Association of Cerebral Arterial Stiffness with Initial Severity in Acute Ischemic Stroke

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Introduction

Stroke still represents one of the major causes of death and the leading cause of disability worldwide1, 2. Initial stroke severity, estimated by the National Institutes of Health Stroke Scale (NIHSS), influences short-term improvement after ischemic stroke, and is a well-established predictor of functional outcomes3. Numerous studies associated arterial stiffness with ischemic stroke and its subtypes based on the Trial of Org10172 in Acute Stroke Treatment (TOAST) classification4 although the results were inconsistent5-11. However, fewer data are available on the association between cerebral arterial stiffness and initial severity of acute ischemic stroke (AIS).

Recently, carotid–cerebral PWV (ccPWV) became available as a means of measuring cerebral arterial stiffness. It mainly measures the segment (C-M segment) stiffness between the common carotid artery (CCA) and the ipsilateral middle cerebral artery.
A previous study demonstrated that cerebral arterial stiffness indicated by ccPWV was independently associated with the presence of C-M segment atherosclerosis, was closely related to the vascular damage of C-M segment, and reflected the vascular structure change of C-M segment in AIS patients. Therefore, it is necessary to evaluate the association of ccPWV with the initial severity of AIS.

**Aim**

The present study’s aim was to evaluate the association between cerebral arterial stiffness confirmed by ccPWV and the initial severity estimated by the NIHSS after AIS.

**Materials and Methods**

**Patients**

This was a hospital-based, observational study. Between June 2012 and August 2018, 1,098 consecutive AIS patients (within seven days of symptom onset) were recorded in our AIS database. Among them, we consecutively enrolled anterior circulation AIS patients who underwent brain multimodal magnetic resonance (MR), ccPWV, echocardiography and carotid ultrasonography during the admission period. We excluded patients who had (1) a history of previous stroke, (2) arrhythmia that could influence assessing PWV accurately, (3) history of radiation therapy due to a head and neck cancer, which may promote cerebral artery atherosclerosis, (4) high or medium risk of potential cardiac sources of embolism based on the TOAST classification, (5) history of endovascular therapy due to anterior circulation disease, which may change the natural stiffness of the corresponding vascular segment, and (6) vascular occlusion at any place on the anterior circulation and an unsuitable temporal window for conducting ccPWV measurements. Written informed consent for this study was obtained from either the patient or his/her family member. The ethics committee of the Second Affiliated Hospital of Guangzhou Medical University approved the study protocol.

**Data Acquisition**

We collected data on sex, age, NIHSS score upon admission, risk factors [including hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, current smoking, body mass index (BMI), and systolic blood pressure (BP)], laboratory data, stroke subtype, and premorbid medication for each patient (Table 1). Hypertension was considered present if subjects had been previously diagnosed according to the World Health Organization/International Society of Hypertension guidelines and were routinely receiving anti-hypertensive therapy. Patients were defined as type 2 diabetics if they had known diabetes treated by diet, oral hypoglycemic drugs, or insulin before the stroke. Hypercholesterolemia was defined as the presence of total cholesterol blood levels ≥ 200 mg/dl. Coronary artery disease was determined based on a history of physician-diagnosed angina, myocardial infarction, or any previous revascularization procedure assessed by a questionnaire. Stroke subtypes were classified using the TOAST classification: (1) Large artery atherosclerosis (LAA); (2) Small vessel occlusion (SVO); (3) Other cause; (4) Undetermined cause. Cerebral angiographic findings for classification were obtained from digital subtraction angiography, MR angiography, or computed tomographic angiography, which were performed at admission. The initial stroke severity was assessed using NIHSS by experienced and qualified neurology physicians on admission. Severe initial stroke severity was defined as an NIHSS score > 6, and mild initial stroke severity was defined as an NIHSS score ≤ 6.

