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Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain

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Chapter 5

Blood pressure is not associated with cerebral blood flow in older persons

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Abstract

Background

Many studies showing a relation between low blood pressure (BP) and adverse health outcomes in older persons suggest that low BP gives rise to reduced cerebral blood flow (CBF). However, limited evidence is available about this association.

Methods

Baseline data of 203 participants in the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial were used (mean age, 81 years, using antihypertensive medication and with mild cognitive deficits). BP, BP changes on standing, and CBF derived from pseudo-continuous arterial spin-labeling magnetic resonance imaging were assessed in all participants. In 102 participants who were randomly assigned to 4-month continuation ($n=47$) or discontinuation of antihypertensive treatment ($n=55$), BP and CBF change were evaluated at 4-month follow-up.

Results

Systolic and diastolic BP were not associated with CBF ($B=-0.21$, $P=0.50$ and $B=-1.07$, $P=0.07$), neither were mean arterial pressure, pulse pressure, and BP changes on standing. In subgroups of participants with small vessel-related cerebral pathologies, including high white matter hyperintensity volume, microbleeds, and lacunar infarcts, or in participants with lower cognition or diabetes mellitus, no association was found between any BP parameters and CBF. Furthermore, compared with the continuation group, CBF change at 4 months was not different in the discontinuation group ($B=-0.12$, $P=0.23$).

Conclusion

Contrary to the notion that lower BP in old age is associated with decreased CBF, our data do not show this association in older persons using antihypertensive medication and with mild cognitive deficits. Also, this association was not present in subgroups of more vulnerable persons, reflected by small vessel-related cerebral pathologies, lower cognition, or diabetes mellitus.

Introduction

Cerebral blood flow (CBF) is essential for providing oxygen and nutrients to the brain to maintain optimal brain function. A constant level of CBF is ensured by means of the cerebral autoregulatory mechanism, where fluctuations in blood pressure (BP) are counteracted via adjusting the resistance of cerebral arterioles.¹ With increasing age and long-standing high BP, arteriosclerosis affects cerebral arterioles, subsequently disrupting cerebral autoregulation.^{2,3} When cerebral autoregulation becomes chronically disrupted, a lower BP can no longer be compensated for and hypoperfusion may occur.^{1,2,4}

Many studies in older persons show an association between the presence of low BP and adverse health outcomes, including increased mortality,⁵⁻⁷ cerebral atrophy,⁸⁻¹⁰ risk of dementia,¹¹ and cognitive impairment.^{12,13} However, a meta-analysis of placebo-controlled double-blind trials in older persons demonstrated a beneficial effect of BP lowering on stroke, cardiovascular events, and heart failure but not on total mortality.¹⁴ It has been hypothesized that, even in the oldest old, lowering BP might prevent or delay cognitive decline. Data from the Systolic Hypertension in Europe (Syst-Eur) trial showed a benefit from antihypertensive treatment in prevention of dementia in persons aged ≥ 60 years.¹⁵ However, hypertension in the very elderly trial (HYVET) failed to demonstrate that lowering BP with antihypertensive treatment improved cognitive functioning in elderly aged ≥ 80 years.¹⁶ Moreover, meta-analyses, including the Syst-Eur and HYVET and other placebo-controlled double-blind trials, suggested that BP lowering with antihypertensive treatment does not reduce the risk of dementia.^{17,18} It has even been proposed that lowering BP in older persons using antihypertensive medication may decrease CBF.^{3,19-21} These observations have led to the suggestion that low BP in old age could result in cerebral hypoperfusion, initiated by impaired cerebral autoregulation. Nevertheless, in older persons with low BP at risk of impaired cerebral autoregulation, limited data are available as to whether CBF is in fact impaired.

The aim of this study was to assess whether BP is associated with CBF in older persons (mean age, 81 years) using antihypertensive medication and with mild cognitive deficits. On the basis of previous reports, we hypothesized that in this population, an association would exist between lower BP and lower CBF and that

an increase in BP in these individuals would lead to an increase in CBF. Especially in subgroups with small vessel-related cerebral pathologies, lower cognition or diabetes mellitus, which are more at risk to have impaired cerebral autoregulation, this association may be more pronounced.

