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Stroke. 2010;41:2801-2806; originally published online October 28, 2010;
doi: 10.1161/STROKEAHA.110.597237
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

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Background and Purpose—Hypertension is a risk factor for cerebral small vessel disease, which includes white matter lesions (WML) and lacunar infarcts. These lesions are frequently observed on MRI scans of elderly people and play a role in cognitive decline. Preferably, one would like to evaluate the effect of hypertension before fluid-attenuated inversion recovery visible macrostructural lesions occur, possibly by investigating its effect on the microstructural integrity of the white matter. Diffusion tensor imaging provides measures of structural integrity.

Methods—In 503 patients with small vessel disease, aged between 50 and 85 years, we cross-sectionally studied the relation between blood pressure, hypertension, and hypertension treatment status and diffusion tensor imaging parameters in both normal-appearing white matter (NAWM) and WMLs. All of the subjects underwent 1.5-T MRI and diffusion tensor imaging scanning. Fractional anisotropy and mean diffusivity were calculated in both NAWM and WMLs.

Results—Increased blood pressure and hypertension were significantly related to lower fractional anisotropy in both NAWM and WMLs and to higher mean diffusivity in WMLs. For hypertensives, odds ratios for the risk of impaired microstructural integrity (fractional anisotropy) were 3.1 (95% CI: 1.8 to 5.7) and 2.1 (95% CI: 1.2 to 3.5) in NAWM and WMLs, respectively, compared with normotensives. Fractional anisotropy odds ratios for treated uncontrolled subjects were 6.5 (95% CI: 3.3 to 12.7) and 2.7 (95% CI: 1.5 to 5.1) in NAWM and WMLs, respectively, compared with normotensives.

Conclusions—Our data show that diffusion tensor imaging may be an appropriate tool to monitor the effect of blood pressure and the response to treatment on white matter integrity, probably even before the development of WMLs on fluid-attenuated inversion recovery. **(*Stroke*. 2010;41:2801-2806.)**

Key Words: hypertension ■ blood pressure ■ diffusion tensor imaging ■ cerebral small vessel disease ■ white matter

Cerebral small vessel disease (SVD) is radiologically characterized by the presence of lacunar infarcts and white matter lesions (WMLs).[1] These are common findings on cerebral MRI scans of both participants from population-based studies and cognitively impaired elderly patients.[2] WMLs are presumably caused by vascular risk factors, especially hypertension.[3] They are related to gait disturbances,[4] cognitive decline, and, ultimately, to dementia in some.[5] However, not all individuals with an apparent identical degree of WMLs on conventional imaging experience the same level of cognitive impairment or have the same risk for dementia.[6] One explanation might be that identical-appearing WMLs on conventional fluid-attenuated inversion recovery (FLAIR) differ in underlying pathology. Another is that the normal-appearing white matter (NAWM) on conventional imaging has undergone structural changes, for example, under the influence of the same vascular risk factors known to be related to WMLs that are beyond the detection limit of FLAIR imaging. There is some pathological proof for both of these explanations.[7,8] However, in vivo assessment of the microstructural integrity of the cerebral white matter has only become available recently with the introduction of diffusion tensor imaging (DTI).

DTI provides quantitative information about the structural integrity of the white matter.[9,10] This technique is based on the principle of molecular diffusion of water and provides, among others, 2 parameters, fractional anisotropy (FA) and mean diffusivity (MD). FA reflects the directionality of diffusion, whereas MD reflects the degree of diffusivity. FA decreases and MD increases are typical indications of impaired structural integrity.[11]

Received July 16, 2010; accepted August 11, 2010.

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Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.597237**

Although hypertension is the preeminent risk factor for SVD, little is known of its effect on the microstructural integrity of the white matter. A small study including 30 elderly (range of age: 60 to 70 years) hypertensive subjects without WMLs on conventional MRI showed no significant differences with respect to the FA in several brain structures, apart from the optic radiation, compared with healthy (range of age: 60 to 76 years) controls.[12] Nitkunan et al[13] found an increase in MD and corresponding decrease in FA in both NAWM and white matter hyperintensities in the centrum semiovale, from normotension, through hypertension to symptomatic cerebral SVD in 134 subjects. Recently, Maclullich et al[14] found a positive and significant correlation between systolic blood pressure and MD in 6 regions of interest in NAWM.

