Original Article

Arterial Stiffness is Associated with Intracranial Arterial Stenosis other than Dolichoectasia in the General Population

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Aims: The relationship between central arterial stiffness and aging-related intracranial arteriopathy is not well investigated in the general population. In a population-based study, we investigated arterial stiffness in relation to intracranial atherosclerotic stenosis and intracranial arterial dolichoectasia.

Methods: This study was a cross-sectional analysis on 1,123 subjects (aged 56.0 ± 9.3 years, 37.9% men) of the population-based Shunyi study in China. Arterial stiffness was assessed by measuring brachial-ankle pulse wave velocity (baPWV). Intracranial atherosclerotic stenosis and intracranial arterial dolichoectasia were evaluated *via* brain magnetic resonance angiography. Multivariate regression models were constructed to investigate the association between baPWV and intracranial large artery diseases.

Results: Increased baPWV was significantly associated with higher prevalence of intracranial atherosclerotic stenosis (odds ratio for the highest quartile of baPWV compared with the lowest quartile, 3.66 [95% confidence interval, 1.57–8.54]), after adjustment for cardiovascular risk factors in multivariate analysis. BaPWV was not associated with the presence of basilar artery dolichoectasia and dilation of basilar artery and internal carotid artery. When the diameters of intracranial arteries were regarded as continuous variables, increased baPWV was inversely related to the internal carotid artery diameter in fully adjusted models ($\beta \pm SE$, -0.083 ± 0.042, $p = 0.047$).

Conclusions: This population-based study demonstrates that arterial stiffness was more likely associated with intracranial stenotic arteriopathy other than intracranial dilative arteriopathy.

Key words: Arterial stiffness, Brachial-ankle pulse wave velocity, Intracranial atherosclerotic stenosis, Intracranial arterial dolichoectasia

Introduction

Arterial stiffness is an independent risk factor for stroke and cardiovascular mortality[1, 2]. It is measured by pulse wave velocity and was previously shown to be related to pathological changes at various sites of the vascular tree, from the aorta to the extracranial carotid arteries[3-6]. Central arterial stiffening may lead to insufficient flow wave dampening and subsequent transmission of excessive pulsatile energy into distal microcirculation. As an organ with low vascular resistance to high flow, the brain may be especially susceptible to aberrant pulsatile hemodynamics. Therefore, by theory and with accumulating evidences, arterial stiffness is an emerging risk factor for structural and functional changes in the brain, which contributes to

cerebrovascular diseases, cognitive impairment, and dementia by reducing the mean cerebral blood flow and increasing pulsatile stress[7-10].

As the intermediary connections bridging the aorta and brain arterioles and capillaries, intracranial large arteries might modify and mediate the association between extracranial pulsatile hemodynamics and brain microvasculature damage. Intracranial atherosclerotic stenosis (ICAS) and intracranial arterial dolichoectasia (IADE) are two distinct pathophysiological manifestations of intracranial large arteries inherent to aging. Whereas ICAS is an atherosclerotic arteriopathy involving endothelial function impairments, IADE is a dilative arteriopathy primarily involving loss of the elastic tissue of the tunica media, representing reduced vascular elasticity and increased stiffness. To date, whether and how the central arterial stiffness correlate with these two disparate intracranial arteriopathies have not been well investigated. Some evidence suggest that subjects with ICAS have increased arterial stiffness compared with those without[11-15]. However, most of the studies were conducted in small groups of selected subjects and investigated the association between arterial stiffness and atherosclerosis only.

Brachial-ankle pulse wave velocity (baPWV) has emerged as a noninvasive and reproducible method to measure arterial stiffness[16]. Although some portions may be determined by peripheral arterial stiffness, baPWV is closely correlated with carotid-femoral PWV, which has been used as the standard method for measuring aortic arterial stiffness[17].

Aim

In the present study, we aimed to investigate the association between arterial stiffness, as assessed by baPWV, and ICAS and IADE in a large population-based cohort.

