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Application value of transcranial contrast-enhanced ultrasonography in evaluating middle cerebral artery stenosis

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Abstract. – OBJECTIVE: To detect the display rate and flow velocity of intracranial circle of Willis (anterior, middle, and posterior cerebral arteries) with transcranial contrast-enhanced transcranial color-coded sonography (CE-TCCS), using digital subtraction angiography (DSA) as the golden diagnostic standard.

PATIENTS AND METHODS: We collected data from 104 patients with suspected stroke treated in our hospital between December 2019 and October 2021. The detection rate of the intracranial circle of Willis, anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) were analyzed based on routine TCCS and CE-TCCS data. Based on digital subtraction angiography (DSA) data, the degree of MCA stenosis was divided into mild stenosis (<50%), moderate stenosis (50-69%), severe stenosis (70-99%), and bilateral middle cerebral artery CE-TCCS examinations were performed. We evaluated MCA color blood flow on CE-TCCS, and recorded the peak systolic velocity (PSV), end-diastolic velocity (EDV), and mean flow velocity (MFV).

RESULTS: The display rates of ACA, MCA, and PCA were significantly improved on the CE-TCCS, and the PSV, EDV and MFV of the MCA stenosis group were higher than those of the normal group. The flow velocity of each stenosis subgroup was increased compared to the normal group. The optimal cutoff values of normal and stenosis under the receiver operating characteristic (ROC) curve were PSV = 168.5 cm/s, EDV = 61.5 cm/s, and MFV = 110.5 cm/s. The optimal cutoff values for mild and moderate stenosis and for moderate and severe stenosis were PSV = 201.5 cm/s and 249.5 m/s, EDV = 95.2 cm/s and 141.5 cm/s, and MFV = 137.6 cm/s and 160.5 cm/s, respectively. PSV and MFV had the most significant sensitivity, specificity, and accuracy.

CONCLUSIONS: Transcranial contrast-enhanced ultrasonography can improve the display rate of intracranial blood vessels and can accurately diagnose MCA stenosis.

Key Words:
Middle cerebral artery, Stenosis, CE-TCCS, DSA.

Introduction

Nowadays, stroke has become the leading cause of death and disability in many countries. The etiology of cerebrovascular disease can be divided into hemorrhagic and ischemic encephalopathy, of which ischemic encephalopathy accounts for as many as 70-80% of the total cases[1]. The middle cerebral artery (MCA) is the most easily detected and the largest of the three major arteries in the brain. MCA plays an important role in the blood supply of the brain and has the highest incidence among the large intracranial arteries stenosis[2]. In cases of severe stenosis in the MCA on one side of the patient, the short-term risk of stroke recurrence is significantly high and can reach 60.7%. Therefore, early detection of MCA stenosis is particularly important for the prevention and subsequent treatment of stroke, since precise evaluation of the degree of stenosis can allow the provision of timely appropriate treatment.

Transcranial color-coded sonography (TCCS) is a special color-coding technique combining two-dimensional grayscale, color Doppler, and spectral Doppler images for displaying the color vessels clearly. At the same time, TCCS can accurately locate and measure blood flow spectrum, enhancing blood vessel information and greatly improving the diagnostic accuracy[3,4]. However, due to the poor sound penetration of the temporal window, visualization of intracranial blood vessels can be significantly poor in elderly individuals. In order to improve the visualization rate of intracranial arteries and accurately locate the intracranial stenosis, this study used CE-TCCS as the research method and digital subtraction angiography (DSA) as the imaging modality to diagnose stenosis. In addition to different degrees of stenosis, we determined the optimal cutoff value that allowed us to distinguish between normal

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from stenotic MCAs and improve the visualization rate of intracranial blood vessels. Furthermore, the purpose of this study was to formulate a reference standard for the flow rate of the MCA stenosis after contrast-enhanced ultrasonography, which can be applied more appropriately and easily in clinical settings.

