Etiology of Intracranial Arterial Stenosis: Are Transcranial Color-Coded Duplex Ultrasound and 3T Black Blood MR Imaging Complementary?

Fabienne Perren, Maria I. Vargas, Odysseas Kargiotis
From the Department of Neurology, Neurovascular and Neurosonology Unit (FP, OK); and Department of Radiology, Neuroradiology Unit, University Hospital and Medical Faculty of Geneva, Geneva (MIV).

ABSTRACT

BACKGROUND: In order to differentiate between the different causes of intracranial stenosis, we compared the diagnostic results of transcranial color-coded duplex (TCCD) sonography with the recently developed 3D high-resolution black blood MR sequence.

METHODS: We studied retrospectively 20 patients referred to our hospital after acute ischemic stroke who were diagnosed with intracranial stenosis and in whom a repetitive TCCD and a 3D MR T1 FAT SAT (black blood) sequence at 3T (TR/TE 350/20 ms, FOV 160×182×120 mm, 0.4×0.4×0.4 size of pixel, 300 slices, Fat Sat spair, acquisition time 6 minutes 14) were performed. Etiological diagnosis was based on one hand on the morphological aspect of the arterial wall (black blood T1 FAT SAT sequence) and on the hemodynamic aspect (TCCD) on the other hand. Analysis of black blood T1 FAT SAT MR sequence and TCCD agreement on the etiological diagnosis was performed using sign test.

RESULTS: TCCD was performed at admission and at least at two different intervals during follow-up. Eleven patients had diffuse intracranial arterial disease and nine had involvement of a single intracranial artery. Etiology of intracranial arterial stenosis included: atheromatosis, thrombosis, vasculitis and reversible vasocostriction syndrome. There was 80% agreement (sign test P = .0059) between these two methods.

CONCLUSIONS: These two combined imaging techniques might be promising for the differentiation of arteriosclerotic changes from stenosis of another origin, especially when follow-up TCCD studies are completed early before a possible regression of the atherosclerotic plaque that might be observed 6 months after initial diagnosis.

Keywords: Transcranial Doppler, color-coded duplex, ultrasound, MRI-VISTA sequence, intracranial stenosis, atherosclerosis.

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Correspondence: Address correspondence to Fabienne Perren, MD PD Médecin adjointe agrégée HUG, University Hospital and Medical Faculty of Geneva Neurovascular and Neurosonology Unit Rue Gabrielle-Perret-Gentil 4 CH-1211 Geneva 14, Switzerland. E-mail: fabienne.perren@hcuge.ch.
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Introduction

Intracranial atherosclerotic disease is a previously underestimated but important cause of ischemic stroke which accounts for 30–50% of ischemic events in Asia and 8–10% in North America and Caucasians making it one of the most common cause of stroke worldwide.1-3 Digital subtraction angiography (DSA) remains the gold standard examination for the detection of intracranial stenosis; however, transcranial Doppler (TCD) and transcranial color-coded duplex (TCCD) sonography, computed tomography (CT) angiography and magnetic resonance imaging [MRI] angiography are all noninvasive imaging modalities that are increasingly being utilized in stroke patients. In an Asian population, asymptomatic intracranial stenosis of the middle cerebral artery was detected by means of TCD in the 7–30% of patients with vascular risk factors, highlighting the importance of intracranial large vessel disease at least in this patient population.4

Apart from atherosclerosis, intracranial stenosis could result from other underlying causes. Atherosclerotic plaques and thromboembolic material are detected in 90% of cases by significant narrowing of the vascular lumen, whereas in the remaining 10% vasculitis, vasospasm, dissection or even moyamoya disease are diagnosed.5 It is essential to differentiate between these conditions since each of them warrant a specific clinical approach.

In the early 1980s, TCD was introduced as a noninvasive method for the detection of blood flow velocities in the intracranial arteries.6 Although TCD is of established value for detecting intracranial stenosis, a single exam is not sufficient to differentiate between vasospasm, vasculitis, atherosclerotic narrowing or emboli.7 Vasospasm and thromboembolic stenosis typically recanalize within days, weeks, or months, whereas atherosclerotic stenosis are supposed not to show significant recanlization, at least during the early follow-ups. Only by repeating studies it may be possible to uncover the pathophysiologic nature of the stenosis.

