Clinical Significance of Hemodynamic Parameters Identified by Ultrasound in the Extracranial Internal Carotid Artery and Posterior Cerebral Artery of Patients with Moyamoya Disease

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Research article

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Abstract

Background

Digital subtraction angiography (DSA), magnetic resonance angiography (MRA) and other imaging methods are limited in the long-term and dynamic examination of hemodynamic changes in moyamoya disease (MMD). The aim of this study was to investigate the hemodynamic changes using ultrasound according to DSA findings and explore the association between ultrasound parameters and clinical manifestations of MMD.

Methods

Hemodynamic parameters of the extracranial internal carotid artery (EICA) and posterior cerebral artery (PCA) identified by ultrasound were classified into 3 groups according to DSA findings, and differences in ultrasound parameters among DSA stages were compared. Then, according to clinical manifestations, 30 patients were divided into the stroke group and the transient ischemic attack (TIA) group. We compared the differences in the EICA and PCA ultrasound parameters between the two groups, and receiver operating characteristic (ROC) curves were used to evaluate the value of ultrasound parameters in diagnosing stroke and TIA in MMD patients.

Results

The diameter (D), peak systolic velocity (PSV), end diastolic velocity (EDV) and flow volume (FV) of EICA decreased as the Suzuki stage advanced (D: $p < 0.001$, PSV: $p = 0.002$, EDV: $p = 0.001$, FV: $p < 0.001$). The PSV and EDV of PCA increased as the scores of the leptomeningeal system from the PCA to the anterior cerebral artery (ACA) and middle cerebral artery (MCA) territory advanced (PSV: $p = 0.002$, EDV: $p < 0.001$). Comparing the ultrasound parameters between the stroke group and the TIA group, the D and FV of EICA, the PSV and EDV of PCA were significantly different. ROC analysis showed that the area under the curve (AUC) based on the FV of EICA, the PSV of PCA and the combination of the two parameters were 0.676, 0.737 and 0.787, respectively, to diagnose stroke and TIA in MMD patients.

Conclusions

Our results suggest that ultrasound parameters are related to DSA results, and that ultrasound is useful in predicting the clinical severity of MMD.

Trial registration:

Clinical Trial Registration-URL: http://www.chictr.org. Unique identifier: ChiCTR1900026075
Moyamoya disease (MMD) is a rare disease of unknown etiology. MMD is characterized by progressive stenosis of the bilateral terminal portions of internal carotid arteries, and their main branches with compensatory abnormal vascular networks at the base of the brain, and was first reported by the Japanese scholars Suzuki and Takaku in 1969 [1]. The incidence and prevalence of MMD is particularly high in East Asian countries, genetic factors play an important role in MMD, and MMD is more common in females. Cerebral ischemia and intracranial hemorrhage due to the rupture of fragile collateral vessels that compensate for ischemia are the main hazards of MMD [2–5]. MMD is an important cause of stroke in children and adults. For those who have affected first-degree relatives and those who cannot receive revascularization surgery for a period of time, undergoing imaging at regular intervals can reduce the risk of permanent disability caused by stroke and improve long-term prognosis.

Digital subtraction angiography (DSA) plays an important role in guiding the clinical treatment and assessing the prognosis of MMD. Suzuki et al. proposed a conventional criterion for the diagnosis and grading of MMD based on vascular morphology by using DSA [1, 6]. However, due to the abundant collateral networks in MMD patients, MMD patients with the same Suzuki stage may have different cerebrovascular reserves and clinical manifestations [1, 6]. Recently, Liu et al. combined the leptomeningeal system from the posterior cerebral artery (PCA) territory to the anterior cerebral artery (ACA) and middle cerebral artery (MCA) territory, which is the most important compensatory system in patients with MMD, and Suzuki stage, proposed a new grading system to better evaluate the clinical characteristics, guide treatment and predict prognosis [7, 8]. However, due to the invasive procedure, high radiation exposure and time consumption of angiography, long-term monitoring of MMD patients and those people who have affected first-degree relatives has many limitations. If people can be examined at regular intervals using a convenient, rapid and noninvasive approach, it is of great significance to predict poor clinical manifestations, especially stroke risk in patients with MMD. Ultrasonography as a noninvasive, economical, and repeatable technique has shown certain value in the diagnosis and prognostic assessment of MMD [9–11]. However, there is still a lack of systematic and in-depth studies on the association between ultrasound parameters, DSA findings and clinical manifestations of MMD patients. In this study, carotid ultrasound and transcranial color-coded duplex sonography (TCCS) were used to detect hemodynamic changes in the extracranial internal carotid artery (EICA) and PCA to realize real-time, long-term monitoring of patients with MMD, providing more information for guiding treatment and predicting poor clinical manifestations in MMD patients.

