded from analysis (Table S2). Average compliance of the participants at 6 months was 98.9% for nilvadipine and 97.7% for placebo.

Missing Data

The missing data rate for the primary and secondary variables ranged from 0% to 15.9%, with overall 89.8% of data available for analysis (Figure 1; Table S3). Missing data in the primary analysis were observed to be missing at random (Little missing completely at random test χ^2_8=9.71; P=0.29), which is in line with the observed reasons why data were missing in this study (Table S3).

Validation of MRI-ASL

We validated the ASL-MRI outcomes by comparing the MRI-ASL CBF measurements using the transcranial Doppler ultrasound measurements as an independent second method. We found a good correlation (ρ=0.35; P=0.047) between these 2 measures (Figure S2).

Effects of Nilvadipine on BP

Nilvadipine induced a significant reduction in BP recorded at the 6-month follow-up visit, compared with placebo (Figure 2). At 6 months, the difference in systolic BP between nilvadipine and placebo (Δ[95% CI]; P value) was −11.5 mm Hg (−19.7 to −3.2; P<0.01).

Effects of Nilvadipine on CBF

Nilvadipine led to an increase in blood flow by 24.4 mL/100 g per minute (4.3–44.5; P=0.02) to the left hippocampus at 6 months while blood flow to the right hippocampus increased by 20.1 mL/100 g per minute (−0.6 to 40.8; P=0.06), reflecting an ≈20% increase in hippocampal CBF (Figure S1). Global CBF remained stable (5.4 mL/100 g per minute [−6.4 to 17.2]; P=0.36; Figure 3), as well as CBF in the PCC (5.2 mL/100 g per minute [−16.5 to 27.0]; P=0.92; Table 2). The sensitivity analyses with the imputed data set, as well as the relative changes in CBF, showed comparable results (Table S4; Figure S1). Also, measurements of CBF in sitting and standing positions (mean CBF velocity) did not differ between nilvadipine and placebo. Post hoc analyses of 2 other regions of interest (precuneus, affected in AD, and the occipital lobe, not affected in AD) demonstrated stable CBF without statistically significant differences between placebo and nilvadipine (Table S6).

Effects of Nilvadipine on Brain Volume and Vascular Lesion Load

Nilvadipine had no effect on whole-brain atrophy or hippocampal atrophy rates nor on change in white matter lesion volume (Table 3). No new infarcts or microbleeds were observed (data not shown).

Table 1. Participant Characteristics

Variable	Nilvadipine	Placebo
n (%)	22 (50)	22 (50)
Sex (female), n (%)	14 (64)	12 (55)
Age, y; mean±SD	72.6±6.9	72.9±5.5
Length, cm; mean±SD	168.7±10.5	167.0±7.8
Weight, kg; mean±SD	71.3±14.5	71.7±10.9
BMI, kg/m^2; mean±SD	24.9±3.6	25.7±3.8
Smoking (yes), n (%)	3 (14)	2 (9)
Years of education, y; n (%)		
<9	7 (32)	2 (9)
9–11	6 (27)	11 (50)
>11	9 (41)	9 (41)
Racial background, n (%)		
White European	28 (64)	26 (59)
Other	1 (2)	2 (5)
Cognitive function		
MMSE, mean±SD	19.7±3.1	21.1±3.7
CDR, n (%)		
0.5	5 (23)	8 (36)
1	13 (59)	12 (55)
2	4 (18)	2 (9)
CDRsob, median (IQR)	6.0 (4.4–8.0)	4.5 (3.9–6.3)
ADAScog, median (IQR)	32.0 (26.0–38.5)	26.5 (25.8–34.3)
Medication, n (%)		
Antihypertensive medication	7 (32)	7 (32)
Cholinesterase inhibitors	20 (91)	19 (86)
Comorbidities, n (%)		
Diabetes mellitus	3 (14)	0 (0)
Vascular comorbidity score (0–7), mean±SD	1.2±1.0	1.6±1.1
BP, mean±SD		
SBP screening, mm Hg	136±14	140±12
DBP screening, mm Hg	78±6	78±7
Home-based SBP, mm Hg (n)	137±17 (18)	135±18 (21)
Home-based DBP, mm Hg (n)	79±8 (18)	75±10 (21)
CBF, mean±SD (n)		
MCBFV sit, cm/s	36.0±8.4 (19)	40.0±11.7 (19)
MCBFV stand, cm/s	35.3±8.0 (17)	38.7±9.6 (16)
CBF global, mL/100 g per min	81.9±22.3 (21)	87.2±19.0 (17)
CBF PCC, mL/100 g per min	107.0±35.4 (21)	111.3±29.8 (17)
CBF hippocampus, left; mL/100 g per min	107.2±31.2 (21)	104.6±26.6 (17)
CBF hippocampus, right; mL/100 g per min	107.7±29.0 (21)	112.2±23.4 (17)
ATT global (s)	0.72±0.03 (21)	0.70±0.04 (17)
ATT PCC (s)	0.83±0.07 (21)	0.81±0.07 (17)
ATT hippocampus, left (s)	0.63±0.06 (21)	0.62±0.06 (17)
ATT hippocampus, right (s)	0.64±0.07 (21)	0.62±0.06 (17)
Structural brain outcomes		
Brain volume (×10^6 mm^3), mean±SD (n)	1.37±0.07 (22)	1.35±0.06 (21)
Hippocampal volume, left (×10^3 mm^3); mean±SD (n)	2.8±0.4 (20)	2.8±0.4 (17)
Hippocampal volume, right (×10^3 mm^3); mean±SD (n)	2.9±0.5 (20)	3.0±0.5 (17)
White matter lesion volume (×10^3 mm^3), median (IQR); n	8.7 (3.6–26.9); 22	9.2 (6.5–21.5); 19
Infarcts, n (%); n	5 (23); 22	4 (18); 21
Microbleeds, n (%); n	5 (23); 21	3 (14); 19