Methods

Participants and procedures

Data were obtained from the magnetic resonance imaging (MRI) sub-study of the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial; a community-based randomized controlled trial evaluating the effect of temporary (4-month) discontinuation of antihypertensive therapy in older persons with mild cognitive deficits in neuropsychological functioning. Participants, aged ≥ 75 years, who were using antihypertensive medication and had a Mini-Mental State Examination score of 21 to 27, were enrolled from Dutch general practices. In addition, a current systolic BP (SBP; based on the last BP measurement obtained from the general practitioners' electronic medical record) of ≤ 160 or ≤ 140 mmHg for persons with diabetes mellitus, myocardial infarction, peripheral artery disease, or coronary reperfusion procedures ≥ 3 years ago, was required. Exclusion criteria were a history of stroke or transient ischemic attack, a recent (≤ 3 years) myocardial infarction or recent coronary reperfusion procedure, current angina pectoris, cardiac arrhythmias, heart failure, the use of antihypertensive medication other than for hypertension, a clinical diagnosis of dementia, or a limited life expectancy.

The DANTE Study Leiden was approved by the Medical Ethics committee of the Leiden University Medical Center and informed consent was obtained from all participants.

In total, 219 of the DANTE participants underwent anatomic and pseudo-continuous Arterial-Spin Labeling (PCASL) MRI scans at baseline to assess the presence and severity of small vessel-related cerebral pathologies and CBF, respectively. Sixteen participants were excluded because of incidental MRI findings, leaving a total of 203 participants for the cross-sectional analyses.

Within a week after the baseline measurement participants were randomly assigned, using block randomization (block sizes of 4 per general practice), in a 1:1 ratio into 2 parallel groups: discontinuation or continuation of antihypertensive treatment. After randomization, for the discontinuation of antihypertensive treatment all general practitioners were instructed to completely or partially withdraw antihypertensive medication. Research staff was blinded to the allocated intervention, whereas general practitioners conducting the intervention and the participants were not. Because of financial limitations, the follow-up PCASL was added in a later phase of the study. Therefore, a random subgroup ($n=102$) of participants received follow-up PCASL scans 4 months after randomization. The longitudinal analyses included 102 participants, of these, half of the participants with a follow-up PCASL had continued using antihypertensive medication ($n=47$) and the other half discontinued using antihypertensive medication ($n=55$) during 4-month follow-up.

Blood pressure

BP was measured by research staff using a fully automatic electronic sphygmomanometer (Omron M6 comfort). First, with all participants in a seated position, BP was measured twice, with 2 minutes between measurements, on the right arm. Thereafter, 3 successive standing BP measurements were performed directly on standing within ≈ 3 minutes, whereby the research staff supported the arm, to keep the cuff at heart level. Similarly, in the subgroup of participants ($n=102$) with a follow-up PCASL MRI scan, BP was measured at 4 months. For analysis, BP measurements were averaged to yield an estimate of the participant's resting BP. Mean arterial pressure was calculated as $1/3(\text{SBP}) + 2/3(\text{diastolic BP [DBP]})$ and pulse pressure as $\text{SBP} - \text{DBP}$. In addition, postural SBP change was calculated as the difference between the mean sitting SBP and the mean standing SBP, the same was done for the DBP. Changes in SBP and DBP on standing were used as indicators of autonomic dysfunction.

Cerebral blood flow and cerebral small vessel disease

MRI scans were acquired with a 3-T whole-body magnetic resonance system. White matter hyperintensity (WMH) volume, defined as hyperintense regions on fluid-attenuated inversion recovery images, was measured in an automated manner. The average grey matter CBF was calculated in mL/100 g per minute with PCASL images. Cerebral microbleeds were assessed on T2*-weighted images and

lacunar infarcts on fluid-attenuated inversion recovery, T2 and 3DT1-weighted images. Detailed description image acquisition and analyses are available in the Supplementary material, which includes brain imaging, WMH volume, CBF, and cerebral microbleeds and lacunar infarcts.

Demographic and clinical characteristics

Demographic and clinical characteristics were obtained at baseline using a standardized interview. Information on medication and medical history were obtained from the general practitioners with the aid of structured questionnaires.

Statistical analyses

Demographic and clinical characteristics of the study participants are presented as numbers with percentages, mean with SDs, or medians with interquartile ranges when appropriate.

