Lower Blood Pressure and Gray Matter Integrity Loss in Older Persons

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In contrast to middle age, it is unclear whether blood pressure (BP) in older persons is associated with cerebral small vessel disease (cSVD). The authors evaluated the association of BP with signs of cSVD as well as gray and white matter integrity in older persons. In 220 participants aged 75 years and older from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) study, cSVD was assessed with conventional magnetic resonance imaging, and microstructural integrity with diffusion tensor and magnetization transfer (MT) imaging. BP measures were not associated with cSVD. However, lower systolic and diastolic BP and mean arterial pressure were associated with decreased gray matter MT ratio peak height and MT ratio in cortical gray matter. Mean arterial pressure was also associated with increased gray matter diffusivity. A lower level of BP was especially associated with worse gray matter integrity. Results suggest that not only upper but preferably lower thresholds of BP values should be observed in older persons. *J Clin Hypertens (Greenwich).* 2015;17:630–637. © 2015 Wiley Periodicals, Inc.

High blood pressure (BP) is related to increased risk of cerebral small vessel disease in middle age, typically including white matter hyperintensities (WMHs),[1–10] lacunar infarcts,[11–13] and microbleeds[14–17] on magnetic resonance imaging (MRI). Apart from these visual focal changes, more widespread subtle changes in the microstructural integrity of the cerebral white matter have been reported.[18–21]

In older persons, the association of BP with MRI findings may be different than in middle-aged persons, since low BP, rather than high BP, has recently been associated with cerebral damage[1,2,22] and worse outcomes such as risk of ischemic stroke[23,24] and mortality.[25] In these studies it has been suggested that this effect may be caused by hypoperfusion, especially in older people with arteriosclerotic damage or a history of cardiovascular disease. Thus, these persons may be better off with higher BP levels, whereby perfusion is maintained and brain integrity preserved.[26,27] To our knowledge, no studies have assessed the relationship between BP and manifestation of small vessel disease in combination with measurements of gray and white microstructural brain integrity in older persons.

The aim of the present cross-sectional study was to explore the associations of BP with manifestations of small vessel disease and microstructural brain integrity in both gray and white matter in older persons.

METHODS

Participants

Participants for this MRI substudy were included from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial, a community-based randomized nonblinded clinical trial assessing the effect of temporary discontinuation of antihypertensive therapy on neuropsychological functioning in older persons with mild cognitive dysfunction. Inclusion criteria were age 75 years and older, use of antihypertensive medication, presence of mild cognitive dysfunction (according to Mini-Mental State Examination score 21–27), and current systolic blood pressure (SBP) ≤160 mm Hg (or ≤140 mm Hg for persons with diabetes, or myocardial infarction, peripheral artery vascular disease, or coronary reperfusion procedures more than 3 years ago). Current BP was determined based on the last BP measurement obtained from the general practitioners' electronic medical record. 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, use of antihypertensive medication other than for hypertension, a clinical diagnosis of dementia, or a limited life expectancy.

The current study used baseline data of the MRI substudy. From the 430 DANTE participants, 220 nonselected persons underwent MRI of the brain. The Medical Ethical committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all participants.

Blood Pressure

SBP and diastolic blood pressure (DBP) were measured twice at baseline in a seated position in all participants using a fully automatic electronic sphygmomanometer

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(Omron M6 Comfort; Omron Healthcare, Inc, Lake Forest, IL). For analyses, the mean of the two measurements was calculated. Mean arterial pressure (MAP) was calculated as 1/3(SBP)+2/3(DBP), and pulse pressure (PP) as SBP–DBP.

MRI Acquisition

All MRI scans were acquired on a whole-body magnetic resonance system operating at a field strength of 3-T with a 32-channel head coil (Philips Medical Systems, Best, The Netherlands). Three-dimensional (3D) T1-weighted images were acquired with repetition time (TR)/echo time (TE)=9.7/4.6 ms, flip angle (FA) =8°, and a nominal voxel size of 1.17×1.17×1.4 mm. Fluid-Attenuated Inversion Recovery (FLAIR) images (TR/TE=11,000/125 ms, FA=90°), T2-weighted images (TR/TE=4200/80 ms, FA=90°), and T2*-weighted images (TR/TE=45/31 ms, FA=13°) were acquired. Diffusion tensor images (DTI) (TR/TE=9592/56 ms, FA=90°, 64 slices, 32 measurement directions, *b* value=1000) and magnetization transfer images (MTI) with and without a saturation pulse (TR/TE=100/11 ms, FA=9°) were acquired. DTI images and MTI images were available for 195 and 216 participants, respectively.

