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Pulsatile and steady components of blood pressure and subclinical cerebrovascular disease: the Northern Manhattan Study

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Abstract

OBJECTIVES—To assess whether pulse pressure (PP) is associated, independently of mean arterial pressure (MAP), with perivascular spaces (PVS), lacunar lesions presumably ischemic (LPI), and white matter hyperintensity volume (WMHV) seen on brain MRI.

METHODS—Participants in the Northern Manhattan Study had their blood pressure (BP) taken during their baseline enrollment visit and again during a visit for a brain MRI a mean of 7 years later. We assessed small and large PVS, lacunar LPI, and WMHV on MRI. We examined the association of systolic (SBP), diastolic (DBP), MAP, and PP at baseline with subclinical markers of cerebrovascular disease using generalized linear models and adjusting for vascular risk factors.

RESULTS—Imaging and BP data were available for 1009 participants (mean age 68 ± 8 years, 60% women, 60% Hispanic). DBP was associated with lacunar LPI and WMHV, while SBP was associated with small and large PVS. Using MAP and PP together disclosed that the effect size for PP was greater for large PVS while the effect of MAP was greater for lacunar LPI and WMHV. The effects of DBP were flat or negative at any degree of SBP > 120 mm Hg for small and large PVS, while a positive association was noted for lacunar LPI and WMHV with any DBP increase over any degree of SBP.

CONCLUSIONS—We report here a segregated association between the pulsatile and steady components of the BP with subclinical markers of cerebrovascular disease. These differential associations may reflect the underlying pathology of these biomarkers.

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Keywords

pulse pressure; perivascular spaces; lacunar infarcts; white matter disease; hypertension

INTRODUCTION

The anatomical integrity of the brain parenchyma is routinely assessed to gauge brain health. With the advent of brain imaging, particularly MRI, macroscopic changes in the brain parenchyma are easily observed and are an area of research interest. Perivascular spaces (PVS), which can be small or large, have been described for more than a century, but their pathological significance has not been settled.[1, 2] It is believed that PVS isolate the vessel from the CSF compartment and are involved in the trafficking of inflammatory cells to and from the brain, as well as drainage of interstitial fluid to the systemic circulation through the lymphatic system.[3] Small and large PVS can be mistaken for lacunar infarcts, which are largely known to be associated with vascular risk factors and other clinical markers of disease such as impaired cognition.[4] Among patients with brain infarcts, white matter hyperintensities (WMH) are common and their prevalence can vary from 7% among those with first-time stroke up to 90 % among those with stroke and other markers of small artery disease. [2, 5] Pathological evidence suggests that these four markers of brain parenchymal health are related to small artery disease.[6–8]

Hypertension has been associated with small and large PVS, lacunar infarcts and WMH.[9, 10] It is believed that the exposure to chronic hypertension damages the small arteries leading to the development of lypohyalinosis, fibrinoid necrosis and loss of vascular integrity.[8, 11, 12] There is substantial evidence that PP is an important predictor of coronary events and overall ischemic stroke, but it is less well known if there is a role for PP in predicting the presence of subclinical cerebrovascular disease attributable to small arterial disease independent of the risk information carried by more classic blood pressure parameters. [13, 14] Pulse pressure encompasses a low or normal diastolic blood pressure (DBP) with a high systolic blood pressure (SBP). As the coronary arteries are perfused during diastole, a lower DBP may compromise the coronary filling, even further among those with pre-existing coronary artery stenoses.[15] Contrary to what is described in coronary arteries, the cerebral blood flow in normotensive individuals is influenced more by the systolic BP than the diastolic BP.[16]

We therefore hypothesized that PP and SBP are associated with subclinical biomarkers of cerebrovascular disease to a greater extent than DBP. We also tested the hypothesis that PP is associated with subclinical biomarkers of cerebrovascular disease, and that this association is independent of that conveyed by other BP measures or clinically-defined hypertension.