Methods

Population

The Shunyi study is a population-based cohort study in China, designed to investigate the determinants and consequences of cardiovascular and age-related diseases. All inhabitants aged 35 years or older and independently living from five villages of Shunyi, a suburb district of Beijing, were invited. From June 2013 to April 2016, a total of 1,586 individuals participated and completed the standard baseline assessments. All participants were invited to undergo brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) examination. Among the 1,586 participants, 329 refused or had contraindica-

tions to MRI, leaving us with 1,257 participants who finally completed brain MRI. Of the 1,257 participants, 1,123 also accomplished baPWV measurement. Thus, the final analysis was conducted on 1,123 subjects (see a flow chart of participants inclusion and exclusion in **Supplemental Fig.1**). Compared with participants who underwent brain MRI and baPWV measurements, those who did not were older (58.4 ± 11.5 years versus 56 ± 9.3 years) and more likely to be male (44.9% versus 37.9%).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Peking Union Medical College Hospital (reference number: B-160). Written informed consent was obtained from all participants.

Measurement of baPWV

baPWV was measured using an automated device (VP-1000, Colin, Komaki, Japan), with the patients in the supine position. This device simultaneously measures pulse waves from the brachial and tibial arteries and arterial blood pressure *via* the oscillometric method[16]. The distance between each sampling point and the heart was estimated automatically according to the subject's height. The transmission time between the brachium and ankle was defined as the time difference between the waveform of the brachium and waveform of the ankle. baPWV on each side was automatically calculated as the PWV = transmission distance / transmission time. The average value of baPWV obtained on both sides was used for further analysis.

Magnetic Resonance Imaging

MRI was performed using a single 3-T Siemens Skyra scanner (Siemens, Erlangen, Germany). Three-dimensional time-of-flight magnetic resonance angiography (TOF-MRA) was performed in axial planes with the following parameters: repetition time (TR) = 21 ms, echo time (TE) = 3.43 ms, field of view (FOV) = 208×229 mm^2, voxel size = $0.3 \times 0.3 \times 0.6$ mm^3, and flip angle = 18°, with a total of 136 axial slices. Three-dimensional T1-weighted images (T1WI) were obtained using magnetization-prepared rapid gradient-echo sequence (TR = 2,530 ms, TE = 3.43 ms, voxel size = $1 \times 1 \times 1.3$ mm^3, flip angle = 8°, 144 sagittal slices).

Assessment of Intracranial Arteries
Intracranial Atherosclerotic Stenosis

Intracranial stenosis was assessed at the site of the most severe degree of stenosis on MRA using the criteria established in the Warfarin–Aspirin Symptomatic Intracranial Disease trial[18]. ICAS was defined as any

degree of stenosis in at least one of the following arteries: internal carotid artery (ICA), middle cerebral artery, anterior cerebral artery, intracranial segment of vertebral artery, basilar artery (BA), and posterior cerebral artery. For each territory, the ordinal degree of narrowing was recorded as no detectable stenosis, stenosis <50%, stenosis ≥ 50%, and occlusion.

Intracranial Arterial Dolichoectasia

Diameters of BA and ICA and basilar artery dolichoectasia (BADE) were assessed via TOF-MRA to evaluate IADE. The maximum diameter of BA and the bilateral ICAs at the vertical portion of cavernous segmentation (C4, Bouthillier classification[19]) were measured. Intracranial artery dilation was defined as ICA or BA having a total intracranial volume (TIV)-adjusted diameter ≥ 2 standard deviation (SD)[20]. TIV was computed as the sum of the volumes of gray matter, white matter, and cerebrospinal fluid, which were automatically segmented on structure T1WI using Statistical Parametric Mapping 12 (http://www.fl.ion.ucl.ac.uk/spm/) and CAT12 (http://www.neuro.uni-jena.de/vbm/) toolbox. Eighty-eight participants with unreliable structural segmentation on T1WI were excluded in the analysis involving ICA and BA dilation. In addition to the diameter of BA, the lateral displacement of BA and the height of BA bifurcation were also evaluated as described previously[21, 22]. BADE was defined as BA diameter >4.5 mm, laterality score >2, or height of bifurcation score >2.