Values are presented as mean (95% CI) for normally distributed variables, median (IQR) for non-normally distributed variables, or n (%) for dichotomous variables. SBP and DBP were measured in sitting position. ADAS, cognitive subscale range from 0 (no impairment) to 70 (severe impairment); CDR, range from 0 (no impairment) to 3 (severe impairment); CDRsob, range from 0 (no impairment) to 18 (severe impairment); and MMSE, range from 0 (severe impairment) to 30 (no impairment). ADAScog indicates Alzheimer Disease Assessment Scale-cognitive subscale; ATT, arterial transit time; BMI, body mass index; BP, blood pressure; CBF, cerebral blood flow; CDR, clinical dementia rating; CDRsob, clinical dementia rating sum-of-boxes; DBP, diastolic blood pressure; IQR, interquartile range; MCBFV, mean cerebral blood flow velocity; MMSE, mini-mental state examination; PCC, posterior cingulate cortex; and SBP, systolic blood pressure.

Discussion

This study investigated the effects of nilvadipine on CBF in patients with mild-to-moderate dementia (Alzheimer clinical syndrome according to the 2018 National Institute on Aging and Alzheimer's Association Research Framework).[29] In a double-blind randomized controlled design, gray-matter CBF was estimated with ASL-MRI at baseline and after 6-month use of either nilvadipine or placebo. In addition to global CBF, 2 regions of interest were defined a priori: the hippocampus and the PCC. The hippocampus was chosen because preclinical data observed an increase in hippocampal CBF after antihypertensive treatment[17,18]; the PCC because it is, as the hippocampus, an area affected early in AD. Post hoc analyses in the precuneus and occipital lobe were added.

The main findings are that BP lowering with nilvadipine led to an increase in hippocampal CBF. There was no statistically significant change in global CBF or in regional CBF in the PCC nor in the other 2 regions of interest (precuneus and occipital lobe).

The observed decrease in BP was expected, given nilvadipine's known antihypertensive properties. Moreover, the magnitude of this decrease (≈10 mm Hg in systolic BP) is in the same range as observed in antihypertensive trials with similar calcium antagonists.[30]

We will first consider the important observation that despite this reduction in BP, there was no reduction in global or regional CBF, confirmed both with MRI and ultrasound under

(*Continued*)