METHODS

The Northern Manhattan Study is an observational, prospective, population-based cohort of stroke-free participants. Participants were enrolled from the Northern Manhattan neighborhood between 1993 and 2001 using random digit dialing, resulting in an overall response rate of 68% as previously described.[17] Between 2003 and 2008, all surviving

participants remaining stroke-free were invited to participate in an MRI Substudy. Participants were eligible for the MRI substudy if >50 years of age and without contraindication to MRI. All participants signed written informed consent and the study was approved by the IRBs at Columbia University and the University of Miami. Sociodemographic and clinical data were recorded at baseline and during follow up as reported elsewhere. [17, 18] Diabetes was defined by self-report, use of glucose-lowering medications, or a fasting glucose ≥ 126 mg/dl. Hypercholesterolemia was defined by self-reported history of high cholesterol, use of cholesterol-lowering medications, or laboratory evidence of a total cholesterol ≥ 200 mg/dl. Current smoking data was obtained by self-report.

Blood pressure measurements

BP measurements were taken twice (> one hour apart) at both the baseline and MRI visits using a pocket aneroid sphygmomanometer. The first manual measurement occurred within the first hour of arrival to the Neurological Institute at Columbia University at each visit and the second BP measurement occurred the same day, at least an hour apart and after 10 minutes of rest preceding each measurement. Hypertension was defined as average within visit systolic (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 , or self-reported history of hypertension or antihypertensive use. All participants were followed annually by telephone and newly diagnosed hypertension or initiation of antihypertensive medications was ascertained. Normotension was defined as a SBP < 140 and DBP < 90 mm Hg at the time of the study visit, as well as well-controlled hypertension among those on antihypertensives. Pulse pressure was calculated by subtracting average DBP from average SBP separately for the baseline visit and for the MRI visit. Mean arterial pressure was calculated with the formula:

$$\text{MAP} = [(2 \times \text{DBP}) + \text{SBP}] / 3.$$

Pulse pressure, SBP, DBP and MAP were standardized due to expected small effect size per mmHg.

Brain MRI acquisition and outcome definitions

Imaging was performed on a dedicated 1.5-T research MRI system (Philips Medical Systems) at the Columbia University Medical Center using a standardized protocol as described before.[19] The MRI sequences used in this study were Fluid Attenuated Inversion Recovery (FLAIR), axial T1, proton density and MRA. All T1 axial sequences were analyzed systematically. First, we rated small voids (i.e. parenchymal hypodensities) of < 5 mm in axial diameter without associated FLAIR hyperintensities as small PVS with a semi-quantitative score reported to have good-to-excellent reliability. [19] Parenchymal voids observed in 3D T1 and FLAIR sequences with a diameter of > 5 mm were individually characterized to obtain their FLAIR appearance, anatomical location and volume. Using a cutoff of 5 mm in axial images yielded a minimum effective diameter of 3 mm typically used to differentiate small from large perivascular spaces or infarcts.[9, 20] To enhance the ability of brain imaging to differentiate large PVS from what we define as lacunar lesions

presumably ischemic (LPI), we created *post-hoc* criteria to classify each lesion seen on MRI using characteristics determined by imaging-pathological correlational studies in other cohorts. A more detailed description can be found in the supplementary data.

A 10% random sample of participants with large voids was used to determine intra- and inter-rater reliabilities. The leading author (JG) rated all the MRI scans and trained a research assistant to apply the same readings. Of the voids seen in the first evaluation, 82 % were identified again by the same reader and 67% were identified by the second reader. In the concordant voids, the intra-reader reliability was good (ICC=0.76) for the void diameters, excellent for complete FLAIR rim and presence of WMH ($\kappa=1.0$ for both), and agreement was moderate-to-good for an absent FLAIR rim ($\kappa=0.60$), ovoid ($\kappa=0.59$) or round shape ($\kappa=0.79$). The inter-reader agreement was good for small PVS score (ICC=0.73), excellent for void diameters (ICC=0.90), and moderate for a thick FLAIR rim ($\kappa=0.60$).