Trained physicians who were blind to the clinical data rated IADE and ICAS independently. The intra-rater agreements were assessed on a random sample of 50 individuals with more than 1-month interval between the first and second readings. The results of the intra-rater agreement were as follows: the intraclass correlation coefficient was 0.93 for the presence of ICAS, 0.95 for BA diameter, and 0.96 for ICA diameter; the weighted κ coefficient was 0.63 for the laterality of basilar artery and 0.73 for the height of basilar artery bifurcation.

Cardiovascular Risk Factor Assessment

Blood pressure was measured three times, and the mean value was used. Diabetes mellitus was defined as self-reported diabetes, or use of oral antidiabetic drugs or insulin, or fasting serum glucose ≥ 7.0 mmol/L, or hemoglobin A1c ≥ 6.5%. Hyperlipidemia was defined as fasting serum total cholesterol >5.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) >3.62 mmol/L, or use of lipid-lowering drugs. Venous blood samples, routinely drawn after an overnight fast, were analyzed for plasma glucose and lipid level. Smoking status was classified as current smoker

(at least within the prior month) or non-current smoker. Body mass index (BMI) (weight/height^2) was calculated.

Statistical Analysis

Binary logistic regression models were used to investigate the association between baPWV and ICAS. The odds ratio (OR) and 95% confidence interval (CI) for the presence of ICAS by increasing quartiles, as well as per SD increase of baPWV, were calculated. All analyses were initially adjusted for age and sex (model 1) and then additionally adjusted for mean blood pressure and antihypertensive medication (model 2). Diabetes mellitus, LDL-C, lipid-lowering medication, BMI, current smoking status, and history of stroke were also included in the model (model 3). Multiple linear regression analysis was conducted to evaluate the relationship between baPWV and burden of ICAS, which was determined according to the number of intracranial arteries with atherosclerosis. Multiple logistic regression model was used to evaluate the relationship between baPWV and ICAS severity, which was categorized as no ICAS, moderate ICAS (<50% stenosis), and severe ICAS (≥ 50% stenosis and occlusion).

Subsequently, intracranial artery dilation and BADE were entered into the logistic regression models to assess the relationship between IADE and baPWV, respectively. Moreover, the diameters of BA and ICA were entered into the linear regression models as continuous variables. Because arterial atherosclerosis interfered with the diameter measurement, when investigating the association between IADE and baPWV, we further conducted analysis confined to participants without ICAS.

All analyses were conducted using SPSS version 19.0 (IBM Co., Armonk, NY, USA), and two-tailed p values <0.05 were considered statistically significant.

Results

The baseline characteristics of the study population are presented in **Table 1**. A total of 1,123 participants were included in the present analysis. The mean age was 56.0 years (SD, 9.3), and 426 (37.9%) of the participants were male. The mean value of baPWV was 15.81 m/s (SD, 3.28), and the cutoff points for quartiles of baPWV were 13.44, 15.28, 17.58 m/s. The prevalence of ICAS in at least one artery was 15.7% (176/1,123). Forty-five (4.0%) participants had BADE, and 47 (4.5%) had ICA or BA dilation.

Compared with participants who had adequate imaging quality for automatic brain structure segmentation, those with inadequate quality (n=88, missing