The correlation power calculation showed that for a sample size of $n=203$ with an α of 5% and a power of 80%, a correlation coefficient of 0.2 could be detected.

The cross-sectional relationship between BP parameters and grey matter CBF was explored by using correlation analyses and linear regression analyses. Unstandardized β and 95% confidence intervals (CIs) were calculated per 10 mm Hg increase in BP parameters. We previously found associations of lower BP with lower volumes of the thalamus, putamen, and hippocampus.²² We also assessed whether BP parameters were associated with CBF within these 3 subcortical structures.

The association between postural BP changes (as indicators of orthostatic hypotension) and grey matter CBF was assessed with linear regression. Unstandardized β and 95% CIs were calculated per mm Hg increase in SBP and DBP changes on standing.

As cerebral small vessel disease has been related to impaired cerebral autoregulation,^{23;24} stratified analyses were performed in subgroups of participants with small vessel-related cerebral pathologies. The subgroups included participants with a WMH volume above the median (>20.5 mL: $n=101$, 49.8%), with cerebral microbleeds ($n=50$, 25.0%) and with lacunar infarcts ($n=56$, 27.6%).

In addition, stratified analyses were performed based on median mini-mental state examination score (26 points; $n=103$, 50.7%) and presence of diabetes mellitus ($n=39$, 19.2%). To further explore the association of BP parameters and grey matter CBF, we performed analyses in subgroups of participants using specific types of antihypertensive medication (including β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, and diuretics) or using platelet inhibitors ($n=39$, 19.2%), statins ($n=71$, 35.0%), or psychotropic medication ($n=34$, 16.7%).

For the longitudinal data analyses, changes in BP and grey matter CBF were calculated by subtracting the baseline measurement from the follow-up measurement. The effect of discontinuation of antihypertensive medication on BP and grey matter CBF was determined with linear regression analyses, in which the randomization was the independent variable and SBP, DBP, or grey matter CBF was the dependent continuous variable.

All cross-sectional and longitudinal analyses were adjusted for age and sex. A P value of ≤ 0.05 was considered statistically significant. The statistical analysis was performed with SPSS software (version 20.0; SPSS, Chicago, IL).

Results

Baseline characteristics of the study population and of the longitudinal sample are summarized in Table. In the entire study population, the mean age was 80.8 (SD, 4.1; range, 75–96) years. Mean SBP was 145 mmHg (SD, 21.0), mean DBP was 81 mmHg (SD, 10.8), and mean arterial pressure was 102 mmHg (SD, 13.1). Mean grey matter CBF was 35.9 mL/100 g per minute (SD, 9.4). All characteristics of the longitudinal sample were similar to the entire study population.

Table 1. Baseline characteristics of the total sample of participants (n=203) and of the longitudinal sample (n=102)

Characteristic	Total sample (n=203)	Longitudinal Sample (n=102)
Demographic		
Age in years, mean (SD)	80.8 (4.1)	80.5 (3.9)
Female, n (%)	115 (56.7)	56 (54.9)
Clinical		
Current smoker, n (%)	14 (6.9)	6 (5.9)
Alcohol ≥ 14 units/week, n (%)	21 (10.3)	11 (10.8)
History of cardiovascular disease, n (%)*	17 (8.4)	11 (10.8)
Presence of chronic disease, n (%)†	125 (61.6)	63 (61.8)
MMSE score, median (IQR)	26 (25-27)	27 (26-27)
Presence of orthostatic hypotension, n (%)‡	96 (47.3)	49 (48.0)
Systolic blood pressure, mm Hg, mean (SD)	145 (21.0)	146 (21.3)
Diastolic blood pressure, mm Hg, mean (SD)	81 (10.8)	82 (10.5)
Mean arterial pressure, mm Hg, mean (SD)	102 (13.1)	103 (13.0)
Pulse pressure, mm Hg, mean (SD)	65 (15.4)	64 (15.7)
Antihypertensive medication, n (%)		
Number of antihypertensive agents ≥ 2	119 (58.6)	60 (58.8)
Beta blocker	74 (36.5)	35 (34.3)
Angiotensin Converting Enzyme-inhibitor	64 (31.5)	34 (33.3)
Angiotensin receptor blocker	75 (36.9)	41 (40.2)
Calcium channel blocker	45 (22.2)	22 (21.6)
Diuretic	107 (52.7)	52 (51.0)
Psychotropic medication, n (%)§	34 (16.7)	18 (17.6)
Cerebral		
Grey matter ml, mean (SD)	498 (47.5)	498 (49.7)
White matter ml, mean (SD)	504 (51.3)	506 (53.7)
WMH ml, median (IQR)	21 (9-56)	19 (7-60)
Presence of cerebral microbleeds, n (%)	50 (25.0)	27 (26.5)
Presence of lacunar infarcts, n (%)	56 (27.6)	33 (32.4)
Grey matter CBF, mL/100g/min (SD)	35.9 (9.4)	36.0 (8.1)

