Cerebral Arterial Stiffness as A New Marker of Early Stage Atherosclerosis of The Cerebral Large Artery in Acute Stroke

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Aim: Carotid–cerebral pulse wave velocity (ccPWV) reflects the segment (C–M segment) stiffness between the common carotid artery and ipsilateral middle cerebral artery. C–M segment atherosclerosis (CMSA) is regarded the most frequent cause of anterior circulation ischemic stroke. We aimed to evaluate the association of ccPWV with early stage CMSA in this study.

Methods: Eighty-one acute ischemic stroke (AIS) patients with 154 C–M segments who were successfully evaluated with digital subtraction angiography, ccPWV, carotid intima–media thickness (cIMT), and brachial–ankle pulse wave velocity were enrolled into this study. Patient demographics and clinical data were retrieved from our AIS databases.

Results: Multivariate analyses showed that CMSA was independently associated with higher systolic BP, ccPWV, and cIMT. ccPWV and cIMT presented good diagnostic values for evaluating early stage CMSA in the receiver operating characteristic curve analyses. The areas under the curve (AUCs) of ccPWV were significantly higher than that of cIMT (Z = 2.204, P = 0.007). The AUC, sensitivity, specificity, Youden index, and cutoff of ccPWV for detecting early stage CMSA were 0.815 (P < 0.001), 86%, 70.7%, 0.567, and 5.4 m/s, respectively. Furthermore, ccPWV was significantly correlated with the stenosis of CMSA at the early stage in Spearman’s correlation analyses (r = 0.877, P < 0.001) and fractional polynomial plot with 95% confidence intervals.

Conclusions: Cerebral arterial stiffness has the potential to be a new marker of early stage atherosclerosis of the cerebral large artery. This finding may help us prevent the occurrence of stroke and decrease the burden of society from stroke patients.

Key words: Early atherosclerosis, Cerebral large artery, Carotid–cerebral pulse wave velocity, Ischemic stroke

Introduction

Ischemic stroke (IS) is the leading cause of premature mortality and morbidity worldwide and has devastating social and economic impacts. Cerebral large artery atherosclerosis diseases are considered important causes of IS because these diseases are responsible for approximately 15%–37% of all IS cases. Therefore, the early detection of cerebral large artery atherosclerosis may help us reduce the occurrence of IS in early therapeutic interventions and is crucial for the primary prevention of IS in communities.

Digital subtraction angiography (DSA), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) are still considered the classical imaging modalities for the evaluation of cerebral large arteries, but there are limitations to their uses in screening early cerebral atherosclerosis. DSA allows the viewing of the entire extracranial and intracranial artery system and provides information about the degree of stenosis, tandem lesions,
Materials and Methods

Patients
We collected patients with acute IS (AIS; within seven days of symptom onset) who were admitted between June 2012 and August 2016. Among these patients, we enrolled anterior circulation AIS patients who underwent brain multimodal MR, DSA, ccPWV, cIMT, and baPWV measurements during the admission period. We excluded patients with (1) arrhythmia that could influence the accurate assessment of PWV, (2) unsuitable temporal windows for conducting ccPWV measurements, (3) high or medium risk potential cardiac sources of embolism on the basis of Trial of Org10172 in Acute Stroke Treatment classification, and (4) history of radiation therapy due to a head and neck cancer, which may promote cerebral artery atherosclerosis. Written informed consent for this study was obtained from each patient or his or her family member. The ethics committee of the Second Affiliated Hospital of Guangzhou Medical University approved the study protocol. Good Clinical Practice guidelines in accordance with the Declaration of Helsinki were used, and the privacy of patients was strictly protected.