White matter hyperintensity volumes (WMHV) were determined in FLAIR images using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. Briefly, WMHV was obtained by the quantification of pixels with intensity 3.5 SDs above the mean of the fitted distribution of brain parenchyma as reported before.[21, 22] To account for head size, WMHV was calculated as a proportion of total cranial volume and transformed into log WMHV to render it normally distributed.

Statistical analysis

We restricted this analysis to participants with BP measurements from both visits and MRI data. Statistical models were created to assess for an association between each dependent measure (subclinical biomarkers of cerebrovascular disease) and the independent variables (SBP, DBP, MAP and PP). We used generalized linear models with Poisson (for counts of small and large PVS and for lacunar LPI count) and linear (for log WMHV) assumptions according to the observed distribution of the data. We assessed for non-linear associations with residual plots and we confirmed only a pattern suggestive of a linear association between the BP parameters used here and the four studied outcomes (see supplemental data). We assessed the relationship between measures and covariates with a model including age, sex, ethnicity, diabetes, hypercholesterolemia, current smoking, and use of antihypertensives. To address the collinearity among BP parameters, we used baseline SBP, DBP, PP and MAP individually. We also used SBP/DBP and PP/MAP together in the same models based on a relatively low collinearity as revealed by a simple linear regression for SBP/DBP ($R^2=0.34$) and PP/MAP ($R^2=0.23$). We acknowledged the redundancy of models using SBP and DBP over MAP and PP, but we presented both models to facilitate clinical interpretation. We also evaluated if the effects of DBP vary at different levels of SBP. Statistical significance was set at $P \leq 0.05$. Analyses were carried out with IBM SPSS Statistics 21 (Release 21.0.0, IBM 2012).

RESULTS

Of 1,290 participants that underwent brain MRI, 1009 had BP data at two visits; their characteristics are shown in table 1. The MRI visit occurred on average 7 (± 2) years after

baseline. The prevalence of hypertension increased from 68% at baseline to 82% at the time of MRI. However, the mean SBP decreased by 3% compared to a 7% drop in the DBP during follow up. As a result, the mean PP in the sample increased during follow-up. Among participants with hypertension at baseline, 55% reported use of antihypertensives and only 13% of them were well-controlled at enrollment. Conversely, 81% of participants with hypertension reported use of antihypertensives at MRI and 45% were well-controlled.

The small PVS score ranged from 0 to 22 (median=4, Figure 1) and only 10% did not have small PVS. Large PVS were present in 37% of the sample (47% infraputaminar, 39% subinsular, 11% subcortical, and 3% basal ganglia excluding infraputaminar large PVS). Among participants with large PVS, 49% had one, and 51% had two or more large PVS. Lacunes of presumed ischemic origin were present in 17% of participants, half of them with evidence of two or more. The most common location for lacunar LPI was subcortical frontal (38 %) and parietal (15%) lobes, and the caudate head (14%). Wedge-shaped cortical LPI (2%) and cerebellar lesions (2%) were labeled probable embolic infarcts, but were not analyzed here.[12]

Brain parenchymal correlates of blood pressure parameters

Higher SBP, DBP, MAP and PP at baseline were individually associated with greater expressions of the four biomarkers of subclinical cerebrovascular disease, although the magnitude of association varied for each of the measures (Table 2). The effect size of DBP and MAP for lacunar LPI and WMHV were the highest compared to the effects of SBP or PP, while PP had the greatest effect size for large PVS compared with SBP, DBP and MAP. The effects size was similar for the four BP parameters and the small PVS score.