Hypertension is an established risk factor for the development of WML. Adequate blood pressure–lowering treatment has been found to be related to a reduced risk of WMLs and their progression in longitudinal studies.[15,16] To date, it is unknown whether similar effects of hypertension treatment on the microstructural integrity of both NAWM and WMLs exist.

We, therefore, hypothesized that blood pressure and hypertension would be negatively related to the microstructural integrity of both NAWM and WMLs and that proper treatment would be positively related to a higher degree of microstructural integrity than those with uncontrolled hypertension, despite blood pressure–lowering treatment. We, therefore, investigated the effect of blood pressure and its treatment status on the microstructural integrity in both NAWM and WMLs among 503 otherwise healthy, independently living elderly subjects with SVD.

Patients and Methods

The Radboud University Nijmegen Diffusion Tensor and MRI Cohort Study was designed to investigate risk factors and cognitive, motor, and mood consequences of brain changes during aging as assessed by (among other techniques) DTI and conventional structural MRI among nondemented elderly with cerebral SVD.

In 2006, consecutive patients from the department of neurology of our hospital who had undergone neuroimaging between October 2002 and November 2006 were selected for possible participation in the study. Inclusion criteria were as follows: (1) age between 50 and 85 years; (2) cerebral SVD on neuroimaging; and (3) acute (n=219) or subacute (n=284) clinical symptoms of SVD. Patients who were eligible because of a lacunar syndrome were included only >6 months after the event to avoid acute effects on the outcomes. Exclusion criteria were as follows: (1) dementia according to the international diagnostic criteria[17–19]; (2) Parkinson(ism) according to the international diagnostic criteria; (3) life expectancy of <6 months; (4) intracranial space occupying lesion; (5) (psychiatric) disease interfering with cognitive testing or follow-up; (6) recent or current use of acetylcholine-esterase inhibitors, neuroleptic agents, L-dopa or dopa-a(nta)gonists; (7) WML mimics (eg, multiple sclerosis and irradiation induced gliosis); (8) prominent visual or hearing impairment; (9) language barrier; and (10) MRI contraindications or known claustrophobia.

From 1004 invited individuals, 727 were eligible and 525 agreed to participate. Complete information, including a cerebral MRI scan, was obtained from 503 individuals, because in 22 individuals exclusion criteria were found during their visit to our research center (14 with unexpected claustrophobia, 1 died before MRI scanning, 1 was diagnosed with multiple sclerosis, in 1 there was a language barrier, 1 subject fulfilled the criteria for Parkinson disease, and 4 met the dementia criteria). The response was 71.3% (503 of 705). These 503 individuals had symptoms of transient ischemic attack or lacunar syndrome (n=219), cognitive disturbances (n=245), motor disturbances (n=97), depressive symptoms (n=100), or a combination thereof. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. All of the participants signed an informed consent form.

Measurement of Blood Pressure

Blood pressure was measured 3 times in the supine position after 5 minutes of rest by an experienced research nurse. The average of these 3 measurements of systolic and diastolic blood pressures was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and/or the use of blood pressure–lowering agents.[20] Information on blood pressure–lowering medication was collected by means of a structured, computerized questionnaire, which was filled in by a resident in neurology.

Other Covariates

Height and weight were measured in light clothing without shoes, and body mass index was calculated as weight divided by height (in meters) squared. Information on smoking behavior (current, former, and never) was obtained through a standardized, structured questionnaire, which was checked during the interview. Diabetes mellitus and hypercholesterolemia were considered to be present if the participant was taking oral glucose–lowering drugs or insulin or lipid-lowering drugs, respectively.