**Methods**

**Patient selection**

We prospectively enrolled MMD patients at our institution between September 2019 and February 2020. The inclusion criteria for our study were as follows: 1) patients who were diagnosed with MMD according to the MMD guidelines [12]; and 2) patients who received ultrasound and DSA examinations with intervals between the two examinations less than 1 month. The exclusion criteria were as follows: 1) patients who were diagnosed with moyamoya syndrome with identified causes, including autoimmune
diseases, meningitis, intracranial tumor, Down syndrome, neurofibromatosis, craniocerebral trauma, and sickle cell anemia, etc.; [12, 13]; 2) MMD patients with two or more risk factors for atherosclerosis, including hypertension, diabetes, hyperlipidemia, smoking, etc.; 3) MMD patients who had diseases that affected cardiac output, including hyperthyroidism, severe anemia, congestive heart failure, atrial fibrillation, etc.; 4) patients who had prior revascularization surgery; and 5) patients with unilateral lesions. Finally, a total of 30 patients were included in our study. Informed consent was obtained from all 30 patients (or their parent or legal guardian in the case of children under 16 years), and the study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University.

**Angiographic Findings**

All 30 patients underwent DSA, including of the bilateral common carotid arteries, internal carotid arteries, vertebral arteries and the late venous phase to evaluate collateral flow. Two independent experienced investigators interpreted the images according to the following diagnostic criteria, they were blinded to the clinical data, and any differences in their results were resolved by consensus.

**Suzuki’s vascular criteria [1] [14]**

StageⅠ: narrowing of internal carotid artery (ICA) apex; stageⅡ: dilatation of the intracerebral main arteries and initiation of the moyamoya; stageⅢ, narrowing of the MCA and ACA and intensification of the moyamoya; stageⅣ, occlusion of the ICA extending to the junction of the posterior communicating artery and minimization of the moyamoya, resulting in enlargement of the collateral vessels from the external carotid artery; stageⅤ: the disappearance of all the main cerebral arteries and further minimization of the moyamoya; and stageⅥ: the complete disappearance of the siphon of the ICA, and disappearance of the moyamoya, resulting in cerebral blood flow supply from the external carotid artery and vertebrobasilar artery systems.

**Grading score of leptomeningeal system from the PCA territory to the ACA and MCA territory**

According to the anatomy extent of pial collateral blood [8], the scores of the leptomeningeal system from the PCA territory to the ACA and MCA territory were the sum of the following three parts, and a score of 0 was assigned if the leptomeningeal anastomoses were absent.

1) Retrograde flow from the parieto-occipital branch of the PCA (pPCA) or posterior pericallosal artery extending to the ACA territory: a score of 1 was assigned if the blood supply extended to the cortical border zone between the ACA and PCA territory; a score of 2 was assigned if the blood supply extended to the central sulcus.
2) A score of 1 was assigned if the anterior temporal branch of the PCA anastomoses to the temporal branch of the MCA.

3) pPCA anastomoses to the MCA: a score of 1 was assigned if the retrograde flow only extended to superficial vessels (M4 segment of MCA); a score of 2 was assigned if the retrograde flow extended into the Sylvian fissure (M3 segment of MCA); and a score of 3 was assigned if the flow extended to the reconstituted vessels at the distal end of the occlusion (M1 or proximal M2 segments of MCA).

**Clinical Manifestations**

According to clinical manifestation at onset, patients were categorized into the stroke group (including ischemic stroke and hemorrhagic stroke) and the TIA group by an experienced research neurologist. Ischemic stroke was defined as a new symptomatic neurologic deterioration lasting at least 24 hours that was not caused by a nonischemic cause, or a new symptomatic neurological deterioration accompanied by neuroimaging evidence of a new cerebral infarction that was not caused by a nonischemic cause. Hemorrhagic stroke is defined as the acute extravasation of blood into the brain parenchyma. TIA was defined as new neurologic deficit or symptoms lasting less than 24 hours with no evidence of cerebral infarction on neuroimaging [15].

