Association Between Carotid-Cerebral Pulse Wave Velocity and Acute Ischemic Stroke: Clinical Trial Protocol

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Background: Pulse wave velocity is commonly regarded as the most effective and noninvasive indicator for evaluating arterial stiffness, while increased arterial stiffness is known to be related to atherosclerosis, which has been proved to play a significant role on the onset of acute ischemic stroke. However, it is still only used in the assessment of central and peripheral arteries. Our previous studies have found that carotid-cerebral pulse wave velocity measured using transcranial Doppler may be a promising method for the assessment of human cerebral arterial stiffness. This trial was designed to examine the association between carotid-cerebral pulse wave velocity and acute ischemic stroke. *Methods:* In a single-center, single-arm, prospective clinical trial, patients with acute ischemic stroke who had anterior circulation infarcts confirmed by magnetic resonance imaging are eligible to receive measurement of carotid-cerebral pulse wave velocity, which is measured in the supine position with transcranial Doppler that using 2-MHz and 4-MHz ultrasound probes by 2 experienced operators. Subjects will be received follow-up for 1 year. Vascular and nonvascular death at follow-up will be assessed as primary outcomes. Secondary outcomes include intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, recurrence or aggravation of ischemic stroke. *Conclusion:* This trial will be the first to evaluate carotid-cerebral pulse wave velocity in patients with acute ischemic stroke using transcranial Doppler. The results may provide more valuable theoretical basis for the prevention, treatment, and prognosis of acute ischemic stroke.

Key Words: Carotid-cerebral pulse wave velocity—acute ischemic stroke—cerebral arterial stiffness—intracranial atherosclerosis

Introduction

Stroke is a devastating disease, which is the third most common cause of physical disability and the second most common cause of death in the world.[1] According to the original TOAST criteria, there are 5 major categories: large artery atherosclerosis, small artery occlusion, cardioembolism, stroke of other determined cause, and stroke of undetermined cause.[2] Ischemic stroke, disease with high rate of disability and mortality, will cause patient much suffering and bring a significant economic burden to family and society, especially in low-income and middle-income countries.[3]

Atherosclerosis, formed by chronic inflammation of the arteries and lipid-rich plaques in blood vessel walls, is the underlying cause of intracranial, coronary, and peripheral arterial diseases with high mortality and morbidity rates in the world.[4,5] Risk factors contributed to atherosclerosis include hypertension, diabetes, dyslipidemia, obesity, and smoking.[6] Intima-media thickness and lipid-rich plaques in large arteries have been demonstrated to be strong evidences of atherosclerosis. With increasing intima-media thickness and lipid-rich plaques of large arteries, the arterial stiffness consistently increased.[7] Arterial wall

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damage and atherosclerosis are caused by increasing arterial stiffness,[8,9] and the association between arterial stiffness and coronary or peripheral artery atherosclerosis had been well established.[10,11] Consequently, the techniques used to measure arterial stiffness we took are available for the assessment of atherosclerosis.

The artery stiffens with aging, a process that is accelerated by a variety of changes involving structural and cellular elements of the arterial wall.[12-14] Interacting factors contributed to arteriosclerosis include atherosclerosis, endothelial dysfunction, oxidative stress, and calcification.[12,14,15] Pulse wave velocity (PWV) is commonly regarded as the most effective and noninvasive indicator for evaluating arterial stiffness.[12-14] Brachial-ankle PWV (baPWV) has been used as the standard measure for peripheral arterial stiffness and carotid-femoral PWV (cfPWV) for central arterial stiffness.[15,16]