Data Acquisition
The baseline characteristics included age, gender, and cardiovascular risk factors (including hypertension, coronary heart disease, diabetes mellitus, hyperlipidemia, current smoking, systolic blood pressure [BP], and body mass index [BMI]). DSA was used to evaluate the CMSA. CMSA was defined when there was at least one angiographically verified atherosclerotic stenosis in the C-M segment. Early stage CMSA was defined when the most severe atherosclerotic stenosis confirmed by DSA in the C-M segment was more than zero but less than 50%. The degree of stenosis in the extracranial cerebral artery was measured using the method in the North American Symptomatic Carotid Endarterectomy Trial and that in the Intracranial Cerebral artery Atherosclerosis trial. In clinical practice, carotid–femoral PWV mainly reflects the stiffness of central arteries, and brachial–ankle PWV (baPWV) reflects the stiffness of central and peripheral arteries.

Recently, carotid–cerebral PWV (ccPWV) measurement, which can be performed noninvasively and easily, has become available as a means of measuring cerebral arterial stiffness. ccPWV mainly measures the segment (C-M segment) stiffness between the common carotid artery (CCA) and ipsilateral middle cerebral artery (MCA). The C-M segment is verified as the specific region that is highly prone to atherosclerosis, and the C-M segment atherosclerosis (CMSA) is also considered a most frequent cause of anterior circulation IS. Therefore, it is necessary to evaluate the association of ccPWV with early stage CMSA.

Aim
In this study, we aimed to evaluate the association of ccPWV with early stage CMSA confirmed by DSA and compare it with cIMT and baPWV.

ccPWV
As described previously, ccPWV was measured with a special two-channel TCD (TCD-2000M; Beijing Chioy Medical Technology Co., Ltd, Beijing, China) by using 2 and 4 MHz ultrasound transducers in the supine position by two experienced operators. The TCD machine used in this study has a built-in program model called arterial pulse wave analysis sys-
The transit time (beside the thyroid notch in the neck of the patient. was placed on the ipsilateral pulsation point of CCA other 4 MHz transducer in the angle fixator of 30°
cally calculated as PWVMCA26). The mean transit time (tem on the basis of the waveform analysis of CCA and
cally measured by the arterial pulse wave analysis sys-
teled between the two insonation sites was automati-
calculated as ccPWV

where26).

5 min of rest. The validity and reproducibility of the
surface distance.
wave analysis system, except the measurement of body
can be automatically completed by the arterial pulse
measurements on both sides of the carotid vessel wall were
made with longitudinal 2D images and were per-
donated as PWV = D/Dmt (cm/s). All of the above
can be automatically completed by the arterial pulse
wave analysis system, except the measurement of body
surface distance.

In all studies, ccPWV was obtained after at least
5 min of rest. The validity and reproducibility of the measurement of ccPWV were previously reported else-
where26).

baPWV
Bilateral baPWV was measured using an auto-
dated device (VP-1000; Colin Co. Ltd., Komaki,
Japan)26, 32). Patients were examined in the supine
position after at least 5 min of rest. This device simul-
taneously measures bilateral brachial and posterior
tibial arterial pulse waveforms and arterial BP by using
the oscillometric method. Transmission time was cal-
culated as the time taken for the waveform to travel
between the right brachium and ankle. The transmis-
sion distance between the right brachium and the
ankle was automatically calculated from the patient’s
height32). The baPWVs on each side were automati-
cally calculated as PWV = transmission distance/trans-
mition time.

cIMT
B-mode ultrasound images were obtained with
an ultrasound machine (Vivid FiVe; GE Ultrasound
Europe, Solingen, Germany) by using a linear array
10 MHz scan head, and the machine was performed by
an experienced operator. For each subject, 10 mea-
surements on both sides of the carotid vessel wall were
made with longitudinal 2D images and were per-
formed from the far wall of the distal common carotid
arteries over a distance of approximately 1 cm prox-
imal to the bifurcation, as described in previous stud-
ies14). All measurements were obtained without prior
clinical information about the subjects. Compared
with an applied standard and the repeated measure-
ments, the intraclass correlation coefficients were ≥
0.85, and the median differences of the pairs of mea-
measurements were < 5%.