Patients and Methods

Patients

A total of 104 patients, 55 males and 49 females, aged 32-81 years old, who were treated in our hospital from December 2019 to October 2021 were included. All patients were suspected of MCA stenosis and underwent DSA examination during the same period. In DSA, stenotic vessels are divided into three grades: mild stenosis (stenosis rate <50%), moderate stenosis (stenosis rate ≥50-69%), and severe stenosis (stenosis rate ≥70-99%)[5]. In this study, patients with MCA were divided into two groups, namely the control group (n = 134 cases) and the stenosis group (n = 74 cases), including 31 cases with mild stenosis, 29 cases with moderate stenosis, and 14 cases with severe stenosis. The control group included patients whose blood vessels were diagnosed as normal by DSA examinations. Exclusion criteria were as follows: patients with severe stenosis or occlusion of internal carotid artery (one or both sides); patients with extremely severe stenosis or occlusion of MCA and multiple stenosis or long stenosis on one side; patients with congenital vascular ring dysplasia and intracranial posterior circulation lesions, diseases which may increase the flow rate of MCA due to compensatory effect.

All patients gave informed consent to enter the study. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Peking University Shenzhen Hospital.

Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound was performed using a PHILIPS EPIQ 7 (C) (Philips, Amsterdam, Netherlands) color Doppler ultrasound instrument, and a phased array probe with a practical frequency of 1.0-5.0 MHz was used. Contrast-enhanced ultrasound uses the conventional ultrasound mode, and adjusts the mechanical index, color gain, and filter to the optimal settings during the imaging process. All patients signed the informed consent form before contrast-enhanced ultrasound. An intravenous channel was established, and SonoVue (Bracco, Milan, Italy) was used as the contrast medium. Before use, 5 mL of normal saline was used to dissolve the contrast medium lyophilized powder, and a dose of 1.0 mL/time was injected into the cubital vein (bolus injection), followed by a rapid injection of 5 mL of normal saline. Color Doppler ultrasonography was performed through the temporal window so as to better understand the display of the intracranial circle of Willis. Furthermore, special care was taken to avoid the blooming artifact, which is caused by excessive contrast agent concentration in the early stage, and we waited for the anterior cerebral artery (ACA), MCA, posterior cerebral artery (PCA), and their branch vessels to be clearly displayed. The peak systolic flow velocity was manually measured, and the shape, course, direction, and the presence or absence of thinning or even interruption of the MCA were then observed. The peak systolic velocity (PSV) and the end-diastolic velocity (EDV) of MCA were calculated manually, whereas the mean flow velocity (MFV) was automatically calculated by a computer based on PSV and EDV values. Following this process, all data were stored and recorded for further use. All CE-TCCS examinations were performed by sonographers with more than five years of experience.

Digital Subtraction Angiography

Intracranial vascular DSA was performed with a vascular contrast agent (GE Company, USA). The Seldinger intubation technique was used to puncture the femoral artery, and the iopromide contrast agent (Ultravist, Bayer AG, Germany) was injected for intracranial angiography to record the presence or absence of vascular stenosis and occlusion so as to reconstruct the DSA image. The diagnosis of DSA was used as the gold standard for evaluating the degree of MCA stenosis.

Statistical Analysis

The SPSS 20.0 statistical software (IBM Corp., Armonk, NY, USA) was used for data processing. Measurement data were expressed as mean ± standard deviation ($x \pm s$), *t*-test and chi-square test were used to compare the data. Using the diagnostic results of DSA as the gold standard, the PSV, EDV, and MFV curves of different stenosis groups were drawn. Furthermore, the area under the curve, Youden index, the best cutoff value,

Table I. Detection rates of the circle of Willis by plain TCCS and CE-TCCS (n = 104).

	TCCS (%)	CE-TCCS (%)	*p*
ACA	85.6 (178)	94.7 (197)	< 0.001
MCA	87.0 (181)	100.0 (208)	< 0.001
PCA	84.6 (178)	98.0 (204)	< 0.001

ACA: anterior cerebral artery, MCA: middle cerebral PCA: artery, posterior cerebral artery, TCCS: transcranial color-coded sonography, CE-TCCS: contrast-enhanced transcranial color-coded sonography.

and the diagnostic sensitivity and specificity were obtained. A value of $p < 0.05$ was considered statistically significant.

Results

Detection Rate of Intracranial Circle of Willis

The detection rates of the intracranial circle of Willis using the conventional TCCS and CE-TCCS are shown in Table I. The MCA had the highest detection rate before contrast-enhanced ultrasound, followed by the ACA and the PCA. After contrast-enhanced ultrasound, the visualization rate of all circles of Willis was significantly improved ($p < 0.001$). A comparison of the images obtained before and after contrast-enhanced ultrasound is shown in Figure 1.