Intracranial atherosclerosis is the leading cause of ischemic stroke due to the increasing prevalence of the disease and the synergism of multiple risk factors.[17,18] Currently the only feasible method to reduce morbidity and mortality of ischemic stroke is primary prevention. Early evaluation of intracranial atherosclerosis may guide us for early therapeutic interventions to reduce the onset of acute ischemic stroke (AIS).[19-21] A study showed high strength evidence that there is a powerful relationship between baPWV and the presence and burden of intracranial artery atherosclerosis.[15] Recent study demonstrated that increased PWV can be used as an indicator of higher risk and mortality of ischemic stroke.[11] However, neither baPWV nor cfPWV can directly measure cerebral arterial stiffness. The common carotid artery (CCA)-middle cerebral artery (MCA) segment atherosclerosis (CMSA) is widely regarded as a most frequent cause contributed to infarction of anterior circulation.[20-22] Recently, an advanced and noninvasive technique named carotid-cerebral PWV (ccPWV) has become available as a means of measuring CCA-MCA segment arterial stiffness.[23,24] From a recent clinical trail, 90 healthy subjects indicated that ccPWV was highly associated with baPWV in evaluation of arterial stiffness, and advancing age and increased diastolic blood pressure had strongly relationship with higher ccPWV.[23] Patients with cerebral artery atherosclerosis show a higher mean ccPWV than those without.[24] At present, no study has yet directly evaluated cerebral arterial stiffness in patients with AIS using ccPWV. This clinical trial was designed to examine the association between ccPWV and AIS. We will additionally analyze whether ccPWV plays critical roles in risk factors, TOAST classification, and prognosis of ischemic stroke.

Methods

Study Design

In a single-center, single-arm, prospective clinical trial, patients with AIS (within 7 days after symptom onset) who had anterior circulation infarcts confirmed by magnetic resonance imaging are eligible to receive measurement of ccPWV. This clinical trial was approved by the Ethical Committee of the Second Affiliated Hospital of Guangzhou Medical University (Reference number: 2018-hs-021) and was registered at Chictr.org.cn (Registration number: ChiCTR1800015449) on 31 March, 2018. According to the Helsinki declaration, all of eligible participants will be required to sign written informed consent before registration. The study will be performed in the Department of Neurology, Second Affiliated Hospital of Guangzhou Medical University by experienced researchers and aims to measure ccPWV value in patients with AIS. Simultaneously, the subjects will be evaluated using modified Rankin Scale, National Institutes of Health stroke scale (NIHSS), and Barthel Index, followed by 1 year. The procedures and details of the study are summarized in Figure 1.

Patient Eligibility

The inclusion and exclusion criteria of the patients are presented in Table 1.

Measurement of ccPWV

ccPWV is measured with a special 2-channels transcranial Doppler (Production license:20110048, Product

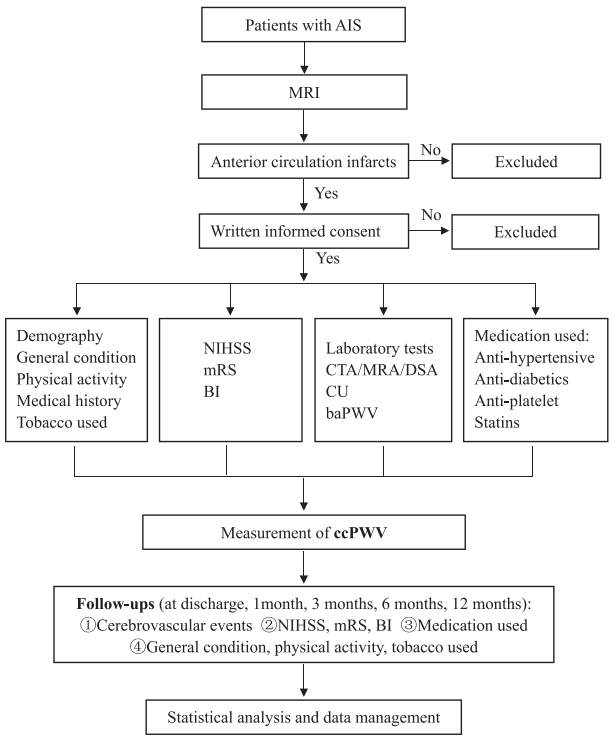

Figure 1. *Procedures and details of the study design. AIS, acute ischemic stroke; baPWV, brachial-ankle pulse wave velocity; BI, Barthel Index; ccPWV, carotid-cerebral pulse wave velocity; CTA, computed tomography angiography; CU, Carotid ultrasonography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale.*