In models including both SBP and DBP, SBP was directly associated with small PVS core ($B=0.033 \pm 0.016$) and large PVS ($B=0.127 \pm 0.052$) and DBP was not. Conversely DBP was associated with lacunar LPI ($B=0.260 \pm 0.075$) and WMHV ($B=0.06 \pm 0.01$), though PP was not (Table 3). In models including both PP and MAP, MAP was associated with lacunar LPI ($B=0.377 \pm 0.031$) and WMHV ($B=0.377 \pm 0.031$) independently of PP, whereas for LPVS, PP ($B=0.090 \pm 0.046$) had a six-time greater effect size than MAP ($B=0.015 \pm 0.045$, Table 3). The effects of increasing DBP over different degrees of SBP confirmed a positive and progressively stronger association of DBP with lacunar LPI count or WMHV at any degree of SBP > 120. The opposite effects of DBP were noted for small and large PVS: as SBP increased, the DBP beta coefficients were negative or evidently less positive than when the SBP was < 120. These effects were similar for men and women, but a statistical interaction was identified between non-white ethnicity and PP for WMHV ($B=0.071$, $P=0.05$), independent of MAP and PP alone (see supplemental data). Further adjustment by length of follow-up or initiation of antihypertensives during follow up had no significant effect on these associations.

Brain parenchymal correlates of longitudinal changes in blood pressure controls

Participants who remained normotensive during follow-up had the lowest expression of subclinical biomarkers of cerebrovascular disease while participants with uncontrolled hypertension at both visits had consistently greater expression of small and large PVS,

lacunar LPI and WMHV (Table 4). Participants with incident hypertension had overall more evidence of subclinical biomarkers of cerebrovascular disease than those without hypertension, but this effect was only significant for large PVS counts. Participants who had hypertension at baseline but were well-controlled at both visits had greater expression of small PVS and WMHV but not of lacunar LPI or large PVS compared to those without hypertension. These results were independent of changes in PP over time, which were not statistically associated with any of the subclinical biomarkers of cerebrovascular disease used in this study.

DISCUSSION

We report here a differential association between peripheral blood-pressure parameters representing steady and pulsatile pressure patterns with distinct parenchymal biomarkers of subclinical cerebrovascular disease. PP and/or SBP, indicators of pulsatile pressure, were associated with the presence of small and large PVS, but not with lacunar LPI and WMHV. DBP and/or MAP, indicators of steady flow, were associated with lacunar LPI and WMHV. The differential association between pulsatility with PVS versus steady BP with lacunar LPI and WMHV suggest a different physiopathology of these imaging biomarkers of cerebrovascular disease and argues against clustering all evidence of subclinical cerebrovascular disease under the same category.

Assessing the effects of DBP on the studied imaging measures at different degrees of SBP demonstrated that among individuals with SBP > 120, the effects of DBP on small and large PVS are minimal or frankly negative. This implies that individuals in whom the SBP rises disproportionately to the DBP (e.g. isolated systolic hypertension) are more likely to have small and large PVS. On the other hand, when both components of the BP rise in a more similar proportion (e.g. mixed hypertension), lacunar LPI and WMHV are the more likely manifestation of subclinical cerebrovascular disease attributable to hypertension. These findings suggest that the “steady component” of the BP is a more important determinant of lacunar LPI and WMHV than its “pulsatile component”, while the opposite applies for small and large PVS. The reported associations were independent of traditional vascular risk factors and antihypertensive use. Furthermore, individuals who remained normotensive during follow up had the lowest expression of subclinical cerebrovascular disease in this sample, and those with incident hypertension during follow-up had lower expression of subclinical cerebrovascular disease compared with those with established hypertension at baseline, suggesting that remaining normotensive may confer the highest protection against the development of subclinical cerebrovascular disease and that the longer a subject has hypertension, the more likely that subclinical cerebrovascular disease will ensue.

