JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2023;19(4):338-343 / https://doi.org/10.3988/jcn.2022.0209

Cerebral Arterial Stiffness as Measured Based on the Pulse Wave Velocity Is Associated With Intracranial Artery Calcification in Patients With Acute Stroke

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Background and Purpose By measuring a newly defined parameter, the carotid–cerebral pulse wave velocity (ccPWV), this study aimed to determine the association of intracranial artery calcification (IAC) with arterial stiffness as reflected by the pulse wave velocity between the carotid and middle cerebral arteries using transcranial Doppler sonography in patients with acute stroke.

Methods We recruited 146 patients with ischemic stroke from our stroke center. Computed tomography of the head was used to assess the presence and severity of IAC. Arterial stiffness was evaluated using ccPWV. Data are presented as quartiles of ccPWV. A multivariable logistic regression model was used to assess the independent relationship between ccPWV and IAC.

Results The IAC prevalence increased with the ccPWV quartile, being 54%, 76%, 83%, and 89% for quartiles 1, 2, 3, and 4, respectively ($p<0.001$) as did IAC scores, with median [interquartile range] values of 0 [0–2], 3 [2–4], 4 [2–5], and 5 [4–6], respectively ($p<0.001$). After additionally adjusting for age and hypertension, a significant correlation was only found between quartiles 3 and 4 of ccPWV and IAC scores. The odds ratio (95% confidence interval) for the IAC scores was 1.78 (1.28–2.50) ($p=0.001$) in quartile 4 of ccPWV and 1.45 (1.07–1.95) ($p=0.015$) in quartile 3 compared with quartile 1.

Conclusions We found that in patients with acute ischemic stroke, ccPWV was positively related to the degree of IAC. Future longitudinal cohort studies may help to identify the potential role of IAC in the progression of cerebral arterial stiffness.

Keywords intracranial arterial calcification; carotid–cerebral pulse wave velocity; computed tomography; arterial stiffness; acute ischemic stroke.

Received May 28, 2022
Revised November 6, 2022
Accepted November 9, 2022

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INTRODUCTION

Intracranial artery calcification (IAC) is a relatively frequent finding on brain computed tomography (CT) in both the general population and patients with ischemic stroke. Our previous clinical studies found a high prevalence of IAC among the general population and patients with stroke or transient ischemic attack.[1,2] Consistent with its high prevalence, several recent population-based studies found increases in the risks of stroke and a poor outcome after stroke.[3-7] IAC can present in either the intimal or medial layers of the arteries; our previous pathological study also found that intimal calcification was often close to the internal elastic lamina and nearly always was within atheromatous plaques, while medial artery calcification might be linked to the increased stiffness of the vessel.[2,8]

The arterial stiffness is influenced by functional and structural changes in the vascular wall, which can mostly be assessed using pulse wave velocity (PWV). Among PWV measurements, although carotid–femoral PWV (cfPWV) is currently considered the gold

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standard for noninvasive measurements of arterial stiffness, brachial–ankle PWV (baPWV) has become the most widely used parameter of large-artery compliance in previous clinical studies and clinical practice. However, baPWV and cfPWV measurements cannot be used to directly assess cerebral arterial stiffness. The measurement of carotid–cerebral PWV (ccPWV), which is simple and noninvasive, has recently become generally available as a measure of cerebral artery stiffness. Moreover, our previous research has also found a strong correlation between ccPWV and baPWV.[9]

Despite numerous recent studies verifying the significant correlation between IAC and arterial stiffness by determining baPWV, few have addressed the association between IAC and cerebral arterial stiffness. In the present study, based on our previous method that used a novel original time and distance assessment technique to directly evaluate the human ccPWV,[9] we aimed to determine the effect of IAC on cerebral artery stiffness among patients with stroke.

METHODS

Subjects

Between September 2018 and June 2020, 146 patients with ischemic stroke who underwent both ccPWV measurement and head CT within 7 days of visiting our stroke center were enrolled in the study.

We included patients who were admitted within 7 days of acute ischemic stroke symptom onset, were 18–80 years old, underwent CT and magnetic resonance imaging (MRI) within 7 days of admission, had complete clinical data or imaging information, and had no history of head injury or tumors. Among the 206 consecutive patients initially examined or considered for inclusion in this study, 32 were excluded because of incomplete or no data on temporal windows for ccPWV measurements, and 28 for not having undergone noncontrast head CT. All patients or their immediate family members provided written informed consent. The study protocol was approved by the clinical ethics committees of the participating hospitals (IRB No. 2021-hs-23).

