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MR and CT evaluation of cardiovascular risk in metabolic syndrome

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Aortic arch stiffness is associated with incipient brain injury in patients with hypertension

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CHAPTER 5

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ABSTRACT

Background: It has been shown that microstructural brain tissue damage can be detected in hypertension patients, while the underlying mechanisms are not fully understood. We aim to explore the association between diffusion tensor imaging (DTI) measures of brain injury and aortic arch pulse wave velocity (PWV) in hypertensive patients without clinically manifest cerebrovascular disease.

Material and Methods: Sixty-six hypertension patients (30 men, mean age 46 ± 14 years) were prospectively included. Aortic arch PWV was assessed using velocity-encoded MRI. Brain tissue integrity was assessed by using DTI. Multivariable linear regression analysis was performed to assess the association between aortic arch PWV and fractional anisotropy (FA), axial diffusivity (AxD), and radial diffusivity (RD).

Results: Increased aortic arch PWV was associated with decreased white matter FA (β = -0.30, p = 0.018), increased grey matter AxD (β = 0.28, p = 0.016), and increased grey and white matter RD (β = 0.30, p = 0.008 and β = 0.35, p = 0.003, respectively). These effects were independent of age, sex, body mass index, smoking, and white matter hyperintensity volume.

Conclusions: Aortic arch stiffness relates to incipient brain injury before overt brain abnormalities may become apparent in patients with hypertension.

INTRODUCTION

Midlife hypertension is an important risk factor for late-life cognitive decline, mild cognitive impairment, and vascular dementia (1). Recently it has been shown that increased systolic blood pressure is associated with subtle brain injury in young adults (2), while the mechanisms underlying this association are not fully understood. Importantly, it has been shown that these measures of brain injury precede development of overt structural brain abnormalities such as white matter hyperintensities (WMH) (3), which in turn have been associated with cognitive impairment and increased likelihood of incident dementia (4,5). There is a strong association between aortic stiffness and hypertension (6). Aortic stiffness is an independent predictor for cardiovascular disease events (7), and clinical guidelines recommend increased aortic stiffness as a negative factor to be considered in the management of patients with hypertension (8). Increased central arterial stiffness may lead to insufficient flow wave dampening and subsequent transmission of excessive pulsatile energy into the periphery where it may cause organ damage (9). The brain is one of the organs that is particularly sensitive to injury secondary to arterial stiffness because its low-impedance vascular system facilitates penetration of excessive pulsatile energy into the microvascular bed (10). Pulse wave velocity (PWV) is a frequently used surrogate marker of aortic stiffness (8). Velocity-encoded (VE) MRI enables non-invasive assessment of PWV with high reproducibility and it has been well-validated against invasive pressure measurements (11). Notably, VE-MRI allows for assessment of regional PWV, also in the aortic arch (12), whereas ultrasound measurements only provide an estimation of global aortic PWV (8). Increased aortic arch stiffness, which integrates and reflects the long-term effect of all identified as well as currently unknown cardiovascular risk factors, can be detected at a stage when organ damage may be reversible (8). Diffusion tensor imaging (DTI) allows in vivo assessment of microstructural brain tissue integrity beyond the detection limit of conventional structural MRI. Water diffusion in the brain is anisotropic due to restriction of lipid bilayers and other cell components. DTI measures the direction and magnitude of water diffusion and provides several imaging metrics including fractional anisotropy (FA), axial diffusivity (AxD), and radial diffusivity (RD) (13). Reduced FA, which measures the directionality of water diffusion, may be indicative of overall impaired brain tissue integrity. AxD and RD are defined as the magnitude of water diffusion parallel and perpendicular to the tract, respectively, within the voxel of interest, and may be used to differentiate axonal injury versus myelin loss (14). We hypothesize that increased aortic arch stiffness plays a central role in causing early sub-clinical brain injury observed in hypertension patients at midlife. Accordingly, we use advanced MRI to explore the relationship between DTI measures of brain injury and aortic arch PWV in a relatively young cohort of hypertension patients without clinically manifest cerebrovascular disease.