The brain is particularly susceptible to end-organ damage due to high pulsatility given its rich vascularization and resultant low-impedance to flow.[23] To better contextualize the results presented here, some biological issues need to be discussed. First, PP rises with age, particularly after 60 years, and it is mainly determined by characteristic impedance (e.g. impedance to pulsatile flow) and cardiac output.[24, 25] With age, cardiac output decreases, leaving characteristic impedance as the major determinant of PP.[24, 26] Characteristic impedance is affected heavily by changes in arterial diameters, particularly the aortic

diameter, to a greater extent compared with other markers of arterial stiffness.[25] As the aorta stiffens, the pulsatility created by the cardiac cycle reaches more distally into smaller branches. As more pulsatile blood flow arrives to the carotid bifurcation, the pulsatility is preferentially transmitted to the internal carotid artery given its lower resistance to flow than the high resistance external carotid artery circulation.[27] As pulsatility reaches the brain parenchyma, chronic exposure to greater hydrostatic pressure as determined by a higher systolic BP facilitates interstitial fluid leakage.[28] Perivascular spaces (also known as Virchow-Robin) are pia-lined extensions of the subarachnoid space surrounding the path of penetrating arteries branching off from large arteries and piercing the brain parenchyma.[29] The function of these spaces might be related to drainage of interstitial fluid back into the circulation.[30] The continued pulsatile barotrauma may trigger inflammation and increase the fluid transit into perivascular spaces.[7] As a result, PVS can enlarge.[31, 32] These proposed mechanisms are consistent with the findings presented here that small and large PVS are associated with a higher SBP and higher PP with minimal contribution for DBP.

The typical pathology of lacunar LPI is consistent with lipohyalinosis (e.g. a disorganized appearance of the wall component of penetrating arteries with lumen reduction), microatheroma, microembolism, or branch occlusive disease.[11] More recent evidence suggests that lacunar LPI may in fact be another phenotypic expression of atherosclerotic disease in the cerebral parent artery more than an exclusive penetrating artery disease.[33, 34] In this same context, WMH has been associated with reduced arteriolar diameters,[35, 36] increased expression of hypoxia-inducible factors by endothelial cells,[37] and fibrosis of the arterioles wall, thus also suggesting small artery disease within the brain.[36] In fact, DBP has consistently been associated with WMHV.[10] Diastolic blood pressure is influenced mostly by the peripheral vascular resistance and sympathetic tone.[38] In this context, it can be postulated that a high DBP may lead to remodeling changes in small arteries and arterioles leading to a compromised lumen and ischemia. An alternative hypothesis includes the possibility that sustained diastolic hypertension may have deleterious effects in cerebral autoregulation thus rendering the brain exposed to fluctuations in systemic hemodynamics.[39] In ethnic minorities, the lack of chronic blood pressure control with perhaps greater stiffness may contribute to the interaction noted here between non-white ethnicity and WMHV.[40]

Other investigators have reported an association between central SBP and silent lacunar infarcts and WMH, independent of more precise measure of arterial stiffness.[41–43] It is uncertain, however, whether the discrepancies noted between these studies and the result presented here may be related to the different methods or populations studied, or whether the concomitant use of DBP or MAP in some of these models would have reproduced the associations reported here. We suggest, based on this discrepancy, that these results should be confirmed in other populations.

The conclusions reached in this study need to be framed in the context of some limitations. For example, the lack of pathological confirmation of the reported MRI findings as well as the relatively low reliability for some imaging measures is a limitation. As a consequence, our proposed classification system for differentiating lacunar LPI versus large PVS remains probabilistic, and thus there is a chance of misclassification. Additionally there is a

significant gap of information pertaining to BP dynamics during the average 7 years of follow-up. However, in studies that have included multiple BP measurements over time, the effects of adding more precision to the measurements of BP strengthen even further its effect size on the measures.[44] Caution is advised in extrapolating these results to other populations with a different ethnic composition.

