Velocity Criteria for Intracranial Stenosis Revisited
An International Multicenter Study of Transcranial Doppler and Digital Subtraction Angiography

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Background and Purpose—Intracranial atherosclerotic disease is associated with a high risk of stroke recurrence. We aimed to determine accuracy of transcranial Doppler screening at laboratories that share the same standardized scanning protocol.

Methods—Patients with symptoms of cerebral ischemia were prospectively studied. Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) criteria were used for identification of ≥50% stenosis. We determined velocity cutoffs for ≥70% stenosis on digital subtraction angiography by Warfarin–Aspirin Symptomatic Intracranial Disease criteria and evaluated novel stenotic/prestenotic ratio and low-velocity criteria.

Results—A total of 102 patients with intracranial atherosclerotic disease (age 57±13 years; 72% men; median National Institutes of Health Stroke Scale 3, interquartile range 6) provided 690 transcranial Doppler/digital subtraction angiography vessel pairs. On digital subtraction angiography, ≥50% stenosis was found in 97 and ≥70% stenosis in 62 arteries. Predictive values for transcranial Doppler SONIA criteria were similar (P>0.9) between middle cerebral artery (sensitivity 78%, specificity 93%, positive predictive value 73%, negative predictive value 94%, and overall accuracy 90%) and vertebral artery/basilar artery (69%, 98%, 88%, 93%, and 92%). As a single velocity criterion, most sensitive mean flow velocity thresholds for ≥70% stenosis were: middle cerebral artery >120 cm/s (71%) and vertebral artery/basilar artery >110 cm/s (55%). Optimal combined criteria for ≥70% stenosis were: middle cerebral artery >120 cm/s, or stenotic/prestenotic ratio ≥3, or low velocity (sensitivity 91%, specificity 80%, receiver operating characteristic 0.858), and vertebral artery/basilar artery >110 cm/s or stenotic/prestenotic ratio ≥3 (60%, 95%, 0.769, respectively).

Conclusions—At laboratories with a standardized scanning protocol, SONIA mean flow velocity criteria remain reliably predictive of ≥50% stenosis. Novel velocity/ratio criteria for ≥70% stenosis increased sensitivity and showed good agreement with invasive angiography. (Stroke. 2011;42:00-00.)

Key Words: digital subtraction angiography • intracranial stenosis • transcranial Doppler

Intracranial atherosclerotic disease (IAD) is increasingly recognized as a major cause of ischemic stroke and an independent risk factor for stroke recurrence.1,2 Digital subtraction angiography (DSA) is the gold standard for the diagnosis of IAD; however, DSA has inherent costs and risks. Thus, validation of noninvasive screening tests is needed. Numerous prior studies evaluated the predictive value of transcranial Doppler (TCD) compared with MR angiography, CT angiography, and DSA.3–11 A multicenter Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) study3 evaluated velocity criteria for ≥50% stenosis in the setting of the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial.12 The main limitation of SONIA findings relates to a lack of standardization of TCD...
scanning protocol and sonographer skills across participating centers.

Meanwhile, patients with stroke with severe (≥70%) IAD are at the highest risk of stroke recurrence.12–14 The initial results of the recently stopped Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) multicenter clinical trial15,16 suggest a high early postintervention stroke risk in these patients that outweighed surprisingly low risk of recurrence with medical therapy alone. Nevertheless, a lower-than-expected risk of stroke with medical therapy alone places further emphasis on noninvasive identification of patients with severe IAD and early initiation of aggressive medical therapy and risk factor modification.

We sought to determine the correlation between TCD and DSA at laboratories that share the same standardized and previously validated TCD scanning protocol. In addition, we aimed to derive screening velocity criteria for evaluation of ≥70% intracranial stenosis.