**Ultrasound Examination**

All subjects underwent ultrasound examination in the ultrasound department of our hospital. All parameters were measured by an experienced sonographer, and the examiner was blinded to the clinical data and radiographic findings.

**Carotid Ultrasound**

Carotid ultrasound was performed on a color-coded ultrasound system (EPIQ 7, Philips Medical Systems, Bothell, WA) with a 3–9 MHz linear array probe. The patient remained in a supine position with their head remaining dropped back and tilted to the opposite side slightly. The sonographer adjusted the gain, depth, pulse-repetition frequency and wall filter to the appropriate conditions, the size of the doppler sample volume was adjusted to 1/3 – 1/4 of the detected vessel, the doppler angle was adjusted to below 60°, and the EICA was measured on the two-dimensional longitudinal section at 1–2 cm above the carotid bulb. The following parameters were measured: diameter (D), peak systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI), and resistance index (RI). Then, the sonographer adjusted the doppler sample volume to the entire width of the vessel, when the signal was stable, the time-averaged mean velocity (TAMV) was measured over a minimum of three cardiac cycles, and the flow volume (FV) was calculated as the product of TAMV and the cross-sectional area (A) of the circular vessel according to the formula $FV = TAMV \times A = TAMV \times [(D/2)^2 \times \pi]$ [16][17].
Transcranial Color-coded Duplex Sonography

Transcranial color-coded duplex sonography was performed on a color-coded ultrasound system (EPIQ 7, Philips Medical Systems, Bothell, WA) with a 1.5-3.0 MHz phased array probe.

The patient remained in a lateral position, the P2 segment of PCA was examined through a transtemporal window. The sonographer adjusted the gain, pulse-repetition frequency and wall filter to the appropriate conditions, the size of the doppler sample volume was adjusted to 3–5 mm, the depth of insonation for PCA was 60–70 mm, and the doppler angle was adjusted to below 60°, when the signal was stable, the PSV, EDV, PI and RI of PCA were measured.

Statistical Analysis

Continuous variables were described as the means ± standard deviation or median (interquartile range), and categorical variables were described as percentages. The Mann-Whitney U test and Jonckheere-Terpstra test were used for continuous variables. A receiver operating characteristic (ROC) curve analysis was applied to identify the performance of each, and the combination of ultrasound parameters for predicting the clinical manifestations of MMD.

Statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY). All calculated p values were 2-tailed, and a p value < 0.05 was considered statistical significance.

Results

Patient characteristics

A total of 30 patients were included in our study, including 13 males and 17 females. All patients had bilateral MMD. The mean age of the patients was 31.97 ± 14.75 years. According to clinical manifestations at onset, 22 patients presented with stroke, and 8 patients presented with TIA. The scores on the modified Rankin scale (mRS) were score 1 in 18 patients, and score 2 in 18 patients. Suzuki stages were as follows: stage I in 3 hemispheres, stage II in 2 hemispheres, stage III in 12 hemispheres, stage IV in 4 hemispheres, stage V in 3 hemispheres, and stage VI in 3 hemispheres.

The grading score of leptomeningeal system from the PCA territory to the ACA and MCA territory were score 0 in 4 hemispheres, score 1 in 1 hemisphere, score 2 in 9 hemispheres, score 3 in 7 hemispheres, score 4 in 21 hemispheres, score 5 in 16 hemispheres, score 6 in 2 hemispheres (Table 1).
Table 1
Baseline characteristics of eligible patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>31.97 ± 14.75</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>13(43.3)</td>
</tr>
<tr>
<td>Clinical diagnoses at onset (patients) (%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>22(73.3)</td>
</tr>
<tr>
<td>TIA</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>mRS on admission (patients) (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>18(60)</td>
</tr>
<tr>
<td>2</td>
<td>12(40)</td>
</tr>
<tr>
<td>Suzuki stage (hemispheres) (%)</td>
<td></td>
</tr>
<tr>
<td>Ⅰ</td>
<td>6(10)</td>
</tr>
<tr>
<td>Ⅱ</td>
<td>14(23.3)</td>
</tr>
<tr>
<td>Ⅲ</td>
<td>26(43.3)</td>
</tr>
<tr>
<td>Ⅳ</td>
<td>8(13.3)</td>
</tr>
<tr>
<td>Ⅴ</td>
<td>5(8.4)</td>
</tr>
<tr>
<td>Ⅵ</td>
<td>1(1.7)</td>
</tr>
<tr>
<td>Grading score of leptomeningeal system (hemispheres) (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4(6.7)</td>
</tr>
<tr>
<td>1</td>
<td>1(1.7)</td>
</tr>
<tr>
<td>2</td>
<td>9(15)</td>
</tr>
<tr>
<td>3</td>
<td>7(11.6)</td>
</tr>
<tr>
<td>4</td>
<td>21(35)</td>
</tr>
<tr>
<td>5</td>
<td>16(26.7)</td>
</tr>
<tr>
<td>6</td>
<td>2(3.3)</td>
</tr>
</tbody>
</table>