CT data acquisition and processing

Imaging was performed using a 64-row multidetector CT scanner without contrast agent. All unenhanced head-tilted brain scans were performed in the axial mode with tilting along the occipitomeatal line, which covered the region from the skull base to the vertex. Axial images were acquired with the following parameters: 5-mm slice thickness, 120 kVp, 170 mAs, and 1-sec rotation time.

A visual grading method was used to assess IAC scores.[10-12] The presence of IAC was defined as a hyperdense artery sign with a peak density exceeding 130 Hounsfield units. Previously established calcification scoring methods that described the severity of IAC were evaluated by grading the values (extent and thickness) of individual cerebral arteries. The extents of calcifications were graded on a five-point scale as follows: absent (0 points), dots (1 point), <90° (2 points), 90°–270° (3 points), and 270°–360° (4 points).

The calcification thickness was classified as follows: no calcification (0 points), 1 mm (1 point), 2 mm (2 points), 3 mm (3 points), and >3 mm (4 points). Peak composite CT scores (sum of the extent and thickness) of 0–2, 3–5, and 6–8 were classified as mild, moderate, and severe degrees of IAC, respectively (Fig. 1).

Measurement of cerebral arterial stiffness

As previously described,[9] bilateral ccPWV measurements were performed by two experienced operators using two-channel (2 and 4 MHz) transcranial Doppler sonography (TCD-2000M, Beijing Chioy Medical Technology, Beijing, China) after a 10–15 min period of rest in the supine position. The 2-MHz ultrasound probe was placed on the temporal window to measure the cerebral blood flow velocity (CBFV) of the middle cerebral artery; the 4-MHz probe, with the angle fixed at 30°, was placed beside the thyroid notch in the neck of the patient to measure the CBFV of the common carotid artery. The mean pulse wave transmission time (Δmt) for ten consecutive cardiac cycles was automatically measured by the arterial pulse wave analysis system. The transit distance (D, in meters) traveled by the pulse wave was calculated by measuring the body surface distance between the

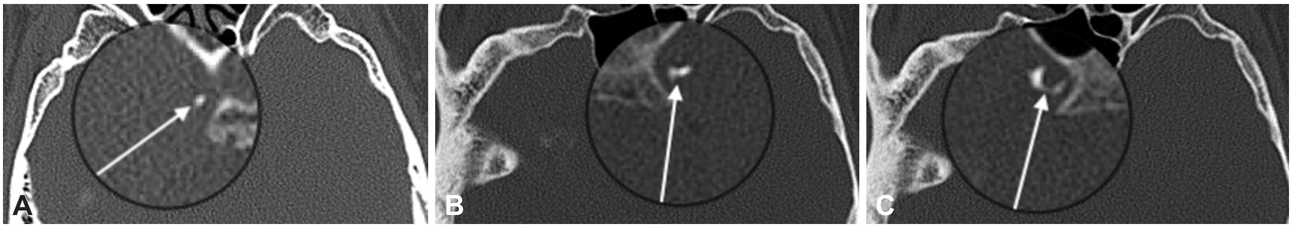

Fig. 1. Examples of IAC scores in computed tomography. According to Babiarz's visual grading scales, IACs were graded as follows: (A) 1 for extent and 1 for thickness (arrow), (B) 2 for extent and 2 for thickness (arrow), and (C) 3 for extent and 3 for thickness (arrow). IAC, intracranial artery calcification.

two recording sites (D1, in meters) plus cosine (30°) of the detecting depth for the common carotid artery (D2, in meters); namely, $D=D1+D2\times\text{cosine}\ (30°)$. ccPWV on each side was therefore calculated as $\text{ccPWV}=D/\Delta mt$ (in centimeters/second). The reproducibility, reliability, and validity of ccPWV measurements were determined in our previous studies.[13-15]

Statistical analysis

Data are presented according to ccPWV quartiles. Within the quartiles, continuous clinical characteristics are presented as mean and standard-deviation values, categorical variables are presented as counts and percentages, and IAC scores are expressed as median (interquartile range) values. The characteristics of the participants were compared according to arterial stiffness severity using the chi-square test for the categorical variables. Continuous variables were compared across quartiles using the Kruskal-Wallis test. Multiple logistic regression analysis was used to examine the independent relationship between ccPWV and the degree of IAC. All reported p-values are based on a two-sided level of significance of less than 0.05. Statistical analyses were performed using SPSS software (version 26.0.0; IBM Corp., Armonk, NY, USA).

RESULTS

After applying the inclusion and exclusion criteria, 146 patients were included. The baseline demographics and clinical characteristics according to ccPWV quartile are listed in Table 1.