Conventional MRI Scanning Protocol

MRI scanning was performed on a 1.5-T scanner (Siemens Magneton Sonata). The protocol included the following whole brain scans: T1 3D magnetization-prepared rapid acquisition with gradient echo imaging (repetition time [TR]/echo time [TE]/inversion time [TI]: 2250/3.68/850 ms; flip angle: 15°; voxel size: 1.0×1.0×1.0 mm); DTI (TR/TE: 10 100/93 ms; voxel size: 2.5×2.5×2.5 mm; 4 unweighted scans, 30 diffusion-weighted scans with b value 900 s/mm^2); FLAIR pulse sequences (TR/TE/TI: 9000/84/2200 ms; voxel size: 1.0×1.2×6.0 mm [including an interslice gap of 1 mm]; number of excitations=2). The complete scanning protocol took 31 minutes. All of the MRI scans were made on the same scanner.

Conventional MRI Analysis

All of the images were evaluated without previous notice of any clinical parameter. WMLs were considered present in case these were hyperintense on FLAIR MRI and not or only faintly hypointense on T1-weighted image. Gliosis surrounding lacunar and territorial infarctions was not considered as WMLs.[21–23] WMLs were manually segmented on the FLAIR image on a Intuos3 graphics tablet (Wacom Co), by 2 experienced raters, with a high interrater agreement (intraclass correlation coefficient for total volume: 0.99). Total WML volume was calculated as the sum of all of the segmented areas multiplied by slice thickness.

Normalization parameters to the ICBM152 linear template (as provided with SPM5, Wellcome Department of Cognitive Neurology, University College London, London, United Kingdom) and gray and white matter tissue probability maps were computed by using SPM5 unified segmentation routines on the T1 magnetization-prepared rapid acquisition with gradient echo images.[24] Total gray and white matter volumes were calculated by summing all of the voxel volumes that had a $P>0.5$ for belonging to the tissue class. Coregistration parameters of the FLAIR image to the T1 image were computed (SPM5 mutual information coregistration) and used to bring both the FLAIR and WML segmentation images into the subject's (anatomic) reference frame. Transformed images were visually checked for coregistration errors. Subsequently, the WML segmentations were resampled to and combined with the white matter maps to yield to a WML map (the intersection of WML and white matter) and NAWM map (the complement of WMLs in white matter) in the T1 reference space.

DTI Analysis

The diffusion-weighted images of each subject were realigned on the unweighted image using mutual information routines from SPM5. Then, the diffusion tensor[25] and its eigenvalues were computed using an SPM5 add-on (http://sourceforge.net/projects/spmtools). Unphysical spurious negative eigenvalues of the diffusion tensor were set to 0, after which the tensor derivatives of the FA and MD were calculated.[26] The mean unweighted image was used to compute the coregistration parameters to the anatomic reference image (SPM5 mutual information coregistration), which were then applied to all of the diffusion-weighted images and results. All of the images were visually checked for motion artifacts and coregistration errors, which resulted in a final sample of 499 subjects because of the exclusion of 4 excessive motion artifacts.

Regions of Interest

FA and MD measurements were obtained for selected areas in which virtually all of the voxels were in the NAWM, using region of interest (ROI) analyses. Four ROIs were hand drawn unilaterally on axial slices of the Montreal Neurological Institute T1 template by an experienced neurologist (F.-E.d.L.). ROIs were a sphere with a diameter of 10 mm. Two slices, including the anterior horns of the lateral ventricles (frontal), and 2 slices, including the posterior horns (occipital), were chosen for assessment of periventricular and subcortical frontal and parieto-occipital NAWM. For each slice, 2 ROIs were placed in the right hemisphere and subsequently mirrored to the left hemisphere. To minimize partial volume effects, ROIs were positioned at a sufficient distance from the edge of the ventricles and the cortical gray matter. ROIs were then translated onto the corresponding FA and MD maps. FA and MD values within each ROI were averaged.

Statistical Analysis

The relation between blood pressure and WML volume was assessed by multiple regression analysis, adjusted for age, sex, and cardiovascular risk factors, including diabetes mellitus, hypercholesterolemia, smoking behavior, and body mass index. The same was done for the relation between blood pressure and DTI parameters (FA and MD) in both NAWM and WMLs.

