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[1, 2]. Cerebral large artery atherosclerosis diseases are considered important causes of IS because these diseases are responsible for approximately 15%–37% of all IS cases[3-5]. 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[3, 6, 7].

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[6-8], but there are limitations to their uses in screening early cerebral atherosclerosis[8-10]. DSA allows the viewing of the entire extracranial and intracranial artery system and provides information about the degree of stenosis, tandem lesions,

and collateral circulation[6]. However, it is invasive and is associated with an elevated risk of transient or permanent neurological complications[9]. MRA and CTA are noninvasive and have shown an overall agreement of up to 90%–97% compared with DSA[6-8]. However, MRA is expensive and time consuming and may not be always used owing to patient noncooperation or magnetic resonance (MR) contraindications. The major disadvantages of CTA are as follows: need for a high dose of iodine contrast and limitations in its use in renal failure, diabetes mellitus, and congestive heart failure patients; therefore, CTA is not appropriate for the study of arteries with a diameter smaller than 0.7 mm[8, 10]. At present, several noninvasive, cost-effective, and portable techniques, including the measurement of carotid intima–media thickness (cIMT) and pulse wave velocity (PWV), have been developed for the early detection of atherosclerosis in asymptomatic but otherwise high-risk subjects with traditional risk factors[11-15]. cIMT is regarded a surrogate marker for the presence and progression of atherosclerosis[11]. Many studies have reported that cIMT is useful for evaluating the risk and incidence of cardiovascular disease and is even associated with cerebrovascular diseases[11, 12, 16]. PWV reflects arterial stiffness, and it is one of the earliest detectable signs of functional and structural changes in the vascular wall[17-20]. Numerous studies have demonstrated that PWV can be used to screen the subclinical atherosclerosis of central or peripheral arteries and detect the subclinical target organ damage and is even regarded a marker of early stage of atherosclerosis[13, 20-25]. 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[17, 18, 21, 24].

Recently, carotid–cerebral PWV (ccPWV) measurement, which can be performed noninvasively and easily, has become available as a means of measuring cerebral arterial stiffness[26]. 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[8], and the C-M segment atherosclerosis (CMSA) is also considered a most frequent cause of anterior circulation IS[3, 6-8, 27]. 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.

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[28], 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

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[29] and that in the intracranial cerebral artery was measured using the method in the Warfarin vs. Aspirin for Symptomatic Intracranial Disease[30].

Measurements

ccPWV

As described previously[26], 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-

tem, 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 for detecting the proximal part of MCA, and MCA was insonated at a depth of 50–55 mm by using standard criteria[31]. To detect CCA, the other 4 MHz transducer in the angle fixator of 30° was placed on the ipsilateral pulsation point of CCA beside the thyroid notch in the neck of the patient. The transit time (Δt, ms) of the pulse wave that traveled between the two insonation sites was automatically measured by the arterial pulse wave analysis system on the basis of the waveform analysis of CCA and MCA[26]. 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 (D_1, cm) between the two probes by using a tape measure plus cosine 30° of detecting depth (D_2, cm) for CCA, namely, $D = D_1 + D_2 \times cosine\ 30°$[26]. Thus, ccPWVs on each side were calculated as $ccPWV = D/\Delta mt$ (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 elsewhere[26].