In summary, small and large PVS are more common among community dwellers with high PP and high SBP, while lacunar LPI and WMH are increased among those in whom MAP and DBP are high, independent of traditional vascular risk factors and of the use of antihypertensives. These differential associations may reflect the underlying pathology associated with these subclinical biomarkers of cerebrovascular disease. Furthermore, participants who remained hypertension-free during follow up had the lowest expression of subclinical cerebrovascular disease while participants with chronically uncontrolled hypertension exhibited its greater expression. We interpret the results as evidence of a special brain susceptibility to hypertension and systemic pulsatility that should be further investigated. As some antihypertensives can differentially target PP and DBP, [25] it would be worthwhile exploring whether the modification of these parameters might limit the brain footprints of systemic arterial hypertension in a more personalized manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Row a demonstrates examples of small perivascular spaces (< 3 mm in effective diameter) in the right subinsular region (a1) and in the subcortical white matter of the frontal lobes (a2) in MRI T1 sequences. Row b has examples of large perivascular spaces (> 3 mm in effective diameter). A large hypodensity can be observed in the left infraputaminar region (b1) without a corresponding hyperintensities in FLAIR (b2), suggesting a perivascular space rather than a lacunar lesions presumably ischemic. Large perivascular spaces can also occur in the subcortical white matter (b3), their largest axis oriented perpendicularly to the lateral ventricles mirroring the radial trajectory of the penetrating medullary arteries in this area. Lacunar lesions presumably ischemic are typically surrounded by thick rim of flair hyperintensities suggestive of perilesional gliosis (c1–3).

Table 1

Demographic and clinical characteristics of the studied sample at baseline and at the time of their brain MRI.

	At baseline visit	At MRI visit
Age (years, $\pm$ SD)	64 $\pm$ 8	72 $\pm$ 8
Female sex (%)	59	
Ethnicity (%)		
Non-Hispanic whites	18	
Non-Hispanic blacks	19	
Hispanics	63	
Hypertension	68	82
Use of antihypertensives	38	66
SBP (mmHg, $\pm$ SD)	140 $\pm$ 19	137 $\pm$ 18
DBP (mmHg, $\pm$ SD)	84 $\pm$ 11	78 $\pm$ 9.7
PP (mmHg, $\pm$ SD)	57 $\pm$ 16	59 $\pm$ 15
MAP (mmHg, $\pm$ SD)	103 $\pm$ 12	98 $\pm$ 11
Diabetes	18	25
Hypercholesterolemia	58	69
Current smoking at baseline visit	17	
Prior cardiac ischemic disease	14	

Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure.

Table 2

Subclinical Biomarkers of Cerebrovascular Disease and blood pressure measurements at baseline used separately in each model

	Small perivascular spaces score	Number of large perivascular spaces	Number of lacunar LPI	Log of WMHV
Per standard deviation	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$
Systolic BP	$0.043 \pm 0.014^{\ddagger}$	$0.092 \pm 0.042^{\ddagger}$	$0.267 \pm 0.061^{\ddagger}$	$0.087 \pm 0.028^{\ddagger}$
Diastolic BP	$0.037 \pm 0.014^{\ddagger}$	0.014 ± 0.041	$0.322 \pm 0.059^{\ddagger}$	$0.136 \pm 0.027^{\ddagger}$
Mean arterial pressure	$0.040 \pm 0.014^{\ddagger}$	0.053 ± 0.041	$0.274 \pm 0.045^{\ddagger}$	$0.339 \pm 0.060^{\ddagger}$
Pulse pressure	$0.036 \pm 0.014^{\ddagger}$	$0.097 \pm 0.043^{\ddagger}$	0.096 ± 0.062	0.096 ± 0.061

‡ P value < 0.05 to 0.001

‡ P value < 0.001

* All models were adjusted for age, sex, ethnicity, diabetes, hypercholesterolemia, current smoking and use of antihypertensives at the time of baseline enrollment.

