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# Noninvasive Detection of Diffuse Intracranial Disease

Vijay K. Sharma, MD, RVT; Georgios Tsivgoulis, MD, RVT; Annabelle Y. Lao, MD;  
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**Background and Purpose**—Intracranial arterial stenosis increases flow velocities on the upslope of the Spencer's curve of cerebral hemodynamics. However, the velocity can decrease with long and severely narrowed vessels. We assessed the frequency and accuracy for detection of focal and diffuse intracranial stenoses using novel diagnostic criteria that take into account increased resistance to flow with widespread lesions.

**Methods**—We evaluated consecutive patients referred to a neurovascular ultrasound laboratory with symptoms of cerebral ischemia. Transcranial Doppler mean flow velocities were classified as normal (30 to 99 cm/s), high and low. Pulsatility index  $\geq 1.2$  was considered high. Focal intracranial disease was defined as  $\geq 50\%$  diameter reduction by the Warfarin Aspirin in Symptomatic Intracranial Disease criteria. Diffuse disease was defined as stenoses in multiple intracranial arteries, multiple segments of one artery, or a long ( $>1$  cm) stenosis in one major artery on contrast angiography (CT angiography or digital subtraction angiography) as the gold standard.

**Results**—One hundred fifty-three patients (96 men, 76% white, age  $62 \pm 15$  years) had previous strokes ( $n=135$ ) or transient ischemic attack ( $n=18$ ). Transcranial Doppler detection of focal and diffuse intracranial disease had sensitivity 79.4% (95% CI: 65.8% to 93%), specificity 92.4% (95% CI: 87.7% to 97.2%), positive predictive value 75.0% (95% CI: 60.9% to 89.2%), negative predictive value 94.0% (95% CI: 89.7% to 98.3%), and overall accuracy 89.5% (95% CI: 84.5% to 94.4%). After adjustment for stroke risk factors, transcranial Doppler findings of low mean flow velocities and high pulsatility index in a single vessel were independently associated with angiographically demonstrated diffuse single vessel intracranial disease, whereas low mean flow velocities/high pulsatility index in multiple vessels were related to multivessel intracranial disease (OR: 19.7, 95% CI: 4.8 to 81.2,  $P<0.001$ ).

**Conclusions**—Diffuse intracranial disease may have a higher than expected frequency in a select stroke population and can be detected with noninvasive screening. (*Stroke*. 2007;38:3175-3181.)

**Key Words:** CT angiography ■ intracranial atherosclerosis ■ stroke ■ transcranial Doppler

Intracranial atherosclerosis leads to cerebrovascular events that account for 8% to 10% of ischemic strokes and are associated with a risk of recurrent stroke approaching 15% per year.<sup>1</sup> With emphasis to identify high-risk patients,<sup>2</sup> recent clinical trials evaluated ways to prevent stroke due to intracranial disease.<sup>3,4</sup>

Transcranial Doppler (TCD) ultrasound noninvasively evaluates cerebral hemodynamics and may be valuable as a screening method to detect  $\geq 50\%$  stenosis in major intracranial arteries.<sup>5,6</sup> Detection, quantification, and progression of intracranial disease have been previously studied using several high-velocity criteria on TCD.<sup>7,8</sup> A short arterial stenosis produces focal velocity increases on the upslope of the so-called Spencer's curve of cerebral hemodynamics (Figure 1).<sup>9,10</sup> However, the relationship between flow velocity and diameter reduction is also affected by the length of the stenosis or the presence of multiple distal lesions.<sup>9,10</sup> There-

fore, flow velocity reduction may occur with elongated arterial stenoses of  $<70\%$  diameter reduction.<sup>5</sup> Moreover, obstruction of more than 3 distal middle cerebral artery (MCA) branches has been associated with decreased velocities in the proximal M1 MCA segment.<sup>11</sup>

TCD also provides information about impedance to flow by calculating pulsatility index, originally described by Gosling and King.<sup>12</sup> Pulsatility of arterial blood flow can be affected by changes in cardiac output as well as proximal and distal vascular resistance.<sup>5,10</sup> Assuming stable central hemodynamics, an increase in the proximal resistance that occurs with a proximal internal carotid artery stenosis or occlusion decreases pulsatility in the MCA. In contrast, an increase in resistance distal to the site of insonation results in an increased blood flow pulsatility.<sup>13,14</sup> With progression of intracranial atherosclerotic process, the resultant long and severely narrowed vessels can reduce blood flow velocities