The mean difference in FA and MD between hypertensives and those without was assessed by means of ANCOVA, adjusted for age, sex, and cardiovascular risk factors. The same difference was calculated for hypertension treatment status in NAWM and WMLs, as well as in ROIs. Subjects who were normotensive with medication were considered treated controlled, whereas subjects who were still hypertensive despite medication were considered treated uncontrolled. Finally, hypertensive subjects without medication were defined as untreated. Mean WML volume values were calculated for the different patient groups, adjusted for age, sex, and cardiovascular risk factors by means of ANOVA. The association among hypertension, hypertension treatment status, and the risk of impaired microstructural integrity (defined as the lower tertile of the FA distribution and the upper tertile of the MD distribution) of the white matter as the outcome variable was assessed by logistic regression, adjusted for age, sex, and cardiovascular risk factors, with normotensive subjects as the reference group. Statistical analyses were performed using the software package SPSS (version 17.0, SPSS Inc).

Results

Table 1 presents the baseline characteristics of the study population. Of the 499 subjects, 43.5% were women. The mean age was 65.6 years (SD: 8.8 years). The mean systolic blood pressure was 140.7 mm Hg (SD: 20.7 mm Hg), and the mean diastolic blood pressure was 78.1 mm Hg (SD: 9.5 mm Hg). Of all participants, 73.5% had hypertension, of whom 54.3% were taking antihypertensive drugs.

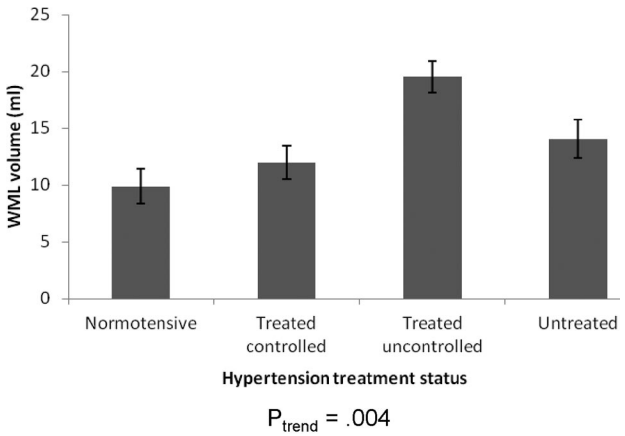
Systolic and diastolic blood pressure levels (per 10-mm Hg increase) were significantly related to WML volume (β=1.68 [95% CI: 0.93 to 2.42; P<0.001] and β=2.6 [95% CI: 1.09 to 4.18; P=0.001]). The Figure presents the relation between hypertension treatment status and WML volume.

Table 1. Characteristics of the Total Study Population

Variable	Data
No. of subjects	499
No. according to age (%)	
50 to 60 y	161 (32.3)
60 to 70 y	161 (32.3)
70 to 85 y	177 (35.4)
Age, y	65.6 (8.8)
Women, n (%)	217 (43.5)
Systolic blood pressure, mm Hg	140.7 (20.7)
Diastolic blood pressure, mm Hg	78.1 (9.5)
Hypertension*	367 (73.5)
Use of antihypertensive drugs, n (%)	271 (54.3)
Diabetes mellitus, n (%)	73 (14.6)
Use of lipid lowering drugs, n (%)	234 (46.9)
Body mass index, kg/m^2	27.1 (4.1)
Smokers, n (%)	
Current	75 (15.0)
Former	275 (55.1)
Never	149 (29.9)
WML volume, mL	7.14 (3.45 to 18.1)
Territorial infarctions, n (%)	59 (11.7)

Data represent mean (SD), median (interquartile range), or n (%).
*Hypertension is indicated by blood pressure ≥140/90 mm Hg and/or use of antihypertensive drugs.

Table 2 shows the relation between blood pressure and DTI parameters in both NAWM and WMLs. An increase in systolic blood pressure (per 10 mm Hg) was significantly related to a decrease of FA in both NAWM (β=−0.19 [95% CI: −0.27 to −0.11]; P<0.001) and WMLs (β=−0.25 [95% CI: −0.39 to −0.12]; P<0.001). The same was true for each 10-mm Hg increase in diastolic blood pressure (β=−0.32



†Values are estimated means (SE), adjusted for age, sex and cardiovascular risk factors.