Abbreviations: SE, standard error; MRI, Magnetic Resonance Imaging; BP, blood pressure, LPI, lesions presumably ischemic.

Table 3

Effects of pulse pressure together with MAP in the association with subclinical biomarkers of cerebrovascular disease

	Small perivascular spaces score	Number of large perivascular spaces	Number of lacunar LPI	Log WMHV
	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$	Coefficient, $\beta \pm SE^*$
Coefficient of DBP and SBP together (Per every 5 mmHg)				
Diastolic BP	0.019 ± 0.016	-0.057 ± 0.050	$0.260 \pm 0.075^{\ddagger}$	$0.128 \pm 0.033^{\ddagger}$
Systolic BP	$0.033 \pm 0.016^{\ddagger}$	$0.127 \pm 0.052^{\ddagger}$	0.110 ± 0.095	0.013 ± 0.034
Coefficient of PP and MAP together				
Pulse pressure	0.022 ± 0.016	0.090 ± 0.046	-0.016 ± 0.092	$-0.075 \pm 0.032^{\ddagger}$
Mean arterial pressure	$0.030 \pm 0.015^{\ddagger}$	0.015 ± 0.045	$0.368 \pm 0.087^{\ddagger}$	$0.377 \pm 0.031^{\ddagger}$
DBP coefficient for degrees of SBP				
DBP in SBP < 120	$0.469 \pm 0.172^{\ddagger}$	-0.022 ± 0.201	-0.270 ± 0.462	-0.203 ± 0.267
DBP in SBP between 120–140	0.059 ± 0.035	-0.119 ± 0.081	$0.412 \pm 0.137^{\ddagger}$	$0.126 \pm 0.067^{\ddagger}$
DBP in SBP > 140	0.011 ± 0.018	-0.016 ± 0.060	$0.223 \pm 0.077^{\ddagger}$	$0.140 \pm 0.037^{\ddagger}$

‡ P value 0.05

‡ P value < 0.001

* All models were adjusted for age, sex, ethnicity, diabetes, hypercholesterolemia, current smoking and use of antihypertensives at the time of baseline enrollment.

Abbreviations: SE, standard error; MRI, Magnetic Resonance Imaging; SBP, systolic blood pressure, DBP, diastolic blood pressure, PP, pulse pressure, LPI, lesions presumably ischemic.

Table 4

Longitudinal changes in blood pressure- parameters and subclinical cerebrovascular disease

	Small perivascular spaces score	Number of large perivascular spaces	Number of lacunar LPI	Log of WMH
	Coefficient, $\beta \pm SE$ *	Coefficient, $\beta \pm SE$ *	Coefficient, $\beta \pm SE$ *	Coefficient, $\beta \pm SE$ *
Normotension	REF	REF	REF	REF
Incident HTN	0.059 ± 0.052	0.246 ± 0.151	-0.155 ± 0.309	0.024 ± 0.095
Controlled HTN in both visits	$0.219 \pm 0.064^{\ddagger}$	0.159 ± 0.200	0.542 ± 0.316	$0.313 \pm 0.124^{\ddagger}$
Uncontrolled HTN in any visit	$0.174 \pm 0.040^{\ddagger}$	$0.363 \pm 0.119^{\ddagger}$	$0.942 \pm 0.210^{\ddagger}$	$0.222 \pm 0.072^{\ddagger}$
Change in PP over time (per 5 mmHg)	-0.026 ± 0.014	-0.002 ± 0.038	-0.029 ± 0.053	-0.003 ± 0.027

 ‡ P value < 0.05 to 0.001 ‡ P value < 0.001

* All models were adjusted for age, sex, ethnicity, diabetes at mri, hypercholesterolemia at mri, current smoking, use of antihypertensives at mri and follow-up time.

Abbreviations: SE, standard error; SBP, systolic blood pressure, DBP, diastolic blood pressure, PP, pulse pressure; LPI, lesions presumably ischemic; HTN, hypertension.