**Subjects and Methods**

Patients with symptoms of cerebral ischemia were prospectively evaluated by TCD at 4 international participating tertiary care centers from March 2008 to August 2010 (Birmingham, AL; Edmonton, Alberta, Greece; Athens, Greece; Singapore). Both inpatients and outpatients first seen by a vascular neurologist for a recent or remote ischemic stroke or transient ischemic attack were eligible for our study if their workup included DSA and TCD. Patients with absent temporal bone windows were excluded. The rate of absent transtemporal windows for TCD examination at our participating centers ranges from 8% for men and 11% for women in Greece up to 15% to 20% in men and 25% to 30% in women (especially older Chinese women) in Singapore (triennium community). All included patients underwent TCD as part of routine workup to determine stroke pathogenic mechanism and subsequent cerebral DSA was done as clinically indicated in the judgment of treating physicians who were unaware of the purposes of this study. Only patients with DSA performed within 1 month of the TCD examination were included. We also recorded demographic data and the National Institutes of Health Stroke Scale scores.

We used 2-MHz, power motion (M-mode) Doppler (PMD-150, Spencer Technologies, Inc) and shared a standardized, previously published insonation protocol.17,18 We used a small spectral sample volume (3 mm) with power motion Doppler units to obtain an optimized spectral waveform.19 Because aliasing, turbulence, and poor signal-to-noise ratios are common with severe stenoses, sonographers optimized waveforms to avoid aliasing, identified the highest velocity cardiac cycle, and applied manual measurements with cursors placed at the peak systolic and end-diastolic velocity values. Software then automatically calculated the mean flow velocities (MFV) for each arterial segment. All sonographers were experienced in TCD (RVT, RVT-eligible, or American Society of Neurochemistry Neurosonology-certified: L.Z., K.B., V.K.S., G.T., H.L.T., A.V.A). DSA was performed and interpreted by neuroendovascular specialists20 who were unaware of TCD velocity measurements. On DSA, intracranial stenosis was graded using WASID criteria for identification of the residual lumen and denominator12 using an autocalibration technique for angiographic workstations because it was used for on-site measurements in the SAMMPRIS trial.15 All patients enrolled at our center into SAMMPRIS were adjudicated as eligible and acceptable for the trial by the central reading. The following MFV cutoffs on TCD were used for identification of ≥50% stenosis (SONIA criteria):11 for middle cerebral artery (MCA) MFV >100 cm/s and vertebral artery (VA)/basilar artery (BA) MFV >80 cm/s. Other vessels were not included in this analysis due to low prevalence of the disease and remain the subject of ongoing study. We also analyzed velocity data to predict cutoffs for ≥70% stenosis on DSA. In addition, we evaluated whether the stenotic-to-prestenotic ratio (SPR) increases the accuracy of velocity prediction of ≥50% and ≥70% stenosis. SPR was calculated by dividing the highest stenotic MFV by the prestenotic MFV (Figure). If stenotic velocities were found in a distal vessel segment, the proximal vessel segment was used to provide prestenotic velocity data. If stenotic velocities were found at the vessel origin, the contralateral depth-corresponding homologous segment velocity was used to calculate the ratio. If stenotic velocities were found in the proximal BA, the distal segment of the BA was used to calculate the ratio. Furthermore, we analyzed “low” velocity findings (corresponding to lesions on the “other” side of the Spencer curve21,22. For the MCA, low velocity was defined as MFV reduction by ≥30% as compared with the contralateral depth-corresponding homologous segment. For the VA/BA, MFV reduction by ≥30% was used as compared with the contralateral homologous segment or the highest VA velocity, respectively (Figure).21,22 To minimize false-positive results due to asymmetry of flow velocities that is commonly found during TCD examinations of tortuous vessels, only low velocities associated with abnormal waveforms23 such as blunted flow signal were selected.

**Statistical Analyses**

We used descriptive statistics for baseline variables and presented continuous variables as mean (±SD) or as median values (interquartile range). The predictive values (sensitivity, specificity, positive predictive value, negative predictive value [NPV], and overall accuracy) with corresponding 95% CIs were calculated after computation of true positive, false-positive, true-negative, and false-negative values. Statistical analyses including receiver operator characteristic (ROC) curve were performed with the PASW Statistics 18.0 (SPSS Inc, Chicago, IL). A level of P<0.05 indicated statistical significance.