Table 1. Characteristics of the study population

	Total (*n*=1,123)	ICAS		IADE			
		ICAS (*n*=176)	Non-ICAS (*n*=947)	Dilation§ (*n*=47)	Non-dilation§ (*n*=988)	BADE (*n*=45)	Non-BADE (*n*=1,078)
Age, mean (SD), years	56.0 (9.3)	61.8 (9.1)	54.9 (8.9)*	57.9 (8.5)	55.8 (9.2)	59.6 (9.2)	55.9 (9.3)*
Male sex, *n* (%)	426 (37.9)	79 (44.9)	347 (36.6)*	13 (27.7)	364 (36.8)	18 (40.0)	408 (37.8)
Body mass index (kg/m²), mean (SD)	26.5 (3.7)	26.9 (3.7)	26.4 (3.7)	27.1 (4.1)	26.5 (3.7)	26.5 (3.6)	26.5 (3.7)
Current smoker, *n* (%)	256 (23.2)	45 (25.7)	211 (22.8)	8 (17)	218 (22.5)	10 (22.2)	246 (23.3)
Hypertension, *n* (%)	579 (51.6)	138 (78.4)	441 (46.6)*	24 (51.1)	504 (51.1)	27 (60.0)	552 (51.3)
Diabetes mellitus, *n* (%)	189 (16.8)	58 (33.0)	131 (13.8)*	8 (17)	158 (16.0)	11 (24.4)	178 (16.5)
Hyperlipidemia, *n* (%)	554 (49.2)	110 (62.5)	444 (46.9)*	20 (42.6)	490 (49.6)	24 (53.3)	530 (49.2)
History of stroke, *n* (%)	58 (5.2)	24 (13.6)	34 (3.6)*	3 (6.4)	46 (4.7)	3 (6.7)	55 (5.1)
Diameter of ICA, mean (SD), mm	4.09 (0.57)	3.83 (0.69)	4.14 (0.54)*	4.72 (0.72)	4.06 (0.55)*	4.37 (0.47)	4.08 (0.58)*
Diameter of BA, mean (SD), mm	3.07 (0.58)	2.93 (0.66)	3.10 (0.56)*	3.71 (0.97)	3.05 (0.53)*	3.87 (0.83)	3.04 (0.54)*
BaPWV, mean (SD), m/s	15.81 (3.28)	17.75 (3.31)	15.44 (3.15)*	15.24 (3.03)	15.78 (3.25)	16.51 (3.46)	15.78 (3.27)

ICA, indicates internal carotid artery; BA, basilar artery; baPWV, brachial-ankle pulse wave velocity; ICAS, intracranial atherosclerotic stenosis; IADE, intracranial arterial dolichoectasia; BADE, basilar arterial dolichoectasia; SD, standard deviation.
§Eighty-eight participants had missing data for dilation status because of inadequate quality of T1-weighted images for automatic structural segmentation.
*$P<0.05$, indicates significant difference. Differences between groups were compared using *t* test (for means) and χ^2 test (for percentages)

Table 2. Association between intracranial atherosclerotic stenosis and arterial stiffness, as measured by baPWV (*n*=1,123)

	BaPWV First Quartile	BaPWV Second Quartile		BaPWV Third Quartile		BaPWV Fourth Quartile		BaPWV (per SD)	
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Model 1	1.00 (reference)	3.46 (1.54-7.76)	0.003	6.40 (2.94-13.91)	<0.001	6.73 (3.05-14.82)	<0.001	1.46 (1.23-1.73)	<0.001
Model 2	1.00 (reference)	2.83 (1.25-6.426)	0.013	4.74 (2.14-10.51)	<0.001	4.15 (1.82-9.48)	0.001	1.26 (1.05-1.52)	0.015
Model 3	1.00 (reference)	2.86 (1.24-6.59)	0.013	4.51 (2.01-10.13)	<0.001	3.66 (1.57-8.54)	0.003	1.19 (0.98-1.45)	0.084

Model 1: adjusted for age and sex. Model 2: adjusted as in model 1+mean arterial pressure, antihypertensive medication. Model 3: adjusted as in model 2+body mass index, low-density lipoprotein cholesterol, current smoker, diabetes mellitus, lipid-lowering medication and history of stroke.
BaPWV, indicates brachial-ankle pulse wave velocity; OR, odds ratio; CI, confidence interval; SD, standard deviation.

TIV and dilation status) were more likely to be male (55.7% versus 36.4%) and current smokers (34.1% versus 22.3%). No significant difference was found with regard to age, baPWV levels, and other vascular risk factors.

Association between ICAS and baPWV

Table 2 presents the association between baPWV and the presence of ICAS. In all models, higher quartiles of baPWV were significantly associated with the presence of ICAS, when compared with the lowest quartile of baPWV. Associations attenuated when adjusted for cardiovascular risk factors and history of stroke (model 3) but still significant for the second, third, and fourth quartiles of baPWV compared with the first quartile, with respective ORs (95% CI) of

2.86 (1.24–6.59), 4.51 (2.01–10.13), and 3.66 (1.57–8.54). Subsequently, we investigated whether baPWV was linearly related to the presence of ICAS, but the linear trend for the association between baPWV (per SD increase) and ICAS was not significant in the full model (OR 1.19 [0.98–1.45]).