Abbreviations: TIA Transient ischemic attack, mRS modified Rankin Scale

Association between Suzuki stage and ultrasound parameters of the EICA in MMD patients
The association between Suzuki stage and ultrasound parameters of the EICA in MMD patients are shown in Table 2.

<table>
<thead>
<tr>
<th>EICA</th>
<th>Suzuki stage (hemispheres)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>stage - II (n = 20)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stage - I (n = 34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stage - 0 (n = 6)</td>
<td></td>
</tr>
<tr>
<td>D(cm)</td>
<td>0.36 (0.31–0.43)</td>
<td>0.30 (0.28–0.36)</td>
</tr>
<tr>
<td>PSV (cm/s)</td>
<td>79.15 (54.75–94.88)</td>
<td>65.30 (47.08–75.60)</td>
</tr>
<tr>
<td>EDV (cm/s)</td>
<td>34.50 (30.03–41.38)</td>
<td>28.40 (22.10–36.83)</td>
</tr>
<tr>
<td>PI</td>
<td>0.77 (0.68–1.02)</td>
<td>0.84 (0.59–1.18)</td>
</tr>
<tr>
<td>RI</td>
<td>0.52 (0.46–0.59)</td>
<td>0.53 (0.42–0.63)</td>
</tr>
<tr>
<td>FV (ml/min)</td>
<td>190.80 (123.08–289.28)</td>
<td>111.01 (74.28–161.14)</td>
</tr>
</tbody>
</table>

Abbreviations: EICA extracranial internal carotid artery, D diameter, PSV peak systolic velocity, EDV end diastolic velocity, PI pulsation index, RI resistance index, FV flow volume

The D of EICA was 0.36 cm (0.31–0.43 cm) in stage II, and it decreased to 0.30 cm (0.28–0.36 cm) in stage I and to 0.18 cm (0.14–0.20 cm) in stage 0. With the increase in the Suzuki stage, the D of EICA was significantly reduced (p<0.001, Fig. 1A).

The PSV and EDV of EICA were 79.15 cm/s (54.75–94.88 cm/s) and 34.50 cm/s (30.03–41.38 cm/s), respectively, in Suzuki II, the values decreased to 65.30 cm/s (47.08–75.60 cm/s) and 28.40 cm/s (22.10–36.83 cm/s) in Suzuki I and to 31.23 cm/s (25.75–46.08 cm/s) and 11.90 (6.60–24.15) cm/s in Suzuki 0. With the increase in the Suzuki stage, the PSV and EDV of EICA were significantly reduced (PSV: p < 0.001, Fig. 1B; EDV: p < 0.001, Fig. 1C).

The FV of EICA was 190.80 ml/min (123.08-289.28 ml/min), 111.01 ml/min (74.28-161.14 ml/min) and 15.82 ml/min (6.17–28.16 ml/min) in stage II, I and 0, respectively, and the difference between the three groups was highly significant (p<0.001, Fig. 1D). Representative cases are shown in Fig. 2.

There was no significant difference in the PI or RI values of EICA between stage II, I and 0 groups.

Association between grading score of leptomeningeal system and ultrasound parameters of the PCA in MMD patients
The association between the grading score of leptomeningeal system from the PCA territory to the ACA and MCA territory and ultrasound parameters of the PCA are shown in Table 3.