Comparison of Blood Flow Velocity Before and After Contrast-Enhanced Ultrasound

The blood flow velocities of the circle of Willis in conventional TCCS and CE-TCCS are shown in Table II. Both TCCS and CE-TCCS clearly showed the circle of Willis: 178 anterior cerebral arteries, 181 middle cerebral arteries, and 153 posterior cerebral arteries. The blood vessels of the DSA-diagnosed control group were selected for contrast before and after contrast-enhanced ultrasound. Before contrast-enhanced ultrasound the blood flow velocity of the MCA was the highest, followed by the ACA and the PCA. After injection of the contrast agent, the blood flow velocity in each artery increased by 18-34%.

Comparison of PSV, EDV, and MFV Among the MCA Stenosis Groups

According to the different degrees of MCA stenosis in the DSA diagnosis results, the 208 vessels were divided into 74 vessels with stenosis and 134 vessels without stenosis. The DSA results of each group are shown in Figure 2. The statistical results revealed that the PSV, EDV, and MFV of the stenosis group were higher compared to shown in Table III. There were 31 cases of mild stenosis, 29 cases of moderate stenosis, and 14 cases of severe stenosis. The PSV, EDV, and MFV of the three different stenosis groups were all higher compared to the normal group, and the flow velocity gradually increased with the aggra-

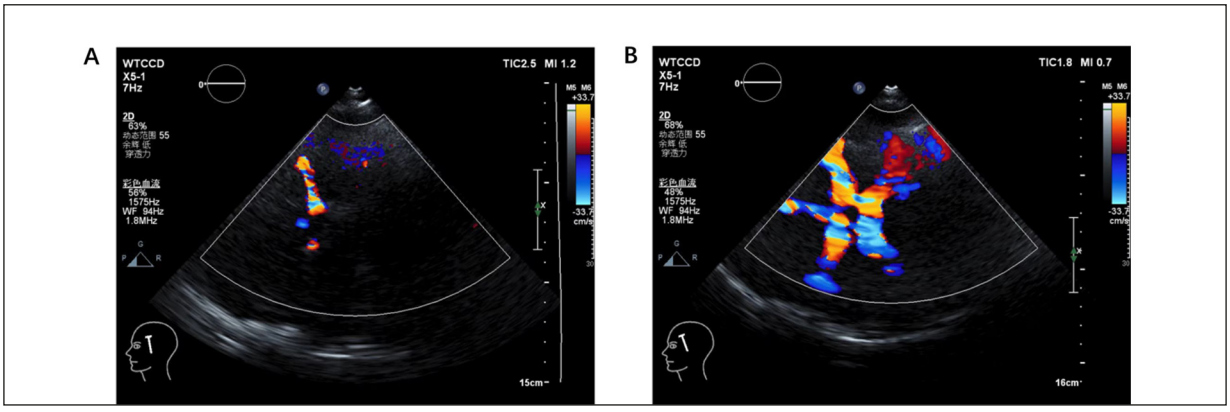

Figure 1. **A**, conventional TCCS showing left MCA of the intracranial circle of Willis. **B**, CE-TCCS showing the entire intracranial circle of Willis.

Table II. Average velocities of the circle of Willis detected by plain TCCS and CE-TCCS (n = 104).

	TCCS (cm/s)	CE-TCCS (cm/s)	*p*
ACA	93.2 ± 15.7	117.1 ± 16.1	< 0.001
MCA	120.8 ± 17.4	141.8 ± 19.4	< 0.001
PCA	67.4 ± 13.9	81.8 ± 15.5	< 0.001

ACA: anterior cerebral artery, MCA: middle cerebral PCA: artery, posterior cerebral artery, TCCS: transcranial color-coded sonography, CE-TCCS: contrast-enhanced transcranial color-coded sonography.

vation of stenosis (p <0.001), as shown in Table IV. The CE-TCCS color doppler flow images and spectral doppler images of all groups are shown in Figure 3.