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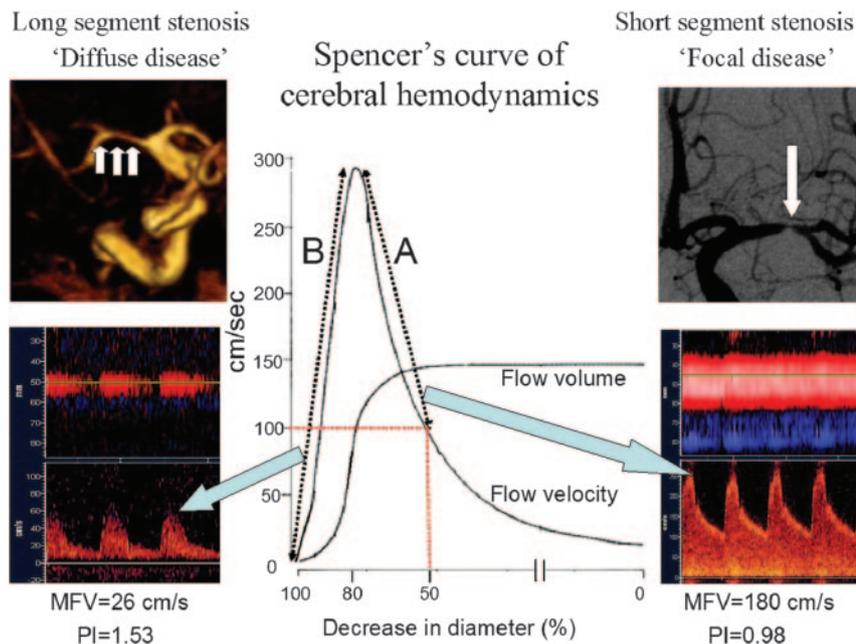
From the Neurosonology and Stroke Research Program (V.K.S., G.T., A.Y.L., M.D.M., A.V.A.), Barrow Neurological Institute, Phoenix, Ariz; the Division of Neurology (V.K.S.), National University Hospital, Singapore; the Department of Neurology (G.T.), University of Athens School of Medicine, Athens, Greece; the University of Santo Tomas (A.Y.L.), Manila, Philippines; and the Comprehensive Stroke Center (G.T., A.V.A.), University of Alabama at Birmingham Hospital, Birmingham, Ala.

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**Figure 1.** The Spencer's curve of cerebral hemodynamics. Dotted line A corresponds to abnormally elevated flow velocities on the "upslope" of the Spencer's curve caused by short and focal stenoses of  $\geq 50\%$ .<sup>20</sup> Upper right DSA image shows a focal  $>50\%$  MCA stenosis with high mean flow velocities on TCD (bottom right image). Dotted line B shows the "downslope" of the Spencer's curve when the velocities decrease due to increasing resistance with most severe or elongated lesions. Upper left CTA image shows a  $>1$ -cm long stenosis in the right MCA with low mean flow velocities and increased PI on TCD (bottom left image).

on the downslope of Spencer's curve (Figure 1).<sup>9</sup> Consequently, pulsatility index (PI) can be used to differentiate velocity reduction due to reduced cardiac output (low PI) from increased distal resistance (high PI).<sup>15,16</sup>

Current diagnostic criteria for intracranial disease such as ones used in the Warfarin Aspirin in Symptomatic Intracranial Disease (WASID) trial and prospective studies in a Chinese population<sup>3,17</sup> take into account only increased flow velocities consistent with a  $\geq 50\%$  focal stenosis. Therefore, a very severe or long stenosis and multiple stenoses in one artery can be missed. We assessed the frequency and accuracy of TCD findings in detection of focal and diffuse intracranial stenoses using novel diagnostic criteria that take into account increased resistance to flow with widespread lesions.

## Subjects and Methods

### Transcranial Doppler

Complete TCD examination was performed in consecutive patients referred to the neurovascular ultrasound laboratory of our tertiary care stroke center with the diagnosis of subacute (3 to 14 days from onset) or chronic ( $>14$  days from onset) ischemic stroke and transient ischemic attack. Demographic characteristics and vascular risk factors information were collected at the time of routine cerebrovascular ultrasound examination.

All TCD studies were performed by stroke neurologists (V.K.S., G.T., A.Y.L., A.V.A.) with specialized training and credentials in cerebrovascular ultrasound (certified by the American Society of Neuroimaging and/or the American Registry for Diagnostic Medical Sonographers). TCD studies were performed using previously described standard insonation protocol with Spencer PMD 100 (Spencer Technologies, Inc).<sup>13</sup> The reviewer for TCD studies was blinded to the angiography results and interpreted the studies independently of the other imaging modalities as part of an ongoing quality control project at our laboratory.