baPWV

Bilateral baPWV was measured using an automated 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 simultaneously measures bilateral brachial and posterior tibial arterial pulse waveforms and arterial BP by using the oscillometric method. Transmission time was calculated as the time taken for the waveform to travel between the right brachium and ankle. The transmission distance between the right brachium and the ankle was automatically calculated from the patient's height[32]. The baPWVs on each side were automatically calculated as PWV = transmission distance/transmission 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 measurements 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 proximal to the bifurcation, as described in previous studies[14]. All measurements were obtained without prior clinical information about the subjects. Compared with an applied standard and the repeated measurements, the intraclass correlation coefficients were ≥ 0.85, and the median differences of the pairs of 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 exhibited 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 software 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 diagnosed 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
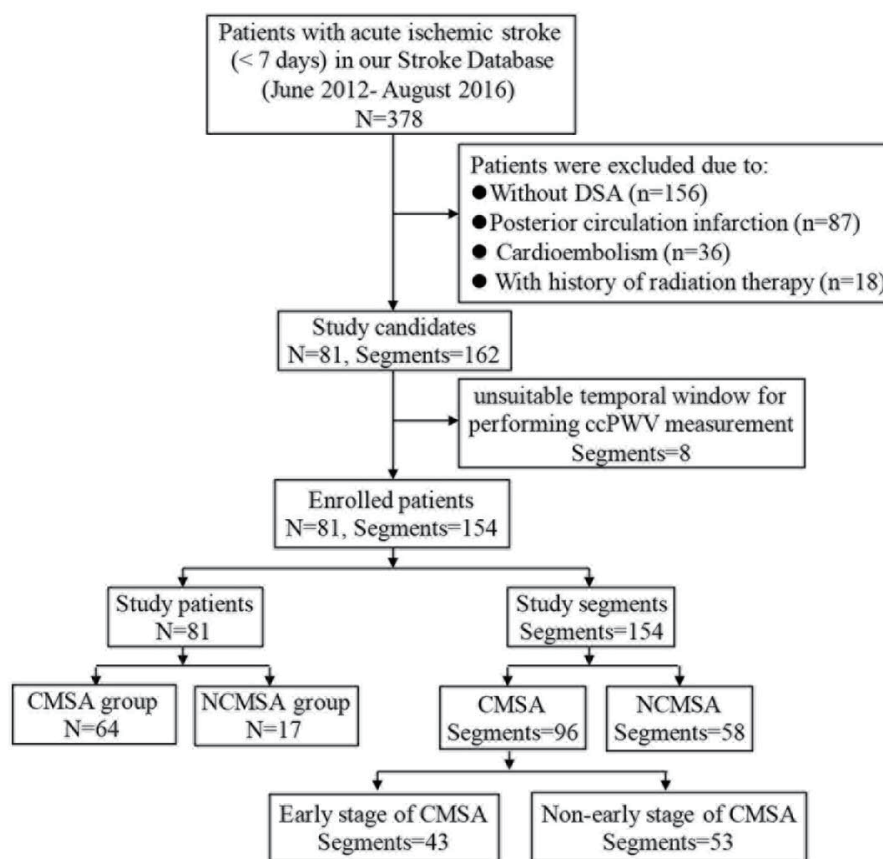
Fig. 1. Study flow chart

DSA, digital subtraction angiography; ccPWV, carotid–cerebral pulse wave velocity; CMSA, the segment atherosclerosis between the CCA and the ipsilateral MCA; NCMSA, non-CMSA.

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=

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/m^2	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.

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.

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

Table 3. Diagnostic characteristics for evaluating CMSA and its early stage using three methods

	CMSA			Early stage of CMSA		
	ccPWV (m/s)	cIMT (mm)	baPWV (m/s)	ccPWV (m/s)	cIMT (mm)	baPWV (m/s)
AUC	0.887*	0.786*	0.606*	0.815[†]	0.730[†]	0.475[†]
(95% CI)	(0.835, 0.938)	(0.711, 0.861)	(0.517, 0.695)	(0.729, 0.902)	(0.630, 0.830)	(0.354, 0.596)
P Value	<0.001	<0.001	0.027	<0.001	<0.001	0.668
Sensitivity,%	70.1	67.7	55.2	86	58.1	48.8
Specificity,%	93.1	82.8	74.1	70.7	82.8	63.8
Youden's index	0.639	0.505	0.293	0.567	0.409	0.126
Cutpoint	5.8	0.95	15.7	5.4	0.95	14.8