We further compared baPWV with the burden and severity of ICAS. Of the 1,123 participants, 93 (8.3%) had ICAS in one artery and 83 (7.4%) in two or more arteries. When adjusted for age and sex, baPWV increased as the number of intracranial arteries with atherosclerosis increased ($\beta \pm SE$, 0.121 ± 0.034, $p<0.001$). Among the population, 109 (9.7%) had moderate ICAS, and 67 (6%) had severe ICAS. In the multiple logistic regression models, we observed increased prevalence of both moderate ICAS and

Table 3. Association of diameters of basilar artery and internal carotid artery with baPWV using multivariate linear regression models

	Model 1		Model 2		Model 3	
	$\beta \pm SE$	p value	$\beta \pm SE$	p value	$\beta \pm SE$	p value
Subjects of ICAS included (n=1,035)						
§Diameter of ICA, per 1 mm	-0.115±0.036	0.002	-0.116±0.041	0.005	-0.083±0.042	0.047
§Diameter of BA, per 1 mm	-0.014±0.037	0.708	-0.010±0.041	0.800	-0.016±0.042	0.694
Subjects of ICAS excluded (n=860)						
§Diameter of ICA, per 1 mm	-0.108±0.039	0.007	-0.136±0.043	0.002	-0.123±0.045	0.007
§Diameter of BA, per 1 mm	0.012±0.040	0.771	0.005±0.045	0.907	0.018±0.047	0.691

Model 1: adjusted for age and sex. Model 2: adjusted as in model 1+mean arterial pressure, antihypertensive medication. Model 3: adjusted as in model 2+body mass index, low-density lipoprotein cholesterol, current smoker, diabetes mellitus, lipid-lowering medication and history of stroke. ICA, indicates internal carotid artery; BA, basilar artery; baPWV, brachial-ankle pulse wave velocity; ICAS, intracranial atherosclerotic stenosis; SE, standard error.
§For diameters of BA and ICA, adjusted for total intracranial volume

severe ICAS in the upper three quartiles of baPWV after adjustment for age and sex. These associations attenuated when further adjusted for the vascular confounding factors **(Supplemental Table 1)**.

Association between IADE and baPWV

No significant association was observed between higher quartiles of baPWV and intracranial artery dilation, as well as the presence of BADE **(Supplemental Tables 2 and 3)**. As presented in **Table 3**, when BA and ICA diameters were regarded as continuous variables, increased baPWV was inversely related to ICA diameter in fully adjusted models ($\beta \pm SE$, –0.083±0.042, p=0.047) and not to BA diameter ($\beta \pm SE$, –0.016±0.042, p=0.694). Because arterial atherosclerosis interfered with the diameter measurement, we further conducted sensitivity analysis confined to participants without ICAS, and the above trends remained.

Discussion

In this large, population-based cohort, we provide evidence that arterial stiffness, measured *via* brachial-ankle pulse wave velocity, is significantly associated with the presence of intracranial atherosclerotic stenosis independent of cardiovascular risk factors. However, association between arterial stiffness and intracranial arterial dolichoectasia, another type of pathological change of intracranial artery, were not pronounced. These results suggested that arterial stiffness was more likely associated with intracranial stenotic arteriopathy other than intracranial dilative arteriopathy.

Previous studies on the association between arterial stiffness and intracranial atherosclerosis reported conflicting results. We observed a strong association between baPWV and ICAS, which is in accordance with some previous studies conducted in patients with ischemic stroke, untreated hypertension, and end-stage renal disease[11-14]. Only one study in community-dwelling older adults of rural Ecuador demonstrated that PWV was correlated with intracranial atherosclerosis, which was diagnosed by carotid siphon calcifications on CT scans[15]. However, such study comprised a relatively small number of subjects. In contrast to the above, there was also a negative report between arterial stiffness and intracranial atherosclerosis[23]. In a study comprising 233 stroke patients, although baPWV was the highest in patients with large artery atherosclerosis subtype of cerebral infarction, it did not differ significantly between patients with and without ICAS.