**Measurement of Cerebral Arterial Stiffness**

We evaluated each patient’s cerebral arterial stiffness by measuring the ccPWV. As described previously, experienced operators measured ccPWV with a special, two-channel Transcranial Doppler (TCD) (TCD-2000M; Beijing Chioy Medical Technology Co., Ltd, Beijing, China), using 2-MHz and 4-MHz ultrasound transducers, with patients in the supine position. The TCD machine used in this study has a built-in program model, called the arterial pulse wave analysis system, which can store, derive, and process signals obtained from transducers on CCA and MCA sites and simultaneously display these signals with expanded waveforms. The 2-MHz probe was held in a temporal window to detect the proximal part of MCA, and MCA was isonated at a depth of 50–55mm using standard criteria. The other 4-MHz transducer in the angle fixator of thirty degrees was placed on the ipsilateral pulsation point of CCA, beside the patient’s thyroid notch in the neck, to detect CCA. The transit time (Δt, ms) of the pulse wave traveled between the two insonation sites was automatically measured by the arterial pulse wave analysis system based on the waveform analysis of CCA and MCA. The mean transit time (Δmt) was then determined from 10 consecutive cardiac cycles. The distance (D, cm) traveled by the pulse wave was defined as the body surface distance (D1, cm) between the two probes, using a tape measure plus cosine 30° of detecting depth (D2, cm) for CCA, namely, D = D1 +
D × cos(30°) (12, 13). Thus, ccPWVs on each side were calculated as ccPWV = D/Am (cm/s). The arterial pulse wave analysis system can take all these measurements, except body surface distance, automatically. In all the studies, ccPWV was obtained after at least five minutes’ rest. The validity and reproducibility of ccPWV measurement were previously reported elsewhere (12).

### Statistical Analyses

All baseline variables were analyzed. Data were expressed as mean ± standard deviation (SD) or median (25th and 75th percentiles) for continuous variables and as frequency and percentage for discrete variables. Comparisons between patients with mild and severe initial severity were performed by unpaired Student’s t-test, or Mann Whitney U test where appropriate, for continuous variables, and chi-square test for categorical variables. To evaluate ccPWV’s discriminatory ability to predict severe initial stroke severity, the receiver operating characteristic (ROC) curve analysis was used. The area under the curve (AUC) was calculated, and baPWV’s optimal cutoff value was the level with the highest Youden index. To identify the association between cerebral arterial stiffness and severity of ischemic stroke, we performed multivariate logistic regression analysis in three different models, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Model 1 was adjusted for age, sex, and significant (P<0.05) variables from the univariate analyses; Model 2 was adjusted for age, sex, risk factors, and significant variables from the univariate analyses; and Model 3 was adjusted for age, sex, risk factors, premorbid medication, and significant variables from the univariate analyses. Furthermore, to better understand the correlations between cerebral arterial stiffness, with severity of ischemic stroke, and TOAST stroke subtypes, we performed a Spearman correlation analysis and established a linear prediction plot with 95% CIs for the NIHSS score according to the level of ccPWV in each stroke subtype, based on the generalized additive regression model. Statistical significance was established at P<0.05. Statistical analyses were performed using the SPSS 17.0 software for Windows (SPSS Inc, Chicago, IL, USA) and Stata 14.0 software for Windows (StataCorp LP, Texas, USA).

### Results

Of the 402 patients who were enrolled in this study, the mean age was 59.10 ± 10.49 years, and 64.18% were men (Fig. 1 and Table 1). The mean ccPWV value was 6.81 ± 2.37 m/s, and the initial NIHSS score at admission was 5 (3-8). Of all, 132 (32.84%) were classified into SVO, which was the most common stroke subtype in the present study. Baseline characteristics are shown in Table 1.

Upon admission, 168 (41.79%) patients had severe initial stroke severity (NIHSS > 6).

The higher ccPWV was significantly (P<0.05) associated with severe initial stroke severity in all patients and subgroups except the LAA and other cause stroke subtypes (Table 2).