MATERIAL AND METHODS

Patients

This study was approved by the local medical ethics committee and all study participants gave written informed consent. Consecutive patients from the hypertension outpatient clinic in whom there was a diagnosis of essential hypertension were considered for study participation between October 2007 and May 2008. All patients were older than 18 years. Compliance to antihypertensive treatment was verified. Exclusion criteria were diabetes (fasting blood glucose ≥ 7.0 mmol/L or current use of antidiabetic agents), evidence of aortic valve stenosis or insufficiency, cerebrovascular disease including stroke and transient ischemic attack (TIA), and general contraindications to MRI. Of the 66 patients in the present study, 50 patients were previously included in Brandts et al (15) study. All DTI analyses were newly and independently analyzed, and the results were not reported previously. Hypertension was defined as systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg at repeated physical examination before antihypertensive therapy was instituted (8). Resistant hypertension was defined as blood pressure that remained above goal in spite of concurrent use of 3 antihypertensive agents of different classes, one of which should be a diuretic (16). Patients whose blood pressure is controlled with 4 or more medications were also considered to have resistant hypertension (16). Goal blood pressure was less than 140 / 90 mmHg. Duration of hypertension was estimated as the time in years that had passed since the reported age of diagnosis until MRI was performed. Participants continued their routine medications during the study. Blood pressure measurements were performed according to current clinical guidelines (8). Brachial cuff blood pressure was obtained immediately after aortic arch PWV imaging using a semiautomated sphygmomanometer (Dinamap, Critikon, Tampa, Florida) with the study participant remaining in supine position on the MRI-table. All patients were fasting at least 4 hours prior to MRI. Imaging was performed in the early evening in all patients.

MRI Protocol

Aortic arch PWV imaging was performed on a 1.5-T MRI scanner (NT 15 Gyroscan Intera; Philips Medical Systems, Best, the Netherlands) (55 patients) or a 3.0-T MRI scanner (Achieva; Philips Medical Systems) (11 patients) with similar protocols. It has been validated previously that aortic arch PWV assessment is not affected by a difference in MRI field strength (15). All brain imaging was performed on the 3.0-T MRI scanner. Aortic and brain imaging were performed consecutively during one session.

Aortic arch PWV

Aortic arch PWV was determined as previously described (17) (see Supplementary information, Appendix S1, available in American Journal of Hypertension online). For both 1.5-T and 3.0-T MRI a maximal number phases was reconstructed to ensure high temporal resolution (true temporal resolution was 2×TR = 10ms). Velocity sensitivity was set to 150 cm/s. Acquisition time for the aortic arch PWV sequence was 3-4 minutes when measured for a mean heart rate of 65 beats per minute and was acquired during free breathing. Aortic arch velocity maps were analyzed by using in-house-developed software package Flow (figure 1) which has been validated previously (18). Aortic arch PWV was calculated as $\Delta x / \Delta t$ in meters per second. We defined Δx as the distance between sampling locations in the ascending and proximal descending aorta. This was manually measured along the centreline in the oblique sagittal view of the aortic arch by using in-house-developed software package MASS which has been validated previously (figure 1) (18). Next, Δt was defined as the transit time between the arrival of the pulse wave at the ascending and the proximal descending aorta, respectively (19). Manual contour drawing in the aorta velocity maps was performed by one researcher (A.A., 3 years of experience in cardiac MRI) under the supervision of a senior researcher (J.J.M.W., 13 years of experience in cardiac MRI).