Statistical Analysis
Values are reported as mean ± SD or number
(percentage) of subjects. According to the DSA results,
patients and C-M segments were respectively divided
into two groups: CMSA and non-CMSA (NCMSA).
To evaluate the potential factors associated with
CMSA, we performed multivariate logistic regression
with adjustments for sex, age, and variables that exhib-
ted a P value < 0.05 in the univariate analyses.
Receiver operating characteristic (ROC) curve analysis
was used to identify the validity of ccPWV, cIMT, and
baPWV for detecting CMSA and its early stage. The
area under the curve (AUC) was calculated, and the
optimal cutoff value of each method was determined
at the level with the highest Youden index (sensitivity
+ specificity - 1). A z-statistic was calculated by the
method of DeLong et al.33). for each comparison
between two ROC curves. To better understand the
relationship between each method and early stage
CMSA, we performed Spearman’s correlation analysis
and established a fractional polynomial plot with 95%
confidence intervals (CIs) for the stenosis of early
stage CMSA according to the level of each method on
the basis of the generalized additive regression model.
Statistical significance was established at P < 0.05.
Statistical analyses were performed using SPSS 17.0 soft-
ware for Windows (SPSS Inc, Chicago, IL, USA) and
Stata 14.0 software for Windows (StataCorp LP, Texas,
USA).

Results
This study enrolled 81 patients (62 males, 19
females) with anterior circulation AIS, and 154 C-M
segments were successfully evaluated with DSA,
ccPWV, cIMT, and baPWV (Fig. 1). The mean age
was 63.2 ± 11.7 years. The values of ccPWV, cIMT,
and baPWV were 6.2 ± 1.7 m/s, 0.89 ± 0.18 mm, and
17.0 ± 3.9 m/s, respectively. On the basis of the results
of DSA, 62.3% (96/154) of C-M segments were diag-
nosed as CMSA and 27.9% (43/154) of segments
were evaluated as early stage CMSA. Among the
patients, 79.0% (64/81) patients were included in
CMSA group. Table 1 and Fig.1 show the baseline

 Associations of ccPWV with Early Cerebral Atherosclerosis
demographics.

**Factors Associated with CMSA**

In univariate analyses, age, male gender, hypertension, systolic BP, ccPWV, cIMT, and baPWV were all significantly associated with CMSA in AIS patients. After adjusting for age, sex, and significant \((P<0.05)\) variables from the univariate analyses, multivariate logistic regression analyses showed that CMSA in AIS patients was independently associated with high systolic BP (odds ratio [OR] 1.55, 95% CI 1.06–2.27, \(P=0.024\)), high ccPWV (OR 6.13, 95% CI 1.54–24.34, \(P=0.010\)), and high cIMT (OR 16.72, 95% CI 1.91–146.32, \(P=0.011\)) (Table 2).

**Three Methods for Detecting CMSA and Early Stage CMSA**

The ROC curves demonstrated excellent diagnostic values for evaluating CMSA of ccPWV, cIMT, and baPWV (Table 3 and Fig. 2A). The AUC, sensitivity, specificity, and Youden index of ccPWV was 0.887, 70.1%, 93.1%, and 0.639, respectively. The cutoff of ccPWV for diagnosing CMSA was 5.8 m/s. The AUC of ccPWV was significantly higher than that of cIMT \((Z=2.892, P=0.001)\) and baPWV \((Z=5.360, P<0.001)\).

Except baPWV \((P=0.668)\), the ROC curves of ccPWV \((P<0.001)\) and cIMT \((P<0.001)\) presented good diagnostic values in detecting early stage CMSA (Table 3 and Fig. 2B). The AUC of ccPWV was significantly higher than that of cIMT \((Z=2.204, P=0.007)\). The AUC, sensitivity, specificity, and Youden index of ccPWV was 0.815, 86%, 70.7%, and 0.567, respectively. The cutoff of ccPWV for detecting early stage CMSA was 5.4 m/s.