High-resolution 3D black blood T1 FAT SAT MR sequence is a newly developed technique that achieves high-quality intracranial vessel wall imaging through improvement of the signal-to-noise and contrast-to-noise ratio.8,9 Moreover, high-resolution MRI is shown to efficiently differentiate between the causes of intracranial vessel abnormality. Signal intensity on T1 and T2 sequences and contrast enhancement reveal distinct
patterns that allow recognizing an atherosclerotic plaque, a dissection, inflammation, or moyamoya disease.10

In the present study we aimed to assess the combination of the two noninvasive modalities, TCCD and HR-MRI, for the differential diagnosis of intracranial artery disease. We performed recurrent TCCD studies to evaluate the progression of the intracranial stenosis and to, subsequently, determine the cause of vessel narrowing. We then compared the TCCD results with the diagnosis of the HR black blood vessels wall MR imaging.

**Methods**

**Patients**

We studied retrospectively patients who have been referred to our hospital for comprehensive work up after ischemic stroke and who were diagnosed with intracranial stenosis. Twenty patients (12 women) were examined using the above-mentioned imaging techniques. Only patients with sufficient transcranial acoustic bone windows were included in the study.

**Transcranial Color-Coded Doppler Sonography**

Repetitive TCCD (2MHz, Philips) examinations through sufficient transcranial acoustic bone windows were performed by experienced sonographers. TCCD was performed at admission and at least at two different intervals during the follow-up (range 2-6 times). All the studies were analyzed by board certified physicians (FP, OK). Velocity criteria used for grading intracranial stenosis according to Baumgartner et al are summarized in Table 1.11 The etiologic diagnosis of the stenosis was based on the results of the repetitive TCCD studies in association with the clinical context and evolution. Additional parameters that were taken into consideration were the presence of collateralization, whether velocity changes were focal or diffuse and the comparison of flow velocities with those of the contralateral arteries. For the cases with suspected vasospasm or vasculitis follow-up was additionally based on measurements of the mean flow velocities and the Lindegaard index.12

**HR-MRI**

All patients were studied with a 3.0T MR (Philips Ingenuity) scanner. The technical protocol included a 3D high-resolution MR T1 FAT SAT (black blood) sequence with the follows technical parameters (TR/TE 350/20 ms, FOV 160×182×120 mm, 0.4×0.4×0.4 size of pixel, 300 slices, Fat Sat spair, acquisition time: 6 minutes 14), an axial Fast spin echo T2 (FST2), coronal fluid attenuation inversion recovery (FLAIR), diffusion weighted imaging (DWI), axial gradient echo T2 (GET2), 3D time of flight (TOF) as well as high-resolution 2D FSE T2 (thickness 1.5, 0.42×0.54 voxel size with reconstruction in 0.2×0.2 mm, TE/TR: 80/3000 mm, 26 slices, acquisition time 6.18 minutes) All studies were analyzed by an experienced neuro-radiologist (MV). Differential diagnosis was guided by the relative intensities of wall thickness on T1 and T2 sequences and by the presence or not of contrast enhancement of the vessel wall.

**Statistical Analysis**

Analysis of HR 3D black blood vessels wall MR imaging and TCCD agreement on the etiological diagnosis was performed using sign test. The results were statistically significant when the P value was less than .05. We also calculated the sensitivity of TCCD in comparison to black blood MRI, by regarding true positive cases as the cases with correct TCCD diagnoses in comparison with black blood MRI and false negative ones as the cases with incorrect TCCD diagnoses.

**Results**

Twenty collaborative patients (12 women, 8 men; 25–88 years; mean age 66.6 years) were examined using both imaging techniques. Eleven patients had diffuse intracranial disease; four had involvement of the middle cerebral artery (MCA); two of the posterior cerebral artery (PCA); one of the basilar artery (BA), one of the intracranial vertebral artery (VA); one of the intracranial internal carotid artery (ICA).

Etiology of intracranial arterial stenosis included: atheromatosis N = 15; thrombosis N = 2; vasculitis N = 2; reversible cerebral vasoconstrictive syndrome (RCVS) N = 1. There was 80% agreement (sign test P = .0059) between the diagnoses of these two methods. The sensitivity of TCCD in comparison to black blood MRI was 80% (CI 95%, 56.34% to 94.27%).

The cases with discordance between TCCD and HR-MRI included 3 patients with atherosclerotic stenosis on HR-MRI that was diagnosed as thrombosis with TCCD and one case with atherosclerotic stenosis and normal TCCD study. The TCCD and HR-MRI diagnosis for each patient is given in Table 2.

TCCD diagnosis was mainly dependent on repetitive examinations. Thus, complete normalization or significant reduction (50%) of peak systolic flow velocities (PSV) during recurrent TCCD examinations (maximum six) within a time period of 1 month in a patient with clearly focal flow velocity accelerations favored the diagnosis of recanalized thromboembolic stenosis. Persistence of the hemodynamic abnormalities without fluctuations and involvement of multiple arteries favored atherosclerotic disease.