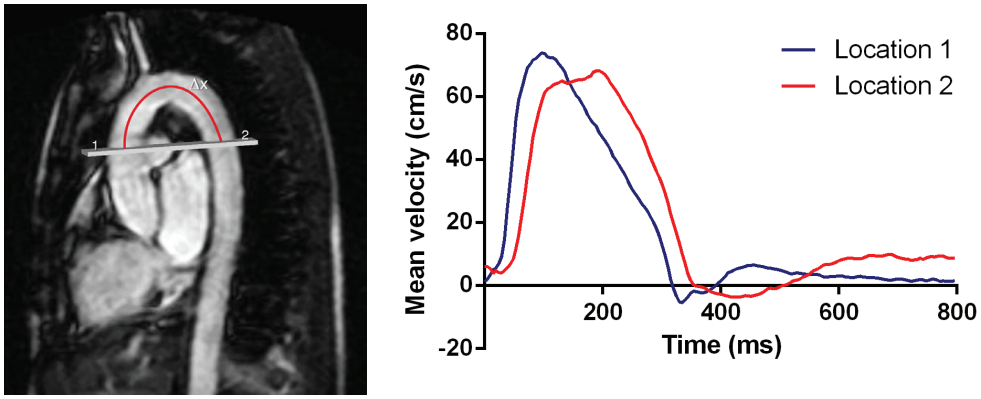

Figure 1. Aortic arch pulse wave velocity assessment
Left: The gray line represents the acquisition plane for velocity-encoded MRI which is positioned perpendicular to the ascending aorta (1) and additionally transects the proximal descending aorta (2).
Right: Pulse wave velocity (PWV) is determined from velocity-time curves recorded at locations 1 and 2.

Brain imaging

For evaluation of brain volumes 3D T1 images were obtained (see Supplementary information, Appendix S2, available in American Journal of Hypertension online). SIENAX software package was used to automatically segment brain from non-brain matter and to calculated

white and grey matter volume (20). A normalization factor was applied to correct for skull size (20). All SIENAX analyses were performed using FMRIB Software Library (FSL) version 2.6. For evaluation of WMH, spin-echo T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences were acquired (15). WMH volume in milliliters was automatically quantified by using a adapted version of a previously validated method (21).

For DTI, a single-shot echo-planar sequence was applied with 15 measurement directions (See Appendix S2). Individual raw diffusion tensor images were preprocessed to create individual fractional anisotropy (FA), axial diffusivity (AxD), and radial diffusivity (RD) images using FDT (FMRIB's Diffusion Toolbox) tools. A diffusion tensor model was fitted to the eddy current corrected images to create individual FA, AxD and RD images. 3D T1-weighted images were skull-stripped using BET and subsequently segmented using FAST (FMRIB's automated segmentation tool) resulting in individual brain masks for white matter and grey matter. Segmented brain structures were aligned into common space using the linear registration tool FLIRT in FSL. Mean FA, AxD and RD values were calculated separately for grey and white matter. Figure 2 demonstrates representative examples of diffusion tensor and FLAIR images in the same study participant.