In ROC analysis, when the continuous value of ccPWV was considered as a predictor of severe initial stroke severity, the AUC was 84.34% (95% CI, 80.22–88.45; P<0.001). The optimal ccPWV cutoff point was 6.87 m/s; at this point, the sensitivity was 73.21%, the specificity was 90.17%, and the Youden index was 0.63.

In the univariate analysis (Supplementary Table 1), the factors associated with severe initial stroke severity (P<0.05) were male sex, older age, higher ccPWV, ccPWV > 6.87 m/s, hypertension, current smoking, higher BMI, higher systolic arterial pressure, higher cholesterol, stroke subtypes, and antihypertensive. Among them, ccPWV > 6.87 m/s was the strongest determinant of severe initial stroke severity [OR (95% CI): 25.08 (14.48–43.44); P<0.001]. In the multivariate logistic regression analysis, ccPWV (as a continuous variable) and ccPWV > 6.87 m/s remained independent determinants of severe initial stroke severity in three different models (Table 3 and Supplementary Table 2). In model 3, the adjusted odds ratio (95% CI) was 1.36 (1.08–1.72) for 1 SD increase in ccPWV (P=0.010), and ccPWV > 6.87 m/s remained significantly associated with severe initial stroke severity [OR (95% CI): 8.13 (3.06–21.58); P<0.001] after adjustment for age, sex, risk factors, premorbid medication, and significant (P<0.05) variables from the univariate analyses.

The Spearman correlation analyses significantly correlated ccPWV with the NIHSS score in relation to TOAST stroke subtypes. The value of ccPWV was more strongly correlated with the NIHSS score in SVO subtype than that in LAA (r=0.82 vs. 0.46, P<0.001), other cause (r=0.82 vs. 0.55, P<0.001), and undetermined cause (r=0.82 vs. 0.32, P<0.001) subtypes (Table 4). On visual inspection, we also found that ccPWV correlated with the NIHSS score in all TOAST stroke subtypes (Fig. 2).

### Discussion

This study, for the first time, systematically evaluated the relationship between cerebral arterial stiffness and initial AIS severity. Numerous studies dis-
Table 1. Clinical characteristics of patients

| Variables                  | Study patients (n = 402) | Variables                  | Study patients (n = 402) |
|----------------------------|--------------------------|----------------------------|--------------------------|
| Male sex                   | 258 (64.18)              | Stroke subtype             |                           |
| Age, y                     | 59.10 ± 10.49            | LAA                       | 108 (26.87)              |
| NIHSS score on admission   | 5 (3-8)                  | SVO                       | 132 (32.84)              |
| ccPWV, m/s                 | 6.63 ± 2.34              | Other                     | 108 (26.87)              |
| Risk factors               |                          | Undetermined               | 54 (13.43)               |
| Hypertension               | 275 (68.41)              | Lesion side of stroke      |                           |
| Diabetes mellitus          | 126 (31.34)              | Left                      | 212 (52.7)               |
| Coronary artery disease    | 99 (24.63)               | Right                     | 190 (47.3)               |
| Hypercholesterolemia       | 92 (22.89)               | Premorbid medication       |                           |
| Current smoking            | 91 (22.64)               | Antihypertensive           | 142 (35.32)              |
| BMI, kg/m²                 | 23.40 ± 3.65             | Hypoglycemic agents        | 59 (14.68)               |
| Systolic arterial pressure, mmHg | 152.52 ± 19.32         | Antiplatelet               | 75 (18.66)               |
| Laboratory findings        |                          | Anticoagulant              | 13 (3.23)                |
| Triglyceride, mmol/L       | 1.55 ± 1.25              | Statin                     | 83 (20.65)               |
| Cholesterol, mmol/L        | 3.92 ± 1.53              |                           |                          |
| Low density lipoprotein, mmol/L | 3.27 ± 1.20         |                           |                          |
| Glucose, mmol/L            | 5.12 ± 1.39              |                           |                          |

Values were presented as mean ± standard deviation, median (interquartile range), or number (%). NIHSS indicates National Institute of Health Stroke Scale; BMI, body mass index; ccPWV, carotid–cerebral pulse wave velocity; LAA, large artery atherosclerosis; and SVO, small-vessel occlusion.