Figure. Relation between WML volume† and hypertension treatment status.

Table 2. Relation Between Blood Pressure (per 10-mm Hg Increase) and DTI Parameters in Both NAWM and WML

	Blood Pressure			
	Systolic		Diastolic	
DTI Parameters†	β	95% CI	β	95% CI
FA				
NAWM	−0.19**	−0.27 to −0.11	−0.32**	−0.49 to −0.16
WML	−0.25**	−0.39 to −0.12	−0.65**	−0.92 to −0.38
MD				
NAWM	0.02*	0.00 to 0.03	0.01	−0.02 to 0.05
WML	0.04*	0.01 to 0.06	0.06*	0.01 to 0.11

Values represent β (per 10-mm Hg blood pressure increase) and 95% CI. Data were adjusted for age, sex, and cardiovascular risk factors.

*$P<0.05$.

**$P<0.001$.

†Data show FA, fractional anisotropy ($\times 10^{-2}$); MD, mean diffusivity ($mm^2/s \times 10^{-7}$).

[95% CI: −0.49 to −0.16; $P<0.001$] and $\beta=-0.65$ [95% CI: −0.92 to −0.38; $P<0.001$]). A 10-mm Hg increase in both systolic and diastolic blood pressures was significantly related to an increase in MD in WML ($\beta=0.04$ [95% CI: 0.01 to 0.06; $P=0.005$] and $\beta=0.06$ [95% CI: 0.01 to 0.11; $P=0.027$]). In NAWM, this was only found for systolic blood pressure ($\beta=0.02$ [95% CI: 0.00 to 0.03]; $P=0.022$). Normalization of WML by intracranial volume did not alter the magnitude of these relations, nor did these relations change when controlling for WML volume as a possible confounder, in particular, in NAWM analyses. Actual values of FA and MD for NAWM and WMLs are presented in Table 3.

Subjects with hypertension had a significantly lower mean FA in NAWM and WMLs than those without (mean difference: 0.80×10^{-2}, $P<0.001$; 0.91×10^{-2}, $P=0.004$). Hypertensives also had a higher MD in both NAWM and WMLs (mean difference: 0.11 $mm^2/s\times10^{-7}$, $P=0.002$; 0.02 $mm^2/s\times10^{-7}$, $P=0.001$) than normotensives. Treated uncontrolled subjects had a significantly lower mean FA value in both NAWM and WMLs (mean difference: 0.73×10^{-2}, $P=0.001$; 0.78×10^{-2}, $P=0.03$) and a higher mean MD value in NAWM (mean difference: 0.09 $mm^2/s\times10^{-7}$; $P=0.03$) compared with treated controlled subjects. Although treated controlled participants did not differ with respect to their mean FA in WML (mean difference: 0.71×10^{-2}, $P=0.06$) from normotensives, they had a significantly lower mean FA in NAWM (mean difference: -0.70×10^{-2}; $P=0.003$; Table 4). Similar results were found in ROI-based analyses (Table 5).

Individuals with hypertension had an increased risk, as estimated by odds ratios, of impaired microstructural integrity of both NAWM and WMLs (odds ratio: 3.1 [95% CI: 1.8 to 5.7]) and 2.1 [1.2 to 3.5]) compared with normotensives. For treated uncontrolled subjects, the odds ratios for impaired microstructural integrity were 6.5 (95% CI: 3.3 to 12.7) and 2.7 (95% CI: 1.5 to 5.1) in NAWM and WMLs compared with normotensives. Similar relations were found for MD (Table 6). Stratified analyses for both acute and subacute manifestations of SVD did not alter the magnitude of the associations (data not shown).

Table 3. FA and MD Values for NAWM and WMLs by Hypertension Treatment Status

	Hypertension Treatment Status			
DTI Parameters*	Normotensives (n=132)	Treated Controlled (n=120)	Treated Uncontrolled (n=151)	Untreated (n=96)
FA				
NAWM	33.6	32.9	31.8	32.9
WML	34.9	33.9	32.6	33.8
MD				
NAWM	8.7	8.9	9.1	8.8
WML	9.7	10.0	10.3	9.9

*FA indicates fractional anisotropy ($\times 10^{-2}$); MD, mean diffusivity ($mm^2/s\times10^{-7}$).