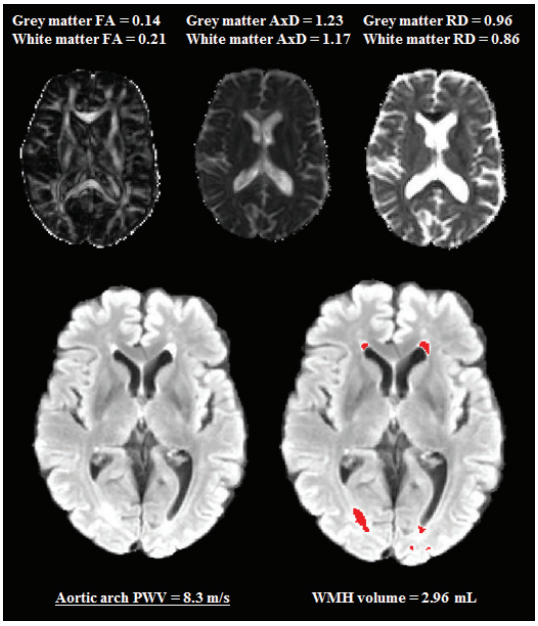

Figure 2. A 65-year-old female with hypertension
Upper panel shows study participant's axial fractional anisotropy (FA, left), axial diffusivity (AxD, middle), and radial diffusivity (RD, right) images. Values of AxD and RD are × 10^{-3} in mm^2/s. Lower panel shows white matter hyperintensities (WMH) in the same study participant on axial T2-weighted FLAIR image (left) and labeled with an intensity threshold (right). PWV: pulse wave velocity.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation unless stated otherwise. Categorical variables are presented as frequencies and percentages. Sex was dummy coded (men = 1 and women = 2). Aortic arch PWV and WMH volume data were non-normally distributed and therefore were log-transformed for analyses. To investigate the association between aortic arch PWV and grey and white matter volume and WMH volume, linear regression analyses were performed, adjusting for age, sex, BMI, and smoking. The correlation between aortic arch PWV and brain DTI measures was tested by Pearson correlation analysis. To explore the association between aortic arch PWV and brain DTI measures, multivariable linear regression analyses were performed adjusting for age, sex, BMI, and smoking. These covariates were entered simultaneously into a multivariable linear regression model. Analyses were repeated after additionally adjusting for duration of hypertension, WMH volume, and systolic and diastolic blood pressure. Finally, analyses were repeated after additionally adjusting for use of specific type of antihypertensive medication (diuretics, beta-blockers, ace-inhibitors, calcium antagonists, and angiotensin II receptor antagonists). Standardized β-coefficients and P-values are reported. Statistical analyses were performed with SPSS version 22. P-values < 0.05 were considered significant.

RESULTS

Clinical characteristics

Nine patients with diabetes (type 1, n = 1; type 2; n = 8) and 9 patients with cerebrovascular disease (stroke, n = 6; TIA, n = 3) were excluded. In total, 66 patients were prospectively included. Mean age was 46 years (range 19 – 72 years) as shown in table 1. There were 30 men (mean age 47 years, range 19 – 72 years) and 36 women (mean age 45 years, range 19 – 71 years). There were 11 patients with resistant hypertension (mean age 52 years, n = 6 males and n = 5 females).

Correlation between aortic arch PWV and brain MRI measures

Table 2 shows a summary of all brain MRI measures. There was no association between aortic arch PWV and brain volume (grey matter β = -0.19, p = 0.067; white matter β = -0.19, p = 0.149) or log WMH volume (β = 0.09, p = 0.494). Pearson correlation analyses showed that log aortic arch PWV was significantly associated with white matter FA (r = - 0.46, p < 0.001), AxD (r = 0.34, p = 0.006), and RD (r = 0.49, p < 0.001) and grey matter AxD (r = 0.41, p = 0.001) and RD (r = 0.47, p < 0.001) (figure 3).

Table 1. Clinical characteristics of patients with hypertension (n = 66)

Age in years	46 ± 14
Male, n (%)	30 (45%)
Height in cm	174 ± 11
BMI in kg/m^2	25 ± 4
Current smoker, n (%)	13 (20%)
Systolic blood pressure, mmHg	150 ± 22
Diastolic blood pressure, mmHg	90 ± 12
Mean arterial pressure, mmHg	109 ± 13
Duration of hypertension in years	5 ± 6
Resistant hypertension, n (%)	11 (17%)
Polytherapy, n (%)	33 (50%)
Diuretics, n (%)	22 (33%)
Beta-blockers, n (%)	20 (30%)
Ace-inhibitors, n (%)	21 (32%)
Calcium antagonists, n (%)	23 (35%)
Angiotensin II receptor antagonists, n (%)	17 (26%)
Aortic arch PWV in m/s	6.9 ± 2.4

BMI: body mass index. Polytherapy: use of > 1 antihypertensive drug or single-pill antihypertensive combinations. PWV: pulse wave velocity.