**Results**

A total of 102 patients had TCD findings indicative of IAD and underwent DSA within 1 month of the TCD examination: mean age 57±13 years; 72% men; 69% white, 18% black, and 13% Asian; median National Institutes of Health Stroke Scale 3 (interquartile range 6). A sample of 102 patients could provide up to 1326 possible TCD/DSA vessel pairs (2 M1 MCA, 2 M2 MCA, 2 internal carotid artery terminus, 2 anterior cerebral artery, 2 posterior cerebral artery, 1 BA, 2 VA). On reviewing of the stored waveforms and DSA images, 636 pairs were excluded due to missing data or poor-quality waveforms (eg, incomplete sweep, aliasing, and poor signal-to-noise ratio) or DSA images (eg, patient motion artifacts or overlapping vessels obscuring the stenosis or reference measurement). On DSA, intracranial stenoses ≥50% (n=97) were located in the MCA in 50% (n=49; M1 44%; M2 6%) and VA/BA 34% (n=32; VA 16%; BA 18%) with 62 lesions being ≥70% (MCA 55%, n=34; BA/VA 32%, n=20). The terminal internal carotid artery, anterior cerebral artery, and posterior cerebral artery were excluded due to a low prevalence of atherosclerotic disease (11%, 4%, and 1%, respectively). Thus, 418 TCD/DSA vessel pairs (of 690) remained for the final analysis.

SONIA criteria for ≥50% stenosis in the MCA had sensitivity 78%, specificity 93%, positive predictive value 73%, NPV 94%, and overall accuracy 90% (Table 1). For ≥50% stenosis in the BA/VA, SONIA MFV criteria >80 cm/s had sensitivity 69%, specificity 98%, positive predictive value 88%, and NPV 93%. Overall accuracy was 92% with no significant differences between MCA and VA/BA.
ROC area was the highest (0.84) when MFV threshold was increased to >90 cm/s for VA/BA ≥50% stenosis (specificity increased by 1%–99%, whereas sensitivity remained unchanged).

Stenotic/prestenotic ratio ≥2 alone had sensitivity of 80% for ≥50% MCA stenosis (Table 1). When SONIA MFV cutoff or SPR ≥2 was applied, sensitivity increased to 82%, specificity decreased by 2%, and the area under ROC curve remained unchanged at 0.868. When SONIA MFV cutoff or SPR ≥2 or low velocity was applied, sensitivity reached 92%, specificity decreased to 81%, and the ROC area remained largely unchanged at 0.864.

For VA/BA ≥50% stenosis, SPR ≥2 alone had sensitivity of 66% (Table 1). When MFV cutoff >90 cm/s or SPR ≥2 were applied, sensitivity increased to 72%, specificity decreased by 0.7%, and the area under ROC curve remained largely unchanged at 0.815. When MFV cutoff >90 cm/s or SPR ≥2 or low velocity were applied, sensitivity reached 88%, specificity decreased to 83%, and the ROC area increased to 0.851.

For ≥70% SAMMPRIS stenosis in the MCA, higher MFV cutoffs were evaluated (range, >110 cm/s to >200 cm/s; Table 2). MFV >120 cm/s had the highest ROC area of 0.809: sensitivity 71%, specificity 91%, positive predictive value 56%, NPV 95%, and overall accuracy 88% (Table 2). With increasing MFV cutoffs from >110 cm/s to >200 cm/s, sensitivity decreased from 71% to 15% and specificity increased from 89% to 99%. For VA/BA ≥70% SAMMPRIS