When compared with participants with the lowest ccPWV values, those with higher ccPWV values were more likely to be older, be diagnosed with hypertension, have higher blood cholesterol levels, have IAC, and have higher IAC scores ($p<0.01$). IAC was present in 74.6% of the population (in 51.3%, 75.7%, 83.3%, and 88.9% of those in quartiles 1–4, respectively; $p<0.01$).

The logistic regression analysis results are listed in Table 2. There was a significant positive correlation between ccPWV and IAC in the logistic regression analysis ($p<0.05$). After additionally adjusting for age and hypertension, the correlation between the quartiles 2–4 of ccPWV and the presence of IAC became insignificant, as well as in the analysis that included ccPWV as a continuous variable ($p>0.05$).

Table 3 lists the results of the logistic regression analysis between ccPWV and calcification scores. The odds ratio (95% confidence interval) values for the IAC scores when comparing quartiles 2–4 of ccPWV with quartile 1 were 1.42 (1.11–1.83), 1.71 (1.30–2.25), and 2.24 (1.65–3.02), respectively ($p<0.05$). After an additional adjustment for age and hypertension, there was also a significant correlation between quartiles 3 and 4 of ccPWV and IAC scores. The odds ratio (95% confidence interval) values for the IAC scores were 1.78 (1.28–2.50) ($p=0.001$) in quartile 4 of ccPWV and 1.45 (1.07–1.95) ($p<0.05$) in quartile 2 compared with quartile 1. ccPWV was also independently associated with IAC

Table 1. Characteristics of the study subjects

Characteristic	ccPWV quartile (cm/s)				*p*
	1 (*n*=37)	2 (*n*=37)	3 (*n*=36)	4 (*n*=36)	
	<716	718.1–847.2	847.8–956.6	≥965.9	
Age, years	54.4±8.8	62.5±6.2	65.1±11.1	68.0±9.9	<0.001
Sex, male	21 (58)	27 (75)	27 (75)	31 (88)	0.325
Hypertension	11 (30)	19 (53)	20 (54)	29 (81)	0.007
Diabetes	8 (22)	4 (11)	8 (22)	10 (28)	0.565
CAD	0	3 (8)	3 (8)	4 (11)	0.287
Current smoking	12 (32)	11 (31)	12 (32)	10 (28)	0.934
Calcification presence	20 (54)	28 (76)	30 (83)	32 (89)	<0.001
Calcification score	0 [0–2]	3 [2–4]	4 [2–5]	5 [4–6]	<0.001
BMI, kg/m^2	22.5±2.4	24.0±2.6	24.3±3.4	22.6±3.0	0.076
SBP, mm Hg	143.9±21.7	146.4±19.4	143.9±19.2	146.2±25.3	0.900
Pulse pressure, mm Hg	53.6±15.9	58.4±15.9	58.0±15.8	62.4±14.9	0.087
TG, mmol/L	1.5±0.8	1.9±1.2	1.9±0.9	1.6±1.5	0.763
HbA1c, %	5.8±0.9	6.3±1.5	6.1±1.2	6.2±1.5	0.266
Cholesterol, mmol/L	4.3±1.0	4.7±0.9	4.2±0.8	3.8±1.1	0.075
LDL-C, mmol/L	2.9±0.8	3.1±0.8	2.7±0.8	2.4±0.8	0.188

Data are mean±standard-deviation, *n* (%), or median [interquartile range] values.
BMI, body mass index; CAD, coronary artery disease; ccPWV, carotid–cerebral pulse wave velocity; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides.

Table 2. Results of the multivariable analysis of ccPWV and calcification presence

ccPWV, cm/s	*n*	Presence, *n* (%)	Nonadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Quartile						
1 (<716)	37	19 (54)	Reference		Reference	
2 (718.1–847.2)	37	28 (78)	2.95 (1.05–8.25)	0.040	1.49 (0.46–4.84)	0.50
3 (847.8–956.6)	36	30 (83)	4.21 (1.40–12.65)	0.010	1.70 (0.50–5.89)	0.40
4 (≥965.9)	36	32 (89)	6.74 (1.96–23.14)	0.002	2.02 (0.50–8.28)	0.33

Data are adjusted for age and hypertension.
ccPWV, carotid–cerebral pulse wave velocity; CI, confidence interval; OR, odds ratio.