White Matter Hyperintensities, Lacunar Infarcts, and Microbleeds

MRI scans were visualized using Philips DICOM viewer R3.0-SP03 software (Philips Medical Systems). Cerebral ischemic damage was evaluated as previously reported.[28] In short, periventricular and subcortical WMHs were scored semiquantitatively. Periventricular WMHs were present when lateral, posterior, and anterior periventricular regions were scored ≥2. A lacunar infarct, assessed on FLAIR and T2- and 3D T1-weighted images, was defined as a parenchymal defect (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. 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 nonhemorrhagic iron deposits, were disregarded. All measurements were obtained blinded to participants' demographic and clinical information.

Image Processing and Analysis

MRI scans were analyzed with FMRIB software version 5.0.1. Library.[29] For the automated measurement of WMH volume, 3D T1-weighted and FLAIR images were skull stripped[30] and co-registered using the FMRIB's Linear Image Registration Tool (FLIRT).[31,32] The FLAIR image was affine-registered to MNI152 standard space using FLIRT. WMHs were extracted from FLAIR images with a conservative MNI152 white matter mask and a threshold was set to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

Using the FDT (FMRIB's Diffusion Toolbox), individual fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD) images were created.[33,34] Using FLIRT to a non–diffusion-weighted reference volume, original images were corrected for effects of head movement and eddy currents in the gradient coils. A diffusion tensor model was fitted to the corrected images to create individual FA, MD, AxD, and RD images. For global quantification of brain tissue FA, MD, AxD, and RD, 3D T1 images were skull stripped,[35] segmented,[36] and aligned to MNI152 using FLIRT. Lower FA and higher MD, AxD, and RD indicate poorer integrity.

For MTI data processing nonsaturated (M0) and saturated (M1) images were co-registered to the 3D T1 image.[36] Individual magnetic transfer ratio (MTR) maps were calculated voxel by voxel. 3D T1 cortical gray and white matter masks were corrected for possible partial volume effects.[37] Per volume-of-interest MTR peak height, normalized for the size for the volume-of-interest, were calculated.[38] MTR peak height value of one participant exceeded three standard deviations and was excluded. Lower MTR peak height indicates poorer integrity.

For the voxel-based analysis, MTR gray matter maps were aligned to MNI152 using nonlinear transformation[39] and averaged to create a reference template for MTR images. Individual gray matter MTR maps were nonlinearly registered to this template.[40] Voxel wise statistics were carried out with FSL randomise using permutation-based nonparametric testing (5000 permutations). Threshold-Free Cluster Enhancement was applied with a significance level set at $P<.05$ Family Wise Error corrected for multiple comparisons. The age and sex of participants were inserted as covariates in the model.

Demographic and Clinical Variables

Demographic and clinical characteristics were obtained using a standardized interview. Education was dichotomized at 6 years of schooling (primary education only) and alcohol use at 14 units per week. Using structured questionnaires, information about medication and medical histories was obtained from the general practitioners.

Statistical Analyses

Characteristics of the study participants are reported as mean (standard deviation), median (interquartile range) for continuous variables when appropriate, and number (percentage) for categorical variables.

For analyses, the SBP and DBP were both grouped into three clinically relevant categories: SBP <140 mm Hg, 140–159 mm Hg and ≥160 mm Hg, and DBP <80 mm Hg, 80–89 mm Hg, and ≥90 mm Hg. Since no clinically relevant cutoff values are known for MAP and PP, these were grouped into tertiles. Accordingly, the associations of clinically relevant groups of SBP, DBP, and tertiles of MAP and PP

with parameters of small vessel disease and microstructural integrity were analyzed using logistic or linear regression analysis adjusting for age, sex, and duration of antihypertensive treatment. WMH volume was logarithmically transformed to ensure a normal distribution. Standardized *z* scores were calculated for the microstructural parameters using the following equation: (=test score−mean)/SD) (Figure 1).