Table 3
Association between the grading score of leptomeningeal system and ultrasound parameters of the PCA

<table>
<thead>
<tr>
<th>PCA</th>
<th>Grading score of leptomeningeal system (hemispheres)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>score 0–2 (n = 14)</td>
<td>score 3–4 (n = 28)</td>
</tr>
<tr>
<td>PSV (cm/s)</td>
<td>65.00(49.50-121.50)</td>
<td>123.50(95.50-172.50)</td>
</tr>
<tr>
<td>EDV (cm/s)</td>
<td>29.50(24.50–55.50)</td>
<td>60.00(41.25–79.25)</td>
</tr>
<tr>
<td>PI</td>
<td>0.84(0.59–0.94)</td>
<td>0.79(0.59–0.95)</td>
</tr>
<tr>
<td>RI</td>
<td>0.54(0.42–0.58)</td>
<td>0.52(0.43–0.57)</td>
</tr>
</tbody>
</table>

Abbreviations: *PCA* posterior cerebral artery, *PSV* peak systolic velocity, *EDV* end diastolic velocity, *PI* pulsation index, *RI* resistance index

The PSV and EDV of PCA were 65.00 cm/s (49.50-121.50 cm/s) and 29.50 cm/s (24.50–55.50 cm/s), respectively, in the score 0–2 group; the values increased to 123.50 cm/s (95.50-172.50 cm/s) and 60.00 cm/s (41.25–79.25 cm/s), respectively, in the score 3–4 group and to 148.00 cm/s (105.00-183.00 cm/s) and 69.00 cm/s (56.25–101.00 cm/s) in the score 5–6 group; The differences of PSV and EDV between the three groups were statistically significant (PSV: \( p = 0.002 \), Fig. 3A; EDV: \( p < 0.001 \), Fig. 3B), while there were no significant difference in the PI or RI values between the score 0–2, 3–4 and 5–6 groups. Representative cases are shown in Fig. 4.

**Comparison of ultrasound parameters between the stroke group and the TIA group in patients with MMD**

The comparison of ultrasound parameters between the stroke group and the TIA group in patients with MMD are shown in Table 4. Compared with the stroke group, the D and FV of EICA were significantly higher in the TIA group (D: \( p = 0.013 \), PSV: \( p = 0.038 \)), and the PSV and EDV of PCA were also significantly higher in the TIA group (PSV: \( p = 0.005 \), EDV: \( p = 0.024 \)).
### Table 4
Comparison of ultrasound parameters between the stroke group and the TIA group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stroke (n = 8)</th>
<th>TIA (n = 22)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EICA D(cm)</td>
<td>0.30(0.25–0.36)</td>
<td>0.37(0.30–0.42)</td>
<td>0.013</td>
</tr>
<tr>
<td>PSV (cm/s)</td>
<td>62.15(40.53–83.38)</td>
<td>66.70(59.70–72.00)</td>
<td>0.498</td>
</tr>
<tr>
<td>EDV (cm/s)</td>
<td>30.55(20.38–39.40)</td>
<td>31.70(24.50–35.40)</td>
<td>0.927</td>
</tr>
<tr>
<td>PI</td>
<td>0.86(0.58–1.10)</td>
<td>0.81(0.72–1.20)</td>
<td>0.646</td>
</tr>
<tr>
<td>RI</td>
<td>0.53(0.41–0.63)</td>
<td>0.53(0.50–0.62)</td>
<td>0.604</td>
</tr>
<tr>
<td>FV (ml/min)</td>
<td>106.86(52.72–172.00)</td>
<td>159.11(116.07–239.64)</td>
<td>0.038</td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSV (cm/s)</td>
<td>105.00(64.50–146.00)</td>
<td>152.50(123.75–204.75)</td>
<td>0.005</td>
</tr>
<tr>
<td>EDV (cm/s)</td>
<td>51.50(31.75–71.00)</td>
<td>68.00(58.00–95.00)</td>
<td>0.024</td>
</tr>
<tr>
<td>PI</td>
<td>0.77(0.57–0.89)</td>
<td>0.80(0.66–0.96)</td>
<td>0.165</td>
</tr>
<tr>
<td>RI</td>
<td>0.51(0.41–0.57)</td>
<td>0.52(0.45–0.58)</td>
<td>0.192</td>
</tr>
</tbody>
</table>

Abbreviations: TIA transient ischemic attack, EICA extracranial internal carotid artery, D diameter, PSV peak systolic velocity, EDV end diastolic velocity, PI pulsation index, RI resistance index, FV flow volume, PCA posterior cerebral artery