CE-TCCS Diagnostic ROC Curve Analysis Results

The area under the curve (AUC) of the receiver operating characteristic (ROC) analysis in CE-TCCS diagnosis demonstrated that the optimal diagnostic velocity values for the normal and the stenotic groups were PSV 168.5 cm/s, EDV 61.5 cm/s, and MFV 110.5 cm/s. The sensitivity, specificity, AUC (95% CI), and Youden index are shown in Table V. The optimal diagnostic velocity values for mild and moderate stenosis were PSV 201.5 cm/s, EDV 95.2 cm/s, and MFV 137.6 cm/s. The sensitivity, specificity, AUC (95% CI) and the Youden index are shown in Table VI. The optimal diagnostic velocity values for moderate

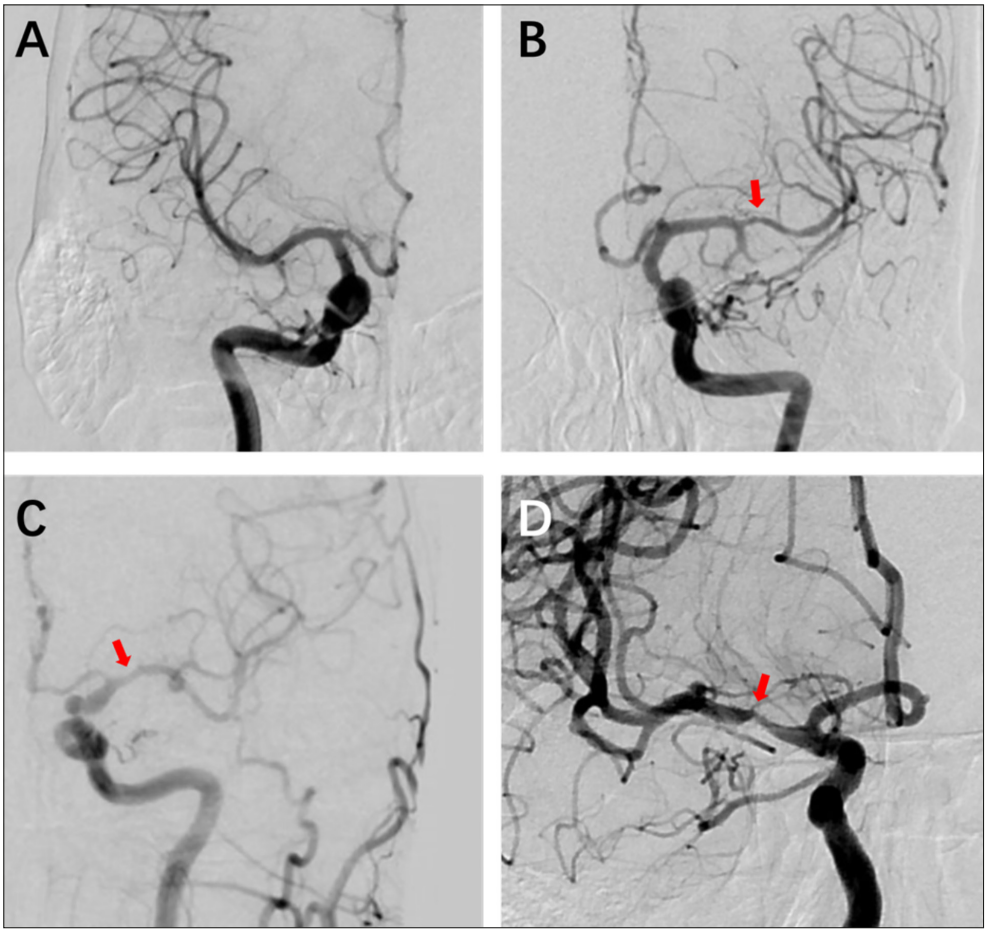

Figure 2. MCA stenosis on DSA was classified as normal (**A**), mild stenosis (< 50%) (**B**), moderate stenosis (50-69%) (**C**), severe stenosis (70-99%) (**D**). The red arrow highlights the stenosis of the vessel.

Table III. Comparison of flow velocity between normal and stenosis group.

	PSV	EDV	MFV
Control group	141.8 ± 19.4	48.2 ± 8.0	95.1 ± 11.8
Stenosis group	220.0 ± 44.0	106.8 ± 15.0	143.6 ± 25.4
t	-10.5	-7.7	-10.5
p	< 0.001	< 0.001	< 0.001

PSV: peak systolic velocity, EDV: end-diastolic velocity, MFV: mean flow velocity.

Table IV. Comparison of flow velocity between normal and stenosis subgroups.

	PSV	EDV	MFV
Control group	141.8 ± 19.4	48.2 ± 8.0	95.2 ± 11.8
Mild stenosis group	177.3 ± 14.8	59.4 ± 13.6	119.6 ± 12.9
Moderate stenosis group	234.2 ± 17.7	81.9 ± 15.2	153.3 ± 12.0
Severe stenosis group	284.8 ± 18.6	132.6 ± 11.3	176.9 ± 11.6
p	< 0.001	< 0.001	< 0.001

PSV: peak systolic velocity, EDV: end-diastolic velocity, MFV: mean flow velocity.