Several possibilities for the association between arterial stiffness and ICAS can be hypothesized. Common determinants of arterial stiffness and atherosclerosis might partly explain the observed association. Additional adjustment for cardiovascular risk factors attenuated the association between baPWV and ICAS, which is consistent with this view. In addition, some evidence demonstrates that atherosclerosis and arterial stiffness may interact as both cause and effect[24]. On one hand, increased arterial stiffness and reduced large artery compliance may increase pulsatile pressure, leading to intracranial large arterial wall remodeling and atherosclerosis[25]. On the other hand, atherosclerosis may by itself, in advanced stages, also impair the elastic properties of the wall and lead to arterial stiffness[26]. In this sense, one would expect to find a strong and synergistic association between arterial stiffness and atherosclerosis in different locations of vascular beds[3-6]. Longitudinal studies are necessary to deter-

mine whether arterial stiffness leads to atherosclerosis or vice versa. This information may have implications for whether the pharmacological agents and medical intervention targeted on arterial stiffness will be effective in preventing the development of ICAS.

Our findings suggest that baPWV, a method for measuring arterial stiffness, might be a noninvasive surrogate marker for the extent of intracranial atherosclerosis. Arterial stiffness measurement might also serve as a potential tool to monitor the management of ICAS in clinical practice. Furthermore, the strong association between arterial stiffness and ICAS observed in our study may provide an additional explanation for the association between arterial stiffness and stroke, as well as cerebral small vessel disease. Future longitudinal studies concerning the association between arterial stiffness and cerebrovascular disease should determine whether arterial stiffness is a risk factor for cerebrovascular disease, independent of its association with ICAS.

Studies investigating the association between central arterial stiffness and intracranial arterial dilation are scarce. BaPWV represents the elasticity of aorta and peripheral arteries of the limbs, which is affected by the property of elastin fibers and medial smooth muscle of the tunica media. Pathologically, progressive luminal dilation of the brain arteries is related to non-atherosclerotic aging, and it is accompanied by rarefaction of the elastic tissue and disruption of the internal elastic lamina. Thus, it was contemplated that brain arterial dilation and increased baPWV are both markers of increased arterial stiffness and loss of vascular elasticity. Theoretically, IADE might synchronously occur with reduced arterial elasticity in the systemic circulation. However, we did not find correlations between baPWV and IADE. It could be partly explained by the low proportion of IADE in this population. Furthermore, the diameter of the arterial lumen is affected by both the atherosclerotic plaque on the vessel wall and the expansion of the lumen. This may explain why increased baPWV was inversely related to ICA diameter, which was in accordance with the association between baPWV and ICAS. On the other hand, previous studies have shown that conventional vascular risk factors were significantly associated with baPWV, whereas only older age was associated with IADE[22], indicating inconsistent underlying mechanisms of arterial stiffness at different vascular beds. First, the aorta exhibits the earliest pathological correlates of stiffness, and subsequently, it progresses centrifugally[27-29]. Intracranial arteries, which have a muscular structure, are more resistant to age-induced stiffening compared with the more proximal elastic arteries[30]. Second, the configu-ration of the Circle of Willis determines the flow distribution at the base of the skull and, consequently, the caliber of the intracranial large arteries. Flow-induced arterial remodeling and IADE prevalence might be affected by the heterogeneous configurations of the Circle of Willis and blood flow distribution[31].

Our results should be framed in the context of various limitations. First, the cross-sectional, observational study design limits our ability to establish casual relationships between baPWV and the development of atherosclerosis and dilation of the intracranial arteries. Second, subjects who refused to participate or those with contraindications to MRI were older than those who underwent MRI, leading to a possibility of selection bias. Third, the lumen-based measurement on MRA may have underestimated both atherosclerotic burden and arterial dilation, as the vessel wall could not be visualized.