**Figure.** A, DSA (center): 58% M1 MCA stenosis; TCD: normal mean flow velocity in the MCA at a depth of 60 mm (insert on the left) and high velocity flow in the mid-MCA at a depth of 49 mm (insert on the right), indicating ≥50% MCA stenosis. B, DSA (center): 71% mid-BA stenosis; TCD: normal mean flow velocity in the BA at a depth of 85 mm (insert on the left) and high velocity flow in the BA at a depth of 94 mm (insert on the right), indicating high-grade (≥70%) mid-BA stenosis. C, DSA (center): 84% proximal BA stenosis; TCD: delayed systolic upstroke in both proximal and midbasilar artery with mean flow velocities of 20 cm/s and 23 cm/s indicating the lesion on “the other side” of the Spencer curve. DSA indicates digital subtraction angiography; MCA, middle cerebral artery; TCD, transcranial Doppler; BA, basilar artery.
stenosis, MFV > 110 cm/s alone had the highest ROC curve of 0.765 with sensitivity 55%, specificity 98%, positive predictive value 79%, NPV 94%, and overall accuracy 92% (Table 3).

For detecting ≥70% stenosis in the MCA, MFV > 120 cm/s or SPR ≥ 3 resulted in increased sensitivity of TCD from 71% to 77%. Application of either MFV > 120 cm/s or SPR ≥ 3 or low velocities increased sensitivity to 91% with the area under the ROC curve of 0.858 and specificity of 80% (Table 2).

For detecting ≥70% stenosis in VA/BA, MFV > 110 cm/s, or SPR ≥ 3 resulted in an increased sensitivity of TCD from 55% to 60%. Application of MFV cutoff > 110 cm/s, SPR ≥ 3, or low velocities increased sensitivity to 80% (Table 3).

Discussion

Our multicenter study showed that at laboratories with a standardized scanning protocol, SONIA, MFV criteria remain reliably predictive of ≥50% MCA stenosis. For ≥70% stenosis, our expanded criteria (abnormally high velocity, stenotic/prestenotic velocity/ratio, or low velocity) demonstrate excellent-to-good sensitivity of TCD screening.

Raising velocity thresholds to predict greater stenosis severity decreases sensitivity and increases specificity of TCD screening. An addition of a stenotic/prestenotic ratio

Table 2. Predictive Values and ROC Areas for ≥70% MCA Stenosis

<table>
<thead>
<tr>
<th>MFV &gt; 110 cm/s</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Overall Accuracy (95% CI)</th>
<th>ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.6 (56.2–82.0)</td>
<td>88.8 (86.5–90.6)</td>
<td>50.0 (39.8–60.1)</td>
<td>95.0 (92.5–96.9)</td>
<td>86.3 (82.3–89.4)</td>
<td>0.797</td>
<td>88.3 (84.4–91.4)</td>
</tr>
<tr>
<td>70.8 (56.5–81.7)</td>
<td>91.1 (88.9–92.9)</td>
<td>55.8 (44.7–66.4)</td>
<td>95.1 (92.8–97.0)</td>
<td>88.3 (84.4–91.4)</td>
<td>0.809</td>
<td>89.9 (86.8–92.1)</td>
</tr>
<tr>
<td>52.9 (40.1–63.2)</td>
<td>95.8 (93.8–97.4)</td>
<td>66.7 (50.5–79.6)</td>
<td>92.8 (90.8–94.3)</td>
<td>89.9 (86.8–92.1)</td>
<td>0.744</td>
<td>89.9 (86.8–92.1)</td>
</tr>
<tr>
<td>41.2 (29.8–49.0)</td>
<td>97.7 (95.9–98.9)</td>
<td>73.7 (53.4–87.6)</td>
<td>91.3 (89.6–92.4)</td>
<td>89.9 (86.8–92.1)</td>
<td>0.694</td>
<td>89.9 (86.8–92.1)</td>
</tr>
<tr>
<td>20.6 (11.8–27.3)</td>
<td>98.1 (96.7–99.2)</td>
<td>63.6 (36.5–84.4)</td>
<td>88.6 (87.3–89.6)</td>
<td>87.5 (85.1–89.3)</td>
<td>0.594</td>
<td>87.5 (85.1–89.3)</td>
</tr>
<tr>
<td>14.7 (7.4–20.2)</td>
<td>98.6 (97.4–99.5)</td>
<td>62.5 (31.3–86.0)</td>
<td>87.9 (86.9–88.7)</td>
<td>87.1 (85.1–88.6)</td>
<td>0.567</td>
<td>87.1 (85.1–88.6)</td>
</tr>
</tbody>
</table>

<sup>*</sup>Original SONIA criteria.