Table 3. Results of the multivariable analysis of ccPWV and calcification scores

ccPWV, cm/s	*n*	Score	Nonadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Quartile						
1 (<716)	37	0 (0–2)	Reference		Reference	
2 (718.1–847.2)	37	3 (2–4)	1.42 (1.11–1.83)	0.006	1.22 (0.91–1.63)	0.176
3 (847.8–956.6)	36	4 (2–5)	1.71 (1.30–2.25)	<0.001	1.45 (1.07–1.95)	0.015
4 (≥965.9)	36	5 (4–6)	2.24 (1.65–3.02)	<0.001	1.78 (1.28–2.50)	0.001

Data are adjusted for age and hypertension.
ccPWV, carotid–cerebral pulse wave velocity; CI, confidence interval; OR, odds ratio.

when it was included in the model as a continuous variable (p=0.001).

DISCUSSION

This study was the first to find that the degree of cerebral arterial calcification was correlated with cerebral arterial stiffness as measured by ccPWV independently from other conventional risk factors in patients with acute ischemic stroke.

PWV, which is virtually synonymous with arterial stiffness for many biomedical professionals, reflects functional and structural changes in the vascular wall compliance. Although cfPWV is considered the gold standard of stiffness measurements, baPWV is widely used in clinical practice due to its simplicity. However, few studies have specifically examined the association between IAC and cerebral arterial stiffness due to limitations when measuring the PWV of cerebral arteries. In the present study, we used a novel time and distance assessment technique based on our previous method to directly measure ccPWV in humans. Compared with baPWV and other PWV measurements, ccPWV could be used to directly assess cerebral arterial stiffness, which may be useful for future studies of intracranial atherosclerotic disease.

In this study, after adjusting for age and hypertension, arterial stiffness as measured using ccPWV was not associated with the presence of IAC, but with the IAC score. This inconsistency can be explained by the high prevalence of IAC in the elderly population; furthermore, the presence of calcification does not necessarily reflect IAC severity. Several previous studies found that vascular calcification was strongly related to aging.[16,17] In coronary artery disease, coronary artery atherosclerosis and calcification have been observed in up to 89% in the elderly population. Furthermore, a high prevalence of calcification has also been found in the aortic arch and extracranial carotid arteries of the elderly. Consistent with these studies, our previous studies found that the IAC prevalence exceeded 70% among the general population and patients with stroke or transient ischemic attack.[1,2]

The arterial stiffness and vascular calcification are independent predictors of cardiovascular morbidity and mortality, and several previous studies have found a significant correlation between them.[18-21] Park et al.[22] found that increased baPWV was closely associated with the degree of cerebral arterial calcification in patients with acute ischemic stroke; however, only 67 patients were included in that study. In a study in China, Zhang et al.[23] also found that increased arterial stiffness was independently associated with intracranial large-artery disease, which presented as intracranial stenosis or calcification. The findings of this research were consistent with those of previous studies on the association between measures of arterial stiffness and vascular calcification.

Several possible mechanisms may be responsible for the relationship between ccPWV and IAC. First, unlike intimal calcification, medial calcification is rarely related to progressive atherosclerotic lesions, but instead to decreased vascular compliance.[24-26] Moreover, IACs are predominantly located medially, and we have previously examined intracranial arteries and found that medial arterial calcification accounted for about 60% of all calcifications and 71% of intracranial internal carotid artery calcifications. Second, IAC and arterial stiffness are known to be independent risk factors for cardiovascular disease. Moreover, these two pathological processes reinforce each other, generating a vicious circle in which endothelial and smooth-muscle cells play key roles.[27] Third, cerebral artery stiffness and IAC share several risk factors including age, sex, hypertension, BMI, and hypercholesterolemia, which are the foundations for linking IAC to cerebral arterial stiffness.[28,29]

This was the first study to use ccPWV to measure cerebral arterial stiffness, and we systematically addressed the correlation between IAC and cerebral arterial stiffness. There were also some limitations to these findings that must be considered. First, as a cross-sectional study, this study could not clarify a temporal relationship between IAC and cerebral arterial stiffness measured using ccPWV. Second, the IAC scores were determined using a visual system rather than an automated measurement process. Third, given the relatively small sample, it was not possible to conduct a subgroup analysis to assess the associations among middle-aged and elderly patients with stroke. Fourth, the body surface distance does not accurately represent the distance of the corresponding artery because the terminal internal carotid artery is circuitous. Fifth, due to the sample-size limitations in this study, we only adjusted for age and hypertension to assess the independent association between ccPWV and IAC, and so there may have also been residual or unmeasured confounders that affected the study results.

In conclusion, we found that ccPWV was positively related with the degree of IAC in patients with acute ischemic stroke. Further longitudinal cohort studies may help to identify the potential role of IAC in the progression of cerebral arterial stiffness.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This study has received seed funding from the PolyU Research Institute for Smart Ageing (RISA).

Acknowledgements

We would like to thank all authors who helped in providing us with the data required for the analysis and for their valuable suggestions.

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