In a relevant clinical context (sudden, intense headache, with or without neurological deficit) and TCCD examination showing multifocal or diffuse stenosis with normalization of flow velocity changes within 3 months (patient 11 in Table 2) reversible cerebral vasoconstrictrion syndrome was regarded as the primary diagnosis. On the contrary, similar initial TCCD hemodynamic changes without complete resolution within 6 months but with fluctuating course depending on treatment efficacy, directed the diagnosis towards vasculitis (patients 7 and 13 in Table 2).

The etiologic diagnosis on HR-MRI was based on the following findings: atherosclerotic stenosis showed eccentric wall thickening without enhancement after contrast injection.
Table 2. TCCD and HR Black Blood MR Imaging Final Etiologic Diagnosis of Intracranial Disease

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender</th>
<th>Age (years)</th>
<th>TCCD Diagnosis</th>
<th>HR-MRI Diagnosis</th>
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<tr>
<td>1</td>
<td>F</td>
<td>7</td>
<td>ATS</td>
<td>ATS</td>
</tr>
<tr>
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<td>F</td>
<td>82</td>
<td>ATS</td>
<td>ATS</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>88</td>
<td>ATS/THR</td>
<td>ATS</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>7</td>
<td>ATS/THR</td>
<td>ATS</td>
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<tr>
<td>5</td>
<td>F</td>
<td>63</td>
<td>ATS</td>
<td>ATS</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
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</tr>
<tr>
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<td>M</td>
<td>55</td>
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</tr>
<tr>
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<td>74</td>
<td>N</td>
<td>THR</td>
</tr>
<tr>
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</table>

M = male; F = female; ATS = atheromatosis; HR-MRI = high-resolution magnetic resonance imaging; N = normal; RVS = reversible cerebral vasoconstriction syndrome; TCCD = transcranial color-coded duplex sonography; THR = thrombosis; VASC = vasculitis.

(Fig 1). Reversible cerebral vasoconstriction syndrome was consistent with diffuse wall thickening without enhancement. These abnormalities disappeared on subsequent control. Cases with central nervous system (CNS) vasculitis presented with smooth, concentric or eccentric wall enhancement and thickening. Follow-up imaging of the two cases showed persistence/resolution of the vessel wall abnormalities.

Discussion
In the present study we evaluated the concordance between two noninvasive imaging studies, such as brain HR black blood MR imaging and TCCD, in the differential diagnosis of intracranial artery disease. In 16 cases out of the 20 studied, there was agreement between the final diagnosis obtained by HR black blood MR imaging and TCCD. In the remaining four cases, the atherosclerotic stenosis observed with black blood MR imaging were either perceived as thromboembolic after normalization of flow velocities on recurrent TCCD studies or not identified on TCCD. Partial regression of the atherosclerotic plaque and moderately high sensitivity of TCCD in detecting intracranial stenosis could account for the discordance in those patients.

For the detection of intracranial stenosis with TCCD, we used peak systolic flow velocity (PSV) cut-off criteria. A recent TCD study by Chen et al. concluded that PSV is more accurate than mean flow velocity (MFV) in detecting and grading middle cerebral artery (MCA) stenosis. The proposed optimal cut-off PSV values were 160, 200, and 280 cm/second for mild, moderate, and severe stenosis respectively, whereas the MFV values were 100, 120, and 180 cm/second, respectively. However, most studies evaluating the performance of TCD for the detection of intracranial stenosis report moderate sensitivity and positive predictive values (PPV). The SONIA trial used MFV cut-offs of >100 cm/second for ≥50% stenosis of MCA and MFV of >80 cm/second for vertebral and basilar artery stenosis, with a PPV of only 50%. In case of severe ≥70% stenosis additional criteria such as MCA MFV of >120 cm/second, or stenotic/prestenotic ratio ≥3, or low velocity, and vertebral/basilar artery MFV of >110 cm/second or stenotic/prestenotic ratio ≥3 improved diagnostic accuracy (Table 3). Similarly, the PPV was 51% and the sensitivity 89% when the intracranial flow was evaluated with the comparison of the local, at the site of the stenosis, blood flow velocities and the blood flow velocities upstream or downstream the stenosis. In case of diffuse intracranial disease, it is proposed that low mean flow velocities and high pulsatility index in a single vessel is associated with diffuse single vessel intracranial disease, whereas low mean flow velocities and high pulsatility index in multiple vessels is indicative of multivessel intracranial disease.