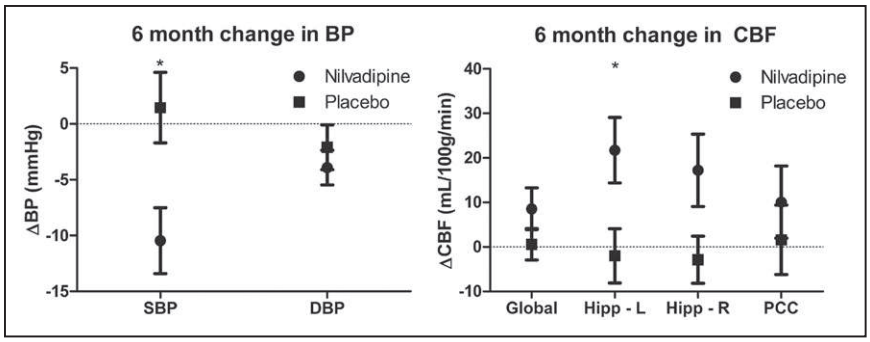

Figure 2. Change in blood pressure (BP) and cerebral blood flow (CBF) between baseline and 6 mo. Estimated mean change, with SEM, over 6 mo for nilvadipine (circle) and placebo (square). DBP indicates diastolic blood pressure; Hipp-L, left hippocampus; Hipp-R, right hippocampus; PCC, posterior cingulate cortex; and SBP, systolic blood pressure. **P*<0.05 between the 2 groups, tested with ANCOVA.

supine, seated, and standing conditions. This indicates that cerebral autoregulation—the mechanism that aims to stabilize CBF—functioned adequately to counteract this reduction in perfusion pressure.[21]

This finding of normal autoregulation is in contrast with the common assumption of impaired autoregulation with aging and in AD. However, our observations align with and extend earlier findings in patients with early-stage AD (mild cognitive impairment).[31] There, BP was lowered acutely with the calcium antagonist nicardipine. Global CBF, measured with O^{15}-Positron Emission Tomography (PET), remained stable.[31] Because one could argue that reductions in CBF may be masked when measured supine by MRI or PET, in the present study, we added transcranial Doppler measurements of CBF (mean CBF velocity) while participants were sitting and standing, including a postural challenge. Also, under these conditions, CBF remained stable.

BP gradients in cerebral arteries can lead to important reductions in perfusion pressure (eg, a 50- to 60-mm Hg reduction in systolic BP), especially in lobar arterioles.[32] This could result in lobar cerebral ischemia when BP is lowered. It is, therefore, important to note that there was no increase in atrophy rate, white matter lesion load, or number of infarcts with nilvadipine.

Next, we will consider the significant increase in hippocampal CBF after BP lowering—an observation that cannot be explained solely by cerebral autoregulation. The increase in hippocampal CBF provides translational evidence for our earlier observations of increased hippocampal CBF after antihypertensive treatment in an AD animal model.[17,18] The angiotensin receptor blocker eprosartan, and not a calcium channel blocker, was used in that study, suggesting that BP lowering per se, rather than a specific drug class effect, is driving the increase in hippocampal CBF.

What potential mechanism could explain this increase in hippocampal CBF? The hippocampus is known to be affected early in the disease by Alzheimer pathology. It is also mainly perfused by branches of the posterior cerebral artery and is more prone to hypoperfusion than other brain regions.[33] In an animal model for familial AD, microvascular pathology in the hippocampus preceded parenchymal amyloid deposition and even amyloid accumulation in the vessel wall.[10] Hypertension may aggravate this AD-related hippocampal microvascular pathology through vascular remodeling and endothelial dysfunction, causing hypoperfusion in this already sensitive area. Antihypertensive treatment may partially reverse this process and restore CBF. Indeed, work in hypertensive patients without dementia has suggested beneficial

Table 2. Treatment Effect of Nilvadipine in Patients With Mild-to-Moderate Alzheimer Disease

	Placebo			Nilvadipine			Between-Group Difference	
Variable	Baseline	6-mo Follow-Up	n	Baseline	6-mo Follow-Up	n	Δ(95% CI)	*P* Value
SBP, mm Hg	137.4±12	138.8±17.1	22	138.7±11.3	128.2±14.3	22	−11.5 (−19.9 to −3)	0.01
DBP, mm Hg	78.6±7.5	76.5±8.5	22	79.9±6.6	76±7.4	22	−1.1 (−5.6 to 3.5)	0.63
Home-based SBP, mm Hg	134.3±20	130.8±22.1	17	138±16.8	132.2±15.5	17	−1.9 (−8.8 to 5.1)	0.59
Home-based DBP, mm Hg	75.0±9.6	77.2±16.7	17	79.4±8.3	76.6±7.8	17	−3.4 (−12 to 5.2)	0.42
CBF global, mL/100 g per min	90.1±18.9	90.7±16.2	14	82.6±23.3	91.2±24.1	18	5.4 (−6.4 to 17.2)	0.36
CBF PCC, mL/100 g per min	114.6±30.1	116.2±24.2	14	106.5±36.7	116.6±42.2	18	5.2 (−16.5 to 27.0)	0.63
CBF hippocampus, left; mL/100 g per min	106.3±26.7	104.4±29.5	14	109.7±32.9	131.4±40.4	18	24.4 (4.3 to 44.5)	0.02
CBF hippocampus, right; mL/100 g per min	110.4±24.7	107.6±28	14	110.6±30	127.8±38.2	18	20.1 (−0.6 to 40.8)	0.06
MCBFV sitting, cm/s	41.4±11.8	40.3±8.5	15	36.1±8.9	36.3±9.3	17	−1.1 (−6.2 to 4.1)	0.68
MCBFV standing, cm/s	39.3±10.3	36.9±9.5	13	36±5.8	35.4±8.8	13	1 (−4.7 to 6.7)	0.73