Fig. 1. Study flow chart
ccPWV indicates carotid–cerebral pulse wave velocity.
cussed the association of central and/or peripheral arterial stiffness with ischemic stroke, but reliable data concerning the relationship between arterial stiffness and initial ischemic stroke severity are lacking. In the present study, we observed that cerebral arterial stiffness, measured using ccPWV, was independently associated with initial stroke severity in AIS patients. The ccPWV values were significantly higher in patients with severe initial stroke severity in all patients and subgroups except LAA and other cause. In the multivariate analysis, adjusting for possible confounding factors in three different models, ccPWV (as

**Table 2.** Subgroup analysis for severity of ischemic stroke and cerebral arterial stiffness

| Patient group | n | ccPWV, m/s | P          |
|---------------|---|------------|------------|
| All patients  |   | Mild (NIHSS ≤ 6; n = 234) | Severe (NIHSS > 6; n = 168) | |
| Sex           |   | 5.51 ± 1.47 | 8.20 ± 2.42 | <0.001 |
| Male          | 258 | 5.98 ± 1.73 | 8.45 ± 2.32 | <0.001 |
| Female        | 144 | 5.01 ± 0.90 | 7.07 ± 2.57 | <0.001 |
| Age, y        |   | ≥ 70 | <70 | |
| ≥ 70          | 81 | 8.69 ± 2.34 | 9.92 ± 2.43 | 0.051 |
| <70           | 321 | 5.21 ± 0.92 | 7.22 ± 1.79 | <0.001 |
| Risk factors  |   | Hypertension | Diabetes mellitus | Coronary artery disease | Hypercholesterolemia | Current smoking | |
|              | 275 | 5.72 ± 1.51 | 7.93 ± 2.27 | <0.001 |
|              | 126 | 5.98 ± 1.89 | 8.57 ± 2.65 | <0.001 |
|              | 99  | 5.76 ± 1.33 | 7.82 ± 1.82 | <0.001 |
|              | 92  | 5.82 ± 1.60 | 8.13 ± 2.48 | <0.001 |
| Stroke subtype|   | LAA | SVO | Other | Undetermined | |
|              | 108 | 8.42 ± 2.00 | 8.45 ± 2.37 | 0.959 |
|              | 132 | 5.51 ± 1.60 | 8.42 ± 2.18 | <0.001 |
|              | 108 | 5.14 ± 0.80 | 4.53 ± 0.20 | 0.067 |
|              | 45  | 4.08 ± 0.43 | 5.16 ± 0.76 | 0.007 |

Values were presented as mean ± standard deviation. ccPWV indicates carotid–cerebral pulse wave velocity; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; LAA, large artery atherosclerosis; and SVO, small-vessel occlusion.

**Table 3.** Association between cerebral arterial stiffness and severity of ischemic stroke in multivariate models

|                      | Unadjusted OR (95% CI) | P         | Adjusted OR (95% CI) | P         |
|----------------------|------------------------|-----------|----------------------|-----------|
| As a continuous variable | ccPWV, per SD (2.34 m/s) | 2.10 (1.81-2.44) | <0.001 | 1.32 (1.06-1.66) | 0.014* |
|                      |                        | 1.34 (1.07-1.68) | 0.012 | 1.36 (1.08-1.72) | 0.010 ‡ |
|                      | At optimal cut-point    | ccPWV > 6.87 m/s | 25.08 (14.48-43.44) | <0.001 | 6.64 (2.62-16.82) | 0.001* |
|                      |                        | 7.39 (2.84-19.26) | <0.001 | 8.13 (3.06-21.58) | <0.001 ‡ |

*Model 1 adjusted for age, sex, and significant (P<0.05) variables from the univariate analyses; †Model 2 adjusted for age, sex, risk factors and significant variables from the univariate analyses; and ‡Model 3 adjusted for age, sex, risk factors, premorbid medication and significant variables from the univariate analyses. OR indicates odds ratio; CI, confidence interval; ccPWV, carotid–cerebral pulse wave velocity; and SD, standard deviation.