Conclusion

In conclusion, the present study provides evidence on the relationship between arterial stiffness and ICAS. baPWV measurement may be performed as a simple procedure to detect candidates for MRA screening in the search of ICAS in the general population. IADE was not relevant to baPWV, indicating that discrepant underlying pathophysiologies of arterial stiffness at various sites of the vascular tree may exist.
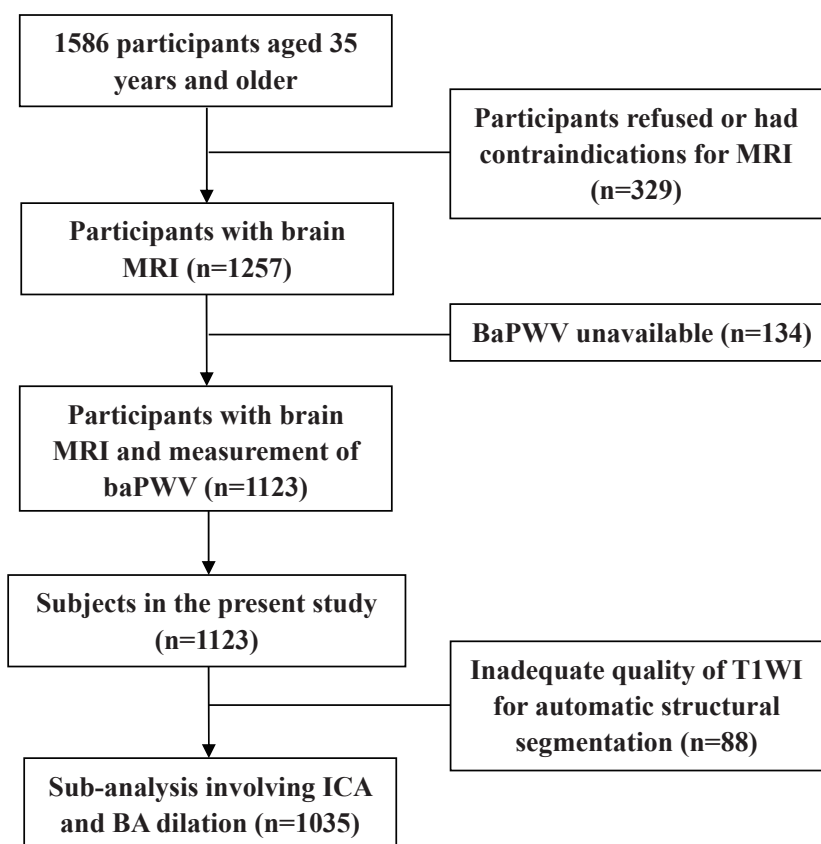
Conflicts of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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┌─────────────────────────┐
│ 1586 participants aged 35│
│     years and older      │
└─────────────────────────┘
             │          ┌──────────────────────────┐
             │──────────│ Participants refused or had│
             │          │ contraindications for MRI  │
             ▼          │         (n=329)            │
┌─────────────────────────┐└──────────────────────────┘
│  Participants with brain │
│      MRI (n=1257)        │
└─────────────────────────┘
             │          ┌──────────────────────────┐
             │──────────│ BaPWV unavailable (n=134) │
             ▼          └──────────────────────────┘
┌─────────────────────────┐
│  Participants with brain │
│  MRI and measurement of  │
│     baPWV (n=1123)       │
└─────────────────────────┘
             │
             ▼
┌─────────────────────────┐
│ Subjects in the present  │
│     study (n=1123)       │
└─────────────────────────┘
             │          ┌──────────────────────────┐
             │──────────│ Inadequate quality of T1WI │
             │          │ for automatic structural   │
             ▼          │   segmentation (n=88)      │
┌─────────────────────────┐└──────────────────────────┘
│ Sub-analysis involving ICA│
│ and BA dilation (n=1035) │
└─────────────────────────┘
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Supplemental Fig. 1. A flow chart of participants inclusion and exclusion in the study

MRI indicates magnetic resonance imaging; T1WI, T1-weighted image; ICA, internal carotid artery; BA, basilar artery; baPWV, brachial-ankle pulse wave velocity.