Baseline and 6-mo follow-up with unadjusted mean±SD and the between-group difference (95% CI) at 6-mo follow-up, corrected for baseline differences, tested with ANCOVA. CBF measured using MRI. MCBFV measured using transcranical Doppler. CBF indicates cerebral blood flow; DBP, diastolic blood pressure; MCBFV, mean cerebral blood flow velocity; PCC, posterior cingulate cortex; and SBP, systolic blood pressure.

Table 3. Effect of Nilvadipine in Patients With Mild-to-Moderate Alzheimer Disease

	Placebo			Nilvadipine			Between-Group Difference	
Variable	Baseline	6-mo Follow-Up	n	Baseline	6-mo Follow-Up	n	Δ(95% CI)	*P* Value
Brain volume ($\times 10^6$ mm^3)	1.36±0.06	1.36±0.07	20	1.37±0.07	1.35±0.07	22	−0.02 (−0.04 to 0.01)	0.13
Hippocampal volume, left ($\times 10^3$ mm^3)	2.81±0.37	2.76±0.39	15	2.8±0.36	2.74±0.35	20	0 (−0.07 to 0.06)	0.91
Hippocampal volume, right ($\times 10^3$ mm^3)	2.93±0.52	2.88±0.54	15	2.87±0.48	2.79±0.48	20	−0.02 (−0.07 to 0.03)	0.41
White matter lesion volume ($\times 10^3$ mm^3)	9.3 (6.5 to 21.5)	11.1 (6.4 to 24.4)	19	8.2 (3.5 to 27.7)	9.2 (3.5 to 30.5)	20	−0.01 (−0.03 to 0.00)*	0.09

Baseline and 6-mo follow-up with unadjusted mean±SD for normally distributed variables, median (IQR) for non-normally distributed variables at 6-mo follow-up, corrected for baseline differences, tested with ANCOVA. IQR indicates interquartile range.

*For estimating the between-group difference in white matter lesion volume, the data were transformed (square-root), tested, and retransformed because of nonnormal distribution.

effects of antihypertensive treatment on CBF using a combination of angiotensin-converting enzyme inhibitors and calcium antagonists.[34] It is striking that the nonsignificant change we observed in whole-brain CBF with 11 mm Hg systolic BP lowering is consistent with the 10% significant increase in CBF that was found with 11 mm Hg BP lowering in that study, which had a similar study design.[34]

The posterior circulation may be more sensitive to the effects of hypertension on CBF, leading to paradoxical reductions in CBF with increases in BP.[35] If this circulation is more sensitive to high BP, it may also benefit more from BP lowering. This could explain why we observe changes in the hippocampus (posterior circulation) and not in global cortical CBF.

The increase in hippocampal CBF could theoretically also be driven by a specific effect of nilvadipine on amyloid-β. Nilvadipine antagonized amyloid-β vasoactivity in vivo and in isolated arteries,[36] resulting in vasodilation of previously constricted vessels. In patients with hypertension and mild cognitive impairment, nilvadipine, but not amlodipine, increased regional CBF.[37] Theoretically, nilvadipine could also reduce amyloid-β deposition in the vascular wall by facilitating clearance[38]; however, it is unlikely that this would show such strong effects in 6 months.

There are some methodological strengths and limitations to discuss. ASL-MRI has not been used before in an RCT setting to evaluate CBF changes in AD. It has, however, already proven its reliability and feasibility in longitudinal and cross-sectional studies.[7,8,24,39]

We minimized between-measurement variability by performing all measurements on the same magnetic resonance scanner. In addition, we corrected for differences in arterial transit time, hematocrit, and effects of atrophy.[40] Without correction for atrophy, CBF effects of nilvadipine were similar; without hematocrit correction, the increase in CBF was significant for left (P=0.03) and right (P=0.04) hippocampus (data not shown).