*cardiovascular diseases include myocardial infarction or percutaneous coronary intervention or coronary artery bypass graft. †chronic diseases include diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease, malignancy, and osteoarthritis. ‡ Orthostatic hypotension was defined as a systolic blood pressure decrease ≥ 20 mm Hg and/or a diastolic blood pressure decrease of ≥ 10 mm Hg within 3 min upon standing. § Psychotropic medication includes use of antipsychotics, antidepressants, or benzodiazepines. || n=3 missing data in n=203 sample. MMSE, mini-mental state examination; BP, blood pressure; WMH, white matter hyperintensities; SD, standard deviation; IQR, interquartile range; CBF, cerebral blood flow.

Per 10 mm Hg increase in SBP, grey matter CBF was 0.21 mL/100 g per minute lower (95% CI, -0.82 to 0.40; $P=0.50$). Similar small non-significant effect sizes were found for the association between DBP, mean arterial pressure, and pulse pressure with grey matter CBF (Figure 1). In addition, there was no association between any of the BP parameters and CBF in the thalamus, putamen, and hippocampus (all $P>0.05$).

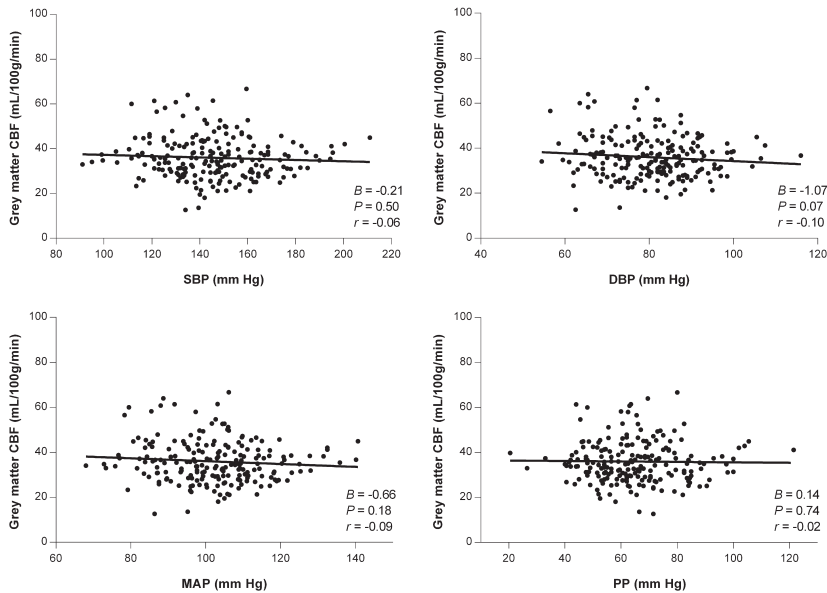


Figure 1. Relationship between blood pressure parameters (per 10 mm Hg increase) and grey matter CBF in mL/100g/min. Unstandardized betas and P -values were calculated by linear regression analyses adjusting for age and gender. All correlation coefficients were non-significant. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; CBF, cerebral blood flow.

The effect of SBP and DBP changes on standing on grey matter CBF are shown in Figure 2. Neither the SBP nor the DBP change on standing were associated with grey matter CBF ($B=-0.11$; 95% CI; -0.22 to 0.01; $P=0.07$ and $B=-0.13$; 95% CI, -0.33 to 0.07; $P=0.21$, respectively).