Maximum mean flow velocities (MFV) were obtained from major arteries of the circle of Willis with a 4-second spectral Doppler data acquisition sweep. MFV was classified as normal (30 to 99 cm/s), high ( $\geq 100$  cm/s), and low ( $<30$  cm/s) for the MCA, anterior cerebral artery, and terminal internal carotid artery. MFV in the

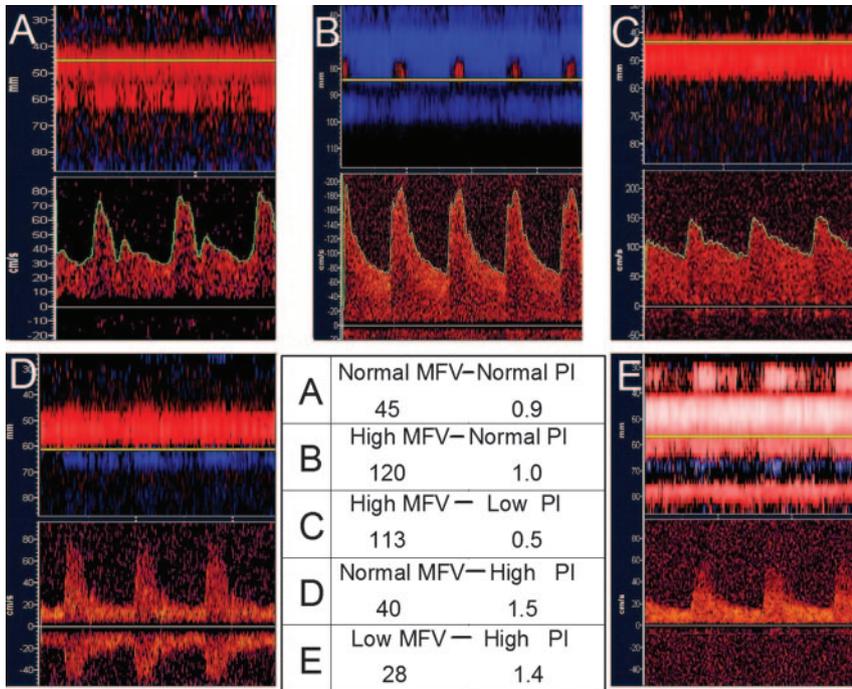
posterior cerebral, basilar, and vertebral arteries were considered normal (20 to 49 cm/s), high ( $\geq 50$  cm/s), and low ( $<20$  cm/s).<sup>5,7</sup>

We used PI of Gosling and King<sup>12</sup> as a reflection of impedance to flow in the cerebral circulation. PI was calculated as (PSV-EDV)/MFV, where PSV is the peak systolic velocity and EDV is the end diastolic velocity. Normotensive individuals breathing room air have PI in the range of 0.6 to 1.1.<sup>5</sup> PI values of  $\geq 1.2$  were considered to indicate increased distal resistance to blood flow. Our group had previously validated PI ranges in consecutive patients with acute stroke to predict acute flow limiting intracranial thromboembolic lesions.<sup>18,19</sup>

A focal  $\geq 50\%$  intracranial stenosis was diagnosed if TCD showed high MFV with variable PI values (Figure 2). Focal stenoses in multiple arteries were diagnosed if high MFV and variable PI were found in different arteries based on depth location and flow direction. Low MFV with low PI found in multiple vessels were attributed to decreased cardiac output.<sup>5</sup> Normal MFV and high PI were attributed to either increased cardiac output or effects of chronic hypertension.<sup>20</sup> Patients with incomplete TCD (absent temporal windows) and known systemic conditions that are associated with elevated flow velocities (anemia or hyperthyroidism) were excluded from the present analyses. We hypothesized that a combination of low MFV and high PI is likely to predict very severe stenosis, a long ( $>1$  cm) intracranial segment stenosis, or multiple stenoses in a single artery (Figure 2).

### Contrast Angiography

CT angiography or digital subtraction angiography (DSA) was used as the gold standard for determining the presence and extent of intracranial lesions. CT angiogram (CTA) was performed in all patients as part of routine diagnostic workup. Patients with contraindications to CTA (renal failure, contrast allergy) were evaluated with DSA. DSA was performed in addition to CTA in selected cases when clinically indicated (extracranial or intracranial angioplasty and stenting, discrepant results between CTA or MR angiography, poor-quality nondiagnostic CTA). Patients without contrast angiographic studies (CTA or DSA) were excluded from the present analyses. The rationale for not including MR angiography in the evaluation of intracranial stenosis was the fact that the commonly performed noncontrast time-of-flight MR angiography has poor sensitivity to slow flow states and overestimates the degree of stenosis.<sup>21</sup> In addition, CTA depicts the normal anatomy of circle of Willis more reliably than MR angiography<sup>22</sup> and has an excellent yield for the detection of intracranial stenooclusive disease (sensi-