Table 2. Brain MRI measures

Brain volumes in cm^3	
White matter	567 ± 62
White matter, normalized	732 ± 45
Grey matter	583 ± 60
Grey matter, normalized	755 ± 62
Whole brain atrophy in %	20 ± 5
WMH volume in mL	5.37 ± 4.5
WMH volume, % of total brain volume	0.36 ± 0.30
WMH volume, % of white matter volume	0.73 ± 0.60
FA	
White matter	0.22 ± 0.01
Grey matter	0.15 ± 0.01
AxD, $\times 10^{-3}$, mm^2/s	
White matter	1.10 ± 0.05
Grey matter	1.12 ± 0.08
RD, $\times 10^{-3}$, mm^2/s	
White matter	0.79 ± 0.05
Grey matter	0.86 ± 0.07

Values are mean ± standard deviation. WMH: white matter hyperintensity. FA: fractional anisotropy; AxD: axial diffusivity; RD: radial diffusivity.

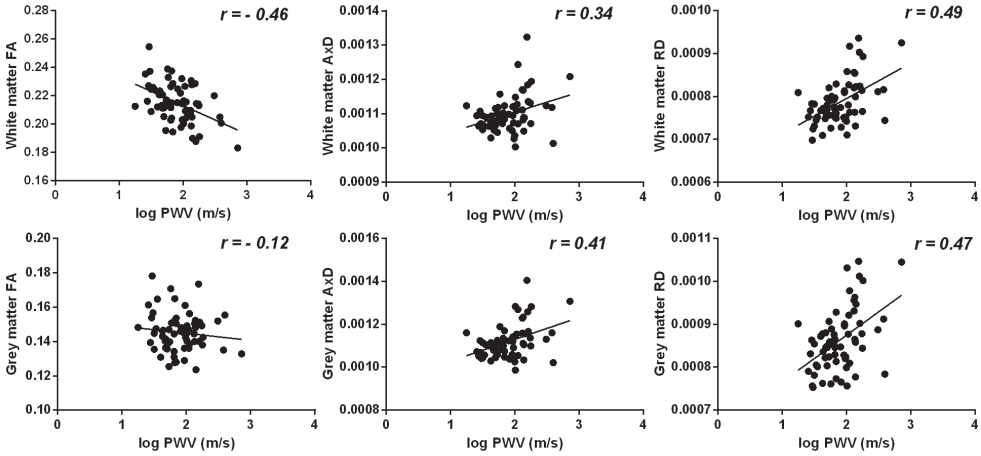

Figure 3. Correlations between aortic arch pulse wave velocity and brain diffusion tensor imaging measures
Pearson correlation coefficients (r) are shown. PWV: pulse wave velocity; FA: fractional anisotropy; AxD: axial diffusivity; RD: radial diffusivity.

Multivariable regression analyses

Results from multivariable regression analysis are shown in table 3 and 4. Increasing age was associated with decreased grey and white matter FA (β = -0.34, p = 0.019 and β = -0.35, p = 0.007, respectively), increased grey matter AxD (β = 0.32, p = 0.009), and increased grey and white matter RD (β = 0.40, p = 0.001 and β = 0.34, p = 0.004, respectively). Male gender was associated with increased grey matter AxD (β = -0.29, p = 0.007) and RD (β = -0.22, p = 0.028). Increasing aortic arch PWV was associated with decreased white matter FA (β = -0.30, p = 0.015), increased grey matter AxD (β = 0.28, p = 0.015), and increased grey and white matter RD (β = 0.30, p = 0.007 and β = 0.35, p = 0.003, respectively). These associations were independent of age, sex, BMI, and smoking. After further adjusting for duration of hypertension, WMH volume, and blood pressure, association between aortic arch PWV and white matter FA (β = -0.30, p = 0.017), grey matter AxD (β = 0.29, p = 0.016), and grey and white matter RD (β = 0.31, p = 0.008 and β = 0.35, p = 0.004, respectively) remained significant. Results did not change materially after further controlling for use of specific type of antihypertensive medication (diuretics, beta-blockers, ace-inhibitors, calcium antagonists, and angiotensin II receptor antagonists).