**Correlations of the Levels of Three Methods with Early Stage CMSA**

Spearman’s correlation analyses demonstrated that ccPWV significantly correlated with the stenosis of early stage CMSA \((r=0.877, P<0.001)\), and cIMT \((r=0.125, P=0.425)\) and baPWV \((r=0.180, P=\)
0.248) did not show similar relationships. **Fig. 3** illustrates the estimated stenosis degree of early stage CMSA according to the levels of three methods. Upon visual inspection, we found that only ccPWV correlated with the stenosis of early stage CMSA.

**Table 1.** Patient demographics and clinical characteristics*

| Variables                      | Study patients (N=81, Segments=154) |
|--------------------------------|-------------------------------------|
| Age, y                         | 63.2 ± 11.7                         |
| Male sex, n/total n (%)        | 62/81 (76.5)                        |
| Hypertension, n/total n (%)    | 51/81 (63.0)                        |
| Coronary heart disease, n/total n (%) | 15/81 (18.5) |
| Diabetes mellitus, n/total n (%) | 15/81 (18.5) |
| Hyperlipidemia, n/total n (%)  | 36/81 (44.4)                        |
| Current smoking, n/total n (%) | 51/81 (63.0)                        |
| Systolic BP, mmHg              | 160.9 ± 19.0                        |
| BMI, kg/m²                     | 23.5 ± 3.7                          |
| ccPWV, m/s                     | 6.2 ± 1.7                           |
| cIMT, mm                       | 0.89 ± 0.18                         |
| baPWV, m/s                     | 17.0 ± 3.9                          |
| Patients with CMSA, n/total n (%) | 64/81 (79.0%) |
| Segments with CMSA, n/total n (%) | 96/154 (62.3) |
| Segments with early stage of CMSA, n/total n (%) | 43/154 (27.9) |
| Stenosis degree of CMSA, %     | 55.7 ± 23.4                         |
| Stenosis degree of early stage of CMSA, % | 33.1 ± 11.0 |

*Values are reported as mean ± SD or number (percentage) of subjects; all medical history based on both self-report and diagnosis in-hospital post stroke.

BMI indicates body mass index; ccPWV, carotid–cerebral pulse wave velocity; cIMT, carotid intima-media thickness; baPWV, brachium-ankle pulse wave velocity; CMSA, the segment atherosclerosis between common carotid artery and the ipsilateral middle cerebral artery; blood pressure.

**Table 2.** Factors associated with CMSA (N=81)*

| Variables                      | Univariate                         | Multivariate† |
|--------------------------------|-----------------------------------|---------------|
|                                | OR (95% CI) | P Value | OR (95% CI) | P Value |
| Age                            | 1.06 (1.01, 1.12) | 0.030 | - | - |
| Male sex                       | 3.03 (0.96, 9.60) | 0.059 | - | - |
| Hypertension                   | 4.34 (1.40, 13.44) | 0.011 | - | - |
| Coronary heart disease         | 1.91 (0.39, 9.43) | 0.426 | - | - |
| Diabetes mellitus              | 4.48 (0.55, 36.78) | 0.163 | - | - |
| Hyperlipidemia                 | 2.26 (0.71, 7.14) | 0.167 | - | - |
| Current smoking                | 1.70 (0.58, 5.01) | 0.339 | - | - |
| Systolic BP                    | 1.13 (1.07, 1.19) | <0.001 | 1.55 (1.06, 2.27) | 0.024 |
| BMI                            | 1.12 (0.95, 1.32) | 0.172 | - | - |
| ccPWV‡                         | 8.05 (2.48, 26.10) | 0.001 | 6.13 (1.54, 24.34) | 0.010 |
| cIMT†                          | 26.79 (5.46, 131.35) | <0.001 | 16.72 (1.91, 146.32) | 0.011 |
| baPWV‡                         | 1.24 (1.05, 1.46) | 0.010 | - | - |

*Values are reported as mean ± SD or number (percentage) of subjects; all medical history based on both self-report and diagnosis in-hospital post stroke.