As SBP <140 mm Hg, 140–159 mm Hg, and ≥160 mm Hg groups included different percentages of persons with diabetes (27.3%, 18.7% and 13.0%, respectively), we performed additional analyses with further adjustment for diabetes.

To assess whether associations found were nonlinear, additional analyses were performed for which the lowest SBP group was grouped into three clinically relevant low BP categories: SBP <120 mm Hg, 120–129 mm Hg, and 130–140 mm Hg. In addition, we evaluated whether J-shaped relationships were present by adding quadratic terms of continuous BP measures to the model.

A *P* value of <.05 was considered statistically significant. Data were analyzed using an exploratory approach, therefore no formal adjustments for multiple comparisons were used. Statistical analysis was performed with SPSS software (version 20.0; SPSS, Chicago, IL).

RESULTS

Table I summarizes the characteristics of the study participants. Mean age was 80.7 (SD 4.1) years; median Mini-Mental State Examination score was 26 (IQR 25–27), reflecting mild cognitive dysfunction; median WMH volume was 22 (IQR 9–56) mL; and lacunar infarcts or

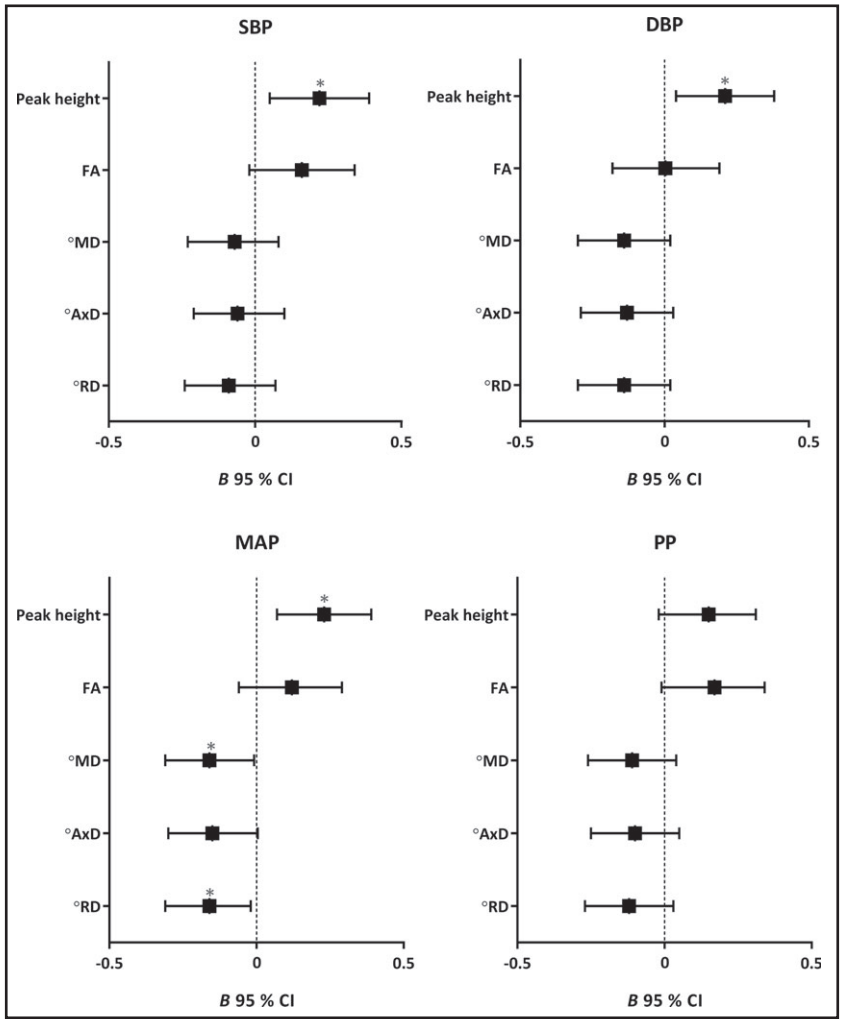

FIGURE 1. β (95% confidence interval [CI]) of the associations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) or pulse pressure (PP) tertiles, with *z* scores of magnetization transfer ratio peak height (peak height), fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD) in gray matter adjusted for age, sex, and duration of antihypertensive treatment. **P*<.05. °Higher diffusivity indicates poorer microstructural integrity.