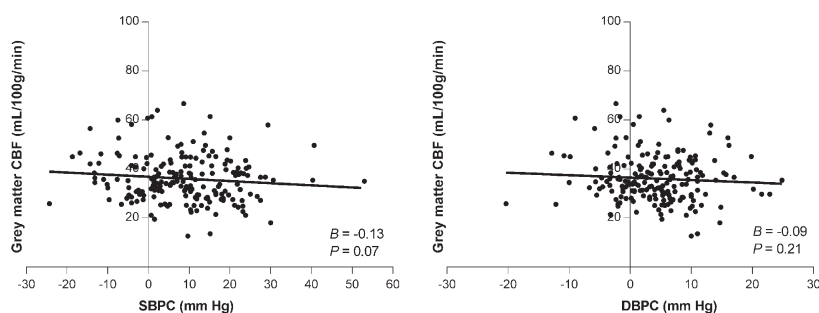


Figure 2. The associations of systolic and diastolic blood pressure change upon standing with grey matter CBF. Unstandardized betas and P-values were calculated per mm Hg increase in blood pressure change with linear regression analysis adjusting for age and gender. A higher blood pressure change indicates that the blood pressure in seated position was higher than blood pressure in standing position. Abbreviations: CBF, cerebral blood flow; SBPC, systolic blood pressure change upon standing; DBPC, diastolic blood pressure change upon standing.

Stratified analyses in subgroups of participants with small vessel disease-related pathologies, that is, high WMH volume ($n=101$), cerebral microbleeds ($n=50$), or lacunar infarcts ($n=56$), or with a mini-mental state examination score ≤ 26 points ($n=103$) or diabetes mellitus ($n=39$), revealed that no statistically significant associations were found between SBP, DBP, mean arterial pressure, or pulse pressure and grey matter CBF in any of these subgroups (all $P>0.05$; Figure 3). Moreover, no significant association were found between any of the BP parameters and grey matter CBF in subgroups of participants using β -blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium antagonists, diuretics, platelet inhibitors, statins, or psychotropic medication (all $P>0.05$).