Table 3. Results from multivariable linear regression analysis to assesses independent predictors of white matter microstructure

	WM FA		WM AxD		WM RD	
	β	P-value	β	P-value	β	P-value
Age	-0.35	0.007	0.22	0.093	0.34	0.004
Sex	0.02	0.860	-0.22	0.051	-0.17	0.085
BMI	0.001	0.996	0.23	0.052	0.17	0.108
Smoking	-0.01	0.928	-0.11	0.353	-0.09	0.395
Log aortic arch PWV	-0.30	0.015	0.24	0.053	0.35	0.003

Standardized β-coefficient and corresponding P-values are shown. BMI: body mass index; PWV: pulse wave velocity. WM: white matter; FA: fractional anisotropy; AxD: axial diffusivity; RD: radial diffusivity.

Table 4. Results from multivariable linear regression analysis to assesses independent predictors of grey matter microstructure

	GM FA		GM AxD		GM RD	
	β	P-value	β	P-value	β	P-value
Age	-0.34	0.019	0.32	0.009	0.40	0.001
Sex	-0.19	0.137	-0.29	0.007	-0.22	0.028
BMI	0.10	0.427	0.18	0.090	0.13	0.222
Smoking	-0.002	0.984	-0.13	0.212	-0.13	0.206
Log aortic arch PWV	0.03	0.809	0.28	0.015	0.30	0.007

Standardized β-coefficient and corresponding P-values are shown. BMI: body mass index; PWV: pulse wave velocity. GM: grey matter; FA: fractional anisotropy; AxD: axial diffusivity; RD: radial diffusivity.

DISCUSSION

The main finding of our study is that increased aortic arch stiffness is associated with incipient brain injury in middle aged hypertensive patients without clinically manifest cerebrovascular disease.

There is an abundant literature showing a relationship between large artery stiffness, brain abnormalities (15,21-25) and cognitive decline (9,26,27). Most of these studies have used pulse pressure or carotid-femoral PWV to estimate global aortic stiffness and conventional structural MRI to assess overt brain abnormalities. Our study extends previous research by evaluating aortic PWV, determined regionally in the aortic arch, and DTI measures of brain tissue integrity in

hypertension patients by using one comprehensive imaging protocol. While previous DTI studies have shown microstructural brain decline in patients with hypertension (2,28,29), the mechanisms underlying these brain changes are not fully understood. Our study findings add to the literature by showing that aortic arch stiffening relates to microstructural brain injury in hypertension patients at midlife.

Our data show that aortic arch PWV is associated with incipient brain injury, independent of several potential confounders. Our findings are in line with two recent studies showing an association between global aortic PWV and DTI measures of brain tissue integrity in older adults (30) and type 1 diabetes patients (31). Important in our analyses was to incorporate age as a covariate, as hypertension and aortic stiffness are closely associated with age (6), and DTI measures are dependent on age as well (32). In addition, while it has been shown previously that reduced brain tissue integrity may be largely explained by WMHs (33), we found that the association between aortic arch PWV and brain injury could not be accounted for by WMH volume. It can be speculated that aortic arch stiffness is involved in the pathogenesis of WMHs (23), as it has been shown that changes in normal-appearing white matter detected by DTI precede development of WMHs (3).

While previous studies found aortic stiffness to be related with WMHs (9,21,25), our data do not shown such an association. Our relatively small sample size may have limited the ability to confirm this association. In addition, the relatively short duration of hypertension could account for our study findings. On the other hand, WMHs may be the final stage of broadly distributed and progressive white matter degeneration (34). It is conceivable that this process of white matter degeneration is not sufficiently advanced in our relatively young non-diabetic cohort.