TABLE I. Characteristics of Participants

Characteristic	(N=220)
Demographics	
Age, y	80.7 (4.1)
Women	125 (56.8)
Lower education (≤6 y)	64 (29.1)
Clinical characteristics	
Current smoking	17 (7.7)
Alcohol ≥14 units per wk	24 (10.9)
History of CVD[a]	20 (9.1)
Presence of chronic diseases[b]	135 (61.4)
MMSE (points)	26 (25–27)
Duration of antihypertensive treatment, y	
<1	5 (2.3)
1–5	57 (25.9)
>5	149 (67.7)
Blood pressure, mm Hg	
Systolic	146 (21)
Diastolic	81 (11)
Mean arterial pressure	102 (13)
Pulse pressure	65 (15)
MRI characteristics	
WMH volume, mL	22 (9–56)
Periventricular WMH	132 (60.0)
Subcortical WMH	113 (51.4)
Lacunar infarcts	59 (26.8)
Microbleeds	55 (25.0)

Abbreviations: MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; WMH, white matter hyperintensity. Data are presented as mean (standard deviation), median (interquartile range), or number (percentage) when appropriate. [a]Cardiovascular disease (CVD) includes myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft. [b]Chronic diseases include diabetes mellitus, Parkinson's disease, chronic obstructive pulmonary disease, malignancy, and osteoarthritis.

microbleeds were present in 59 (27%) and 55 (25%) of participants, respectively.

No significant associations were found between SBP or DBP with volumes of WMH, presence of periventricular or subcortical WMH, lacunar infarcts, or microbleeds. There was also no significant association of MAP or PP with any of these parameters (Table II).

The associations of BP measures with microstructural parameters (MTI and DTI) are shown in Table III. Our data show that both lower SBP and DBP were significantly associated ($P<.05$) with decreased gray MTR peak height. Accordingly, lower MAP was also significantly associated with decreased gray matter MTR peak height ($P=.01$). Moreover, lower MAP was significantly associated with decreased white matter MTR peak height and with increased MD and RD in the gray matter (all $P<.05$). There were no significant associations between PP and any of the parameters of microstructural integrity.

The additional adjustments for diabetes, to explore whether associations could be affected by higher percentage of persons with diabetes in the subgroup having lower SBP, did not alter associations. SBP and DBP were still significantly associated with gray matter MTR peak height (β=2.4, [95% CI, 0.6–4.2] $P=.01$ and $B=2.3$ [95% CI, 0.4–4.2] $P=.02$, respectively). Whereas, MAP was still significantly associated with gray matter MTR peak height, MD, and RD in the gray matter (β=2.5 [95% CI, 0.7–4.3] $P=.01$, β=−10.7 [95% CI, −21.0 to −0.4] $P=.04$, and β=−10.8 [95% CI, −20.8 to −0.9] $P=.03$, respectively) and with white matter MTR peak height (β=3.4 [95% CI, 0.4–6.5] $P=.03$).

Modeling SBP in low BP groups and the analyses performed with quadratic terms of BP measures confirmed a linear relation. The effect size of the low clinical SBP categories and gray matter MTR peak height was β=2.2 (95% CI, −0.6 to 5.0), which was comparable to the associations found in the entire group; however, because of the small numbers in the low SBP groups (<120 mm Hg: n=23; 120–129 mm Hg: n=24; and 130–140 mm Hg: n=42), this association was not statistically significant. Quadratic terms of continuous SBP, DBP, MAP, and PP were all not statistically significant.

Figure 1 shows forest plots of all BP measures and MTR peak height, FA, MD, AxD, and RD in gray matter. The direction of all of the associations is similar and indicates that SBP, DBP, and MAP are significantly associated with lower gray matter MTR peak height and lower MAP with higher MD and RD in the gray matter.

To investigate potential preferential focal associations between BP measures and MTR in cortical gray matter, VBM analysis was performed. Results of these voxel-based analyses are shown in Figure 2, indicating that mainly lower SBP, DBP, and MAP were statistically significantly associated with a decrease of MTR in cortical gray matter with a symmetrical diffuse pattern in both hemispheres, with a slight preference for the frontal lobe. For PP, no cortical areas that demonstrated a significant association with MTR was found.