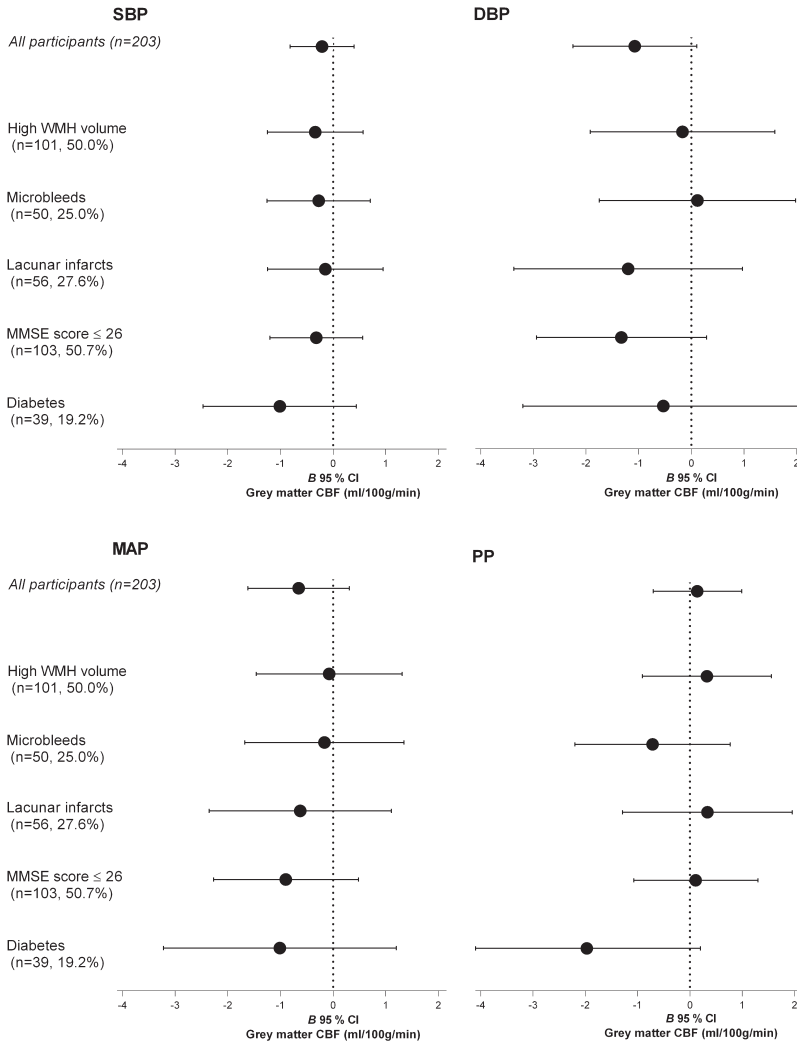


Figure 3. The association between blood pressure parameters (per 10 mm Hg increase) and grey matter CBF stratified for cerebral small vessel-related pathologies. Unstandardized betas (95% CI) were calculated by linear regression analyses adjusting for age and gender. A negative beta indicates that per 10 mm Hg BP increase, grey matter CBF decreases. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; WMH, white matter hyperintensity.

Figure 4 shows the 4-month change in SBP, DBP, and CBF in both the continuation group and the group that discontinued antihypertensive medication. Discontinuation of antihypertensive medication resulted in a statistically significant increase of both SBP (9.4 mm Hg; SE, 4.5) and DBP (5.0 mm Hg; SE, 2.2), compared with the group that continued antihypertensive medication ($B=0.20$; 95% CI, 0.01–0.40; $P=0.04$ and $B=0.22$; 95% CI, 0.03–0.41; $P=0.02$, respectively). However, in the discontinuation group, grey matter CBF did not change significantly when compared with the continuation group ($B=-0.12$; 95% CI, -0.32 to 0.08; $P=0.23$).

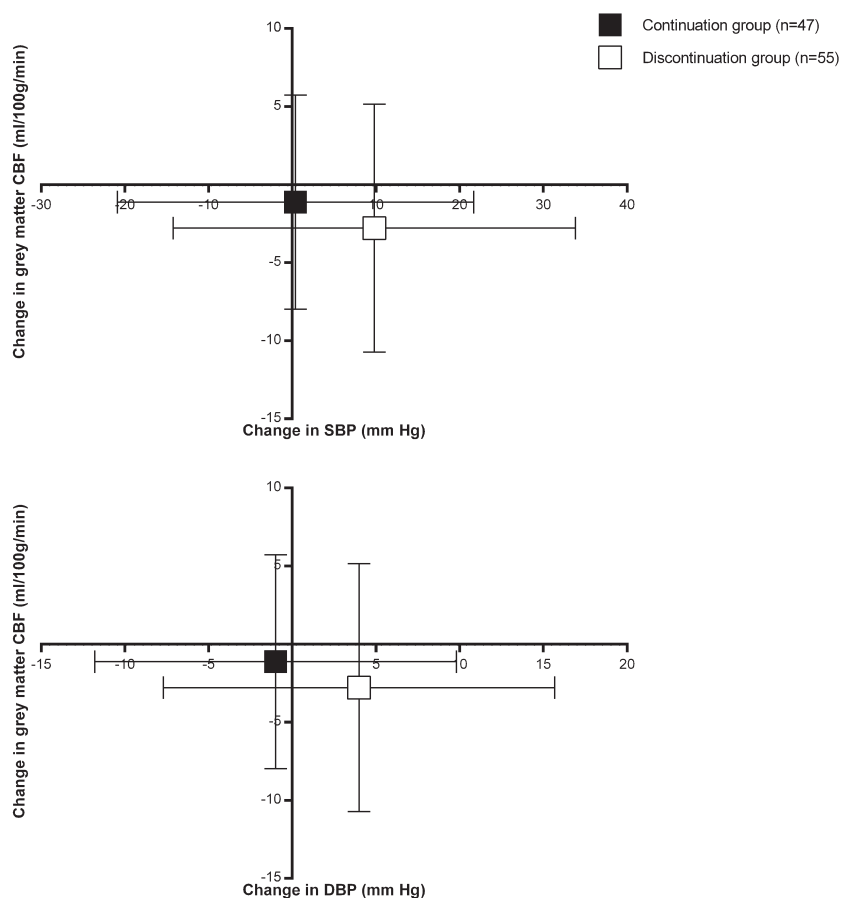


Figure 4. Four-month change in systolic, diastolic blood pressure and cerebral blood flow in the continuation group and the group that discontinued antihypertensive medication. Bars represent the means and standard deviations. The discontinuation group had significantly higher SBP and DBP change than the continuation group ($p<0.05$). CBF change was not significantly different between the discontinuation and continuation group. Abbreviations: SBP, systolic blood pressure; CBF, cerebral blood flow; DBP, diastolic blood pressure.