ROC indicates receiver operating characteristic; MCA, middle cerebral artery; PPV, positive predictive value; NPV, negative predictive value; MFV, mean flow velocity; SPR, stenotic-to-prestenotic ratio; VA, vertebral artery; BA, basilar artery; CI, confidence interval.
helps to identify velocity increases predictive of severe disease regardless of the actual velocity value (similar to the internal carotid artery/common carotid artery ratio for carotid duplex). For the evaluation of ≥50% MCA stenosis, the use of SPR ≥2 (22 false-negative/false-positive cases) resulted in 3 less false-negative/false-positive cases than the MFV >100 cm/s cutoff (25 false-negative/false-positive cases). For ≥70% MCA stenosis, the application of SPR ≥3 (20 false-negative/false-positive cases) resulted in 9 less false-negative/false-positive cases than the MFV >120 cm/s cutoff (29 false-negative/false-positive cases). Ratios also help to control for variable cardiac output, blood pressure, viscosity, etc. Furthermore, our criteria particularly aim at uncovering lesions on “the other side” of the Spencer curve where the actual velocity decreases with most severe or elongated stenoses.

Our study is in general agreement with previous studies that validated various blood flow velocity criteria for intracranial stenoses. The SONIA trial evaluated the performance of TCD against invasive angiography for identification of ≥50% intracranial stenosis. The trial demonstrated that TCD can reliably exclude the presence of intracranial stenosis (NPV >80%) similarly to our findings (NPV range, 93%–98%). Sensitivity of TCD screening in our study was better than in SONIA likely due to the fact that our multicenter group shared a standardized scanning protocol (such standardization was not performed before the SONIA trial). Another potential reason is the uniform use of a recent power motion-mode Doppler–TCD technology (largely unavailable to SONIA trialists at that time) that was shown particularly useful in evaluation of the posterior circulation. Furthermore, to our knowledge, no study has been performed so far to evaluate TCD velocity criteria for the detection of ≥70% intracranial stenosis in comparison with DSA and a prospective validation study of these newly derived criteria is necessary.

Our study has limitations. First, although we had 4 tertiary care academic centers, our study is limited by a relatively small number of patients, and at the moment, we cannot provide accuracy data for vessels such as internal carotid artery, anterior cerebral artery, and posterior cerebral artery. Second, we did not perform DSA in all patients with stroke who had TCD and the decision-making management to perform DSA could have been influenced by TCD results. Our results may be affected by this potential verification bias. However, to minimize this verification bias, we compared not only the symptomatic vessel on DSA and TCD, but also other vessels that may or may have not had IAD within the same subject. Furthermore, often inevitable time delays between TCD and DSA and vice versa precluded us from reliably ruling out the influence of recanalization of a thrombus superimposed on an intracranial stenosis. To minimize this bias, we did not include arteriograms postunsuccessful thrombectomy or partial recanalization. Furthermore, to avoid unnecessary angiograms, we have several diagnostic criteria to differentiate velocity increases with IAD and other conditions such as collaterals with the precerebral carotid artery disease.

In conclusion, our study showed that SONIA MFV criteria remain reliably predictive of ≥50% stenosis at laboratories that use a standardized TCD scanning protocol. Our novel velocity/ratio criteria for detection of ≥70% intracranial stenosis show good agreement with invasive angiography. Adjustment of MFV cutoffs, stenotic/prestenotic ratio, or low-velocity criteria could lead to improved sensitivity of TCD testing if one plans to use these criteria. Our criteria, if prospectively validated, could provide a reliable alternative to DSA in identification of patients with severe IAD if “best medical therapy” is to become a standard in aggressive pharmacological treatment and risk factor modification for this condition.

Disclosures
A.V.A. and M.R.H. serve on the Steering Committee of the SAMMPRIS trial funded by the National Institutes of Health.
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References
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