DISCUSSION

In older persons with mild cognitive impairment using antihypertensive medication, BP measures were not associated with WMHs, lacunar infarcts, or microbleeds. However, significant associations were present for SBP, DBP, and MAP with MTR peak height, mean and/or radial diffusivity, and MTR in cortical gray matter, indicating that lower BP was associated with poorer gray matter microstructural integrity.

In line with our results, results of the Rotterdam Scan Study showed no association of increasing SBP or DBP with increasing WMH in persons older than 74 years, whereas in persons up to 74 years such associations existed.[1,22] Even though data from the Framingham Heart Study showed an association of increasing SBP and DBP with accumulating white matter microstructural damage in healthy young adults,[21] and it has been shown that in middle-aged persons with signs of small vessel disease, a linear relationship between SBP and DBP levels (per 10 mm Hg) and white matter microstructural damage was present.[18] Our data

TABLE II. Parameters of Small Vessel Disease in Groups of Systolic and Diastolic Blood Pressure and Tertiles of Mean Arterial Pressure and Pulse Pressure

	Systolic Blood Pressure, mm Hg					Diastolic Blood Pressure, mm Hg				
Parameters of Small Vessel Disease	<140 (n=88)	140–159 (n=75)	≥160 (n=57)	β/OR (95% CI)	*P* Trend	<80 (n=99)	80–89 (n=78)	≥90 (n=43)	β/OR (95% CI)	*P* Trend
Volume WMH, mL	34.8 (4.1)	38.7 (5.1)	38.1 (37.9)	0.02 (−0.19, 0.24)	.84	33.2 (3.3)	40.4 (5.1)	46.2 (7.1)	0.09 (−0.14, 0.31)	.45
Periventricular WMH, No. (%)	54 (61.4)	45 (60.0)	33 (57.9)	0.93 (0.65, 1.32)	.68	54 (54.5)	51 (61.4)	27 (62.8)	1.34 (0.92, 1.95)	.13
Subcortical WMH, No. (%)	46 (52.3)	38 (50.7)	29 (50.9)	1.04 (0.73, 1.48)	.83	52 (52.2)	39 (50.0)	22 (51.2)	0.98 (0.68, 1.41)	.90
Lacunar infarcts, No. (%)	21 (24.1)	21 (28.0)	17 (29.8)	1.18 (0.79, 1.76)	.41	27 (27.6)	20 (26.6)	12 (27.9)	1.04 (0.69, 1.57)	.86
Microbleeds, No. (%)	19 (22.1)	18 (25.0)	18 (32.1)	1.38 (0.92, 2.08)	.12	20 (20.6)	24 (32.0)	11 (26.2)	1.45 (0.95, 2.21)	.09
Basal, No. (%)	11 (12.8)	12 (16.7)	10 (17.9)	1.34 (0.82, 2.19)	.25	12 (12.4)	13 (17.3)	8 (19.0)	1.61 (0.96, 2.70)	.07
Lobar, No. (%)	14 (16.3)	13 (18.1)	14 (25.0)	1.33 (0.84, 2.10)	.23	15 (15.5)	18 (24.0)	8 (19.0)	1.40 (0.87, 2.27)	.17