Supplemental Table 1. Association of ICAS severity with baPWV using multiple logistic regression model (*n*=1,123)

	BaPWV First Quartile	BaPWV Second Quartile		BaPWV Third Quartile		BaPWV Fourth Quartile	
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Model 1							
Moderate vs no ICAS	1.00 (reference)	3.19 (1.15-8.85)	0.025	5.36 (2.02-14.25)	0.001	6.72 (2.52-17.96)	<0.001
Severe vs no ICAS	1.00 (reference)	3.90 (1.08-14.06)	0.037	8.27 (2.42-28.24)	0.001	6.50 (1.83-23.07)	0.004
Model 2							
Moderate vs no ICAS	1.00 (reference)	2.64 (0.94-7.40)	0.064	4.02 (1.48-10.92)	0.006	4.23 (1.52-11.77)	0.006
Severe vs no ICAS	1.00 (reference)	3.14 (0.86-11.45)	0.082	6.02 (1.72-21.09)	0.005	3.87 (1.04-14.41)	0.044
Model 3							
Moderate vs no ICAS	1.00 (reference)	2.59 (0.92-7.32)	0.072	3.62 (1.32-9.91)	0.012	3.49 (1.27-10.13)	0.016
Severe vs no ICAS	1.00 (reference)	3.35 (0.89-12.56)	0.073	6.31 (1.76-22.62)	0.005	3.56 (0.92-13.72)	0.066

Model 1: adjusted for age and sex. Model 2: adjusted as in model 1+mean arterial pressure, antihypertensive medication. Model 3: adjusted as in model 2+body mass index, low-density lipoprotein cholesterol, current smoker, diabetes mellitus, lipid-lowering medication and history of stroke. ICAS, indicates intracranial atherosclerotic stenosis; baPWV, brachial-ankle pulse wave velocity; OR, odds ratio; CI, confidence interval.

Supplemental Table 2. Association between intracranial artery dilation[§] and baPWV (subjects of ICAS excluded, *n*=860)

	BaPWV First Quartile	BaPWV Second Quartile		BaPWV Third Quartile		BaPWV Fourth Quartile	
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Model 1	1.00 (reference)	1.14 (0.51-2.54)	0.758	0.61 (0.24-1.58)	0.308	0.35 (0.12-1.06)	0.063
Model 2	1.00 (reference)	1.10 (0.49-2.51)	0.816	0.56 (0.20-1.54)	0.261	0.32 (0.10-1.06)	0.062
Model 3	1.00 (reference)	1.10 (0.48-2.51)	0.830	0.54 (0.20-1.49)	0.233	0.30 (0.09-1.03)	0.055

Model 1: adjusted for age and sex. Model 2: adjusted as in model 1+mean arterial pressure, antihypertensive medication. Model 3: adjusted as in model 2+body mass index, low-density lipoprotein cholesterol, current smoker, diabetes mellitus, lipid-lowering medication and history of stroke. ICAS, indicates intracranial atherosclerotic stenosis; baPWV, brachial-ankle pulse wave velocity; OR, odds ratio; CI, confidence interval.
[§]Eighty-eight participants had missing data for dilation status because of inadequate quality of T1-weighted images for automatic structural segmentation.

Supplemental Table 3. Association between basilar arterial dolichoectasia and baPWV (subjects of ICAS excluded, *n*=947)

	BaPWV First Quartile	BaPWV Second Quartile		BaPWV Third Quartile		BaPWV Fourth Quartile	
		OR (95%CI)	*p* value	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Model 1	1.00 (reference)	1.57 (0.55-4.50)	0.401	2.03 (0.71-5.78)	0.185	1.65 (0.53-5.16)	0.388
Model 2	1.00 (reference)	1.50 (0.52-4.37)	0.454	1.86 (0.62-5.62)	0.270	1.45 (0.42-5.02)	0.555
Model 3	1.00 (reference)	1.47 (0.50-4.27)	0.483	1.78 (0.59-5.37)	0.307	1.29 (0.36-4.58)	0.695

Model 1: adjusted for age and sex. Model 2: adjusted as in model 1+mean arterial pressure, antihypertensive medication. Model 3: adjusted as in model 2+body mass index, low-density lipoprotein cholesterol, current smoker, diabetes mellitus, lipid-lowering medication and history of stoke. ICAS, indicates intracranial atherosclerotic stenosis; baPWV, brachial-ankle pulse wave velocity; OR, odds ratio; CI, confidence interval.