Discussion

In our population of older persons with mild cognitive deficits using antihypertensive medication, no relation was found between any BP parameter and CBF. Moreover, BP changes after the orthostatic challenge were not associated with CBF, and no association was found between BP and CBF in subgroups of persons with small vessel disease–related pathologies, lower cognition, or diabetes mellitus. In addition, our longitudinal data showed that a change in BP during 4 months because of the discontinuation of antihypertensive medication had no effect on CBF.

During the past decades, a considerable number of observational and longitudinal studies in older persons have revealed an association between low BP and adverse health outcomes. In the Leiden 85-plus Study, it was shown that 85-year-old persons with low BP had an increased mortality risk.⁷ Similar observations of unfavorable outcomes in older persons with low BP are at an increased risk of dementia¹¹ and cognitive impairment.^{12,13} In a combined study of 2 prospective population-based studies, low baseline BP conferred a higher risk of dementia 2 years later, especially in persons using antihypertensive medication.¹¹ A possible explanation for these findings has been that in older persons low BP or a decrease in BP might be associated with a low CBF. Furthermore, it has also been proposed that in older persons in addition to low BP, atherosclerosis, and possibly, the treatment of hypertension may induce cerebral hypoperfusion, ischemia, and hypoxia. Our data show that even in older persons using antihypertensive medication and at increased risk of having chronic hypoperfusion, lower BP is not associated with low CBF. Although effects were only minor and not statistically significant, our data pointed to the opposite direction. Therefore, the commonly used explanation for previous findings, namely that BP increases the risk of adverse health outcomes by means of a subsequently lowered CBF, is not supported by our findings.

Opposing our hypothesis, we found no association between low BP and low CBF. In agreement with previous literature, BP changes after the orthostatic challenge were not associated with CBF.⁴ In our study, the median WMH volume (21 mL [IQR, 9–56]) was relatively high compared with median WMH volume in other studies that included older persons. Previous studies reported a mean white matter lesion volume of 5 to 11 mL in participants with a mean age of 72 to

75 years.²⁵⁻²⁷ The prevalence of cerebral microbleeds and lacunar infarcts in our study population (25.0% and 27.6%, respectively) was slightly higher than that in other studies, reporting a prevalence of cerebral microbleeds of 17.2%²⁷ or 23.5% and a prevalence of lacunar infarcts of 18.2%.^{26,28} Although cerebrovascular reactivity may be reduced in persons with small vessel disease,^{23,24} BP was not related to CBF in subgroups of persons with overt signs of small vessel disease-related pathologies. Furthermore, our results revealed that after the 4-month discontinuation of antihypertensive medication, a significantly increased BP had no effect on CBF. Only few studies have investigated whether BP is associated with CBF. In one of these studies, including younger persons (mean age, 58 years), SBP and DBP were also not associated with CBF.²⁹ Another study, not only in a healthy but also younger population (mean age, 67 years), showed that only in men higher BP was associated with lower CBF.³⁰ However, no association between low BP and reduced CBF was found in any of these studies. Furthermore, higher BP among persons with atherosclerosis was associated with a decline in CBF during 5-year follow-up,³¹ and previous findings in hypertensive older persons aged ≥ 70 years showed that CBF increased in persons who were more intensively treated for hypertension.³²

An explanation for our results may be that in our population, consisting of older persons with mild cognitive deficits, BP stays within the range of cerebral autoregulation, whereby CBF remains constant. Because no relation with CBF was found with indicators of autonomic dysfunction, namely BP changes on standing or with BP in subgroups of persons with small vessel disease-related pathologies (prone to have disrupted cerebral autoregulation), we can only speculate that this BP range of maintained cerebral autoregulation seems relatively wide, so that CBF remains stable.

To our knowledge, this is the first study to investigate the relationship between BP and CBF in subgroups of older persons with small vessel-related cerebral pathologies, in addition to BP change on standing and CBF. Also, the assessment of BP and CBF change because of the discontinuation of antihypertensive treatment is unique. A limitation of this study may be that, despite the fact that our study population consisted of older old persons with small vessel disease-related pathologies, the inclusion of participants without stroke or (recent) other cardiovascular events may have resulted in a selection of relatively healthy older

old persons. This selection limits our ability to extrapolate the results to all older old persons. Also, BP change on standing was related to CBF measured in a supine position, measuring CBF on standing would be preferable. In addition, although the large range in BP and CBF values may have hampered finding small associations, there was sufficient statistical power to find a correlation coefficient of 0.20. Our relatively small number of persons with a low BP may have prevented us from finding an association with reduced CBF. Yet, it is notable that we consistently found no relationship between BP parameters and CBF.