	Mean Arterial Pressure, mm Hg					Pulse Pressure, mm Hg				
	<97 (n=73)	97–107 (n=73)	>107 (n=74)	β/OR (95% CI)	*P* Trend	<58 (n=74)	58–69 (n=72)	>69 (n=74)	β/OR (95% CI)	*P* Trend
Volume WMH, mL	32.8 (3.8)	41.0 (5.1)	38.1 (5.1)	0.02 (−0.19, 0.23)	.85	33.5 (4.4)	37.1 (4.9)	40.3 (4.9)	0.06 (−0.15, 0.26)	.59
Periventricular WMH, No. (%)	43 (58.9)	47 (64.4)	42 (56.8)	0.95 (0.46, 1.43)	.78	46 (62.2)	46 (63.9)	40 (54.1)	0.81 (0.58, 1.15)	.81
Subcortical WMH, No. (%)	37 (50.7)	42 (57.5)	34 (45.9)	1.43 (0.67, 1.33)	.74	38 (51.4)	36 (50.0)	39 (52.3)	1.11 (0.79, 1.56)	.53
Lacunar infarcts, No. (%)	18 (25.0)	22 (30.1)	19 (25.7)	1.04 (0.71, 1.52)	.86	18 (24.7)	19 (26.4)	22 (29.7)	1.16 (0.79, 1.71)	.46
Microbleeds, No. (%)	15 (21.1)	18 (25.7)	22 (30.1)	1.40 (0.94, 2.10)	.10	17 (23.9)	19 (27.1)	19 (26.0)	1.03 (0.69, 1.53)	.89
Basal, No. (%)	9 (12.7)	15 (12.9)	9 (20.5)	1.59 (0.97, 2.62)	.07	10 (14.1)	11 (15.7)	12 (16.4)	1.06 (0.68, 1.76)	.71
Lobar, No. (%)	11 (15.5)	13 (18.6)	17 (23.3)	1.39 (0.88, 2.20)	.16	12 (16.9)	14 (20.0)	15 (20.5)	1.05 (0.68, 1.63)	.83

Abbreviation: WMH, white matter hyperintensity. Missing values: n=3 for volume WMH, n=1 for lacunar infarcts, and n=6 for microbleeds. Data are presented as mean (standard error) or number (percentage), and β or odds ratios (ORs) (per increase in blood pressure group or tertile) (95% confidence interval [CI]), adjusted for age, sex, and duration of antihypertensive treatment.

TABLE III. Gray and White Matter Microstructural Parameters in Groups of Systolic and Diastolic Blood Pressure and Tertiles of Mean Arterial Pressure and Pulse Pressure

	Systolic Blood Pressure, mm Hg					Diastolic Blood Pressure, mm Hg				
Microstructural Parameters	<140 (n=88)	140–159 (n=75)	≥160 (n=57)	β (95% CI)	*P* Trend	<80 (n=99)	80–89 (n=78)	≥90 (n=43)	β (95% CI)	*P* Trend
Gray matter										
Peak height	65 (1.1)	66 (1.2)	70 (1.6)	2.4 (0.6, 4.2)	**.01**	65 (1.1)	67 (1.2)	70 (1.70	2.3 (0.4, 4.1)	**.02**
FA	166 (0.9)	170 (1.0)	168 (1.2)	1.4 (−0.2, 2.9)	.08	168 (0.8)	169 (1.1)	168 (1.3)	0.0 (−1.6, 1.6)	.97
MD	1151 (7.7)	1149 (7.5)	1146 (10.9)	−5.1 (−15.8, 5.9)	.35	1156 (7.3)	1155 (7.6)	1122 (11.8)	−9.2 (−20.2, 1.7)	.10
AxD	1339 (8.3)	1341 (8.1)	1335 (11.8)	−4.2 (−15.7, 7.4)	.48	1346 (7.9)	1345 (8.0)	1310 (12.9)	−9.4 (−21.2, 2.4)	.12
RD	1057 (7.5)	1054 (7.3)	1051 (10.5)	−5.6 (−16.0, 4.7)	.28	1061 (7.1)	1059 (7.4)	1028 (11.3)	−9.1 (−19.7, 1.4)	.09
White matter										
Peak height	103 (1.9)	107 (2.0)	109 (2.7)	2.8 (−0.4, 5.9)	.08	104 (1.7)	107 (2.1)	110 (3.0)	2.3 (−0.9, 5.5)	.16
FA	243 (2.0)	248 (2.3)	242 (2.6)	0.4 (−2.9, 3.7)	.83	244 (1.9)	245 (2.4)	244 (2.9)	−1.5 (−4.8, 1.9)	.40
MD	1009 (6.5)	1006 (6.7)	1011 (9.0)	−1.3 (−10.7, 8.1)	.78	1011 (6.4)	1013 (6.9)	994 (9.2)	−1.6 (−11.3, 8.1)	.75
AxD	1243 (6.2)	1245 (6.2)	1245 (8.5)	−0.5 (−9.2, 8.3)	.91	1246 (6.0)	1250 (6.2)	1228 (8.9)	−2.1 (−11.1, 6.8)	.64
RD	893 (6.8)	887 (7.1)	894 (9.4)	−1.7 (−11.7, 8.2)	.73	894 (6.6)	895 (7.3)	877 (9.5)	−1.3 (−11.5, 9.0)	.81