The retention of participants was high, minimizing distortion of the results. However, there were ≈10% missing data in the main outcomes. Because this was predominantly because of logistic or technical problems rather than patient-related factors (Table S3), these were data missing completely at random. This is confirmed by the similar results for imputed and complete-case datasets (Table S4).

Although this was a relatively small group of participants, their characteristics were similar to ≈500 participants in the main NILVAD study (Table S2), indicating that they formed a representative sample of that population. However, racial diversity was limited mainly to white Europeans, which limits extrapolation to other populations.

We had no amyloid or τ biomarkers to confirm Alzheimer pathology. Following the 2018 National Institute on Aging and Alzheimer's Association Research Framework, our patients would now be best described as having Alzheimer clinical syndrome.[29] In similar patient samples in this age range, the prevalence of PET-amyloid positivity was 88%[41] and of PET-τ positivity was 90%,[42] indicating that adding these biomarkers would have yielded little extra information at incremental costs and patient burden. Patients were diagnosed as probable AD based on 2011 National Institute on Aging and Alzheimer's Association criteria, using neuropsychology and MRI biomarkers, and clinical (>2 years) and MRI follow-up (at 6 months and 1.5 years) were consistent with AD and excluded other causes of dementia (vascular dementia, frontotemporal dementia, and Lewy body dementia). For example, volumetric changes in our sample were consistent with the literature, for example, in whole brain (1.2%)[43] and hippocampal atrophy rate (2.3%)[44] (Table S5).

Our findings cannot yet be translated to earlier stages of the disease, although a previous study in a small group of mild cognitive impairment because patients with AD showed similar results.[37]

Patients with a diastolic pressure <60 mm Hg and a pulse pressure >60 mm Hg, which could indicate increased vascular stiffness, may be at increased risk of lobar ischemia after BP lowering.[32] None of our participants met these criteria, and, therefore, our findings cannot be extrapolated to such patients.

Perspectives

This study shows that BP reduction with nilvadipine resulted in an increase in hippocampal CBF while global CBF remained stable. An important question is whether this observed increase in CBF translates to clinical benefits. Unfortunately, sample sizes were too small and follow-up time too short to reliably study the effects of this CBF increase on structural brain measures and cognitive measures (Table 3; Figure S3). The main NILVAD trial found no beneficial effects of nilvadipine on cognitive function; however, subgroup analyses

suggested a potential benefit in earlier stages of disease.[45] It would, therefore, be important to investigate, in a larger study with longer follow-up, whether the improvement in hippocampal CBF leads to cognitive benefits in earlier stages of disease (mild cognitive impairment or earlier), where the potential for prevention of cognitive decline may be much higher.

The observation that BP lowering does not lead to a decrease in CBF is also a relevant finding in light of treatment of hypertension in AD. Current hypertension guidelines lack specific advice about patients with AD, as there was no evidence on which to base the ratio between safety and benefit.[46] One of the risks of BP lowering in this patient group is to compromise CBF, since cerebral autoregulation might be affected.[32] However, we previously showed that dynamic cerebral autoregulation remains effective in AD,[21] and the present study confirms that BP lowering was achieved without causing cerebral hypoperfusion.

Conclusions

Nilvadipine increased hippocampal CBF while lowering BP. These findings indicate that the known decrease in CBF in patients with AD can in some regions be reversed. In addition, this study demonstrates that ASL-MRI is a feasible and valid method to evaluate physiological changes in a relatively small sample of AD patients.

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Disclosures

B.A. Lawlor reports a pending patent for nilvadipine. The other authors report no conflicts.

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Novelty and Significance

What Is New?

- This is the first study on the effects of blood pressure lowering on cerebral blood flow in patients with dementia because of Alzheimer disease.

What Is Relevant?

- Systolic blood pressure was reduced on average by 11.5 mm Hg.
- At 6 months, whole-brain gray-matter cerebral blood flow remained stable, and there was no evidence for regional hypoperfusion.
- Hippocampal blood flow increased significantly.

Summary

Moderate antihypertensive treatment had no adverse effects on cerebral blood flow in patients with mild-to-moderate Alzheimer dementia and improved hippocampal blood flow. Whether this translates into clinical benefit remains unknown.