TCD/TCCD detection and follow-up of intracranial vasospasm combines MFV measurements and the calculation of Lindegaard index. A meta-analysis found 99% specificity, 67%
sensitivity, 97% PPV and 78% negative predictive value (NPV) for the TCD detection of subarachnoid hemorrhage (SAH) induced vasospasm.\textsuperscript{18} Regarding reversible cerebral vasocostriction syndrome, there are currently no TCD diagnostic criteria, although it is suggested to use the validated criteria for SAH induced vasospasm in order to assess the risk of ischemic complications.\textsuperscript{19} The flow velocities return to normal values within 12 weeks, although resolution of vasocostricion is often seen as early as 1 to 4 weeks.\textsuperscript{20,21} TCD studies in patients with vasculitis typically show bilateral patchy flow velocity accelerations, whereas during remission the velocities are largely within normal limits.\textsuperscript{22}

High resolution, contrast enhanced MRI can reliably assess the intracranial vessel wall and differentiate between the possible causes of arterial abnormality. Atherosclerotic stenosis present with focal, eccentric vessel wall thickening without enhancement, whereas unstable plaques may show eccentric enhancement and heterogeneous signal intensity.\textsuperscript{23} In patients with vasculitis MRI reveals diffuse, concentric vessel wall stenosis with contrast uptake. Cases with intracranial vessel dissections show intramural hematoma and have intimal flap and double lumen.\textsuperscript{24} Moya-moya disease is characterized by small, concentric vessel wall thickening and the absence of enhancement.\textsuperscript{25} Reversible cerebral vasoconstrictive syndrome can be distinguished from cerebral vasculitis by the presence of diffuse, uniform wall thickening without enhancement.\textsuperscript{26} The hallmark of intracranial vasculitis is intramural wall enhancement.\textsuperscript{27} Moreover, black blood MR imaging may visualize important characteristics of the atherosclerotic plaque that determine its vulnerability. FAT SAT T1-weighted sequences and time-of-flight angiography may reveal intraplaque hemorrhage and T2-weighted and proton density weighted sequences differentiate between the lipid core and plaque cap. Wall enhancement is indicative of plaque inflammation and subsequent increased rupture risk.\textsuperscript{10}

Our study has some important limitations. First, TCCD and MRI results were not compared with a “gold standard” examination such as DSA. The total number of patients was relatively small and, although the evaluating physicians were “blinded” to each other’s results, they were not blinded to patient’s clinical data and follow-up. Moreover, TCCD can only distinguish between stable versus regressive stenosis and clinical context is necessary in order to reach a diagnosis. For this reason, our study compares between a one time MRI imaging versus serial TCCD imaging plus clinical context and evolution which results in a strong bias in favor of TCCD. Finally and according to some reports, stenosis regression might be observed in follow-up TCCD studies 6 months after the initial diagnosis in some patients (up to 29%) with atherosclerotic disease.\textsuperscript{28,29} In our study, the majority of follow-up studies were completed before 6 months, making significant atherosclerotic plaque regression less probable. However, a TCCD misdiagnosis of thrombosis instead of atherosclerosis in 3 of our patients (patients 3, 4 and 12 in Table 2) could be explained by a significant plaque regression during follow-up. On the other hand, the case with intracranial thrombosis that had a normal TCCD study (patient number 10) can be explained by the presence of a hemodynamically nonsignificant stenosis by the time of the TCCD study.

On the other hand and to the best of our knowledge, this is the first time that the etiologic diagnostic efficacy of HR black blood MR imaging in association with TCCD is being assessed in patients with intracranial stenosis. The cause of intracranial vessel pathology determines patient’s appropriate management. Distinguishing atherosclerotic stenosis from thromboembolic material may allow for optimal selection of the antithrombotic medication and for early initiation of aggressive medical treatment in case of high-grade, stenotic and symptomatic intracranial atheromatosis.\textsuperscript{30} This is of great importance since intracranial atherosclerotic disease is associated with increased risk for recurrent ischemic events and “best” medical treatment can largely improve patient’s outcome.\textsuperscript{31,32} Moreover, immunosuppressive therapy could be withheld in cases with strong evidence of reversible cerebral vasocostriction syndrome diagnosis instead of cerebral vasculitis.\textsuperscript{21}

In conclusion, the present study highlights the significant diagnostic agreement between HR black blood MR imaging and TCCD for the etiologic approach of intracranial stenosis. Although not tested against a “gold standard” examination, our results show evidence that the combination of the two noninvasive techniques might be sufficient for the differential diagnosis of intracranial vessel disease, especially when follow-up TCCD studies are completed before a possible regression of the atherosclerotic plaque that might be observed 6 months after initial diagnosis.

References