	Mean Arterial Pressure, mm Hg					Pulse Pressure, mm Hg				
	<97 (n=73)	97–107 (n=73)	>107 (n=74)	β (95% CI)	*P* Trend	<58 (n=74)	58–69 (n=72)	>69 (n=74)	β (95% CI)	*P* Trend
Gray matter										
Peak height	64 (1.2)	67 (1.3)	69 (1.3)	2.5 (0.8, 4.2)	**.01**	65 (1.3)	67 (1.2)	67 (1.4)	1.6 (−0.2, 3.3)	.08
FA	167 (1.0)	169 (1.0)	168 (1.1)	1.0 (−0.5, 2.5)	.18	167 (1.0)	169 (1.1)	169 (1.0)	1.4 (−0.0, 2.9)	.06
MD	1159 (8.4)	1150 (8.4)	1139 (8.5)	−10.7 (-20.9, −0.6)	**.04**	1149 (7.9)	1148 (8.7)	1149 (8.7)	−7.8 (−17.9, 2.4)	.13
AxD	1348 (9.0)	1342 (9.1)	1327 (9.2)	−10.7 (−21.7, 0.3)	.06	1338 (8.5)	1339 (9.5)	1339 (9.3)	−7.2 (−18.2, 3.7)	.20
RD	1065 (7.8)	1055 (8.1)	1044 (8.3)	−10.8 (−20.6, −1.0)	**.03**	1155 (7.7)	1153 (8.4)	1154 (8.5)	−8.1 (−17.9, 1.7)	.10
White matter										
Peak height	102 (1.9)	106 (2.3)	109 (2.2)	3.3 (0.3, 6.3)	**.03**	103 (2.3)	107 (1.9)	107 (2.2)	2.3 (−0.7, 5.3)	.13
FA	243 (2.3)	245 (2.1)	245 (2.4)	0.9 (−2.3, 4.0)	.59	242 (2.2)	246 (2.4)	245 (2.2)	2.1 (−1.1, 5.2)	.19
MD	1014 (7.4)	1011 (6.8)	1002 (7.4)	−6.0 (−15.0, 3.0)	.19	1011 (7.1)	1006 (7.2)	1008 (7.3)	−7.3 (−16.2, 1.6)	.11
AxD	1247 (6.9)	1248 (6.5)	1237 (6.9)	−5.1 (−13.4, 3.3)	.24	1246 (6.7)	1242 (6.7)	1244 (6.9)	−6.4 (−14.6, 1.9)	.13
RD	897 (7.8)	893 (7.1)	884 (7.8)	−6.4 (−15.9, 3.1)	.19	894 (7.4)	888 (7.6)	890 (7.6)	−7.8 (−17.2, 1.6)	.10

Abbreviations: AxD, axial diffusivity $mm^2/s \times 10^6$; FA, fractional anisotropy value $\times 10^3$; MD, mean diffusivity $mm^2/s \times 10^6$; peak height, normalized magnetization transfer ratio peak height value $\times 10^3$; RD, radial diffusivity $mm^2/s \times 10^6$. Missing values: n=5 for MTR peak height, n=15 for FA, MD, AxD, and RD. Data are presented as mean (standard error) and β (per increase in blood pressure group or tertile) (95% confidence interval [CI]), adjusted for age, sex, and duration of antihypertensive treatment. Bold values indicate significance.