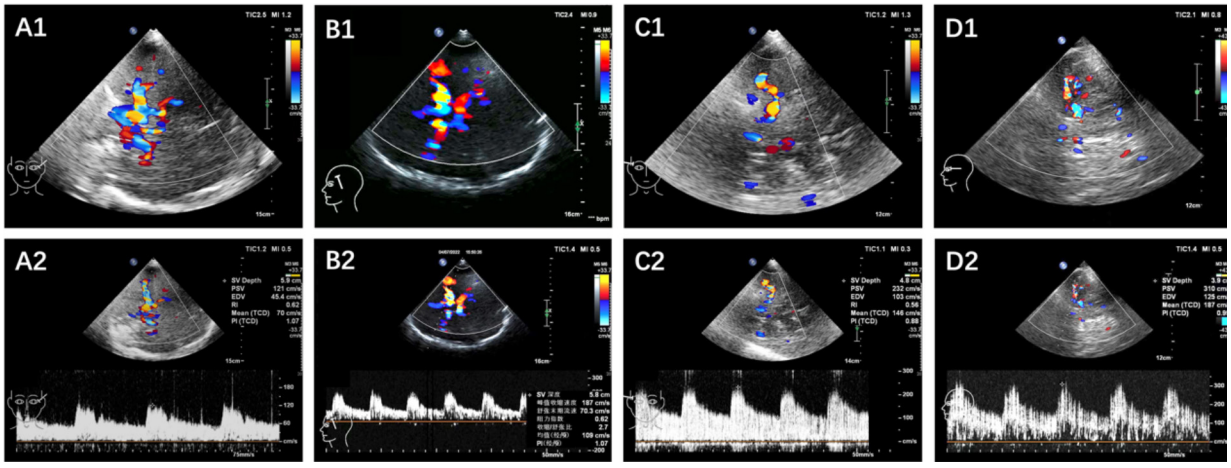

Figure 3. A1, Color Doppler Flow Image showed normal left MCA; **A2**, Spectral Doppler image showed PSV of approximately 121 cm/s; **B1,** Color Doppler Flow Image showed mild stenosis in the left MCA; **B2**, Spectral Doppler image showed a PSV value of approximately 187 cm/s; **C1**, Color Doppler Flow Image showed moderate stenosis in the right MCA; **C2**, Spectral Doppler image showed that PSV was approximately 232 cm/s; **D1**, Color Doppler Flow Image showed severe stenosis in the left MCA; **D2**, Spectral Doppler image showed that PSV was approximately 310 cm/s.

and severe stenosis were PSV 249.5 cm/s, EDV 141.5 cm/s, and MFV 160.5 cm/s. The sensitivity, specificity, AUC (95% CI), and the Youden index are shown in Table VII.

Discussion

Population aging has become an increasingly prominent phenomenon on a global scale, and

Table V. The optical cutoff velocity value between normal and stenosis group

	Cutoff value (cm/s)	Sensitivity	Specificity	AUC (95% CI)	The Youden index
PSV	168.5	0.892	0.947	0.977 (0.958-0.995)	0.839
EDV	61.5	0.635	0.957	0.884 (0.829-0.940)	0.792
MFV	110.5	0.905	0.947	0.975 (0.955-0.995)	0.852

Table VI. The optical cutoff velocity value between mild and moderate stenosis group.

	Cutoff value (cm/s)	Sensitivity	Specificity	AUC (95% CI)	The Youden index
PSV	201.5	1.000	0.992	1.000 (0.999-1.000)	0.992
EDV	95.2	0.814	0.896	0.997 (0.957-0.997)	0.710
MFV	137.6	0.953	0.968	1.000 (0.999-1.000)	0.852

PSV: peak systolic velocity, EDV: end-diastolic velocity, MFV: mean flow velocity, AUC: area under curve, CI: confidence interval.

Table VII. The optical cutoff velocity value between moderate and severe stenosis group.