Table 4. DTI Parameters in NAWM and WML by Treatment Status

		Hypertension Treatment Status		
DTI Parameters§	Hypertension, All†	Treated Controlled (n=120)	Treated Uncontrolled (n=151)	Untreated (n=96)
FA				
NAWM	−0.80**	−0.70*	−1.43**	−0.41
WML	−0.91*	−0.71	−1.50**	−0.66
MD				
NAWM	0.11*	0.12*	0.21**	0.02
WML	0.02*	0.21*	0.33**	0.07

Values are estimated mean differences calculated by ANCOVA, adjusted for age, sex, and cardiovascular risk factors. Normotensives are the reference group.

*$P<0.05$.

**$P<0.001$.

†Hypertension is shown by systolic blood pressure ≥140 mm Hg or systolic blood pressure ≥90 mm Hg and/or use of antihypertensive drugs.

§FA indicates fractional anisotropy ($\times 10^{-2}$); MD, mean diffusivity ($mm^2/s\times10^{-7}$).

Table 5. Fractional Anisotropy in NAWM From ROIs, by Hypertension Treatment Status

		Hypertension Treatment Status		
Fractional Anisotropy, ROI§	Hypertension, All†	Treated Controlled (n=120)	Treated Uncontrolled (n=151)	Untreated (n=96)
Frontal	−0.99	−0.88	−2.00*	−0.32
Frontal periventricular	−1.98*	−1.54*	−3.66**	−1.09
Parieto-occipital	−2.84**	−3.33**	−4.08**	−1.37
Parieto-occipital periventricular	−0.92	−0.58	−2.47*	−0.05

Values are estimated mean differences calculated by ANCOVA, adjusted for age, sex, and cardiovascular risk factors. Normotensives are the reference group.

*$P<0.05$.

**$P<0.001$.

†Hypertension is shown by systolic blood pressure ≥140 mm Hg or systolic blood pressure ≥90 mm Hg and/or use of antihypertensive drugs.

§FA indicates fractional anisotropy ($\times 10^{-2}$).

Table 6. Relation Among Hypertension, Treatment Status, and Severe Microstructural Integrity Changes (OR and 95% CI)

DTI Parameters†	Hypertension, All	Hypertension Treatment Status		
		Treated Controlled (n=120)	Treated Uncontrolled (n=151)	Untreated (n=96)
FA				
NAWM	3.1 (1.8 to 5.7)**	2.8 (1.4 to 5.5)*	6.5 (3.3 to 12.7)**	1.7 (0.8 to 3.5)
WML	2.1 (1.2 to 3.5)*	2.1 (1.1 to 4.0)*	2.7 (1.5 to 5.1)*	1.6 (0.8 to 3.0)
MD				
NAWM	1.9 (1.0 to 3.6)	1.9 (0.9 to 4.2)	4.2 (2.0 to 9.1)**	0.7 (0.3 to 1.7)
WML	2.2 (1.2 to 4.0)*	2.1 (1.0 to 4.3)*	4.0 (2.0 to 8.1)**	1.2 (0.6 to 2.5)

Data are OR (95% CI) adjusted for age, sex, and cardiovascular risk factors. Normotensives are the reference group. FA indicates fractional anisotropy ($\times 10^{-2}$); MD, mean diffusivity ($mm^2/s \times 10^{-7}$).

*$P<0.05$.

**$P<0.001$.

†Values represent the lower tertile of the FA and the upper tertile of the MD severity distribution.