A ROC analysis was performed for the FV of EICA, the PSV of PCA and the combination of the two parameters to diagnose stroke and TIA in MMD patients (Table 5). The area under the ROC curve was 0.74 for the PSV of PCA, 0.68 for the FV of EICA, and 0.79 for the combination of the two parameters (Fig. 5). The ROC analysis showed that the diagnostic value of the combination of the two parameters is superior to that of the PSV of PCA and the FV of EICA.
Table 5
Diagnosis of stroke and TIA by the ultrasound parameters

<table>
<thead>
<tr>
<th></th>
<th>AUC(SD)</th>
<th>95% CI of AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>EICA&lt;sub&gt;FV&lt;/sub&gt;</td>
<td>0.676(0.074)</td>
<td>(0.531, 0.828)</td>
</tr>
<tr>
<td>PCA&lt;sub&gt;PSV&lt;/sub&gt;</td>
<td>0.737(0.073)</td>
<td>(0.593, 0.880)</td>
</tr>
<tr>
<td>EICA&lt;sub&gt;FV&lt;/sub&gt; plus PCA&lt;sub&gt;PSV&lt;/sub&gt;</td>
<td>0.787(0.060)</td>
<td>(0.670, 0.904)</td>
</tr>
</tbody>
</table>

Abbreviations: EICA<sub>FV</sub> flow volume of extracranial internal carotid artery, PCA<sub>PSV</sub> peak systolic velocity of posterior cerebral artery

Discussion

In this study, we investigated the hemodynamic changes in the EICA and PCA using ultrasound according to the DSA findings of Suzuki stage and grading score of leptomeningeal system from the PCA to the ACA and MCA territory in MMD patients. The D, PSV, EDV and FV of EICA decreased as the Suzuki angiographic stage advanced, the PSV and EDV of PCA increased as the scores of the leptomeningeal system from the PCA to the ACA and MCA territory advanced. MMD patients who presented with TIA were more likely to obtain higher D, and FV values of the EICA and higher PSV, and EDV values of the PCA than those who presented with stroke. Our results suggest that ultrasound parameters are related to DSA results, and detection of ultrasound parameters might be useful in predicting the clinical severity of MMD.

At present, DSA is the gold standard for the diagnosis of MMD, however, DSA is invasive, radiative and can even cause serious complications. For people who cannot undergo DSA examination, magnetic resonance imaging (MRI) combined with MRA can be used as an alternative method [12], but MRI combined with MRA is time-consuming and expensive, and neither of these imaging methods can provide hemodynamic information. However, Clinicians expect to dynamically detect the hemodynamic changes in MMD patients through simple and noninvasive means. The application of these methods in screening and long-term monitoring of MMD are limited. Ultrasonography is a noninvasive, economical, and repeatable technique, that has been used in the diagnosis of MMD, detecting the patency of bypass vessels, and evaluating postoperative hemodynamic changes [18–20]. Monitoring the progression of MMD may show great value for clinical use.

The histopathological change in the involved artery in MMD patients is eccentrically laminated thickening of the intracranial artery, as the disease advances, fibrocellular intimal thickening involves the EICA [21–23]. Although most researchers have focused on the intracranial portions of the ICA and their branches in MMD, considering the histopathology aspects, MMD causes extracranial stenosis of the proximal portion of the ICA in some cases, the so-called bottleneck sign, which is a typical vascular finding of MMD [23]. Yasuda et al. reported that the bottleneck sign began to appear in patients with Suzuki stage III or higher [24]. Our results demonstrated that as the Suzuki stage advanced, the diameter of EICA decreased. MMD
is characterized by progressive stenosis of the bilateral terminal portions of internal carotid arteries, and their main branches, resulting in increased resistance in the distal vessel and decreased velocity and blood flow volume in the proximal vessel. Ruan et al. showed that the time-averaged mean flow velocity of ICA in MMD patients was lower than that in normal controls, and the RI was higher than that in normal controls [25]. Our findings seemed to be consistent with previous studies, our results showed that as the Suzuki stage advanced, the PSV, EDV and FV of EICA decreased.