*[†] $P \leq 0.001$.
CMSA indicates the segment atherosclerosis between common carotid artery and the ipsilateral middle cerebral artery; ccPWV, carotid–cerebral pulse wave velocity; cIMT, carotid intima-media thickness; baPWV, brachium-ankle pulse wave velocity; AUC, area under the curve; CI, confidence interval.
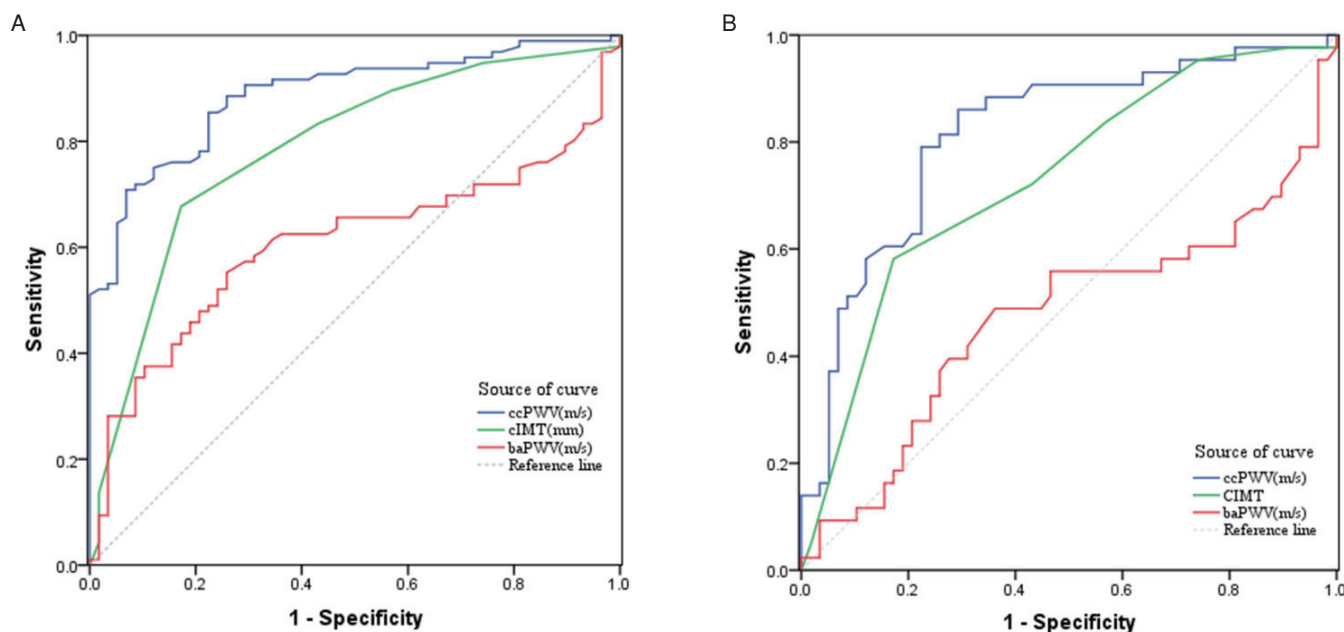
**Fig. 2.** ROC curves of three methods for diagnosing CMSA and its early stage
A. ROC curves of ccPWV, cIMT, and baPWV for evaluating CMSA. The AUCs of the three methods are significantly different ($P \leq 0.001$). B. ROC curves of ccPWV, cIMT, and baPWV for detecting early stage CMSA. The AUCs of the three methods are significantly different (P <0.001). ROC, receiver operating characteristic; CMSA, the segment atherosclerosis between CCA and the ipsilateral MCA; AUC, area under the curve; ccPWV, carotid–cerebral pulse wave velocity; cIMT, carotid intima–media thickness; baPWV, brachium-ankle pulse wave velocity.