**Table 4.** Correlations of cerebral arterial stiffness with severity of ischemic stroke in relation to TOAST stroke subtype

| TOAST stroke subtype | t/Z | P         |
|----------------------|-----|-----------|
| LAA                  | 0.46| <0.001    |
| SVO                  | 0.82| <0.001    |
| Other                | 0.55| <0.001    |
| Undetermined         | 0.32| 0.017     |
| SVO vs. LAA          | -0.02| 0.001     |
| SVO vs. Other        | -0.10| <0.001    |
| SVO vs. Undetermined | -0.98| <0.001    |

TOAST indicates the Trial of Org10172 in Acute Stroke Treatment; LAA, large artery atherosclerosis; and SVO, small-vessel occlusion.
with initial severity during the acute phase of stroke.

In the present study, we also discussed the correlations of cerebral arterial stiffness with initial severity in different stroke subtypes based on the TOAST classification. We observed that higher ccPWV was significantly associated with severe severity in SVO and undetermined cause subgroups, and the value of ccPWV was most strongly correlated with the NIHSS score in subjects with SVO among all stroke subtypes. These findings suggest that cerebral arterial stiffness may be more strongly correlated with initial SVO severity than those of other subtypes. Several studies also associated central and/or peripheral arterial stiffness with the SVO subtype, which was similar to our results. Cerebral arterial stiffness might share several multifactorial mechanisms with the progressive neurological deficit that develops in SVO patients. Higher cerebral arterial stiffness impairs compliance of the cerebral vessel walls, increases the pulse pressure.

Fig. 2. The relationships between cerebral arterial stiffness, measured using carotid–cerebral pulse wave velocity (ccPWV), and severity, evaluated by the NIHSS score, in four stroke subtypes A to D. Black lines and gray shadows represent the estimated probability and the 95% CI for the NIHSS score at the ccPWV level based on the generalized additive model. The x axis is limited from the 5th to the 95th percentile of ccPWV.
The excessive pulsatile energy is transmitted into the cerebral small arteries, which are vulnerable to highly pulsatile systemic pressure with a possible “tsunami effect”3, 9, 11) . It relates to the arteriosclerotic microcirculatory impairment and may also increase SVO risk and severity. Additionally, the vascular endothelial impairment, indicated by PWV, is associated with blood–brain barrier failure3, 9, 11). Through these presumed mechanisms, cerebral arterial stiffness might contribute to the initial severity associated with SVO.

The present study has both strengths and limitations. The first strength is that this study, for the first time, systematically discussed the association between cerebral arterial stiffness and initial AIS severity. Second, all patients were carefully phenotyped for both AIS origin and consequences using validated scales and imaging techniques. Third, ccPWV was measured by experienced operators, with intensive training, using gold standard techniques. However, the present study was performed at a single center and included a population with a single ethnicity. Furthermore, the small number of patients enrolled in this study should be a key limitation. Also, more than half of initially-enrolled patients were excluded, which might have caused a selection bias.

**Conclusions**

In conclusion, cerebral arterial stiffness, measured using ccPWV at admission, was independently associated with initial severity in AIS patients and may be more strongly correlated with initial severity of SVO than those of other subtypes.

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**Conflict of Interest**

The authors declare no conflict of interest.