As MMD progresses, blood flow decreases in the anterior circulation, and patients may have a TIA or even a stroke. To sustain adequate cerebral perfusion, PCA could develop collateral branches to compensate for the ischemic brain, and the leptomeningeal system from the PCA plays an important role in supplying the ischemic cortex of the MCA and ACA territories. Liu et al. proposed a new grading system for assessing the collateral circulation of MMD patients, according to the anatomic extent of collateral circulation from the PCA to the ACA and MCA territory, the grading score of the leptomeningeal system was scored from 0 to 6 [8]. As collateral circulation mainly comes from the P2 segment of PCA, in our study, we selected the P2 segment to measure ultrasound parameters. We found that the low-speed blood flow of the PCA was more common in low-score groups. In contrary, in high-score groups, high speed blood flow of the PCA was more easily detected. The reason was that the high velocity could provide enough blood flow for the collateral circulation. When the P1 segment of PCA was involved, a low-velocity and low-resistance blood flow signal of the P2 segment was noted, and the low-velocity in P2 segment could not supply enough blood flow for the establishment of collateral circulation [26]. Therefore, the more abundant collateral circulation formed by the PCA, the higher flow velocity of the P2 segment we detected.

The main symptoms at presentation of MMD are stroke and TIA. Hypoperfusion increases the susceptibility to ischemia, hemodynamic abnormalities are the main mechanism of ischemic stroke [8] [27]. Hemorrhagic stroke is a deleterious consequence of compensatory mechanisms in response to ischemia [14]. As progressive narrowing of the ICA, poor collateral circulation, rupture of fragile, dilated moyamoya vessels under unusually increased hemodynamic stress is the main cause of cerebral hemorrhage [28]. For those who do not pay enough attention to TIA symptoms and pediatric patients who cannot accurately describe their TIA symptoms, delayed diagnosis and treatment could increase the risk of permanent disability due to stroke. The association between ultrasound parameters and clinical manifestations has rarely been reported. We assumed that the blood flow in the EICA reflects the blood supply of anterior circulation. Our findings have confirmed our hypothesis, a higher Suzuki stage represents a reduction in the ICA blood flow, indicating intracranial shrinkage of the anterior circulation, which is a risk factor for stroke. According to our study, the blood flow in EICA were significantly correlated with the clinical manifestations, patients who presented with stroke were more likely to have less blood flow in the EICA, but those who presented with TIA symptoms were more likely to have more blood flow in EICA. PCA is the main pathway of collateral circulation in MMD patients, and plays an important role in the compensation of cerebral blood flow when principal conduits are insufficient. Successful compensatory collateralization is considered a preventive measure against stroke in MMD patients [29]. In our study, we investigated the effect of the PCA ultrasound parameters on clinical
manifestations. We found that the increased velocity of PCA results in good collateral circulation could better prevent the occurrence of stroke. Our results showed that compared with the TIA group, patients in the stroke group presented a lower velocity of PCA. In our study, we used ultrasound parameters of the EICA and PCA to predict the risk of stroke in MMD patients. As a result, the combination of ICA and PCA parameters was found to be superior to each single parameter for predicting stroke risk in MMD patients. Our results indicate that ultrasound parameters are related to clinical manifestations.

Our study had some limitations. First, because of the relatively small sample size, our patients were only divided into the stroke group and the TIA group according to their clinical manifestations, stroke includes ischemic stroke and hemorrhagic stroke, but hemorrhagic stroke is a deleterious consequence of compensatory mechanisms in response to ischemia in MMD patients. In our study, we did not further classify the stroke group, it would have been better if our study had divided the stroke group into ischemic stroke and hemorrhagic stroke in separate groups. Second, in this study, we only investigated the hemodynamics of the EICA and PCA in patients with MMD, Although PCA is the main pathway of collateral circulation in MMD patients and which plays an important role in the compensation of cerebral blood flow, transdural collaterals from the external carotid artery (ECA) can also supply the ischemic brain. As ECA has many branches, the hemodynamic changes in one or two branches have little effect on the trunk, therefore, in this study, we did not include the parameters of the ECA [1] [30]. Further studies are needed to study the impact of the ECA to better predict the risk of stroke in patients with MMD.

Conclusions

Our results suggest that the DSA results of the Suzuki stage and the scores of leptomeningeal system from the PCA territory to the ACA and MCA territory are related to EICA and PCA ultrasound parameters, respectively. Ultrasonography is a noninvasive, nonradiative and economical technique, that can be used for preliminary screening and periodic monitoring of patients with MMD, and detection of ultrasound parameters might be useful in predicting the poor clinical manifestations of MMD patients.