In conclusion, although it is frequently thought that lowering BP in older persons with impaired vascular resistance reduces CBF, our data show that in older persons with mild cognitive deficits who are using antihypertensive medication, low BP is not associated with decreased CBF, indicating this hypothesis is unlikely.

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Supplementary material

Brain imaging

All MRI scans were acquired on a whole-body magnetic resonance system operating at a field strength of 3-T (Philips Medical Systems, Best, the Netherlands), equipped with a 32-channel head coil. PCASL images were obtained with repetition time (TR)/ echo time (TE)=4000/14 ms, flip angle (FA)=90° field of view (FOV)=240'133' 240 mm, matrix size=80'80 mm, slices 19, background suppression (inversion pulses at 1680 and 2830 ms), and with a labelling time of 1650 ms and postlabeling delay of 1525 ms. An M0-scan was acquired with similar settings, but without background suppression and a TR of 6000 ms. 3DT1-weighted images were acquired with TR/TE=9.7/4.6 ms, FA=8°, and 224'177'168 mm FOV, resulting in a nominal voxel size of 1.17'1.17'1.4 mm. Fluid attenuated inversion recovery (FLAIR) images were acquired with TR/TE=11 000/125 ms, FA=90°, FOV=220'176'137 mm, matrix size=320'240, 25 transverse slices, 5-mm thick. T2*-weighted images (TR/TE=45/31 ms, FA=13°, FOV=250'175'112 mm) and T2-weighted images (TR/TE=4200/80 ms, FA= 90°) were acquired.

White matter hyperintensity volume

White matter hypertensity volume quantifications were conducted with FMRIB Software Version 5.0.1. Library.¹ White matter hyperintensity volume, defined as hyperintense regions on FLAIR, was measured in an automated manner. The 3DT1-weighted images were first skull stripped,² and FLAIR and 3DT1 images were linearly co-registered.^{3,4} The brain extracted FLAIR image was affine-registered to MNI152 standard space. A conservative MNI152 white matter mask was used to extract the white matter from FLAIR image. Subsequently, a general threshold was set to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

Cerebral blood flow

Different tools of FMRIB Software Version 5.0.1. Library¹ were used for the PCASL analyses. First, PCASL images were corrected for gradient nonlinearities in all three directions, then the perfusion-weighted maps were quantified into cerebral blood flow (CBF) maps using a single-compartment model with an additional correction for the decrease in labeling efficiency due to the background suppression pulses^{5,6} followed by the removal of non-brain tissue.² T1-weighted

images were skull stripped² and tissue type segmentation with partial volume estimation was performed to calculate separate estimates of grey and white matter volumes.⁷ Subsequently, T1-weighted images were aligned to MNI152 using linear and non-linear registration.^{3,4} Next, the CBF maps were aligned to MNI152 using previously calculated linear and non-linear transformations with the conversion matrix based on the grey matter T1-weighted images. After correcting for an individual binarized white matter hyperintensity volume map, using the individual scan dependent grey matter mask, the average grey matter CBF was calculated in mL/100g/min.

Cerebral microbleeds and lacunar infarcts

Cerebral microbleeds and lacunar infarcts were scored by a single rater (JFD) who was blinded to clinical data, and who was supervised by a second rater (JG), having more than 15 years neuroradiological experience. Cerebral microbleeds were defined as focal areas of signal void (on T2 images), which increased in size on T2*-weighted images (blooming effect). Symmetric hypointensities in the basal ganglia, likely to represent calcifications or non-hemorrhagic iron deposits, were disregarded. Lacunar infarcts, assessed on FLAIR, T2 and 3DT1-weighted images, were defined as parenchymal defects (signal intensity identical to cerebrospinal fluid on all sequences) of at least 3 mm in diameter, surrounded by a zone of parenchyma with increased signal intensity on T2-weighted and FLAIR images.

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