	Cutoff value (cm/s)	Sensitivity	Specificity	AUC (95% CI)	The Youden index
PSV	249.5	1.000	0.961	0.994 (0.986-1.000)	0.961
EDV	141.5	0.857	0.740	0.927 (0.874-0.981)	0.697
MFV	160.5	1.000	0.942	0.988 (0.972-1.000)	0.942

PSV: peak systolic velocity, EDV: end-diastolic velocity, MFV: mean flow velocity, AUC: area under curve, CI: confidence interval.

the prevalence, disability, and mortality rates of stroke are increasing every year. Currently, DSA is well-accepted to be the gold standard for the diagnosis of arterial stenosis. However, DSA is a complex, invasive, and expensive imaging modality, and thus cannot be used as a routine screening method. In addition, CTA (CT angiography) and magnetic resonance angiography (MRA) are expensive and are contraindicated in patients with contrast medium allergy, internal metal implants, and claustrophobic patients. As a result, both methods cannot be widely used in stroke-screening programs[6-9].

TCCS is a noninvasive, accurate, and inexpensive examination method, which can detect the early stenosis of intracranial blood vessels[10]. Transcranial Doppler (TCD) ultrasonography is an examination with similar physical principles to TCCS. It is particularly appropriate for daily evaluations and obtaining information regarding the collateral flow across various branches of the circle of Willis in patients with cerebrovascular disorders. The measured flow velocity data can assist in the early diagnosis and monitoring of the progression of cerebral vasospasm after subarachnoid hemorrhage (SAH), thereby, preventing and treating promptly with the aim of avoiding complications of late-onset cerebral infarction[11]. However, due to the obvious attenuation of the ultrasound beam after penetrating the skull, some elderly people, especially elderly women and patients with poor acoustic window sound transmission, may show poor intracranial structures. CE-TCCS can enhance the intensity of the backscattered signal, so that the nonlinear effect can generate stronger harmonics, enhance the echo contrast between the blood flow and the tissue, improve the signal-to-noise ratio, and significantly improve the display rate of color blood flow signals, thereby improving the display rate of the circle of Willis[12-15]. Furthermore, CE-TCCS has the ability to display the secondary and tertiary branches of the main arteries, which provide the basis for visualizing stenotic arteries, and it can visually display abnormal blood flow signals in the stenotic parts of the intracranial arteries[16], increasing the accuracy of arterial stenosis detection in the elderly and in patients with poor acoustic window. Consequently, this imaging tool can provide a reliable basis to identify potential stenosis sites. In this paper, we compared the display rate of intracranial arteries before and after contrast-enhanced ultrasound, and it was confirmed that the display rate of the circle of Willis was significantly improved after contrast-enhanced ultrasound. The peak flow velocity of the anterior, middle, and posterior cerebral arteries was statistically compared, and it was found that the flow velocity was faster compared to before using CE-TCCS. The experimental results showed that CE-TCCS had great clinical application value in the diagnosis of MCA stenosis. However, there is no unified standard for quantitatively evaluating the degree of MCA stenosis based on the CE-TCCS diagnosis of MCA flow velocity. In this study, DSA

was used as the gold standard for the diagnosis of MCA stenosis. The threshold value of CE-TCCS flow rate was measured to quantitatively diagnose the degree of MCA stenosis, which can in turn improve the confidence of ultrasound diagnosis and provide rich hemodynamic information for clinical practice.

In this study, we excluded several factors, such as severe stenosis or occlusion of one or both internal carotid arteries that may cause slowing of MCA flow velocity, congenital vascular ring development abnormalities (absence of A1 on one side, embryonic PCA), and diseases, such as acquired ischemic lesions of the intracranial posterior circulation that may cause a compensatory increase in MCA flow velocity. Our findings revealed that CE-TCCS could efficiently differentiate normal from stenotic MCAs with different degrees of stenosis. The differences in flow velocity between normal and stenotic groups and among groups with different degrees of stenosis were statistically significant (p <0.001).