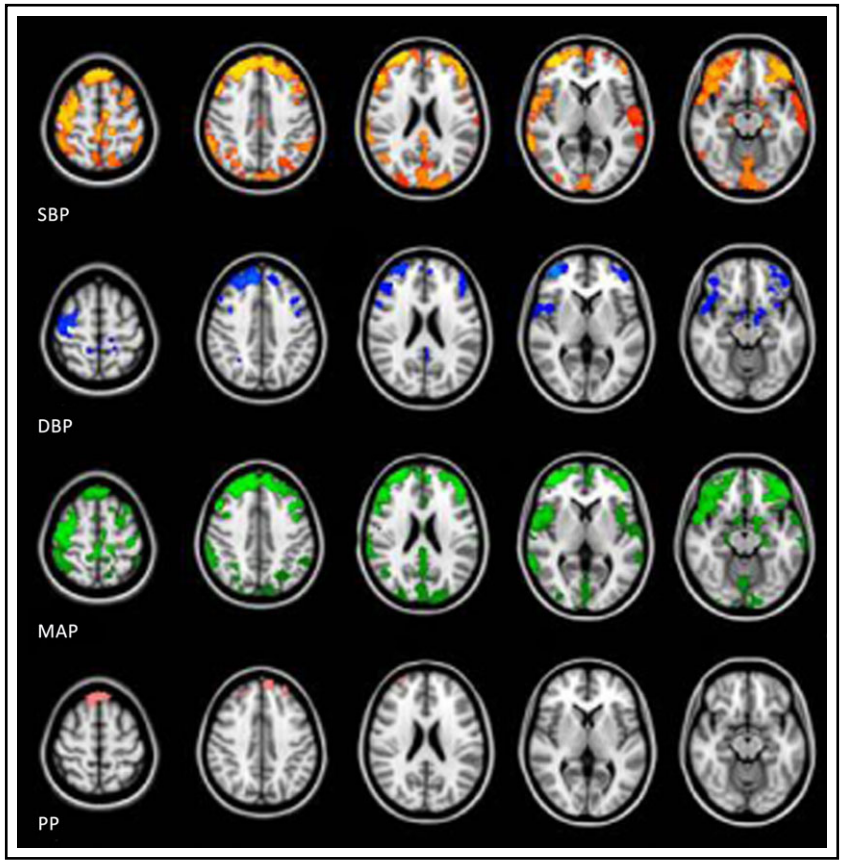

FIGURE 2. Voxel-based analyses of blood pressure measures associated with cortical gray matter magnetization transfer ratio (MTR). Results are projected on the MNI152 standard space image. Areas show statistically significant associations ($P<.05$) of lower blood pressure with a decrease in gray matter MTR (adjusted for age and sex). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

indicate that, besides no associations of BP with manifest vascular white matter damage, more sensitive techniques to pick up ischemic changes, DTI and MTI, did not reveal any association of BP (SBP, DBP, MAP, or PP) with white matter damage.

In contrast, our data show that BP measures were mainly associated with gray matter integrity. Rather than higher BP, lower SBP, DBP, and MAP were all associated with gray matter tissue damage, reflected by the lower MTR peak height values, higher MD and RD in gray matter, and lower MTR in cortical gray matter. No associations were found between BP measures and FA and AxD, as these predominantly represent axonal and myelin integrity in the white matter related to preferred diffusion directionality. The MD and RD parameters are indicators for both white and gray matter microstructure, and it has been suggested that these are higher in damaged gray matter tissue as a result of increased free diffusion.[41–43]

The findings of lower BP with subtle gray matter damage fit the observation of the diminished or even reversed detrimental effect of elevated BP in older persons. It is plausible that in our study population of older persons with hypertension, cerebral autoregulation has become impaired by arteriosclerotic damage in such a way that it no longer compensates for reduced cerebral blood flow. While previous studies have shown that white matter is more sensitive than gray matter for hypoperfusion,[44] our data in a sample of older persons with hypertension show that gray rather than white matter integrity is associated with low BP, indicating that there may be a difference in hemodynamic physiology between gray and white matter. On the other hand, a second explanation for our findings cannot exclude the possibility that lower gray matter microstructural integrity may have been the cause rather than the consequence of low BP and cerebrovascular homeostasis.

STUDY LIMITATIONS

The stringent selection criteria resulted in a group of relatively healthy older people, which limits the generalizability of our findings. In addition, due to the cross-sectional design of our study, no causal inference can be made; therefore, future studies are necessary to elucidate whether low BP precedes gray matter integrity in older persons or vice versa.

CONCLUSIONS

Our data show that in our population of older persons, lower BP is associated with subtle cerebral ischemic changes specifically in the gray matter. These findings imply that in older persons with mild cognitive dysfunction using antihypertensive medication, not only upper thresholds of BP values, but preferably lower thresholds, should be observed.

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