registration:20152230181, Beijing Chioy Medical Technology Co., Ltd, Beijing, China.) using 2-MHz and 4-MHz ultrasound transducers in the supine position by 2 experienced operators.[23,24] The machine used in this study has a built-in program model called 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.[23,24] The 2-MHz probe will be held in a temporal window for detecting the proximal part of MCA, and MCA was insonated at a depth of 50-55 mm using standard criteria.[25] The other 4-MHz transducer in the angle fixator of 30° will be placed on the ipsilateral pulsation point of CCA beside the thyroid notch in the neck of the patient to detect CCA. The transit time (Δt, ms) of the pulse wave traveled between the 2 insonation sites will be automatically measured by the arterial pulse wave analysis system based on the wave form analysis of CCA and MCA. The mean transit time (Δmt) will be determined from10 consecutive cardiac cycles. The distance (D, cm) traveled by the pulse wave will be defined as the body surface distance (D1, cm) between the 2 probes using a tape measure plus cosine30° of detecting depth (D2, cm) for CCA, namely, $D = D1 + D2 \times \cos 30°$. Thus, ccPWVs on each side were calculated as $ccPWV = D/\Delta mt(cm/s)$. All the above can be automatically completed by the arterial pulse wave analysis system except the measurement of body surface distance.[23,24]

In all the studies, ccPWV should be obtained in a temperature-controlled environment; ideally 24°C-26°C. Tobacco used, alcohol consumption, and caffeinated drinks should be avoided at least 12 hours before measurement. Subjects will be advised to rest for a minimum of 5 minutes.

Follow-Up

Subjects will be received regular basis (at the time of discharge, 1 month, 3 months, 6 months, 12 months) follow-up through face-to-face. Researchers will record their general condition, physical condition, muscle strength, tobacco used, alcohol consumption, and stress. The medication used include antihypertensive, antidiabetics, antiplatelet aggregation, and statins. Each subject will be evaluated in neurology with modified Rankin Scale, NIHSS, and Barthel Index, and then judge whether subjects suffer from transient ischemic attack, aggravation or recurrence of ischemic stroke. Subjects who suffer from serious internal medical diseases or are unable to maintain will be excluded during follow-up. All the data will be uploaded to the case report form (CRF) by data collectors who had been trained rigorously.

Outcomes

Vascular and nonvascular death at follow-up will be assessed as primary outcomes. Secondary outcomes include intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, recurrence or aggravation of ischemic stroke.

Sample Size and Statistical Analysis

As this trial is a preliminary single-arm study aiming to examine the association between ccPWV and AIS, sample size based on statistical calculations is not determine.[26] An alternative method is that participants will be divided into 4 groups (150 in each group) according to the value of ccPWV. Considering 10% loss to follow-up, which is based on previous training with this population, the total of participants will be set at 666.

Statistical analysis will be handled by a single statistician who is blind to the group and performed using SPSS 22.0 statistical software for windows. The values of ccPWV will be presented as mean ± standard deviation, or percentages of subjects. Student *t* test will be employed to evaluate differences in value of ccPWV between NIHSS scores more than or equal to 6 and NIHSS scores less than 6 patients with AIS. Chi-square test will be used for categorical variables. To identify the relativity between risk factors contributed to AIS and ccPWV, we will perform multiple logistic regression analysis with adjustments for age, sex, hypertension, diabetes mellitus, hyperlipidemia,

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria
1. Male or female pts (aged between 18 and 80 years)
2. Patients with anterior circulation AIS confirmed by MRI
3. No more than 7 days from AIS onset
4. NIHSS scores from 0 to 10
5. Suitable temporal window for measuring of ccPWV
6. Sign written informed consent before registration
Exclusion criteria
1. Serious diseases such as severe heart failure, hepatic or renal system diseases
2. History of malignant tumor
3. Patients with head or neck tumors treated with radiotherapy
4. Patients with carotid or cerebral artery stenting
5. Patients with C-M segment occlusion
6. Factors that lead to inaccuracy of ccPWV measurement
7. Cardiogenic or nonatherosclerotic cerebrovascular diseases
8. Pregnancy or breastfeeding
9. Be unable to maintain compliance and follow-up
10. Patients judged inappropriate by the researchers