DTI is sensitive to the intrinsic properties of water diffusion in brain tissue. Previous findings from a mouse model of retinal ischemia demonstrate differential changes in DTI measures, where axonal damage was associated with decreased AxD, while an increase in RD was more related to demyelination in the white matter (14). These data suggest that AxD and RD may be used to differentiate axonal injury versus myelin loss. Our finding that increased aortic arch PWV was associated with decreased FA and increased RD in the white matter suggests impaired brain tissue integrity which may be due to break down of myelin (13,14). However, it should be noted that interpretation of variation in specific diffusivity measures is still under debate. For example, where increased AxD is frequently presented as an indicator of brain tissue integrity, one previous study showed that greater water diffusivity along the axon was associated with clinically relevant deterioration of cognitive function in cognitively normal elderly individuals (35).

The following biological mechanism may be involved in the brain abnormalities observed in our study. White matter may be more susceptible to pressure fluctuations than grey matter because of the vulnerable small vessels penetrating the white matter. It has been proposed that vascular

dysautoregulation due to arterial remodeling causes transient reductions in blood flow to white matter watershed areas of vascular supply, which in turn results in hypoxemia and subtle myelin damage (36). However, the aforementioned biological mechanism explains neither the diffuse grey matter atrophy that has been observed previously (37) nor our finding that aortic arch PWV was also associated with increased AxD and RD in the grey matter. Our data suggest that increased aortic arch stiffness may affect grey matter microstructure as well, but the underlying mechanism remains to be elucidated. It might be the case that there is a close spatial association between atrophy and increases in water diffusivity (38), and increased diffusivity in the remaining brain tissue may be due to reduced cellular density and aberrant cellular organization.

Data from the following studies may also explain the association between aortic arch PWV and DTI measures of brain injury observed in our study. One recent study showed that substantial diastolic flow reversal exists in the descending thoracic aorta, and this aortic flow reversal is primarily determined by aortic stiffness (39). Aortic reverse flow contributes to carotid diastolic antegrade flow, and it has been suggested that exaggerated flow reversal may predispose hypertension patients with aortic atherosclerosis to ischemic stroke through retrograde plaque embolism (39). Another recent study investigated the association between several central hemodynamic measures including aortic reservoir characteristics and structural brain changes (40). This study showed that the excess pressure component from central aortic pressure wave form analysis, representing excess left ventricular work required for stroke volume ejection, was related to brain matter atrophy in healthy individuals. One interpretation of these findings is that greater pressure and/or flow transmission from the aorta to the cerebral circulation may cause end-organ damage (40).

In young, healthy adults, wave reflection at the interface between the normally compliant aorta and relatively stiff first-generation arteries represents a protective mechanism that limits transmission of excessive pulsatility into the periphery (10). However, previous studies suggest that there is a disproportionate increase in aortic arch stiffness but little change in carotid artery stiffness with advancing age and in the presence of vascular risk factors (9). Disproportionate stiffening of the aortic arch with little change in carotid artery stiffness reduces wave reflection at this important interface and may thereby facilitate transmission of excessive pulsatile energy into the cerebral microcirculation (9). In contrast to previous studies that almost exclusively assessed global estimates of aortic stiffness, we used VE-MRI which enabled us to assess PWV regionally in the aortic arch. Increased aortic arch stiffness integrates and reflects the long-term effect of all identified as well as currently unknown cardiovascular risk factors (8). It is likely that stiffening of the aortic arch is of particular importance with regards to previously reported associations between global aortic stiffness and brain abnormalities (15,21-25).

Strengths of this study are use of an advanced MRI protocol for combined assessment of aortic arch stiffness and brain structure. We included a relatively young cohort of hypertension patients without cerebrovascular disease patients which enabled us to investigate the association between aortic arch stiffness and subtle brain injury before more overt brain abnormalities may become apparent. Our study has some limitations. It involves a cross-sectional design with a relatively small sample size. Due to the observational nature of our study it is not possible to infer causality. Longitudinal studies are needed to further elucidated associations between aortic arch stiffness and evolution of subtle brain injury. Furthermore, future studies should focus on aortic arch stiffness as a potential treatment target.

In conclusion, increased aortic arch stiffness is associated with incipient brain injury in middle aged hypertensive patients without clinically manifest cerebrovascular disease.

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