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**Supplementary Table 1.** Univariate analysis of the determinants of severity of ischemic stroke

| Variables                             | OR (95% CI)      | \( P \)  |
|---------------------------------------|------------------|---------|
| Male sex                              | 0.24 (0.15-0.39) | < 0.001 |
| Age, y                                | 1.13 (1.10-1.16) | < 0.001 |
| ccPWV, m/s                            | 2.10 (1.81-2.44) | < 0.001 |
| ccPWV > 6.87 m/s                      | 25.08 (14.48-43.44) | < 0.001 |
| Left side lesion of stroke            | 0.82 (0.55-1.22) | 0.318   |
| Risk factors                          |                  |         |
| Hypertension                          | 2.33 (1.48-3.67) | < 0.001 |
| Diabetes mellitus                     | 1.23 (0.80-1.88) | 0.344   |
| Coronary artery disease               | 1.36 (0.86-2.15) | 0.187   |
| Hypercholesterolemia                  | 1.54 (0.97-2.46) | 0.070   |
| Current smoking                       | 1.99 (1.24-3.20) | 0.004   |
| BMI, kg/m²                            | 1.07 (1.02-1.14) | 0.014   |
| Systolic arterial pressure, mmHg      | 1.08 (1.06-1.10) | < 0.001 |
| Laboratory findings                   |                  |         |
| Triglyceride, mmol/L                  | 1.20 (0.99-1.46) | 0.056   |
| Cholesterol, mmol/L                   | 1.27 (1.11-1.45) | 0.001   |
| Low density lipoprotein, mmol/L       | 0.95 (0.81-1.13) | 0.577   |
| Glucose, mmol/L                       | 1.03 (0.89-1.19) | 0.695   |
| Stroke subtype                        |                  |         |
| LAA                                   | 12.75 (7.29-22.28) | < 0.001 |
| SVO                                   | 1.89 (1.24-2.88) | 0.003   |
| Other                                 | 0.05 (0.02-0.11) | < 0.001 |
| Undetermined                          | 0.09 (0.03-0.25) | < 0.001 |
| Premorbid medication                  |                  |         |
| Antihypertensive                      | 5.18 (3.33-8.06) | < 0.001 |
| Hypoglycemic agents                   | 1.67 (0.96-2.90) | 0.072   |
| Antiplatelet                          | 1.19 (0.72-1.98) | 0.491   |
| Anticoagulant                         | 1.65 (0.55-5.01) | 0.375   |
| Statin                                | 1.48 (0.91-2.40) | 0.116   |

OR indicates odds ratio; CI, confidence interval; ccPWV, carotid-cerebral pulse wave velocity; BMI, body mass index; LAA, large artery atherosclerosis; and SVO, small-vessel occlusion.
**Supplementary Table 2.** Multivariate analysis of the determinants of severity of ischemic stroke

| Variables                  | Adjusted OR (95% CI) | \( P \)  |
|----------------------------|----------------------|--------|
| **Model 1**                |                      |        |
| Current smoking            | 2.33 (1.17-4.67)     | 0.017  |
| LAA                        | 24.29 (6.83-86.40)   | <0.001 |
| SVO                        | 8.59 (2.65-27.91)    | <0.001 |
| ccPWV >6.87 m/s            | 6.64 (2.62-16.82)    | 0.001  |
| **Model 2**                |                      |        |
| Current smoking            | 2.56 (1.25-5.24)     | 0.010  |
| LAA                        | 17.10 (4.80-60.87)   | <0.001 |
| SVO                        | 6.22 (1.91-20.27)    | 0.002  |
| ccPWV >6.87 m/s            | 7.39 (2.84-19.26)    | <0.001 |
| **Model 3**                |                      |        |
| Current smoking            | 2.57 (1.26-5.27)     | 0.010  |
| LAA                        | 17.88 (4.98-64.15)   | <0.001 |
| SVO                        | 6.40 (1.96-20.94)    | 0.002  |
| ccPWV >6.87 m/s            | 8.13 (3.06-21.58)    | <0.001 |

*Model 1 adjusted for age, sex, and significant \( P<0.05 \) variables from the univariate analyses;  
†Model 2 adjusted for age, sex, risk factors and significant variables from the univariate analyses; and  
‡Model 3 adjusted for age, sex, risk factors, premorbid medication and significant variables from the univariate analyses. OR indicates odds ratio; CI, confidence interval; and ccPWV, carotid-cerebral pulse wave velocity.