Abbreviation: AIS, acute ischemic stroke; ccPWV, carotid-cerebral pulse wave velocity; and C-M segment, the segment between common carotid artery and ipsilateral middle cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

atrial fibrillation or flutter, obesity, tobacco used, alcohol consumption, diet quality, physical inactivity, stress, life events, and depression. The association between ccPWV and each subtype in the TOAST criteria will be analyzed with a multiple logistic regression model. The level of statistical significance will be set at $P \leq .05$.

Data Collection and Management

Project administrator set out strict procedures to ensure that the data is well preserved and can be traceable. During this trial, the original data from patients and clinical assessment will be collected by data collectors on the CRF made by statistician. Furthermore, all of this data will be precisely entered into a password-protected computer 2 week after data collection. The data collectors will hand CRF and written informed consent to administrator for keeping after all of data are entered.

Quality Control

To assure an integrated, scientific, and effective study, the operators, data collectors, data analysts, data managers will receive strict and specific training before the implementation of clinical protocol. The operators who is the most basic and critical to ensure the reliability of the trial will be required to improve theory and practical ability about ccPWV. The operators, data collectors, and data analysts are totally blind to enrollment of patients. In addition, in order to make subjects can better during the study, the operators will relieve the negative reaction of subjects by particularly taking some communicating methods and skills. Data collectors will fill the original data in the CRF in a timely, integrated, and accurate way.

Discussion

PWV is extensively used to assess arterial stiffness because of its prominent merits which include noninvasive, reproducible, portable.[16,17] baPWV has commonly regarded as the standard measure for peripheral arterial stiffness and cfPWV for central arterial stiffness.[16,17] In the field of neurology, cerebral arterial stiffness is increasingly the focus of attention, especially the segment from CCA to the ipsilateral MCA, this is because this segment atherosclerosis is widely described as one of the most frequent causes contributed to infarction of anterior circulation.[20-22] However, both baPWV and cfPWV were unable to evaluate cerebral arterial stiffness in a direct way, although some studies indicated that patients with AIS show a higher mean PWV than those without.[10,15,27] With the update of arterial pulse wave analysis system, ccPWV has been greatly improved in recent years and has become available as a promising technique for measuring CCA-MCA segment arterial stiffness.[23,24] Our previous studies demonstrated that ccPWV was independently associated with baPWV in evaluation of arterial stiffness and had proven to be highly associated with the presence of CMSA.[23,24] Whether ccPWV has significant impact on the onset and prognosis of AIS is difficult to predict. Therefore, this clinical trial aims to measure CCA-MCA segment arterial stiffness in AIS and systematically examine the association between ccPWV and AIS.

In theory, ccPWV may closely relate to risk factors (age, hypertension, diabetes mellitus, hyperlipidemia, obesity, tobacco used, alcohol consumption, etc.) contributed to AIS and play a certain role in TOAST classification. ccPWV may yet be a noninvasive technique for evaluation of CMSA in the early stage and guide us for early therapeutic interventions to reduce the onset of AIS.[24] The values of ccPWV in AIS may guide us for systematic therapy in the hope of relieving the sufferings and reducing recurrent rate of AIS.

However, 2 limitations of this study have to be considered. First, this trail is a single-center study. Second, not all patients have suitable temporal window for measuring of ccPWV, there are expected to avoid the issue by improving practical experience.

Conclusion

To our knowledge, this clinical trial will be the first to examine the association between ccPWV and AIS. The results of this clinical trial may indicate that ccPWV is closely associated with AIS and will provide more valuable theoretical basis for the prevention, treatment, and prognosis of AIS.

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