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
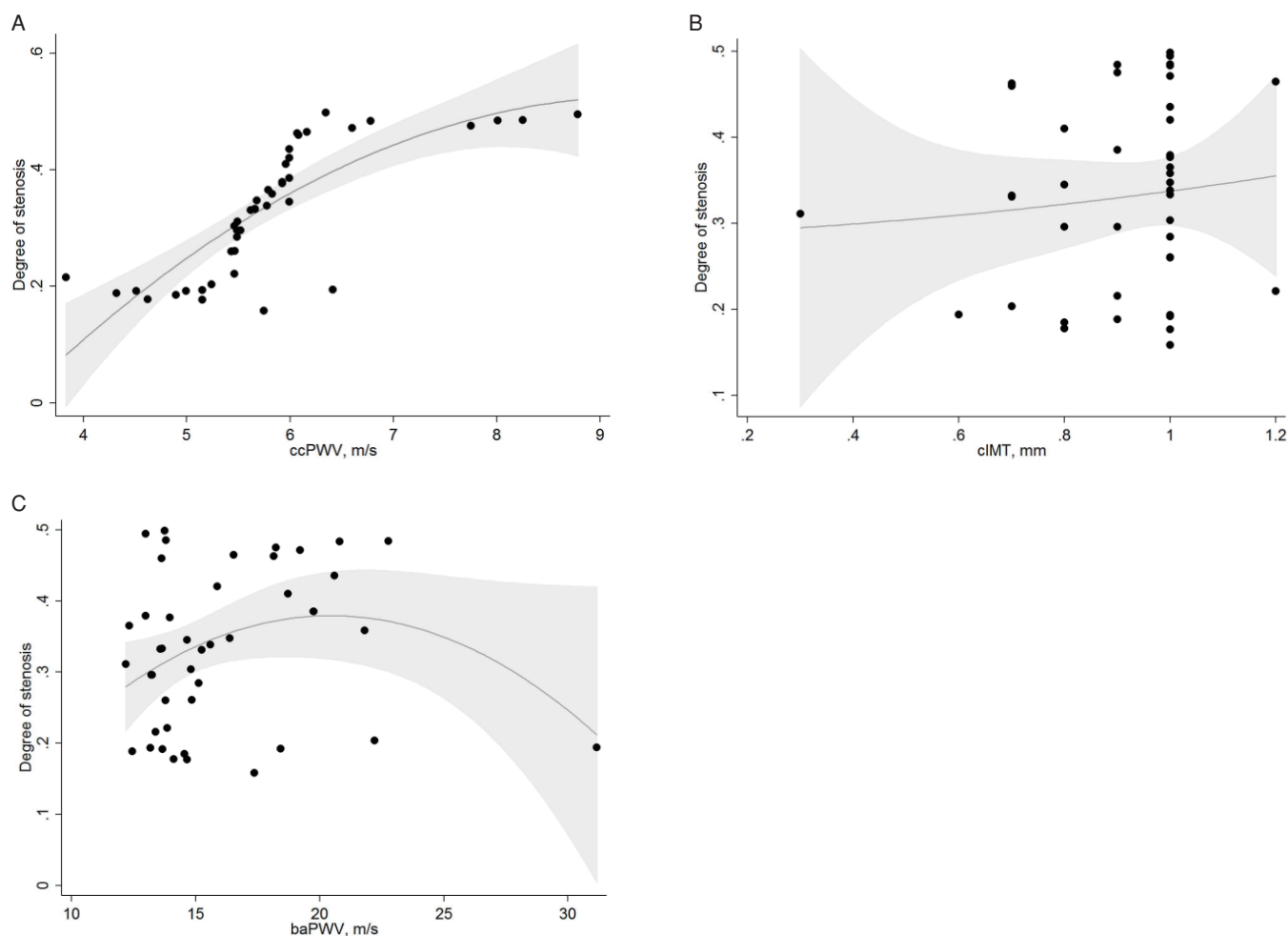
Fig. 3. Relationships between the levels of three methods and the stenosis degree of early stage CMSA

Black lines and gray shadows represent the estimated probability and 95% CIs for the stenosis of early stage CMSA at the level of methods on the basis of the generalized additive model. The x axis is limited from the 5th to the 95th percentile of the level of the method. A. Relationship between ccPWV and stenosis degree of early stage CMSA. B. Relationship between cIMT and stenosis degree of early stage CMSA. C. Relationship between baPWV and stenosis degree of early stage CMSA. CMSA, segment atherosclerosis between the CCA and the ipsilateral MCA; CI, confidence interval; ccPWV, carotid–cerebral pulse wave velocity; cIMT, carotid intima–media thickness; baPWV, brachium-ankle pulse wave velocity.

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 [13, 20-25]. 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 [36, 37]. 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 regressThe 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 [26]. 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.

Sources of funding

Disclosures of Conflict of Interest

None.

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