Discussion

We found a linear relation between blood pressure levels and the microstructural integrity of both NAWM and WMLs. In hypertensives, the microstructural integrity of the cerebral white matter was significantly more affected than in normotensives. This is supported by a recent study which showed that high blood pressure was associated with lower FA values in the dorsal anterior cingulate and in multiple frontostriatal and frontotemporal white matter regions in 41 patients (mean age: 70.1 years) with major depression.[27] Our data further suggest that effective treatment of hypertension may reduce the risk of impaired microstructural integrity, although we did not perform an intervention study. These data are consistent with the results from previous longitudinal population-based studies that investigated the role of hypertension and its treatment status on the presence of WML on conventional FLAIR MRI.[15,16,28] More interestingly, we found loss of microstructural integrity in the NAWM as well, which could explain the fact that cognitive performances can differ between individuals with an apparent identical degree of white matter hyperintensities on conventional imaging. This is supported by recent work, in which microstructural integrity of both WMLs and NAWM was associated with cognitive function, regardless of white matter atrophy and WML volume.[29] Microstructural changes in the white matter, not visible on FLAIR, may, therefore, add to cognitive decline.

The underlying neuropathology of impaired microstructural integrity as assessed with DTI is not fully elucidated, but it has been suggested that it is composed of a combination of axonal loss and gliosis, as seen in postmortem studies on SVD.[30] Recently, a quantitative postmortem MRI study on the heterogeneity of white matter hyperintensities in Alzheimer disease showed that, in Alzheimer disease, the degree of axonal density was an independent determinant of FA.[31] More proof for the assumption of impaired microstructural integrity comes from an MRS study that found a relation between *N*-acetylaspartate, a marker for axonal loss/dysfunction, and increase in MD and reduction of FA in symptomatic SVD subjects with white matter hyperintensities.[13] Because hypertension is a strong risk factor for SVD, it is plausible that the hypertension-associated DTI changes found in this study may reflect similar underlying pathology.

To our knowledge, this is the largest study to date that investigated the effect of hypertension on the microstructural integrity of cerebral white matter. Moreover, the association between treatment of hypertension and microstructural integrity of cerebral white matter has never been studied before.

Strong elements of our study include the fact that our study is single center with a high response (71.3%) and the use of standardized, structured assessment of both the risk factor and treatment status, as well as the other covariates. All of the WMLs were manually segmented by 2 experienced researchers, blinded to clinical data, with high interrater agreement. However, some methodological issues need to be considered.

Although blood pressure measurement was based on 3 measurements after 5 minutes of rest, one cannot exclude misclassification. Nonetheless, all of the measurements were done without information on the degree of WML or the structural integrity of the white matter, so we consider it unlikely that this misclassification is related to DTI parameters. Therefore, any possible measurement error is likely to be random and would have biased our findings to the null, leading to an underestimation of the strength of our associations. In our analyses, the relatively less structurally impaired integrity in the untreated group compared with treated controlled and treated uncontrolled subjects seems initially contradictory. One likely explanation for this finding could be that misclassification has occurred in this group. Because classification of "untreated hypertension" was based on 3 single measurements on 1 single day, it could be, at least in some, that their blood pressure was elevated because of a white coat effect. This effect may have led to an overestimation of the proportion of true hypertensive subjects in this group. Consequently, these individuals do not exhibit the accompanying impairment in the white matter's structural integrity, simply because they are not truly hypertensive. Another explanation could be that the duration of hypertension among those participants with hypertension in this untreated group is short and, therefore, without organ failure or symptoms that prompted them to visit a doctor.

In conclusion, DTI may add to our understanding of the very early loss of microstructural integrity of the white matter given our finding of a relation between the level of blood pressure and of the DTI parameters in the NAWM, beyond the limits of visibility on conventional FLAIR imaging. Follow-up studies are needed to study whether areas of reduced microstructural integrity ultimately develop into FLAIR-visible WML. Adequate hypertension treatment was related to a higher degree of microstructural integrity of the cerebral white matter and thereby offers the possibility of postponing or preventing the emergence of FLAIR-visible WML, although this needs to be investigated in prospective intervention studies.

Future studies should not only investigate more in-depth pathophysiological mechanisms of the transition from NAWM to WMLs but also take its cognitive or motor consequences into account. When proven, DTI parameters could play a role as biomarkers for disease progression. Longitudinal studies are needed to assess this potential clinical application of DTI.

Sources of Funding

F.-E.d.L. received a personal fellowship from the Dutch Brain Foundation (H04-12) and a clinical fellowship from The Netherlands Organization for Scientific Research (project No. 40-00703-97-07197).

Disclosures

None.

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