†Adjusted for age, sex, and significant (P<0.05) variables from the univariate analyses.

‡The higher values of both sides were used for univariate and multivariate logistic regression analysis.

CMSA indicates the segment atherosclerosis between common carotid artery and the ipsilateral middle cerebral artery; CI, confidence interval; BP, blood pressure; BMI, body mass index; ccPWV, carotid–cerebral pulse wave velocity; cIMT, carotid intima-media thickness; baPWV, brachium-ankle pulse wave velocity.

**Discussion**

To evaluate the validity of ccPWV for detecting early stage CMSA in this study, we took catheter angiography as a golden standard. Early stage CMSA was
defined, and the most severe stenosis of CMSA was angiographically verified to be <50%. Two noninvasive methods that are regarded markers of the early stage of atherosclerosis, such as cIMT and baPWV, were compared with ccPWV in the detection of early stage CMSA in this study.

Multivariate analysis showed that ccPWV was independently associated with CMSA. Therefore, the results in this study suggest that ccPWV may have potential as a new risk marker of CMSA. In the ROC curve analyses, ccPWV had excellent diagnostic values for evaluating CMSA, and its AUC was significantly higher than that of cIMT and baPWV. It means that ccPWV is a valid method of diagnosing CMSA and was more accurate than cIMT and baPWV probably because ccPWV directly reflects the stiffness of the entire C-M segment; by contrast, cIMT only focuses on the carotid artery, and baPWV mainly focuses on central and peripheral arteries.17, 34, 35

In evaluating the validity of ccPWV for detecting...
early stage CMSA, the ROC curve of ccPWV presented good diagnostic values in this study. This result was consistent with previous findings that showed that PWV can be used to screen the subclinical atherosclerosis of central or peripheral arteries and can be used as a marker of early stage atherosclerosis. Previous studies demonstrated that PWV was a more useful measurement than cIMT in the determination of vascular damage in some diseases, particularly in the early stage of disease duration. We also noted that ccPWV was more accurate than cIMT in detecting early stage atherosclerosis in the present study. Furthermore, we observed that ccPWV closely correlated with the stenosis of early stage CMSA in Spearman’s correlation analysis. Upon visual inspection, we also found that only ccPWV correlated with the stenosis of early stage CMSA in the fractional polynomial plot with 95% CIs for the stenosis of early stage CMSA according to the level of each method on the basis of the generalized additive model. The machine for measuring cerebral arterial stiffness is a special two-channel TCD with a built-in arterial pulse wave analysis system, which can store, derive, and analyze the pulse waves and automatically calculate the value of ccPWV. Therefore, the measurement of cerebral arterial stiffness is a noninvasive, cost-effective, and portable method, and its operation is quite simple. The validity and reproducibility of the measurement of ccPWV were previously reported elsewhere. Therefore, ccPWV is reliable and suitable for the screening of the
general population.

This study has certain limitations. First, all data for this study were retrieved from our AIS database between June 2012 and August 2016. Owing to the limitations of patients with catheter angiography and the suitable temporal window for measuring ccPWV, there were only 81 patients and 154 C-M segments enrolled into this study. However, these issues are likely to have a minimal influence on the findings. In the follow-up study, this method will be used to screen early stage CMSA in the community population with a large sample size. Second, ccPWV was not compared with MRA and CTA for evaluating early stage CMSA in this study because we had selected DSA as the gold standard.

In conclusion, ccPWV has the potential to be a new marker of early stage CMSA, which may help us prevent the occurrence of stroke and decrease the burden on society more effectively.

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**Disclosures of Conflict of Interest**

None.

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