Abbreviations

DSA: digital subtraction angiography; MRA:magnetic resonance angiography; MMD:moyamoya disease; EICA:extracranial internal carotid artery; PCA:posterior cerebral artery; TIA:transient ischemic attack; ROC:receiver operating characteristic; D:diameter; PSV:peak systolic velocity; EDV:end diastolic velocity; FV:flow volume; ACA:anterior cerebral artery; MCA:middle cerebral artery; AUC:area under curve; TCCS:transcranial color-coded duplex sonography; ICA:internal carotid artery; pPCA:parieto-occipital branch of the PCA; PI:pulsatility index; RI:resistance index; TAMV:time-averaged mean velocity; A:cross-sectional area; mRS:modified Rankin Scale; MRI:magnetic resonance imaging; ECA:external carotid artery.

Declarations

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Availability of data and materials

The datasets supporting the conclusions of this study are available from the corresponding author on reasonable request.

Authors’ contributions

SZ, PG, JW and WH: conception and design. SZ, PG, JW, ZS, YL and JZ: acquisition of data. SZ, PG: analysis and interpretation of data. SZ: drafting the article. All authors critically revising the article and approved the final version of the manuscript. LC, DZ and WH: study supervision

Ethics approval and consent to participate

The study was approved by Beijing Tiantan Hospital Ethics Committee, Capital medical university. Informed consent was written obtained when patients were admitted to Department of ultrasound.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

References


Figures
Figure 1

Association between the Suzuki stage and ultrasound parameters of the EICA. (A-D) The D, PSV, EDV and FV of EICA between stage I-II, stage III-IV and stage V-VI groups were statistically significant (D: p<0.001, PSV: p=0.002, EDV: p=0.001, FV: p<0.001). Abbreviations: EICA extracranial internal carotid artery, D: diameter, PSV: peak systolic velocity, EDV: end diastolic velocity, FV: flow volume.
Figure 2

Representative cases. (A) A 32 year old man with MMD had a Suzuki stage II artery on the left. The carotid ultrasound showed high values of D (0.37 cm), PSV (80 cm/s), EDV (30 cm/s), TAMV (26 cm/s) and FV (170 ml/min) in the left EICA. (B) A 37-year-old woman with MMD had a stage V artery on the right. Carotid ultrasound showed low values of D (0.19 cm), PSV (41 cm/s), EDV (14 cm/s), TAMV (11 cm/s) and FV (18 ml/min) in the right EICA. Abbreviations: MMD moyamoya disease, D diameter, PSV peak systolic velocity, EDV end diastolic velocity, TAMV time-averaged mean velocity, FV flow volume, EICA extracranial internal carotid artery.
Figure 3

Association between the grading score of the leptomeningeal system and ultrasound parameters of the PCA. (A-B) The PSV and EDV of PCA between the score 0-2, score 3-4 and score 5-6 groups were statistically significant (PSV: p=0.002, EDV: p<0.001). Abbreviations: PCA posterior cerebral artery, PSV peak systolic velocity, EDV end diastolic velocity.
Figure 4

Representative cases. (A) A 24 year old man with MMD scored 2 points in the leptomeningeal system on the right (white arrows). The TCCS showed low values of PSV (66 cm/s) and EDV (29 cm/s) in the right PCA. (B) A 33 year old woman with MMD scored 5 points in the leptomeningeal system on the right (white arrows). The TCCS showed high values of PSV (159 cm/s) and EDV (64 cm/s) in the right PCA.

Abbreviations: MMD moyamoya disease, TCCS transcranial color-coded duplex sonography, PSV peak systolic velocity, EDV end diastolic velocity, PCA posterior cerebral artery.
Figure 5

The ROC curve of ultrasound parameters in diagnosing stroke and TIA of MMD patients. The area under the ROC curve was 0.676 (95% CI, 0.531-0.828) for the FV of EICA, 0.737(95% CI, 0.593-0.880) for the PSV of PCA and 0.787(95% CI, 0.670, 0.904) for the combination of the two parameters. Abbreviations: ROC receiver operating characteristic, TIA Transient ischemic attack, MMD moyamoya disease, EICA_FV flow volume of the extracranial internal carotid artery, PCA_PSV peak systolic velocity of the posterior cerebral artery.