In this study, we found that the process of depicting intracranial arteries by CE-TCCS can be affected by several factors. For instance, the scanning method and direction, and the correct identification of each segment of the blood vessels were particularly important. The anterior, middle, and posterior temporal windows can be selected according to the actual situation[2]. Transient "blooming artifacts" which refer to artifacts stemming from oversaturated color Doppler signals during the peak period of contrast-enhanced ultrasound enhancement, may occur after the injection of a low-concentration contrast bolus[17]. Therefore, it is necessary to select the operation timing to reduce the color gain. Based on our experience, we diluted the ultrasound contrast agent to 5 mL, injected 1.5 mL in a bolus, observed the carotid artery, and then observed the intracranial blood vessels after approximately three minutes. Consequently, this approach managed to suppress potential spillover effects in the color blood flow image, and relatively reduce the spectral, rendering this time interval advantageous for imaging processes. However, based on differences in the heart rate, cardiac function, and contrast agent metabolism rate between different patients, it is necessary to adjust the examination time appropriately and flexibly. Therefore, repeated injection of contrast agents is necessary. In addition, the same angle should be used when obtaining blood flow velocities before and after injection of the agent, so as to enhance the credibility of the flow velocity contrast. Proper body position adjustment (supine or lateral position) during the examination is also conducive to the clear display of blood vessels and the accurate acquisition of flow velocity.

Based on the current research results, it is still controversial whether the hemodynamic parameters increase after contrast-enhanced ultrasound. Some studies[18] have suggested that the PSV of intracranial arteries can be increased by 15-36% after injection of the contrast agent, with an average increase of 24.00±7.40%. Additional studies[19] have shown that the difference in the PSV before and after the injection of the contrast agent is not significant. Our study compared the hemodynamic parameters of normal intracranial arteries before and after contrast-enhanced ultrasonography and confirmed that the PSV was significantly different before and after contrast-enhanced ultrasound, and the blood flow velocity of each artery increased by 18-34%. The reasons for these findings may be as follows: (1) the ultrasonic spectrum measurements were greatly affected by the angle between the blood flow direction and the sound beam angle. Due to the poor blood flow display during TCCS, it was difficult to adjust the blood flow direction and the sound beam correctly during spectrum acquisition. Therefore, the measurement speed may often be slower, and the clear display of intracranial blood flow by CE-TCCS can solve this problem; (2) because the strength of the Doppler spectrum signal was used to indicate the level of the reflected sound wave energy, some reflected waves with high flow velocity but low energy may be filtered out by the conventional ultrasound. However, these reflected waves can be enhanced after injection of the contrast agent and can thus be detected during this process. Therefore, we believe that the blood flow spectrum after contrast-enhanced ultrasound can truly reflect more the blood flow in the sampling volume.

In both domestic and foreign literature, the use of CE-TCCS to evaluate the stenosis degree of MCA has not been explored much, yet there is no unified standard so far. Currently, the majority of studies[20,21] use either MRA or CTA as the standard for research purposes, and the most commonly used indicator is PSV, while the diagnostic accuracy of MRA and CTA for intracranial stenosis is significantly lower than that of DSA. In our study, we used CE-TCCS to compare the blood flow velocities of PSV, EDV, and MFV

at the stenosis sites, and we found that all three blood flow velocities could efficiently evaluate different degrees of MCA stenosis. Furthermore, our findings revealed that the AUC of PSV and MFV, including sensitivity and specificity were larger than EDV, and the assessment had the highest accuracy.

Racial differences in intracranial and extracranial atherosclerosis have been reported in previous studies[22], suggesting a higher degree of intracranial stenosis in patients of Chinese origin. Our study is a single-center study, hence all patients included were Chinese. However, the sample size of this study was small as only 104 patients were included with a total of 208 MCAs. The final diagnosis by DSA was 134 normal and 74 stenotic, of which we identified 31 cases of mild stenosis, 29 cases of moderate stenosis, and 14 cases of severe stenosis. Due to the small sample size, single ethnicity, and unbalanced sample size of each stenosis group, determination of the optimal diagnostic velocity value of normal and stenosis and different degrees of stenosis may have been affected[22]. Future studies should include a larger sample size and patients from different ethnic groups.

Conclusions

Current results contribute to the fact that we determined the optimal cutoff value that allowed us to distinguish between normal from stenotic MCAs and improve the visualization rate of intracranial blood vessels. Furthermore, we formulate a reference standard for the flow rate of the MCA stenosis after contrast-enhanced ultrasonography. In summary, CE-TCCS flow velocity measurements can effectively evaluate and grade MCA stenotic disease, and thus provide a basis for early clinical intervention, prevention of ischemic stroke, and prognostic improvement.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Ethics Committee of Peking University Shenzhen Hospital. The approval number is IRB of Peking University Shenzhen Hospital (2019) 19th. The IRB date is January 22nd, 2019.

Informed Consent

Informed written consent has been obtained from each patient following explanation of any study-related procedures.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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