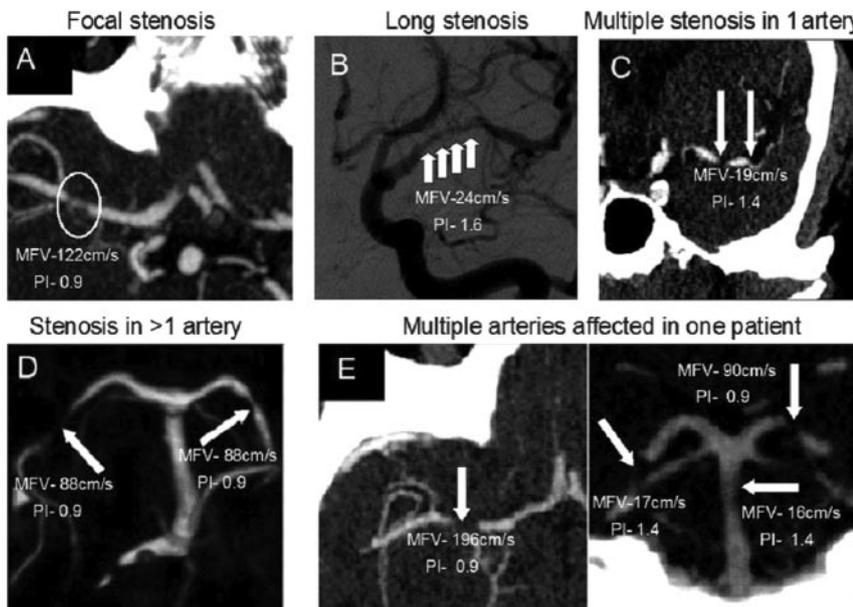
**Figure 2.** M-mode and corresponding spectral TCD findings in patients with focal and diffuse intracranial disease. MFV and PI values are shown in the table inset.

tivity 100%, positive predictive value 93.4%) when compared with DSA.<sup>23</sup> Moreover, Bash et al have recently shown that CTA has a higher sensitivity and positive predictive value (98% to 100% and 93% to 100%, respectively) than MR angiography (70% to 87% and 59% to 65%, respectively) for the diagnoses of both intracranial arterial stenosis and occlusion.<sup>24</sup> Interestingly, a study with higher interobserver reliability was also documented with CTA (correlation coefficient 0.95, 95% CI: 0.93 to 0.96).<sup>24</sup>

High-resolution brain CTA with a multidetector helical scanner (4i Lightspeed; GE Medical Systems, Milwaukee, Wis) was routinely performed in all patients with no contraindications for CTA as part of clinically indicated stroke diagnostic workup. CT scans were obtained at a 1.3-mm slice thickness with a 1-mm interval during a bolus injection of 70 mL of contrast material. Multiplanar reformats were created in the axial, coronal, and sagittal planes. An attending-level staff neuroradiologist and stroke neurologist evaluated neurodiagnostic imaging studies independently of TCD results. In patients

who underwent both DSA and CTA, DSA was used for final analysis. If multiple angiographic studies were available, we used the one obtained closest in time to TCD.

Focal intracranial disease on angiography was defined as a  $\geq 50\%$  diameter reduction by the WASID criteria.<sup>3</sup> Diffuse intracranial disease was defined as stenosis in multiple intracranial arteries, multiple segments of stenosis in one artery, or a long ( $>1$  cm) stenosis in one major artery (Figure 3). We chose the arbitrary cutoff of 1 cm for discriminating focal from elongated diffuse intracranial arterial stenotic lesions after taking into account the average length of the insonated vessels during a standard TCD evaluation: M1 MCA (14 to 16 mm), anterior cerebral artery (12.7 mm), basilar artery (33.3 mm), vertebral artery (35 to 40 mm).<sup>25–27</sup> Because the average length of terminal internal carotid artery and P1 posterior cerebral artery was  $<1$  cm, all lesions in the former vessels were classified as focal. In a recent study that assessed vertebral artery stenosis using transcranial color Doppler flow imaging, the same angiographic



**Figure 3.** Spectrum of focal and diffuse intracranial lesions on contrast angiography with corresponding flow velocity and PIs. A, A focal stenosis in the M1 segment of the right MCA. B, A long ( $>1$  cm) stenosis in the left MCA. C, Multiple segments with focal stenosis in left MCA. D, Stenoses in multiple segments of posterior circulation arteries. E, Multiple stenoses in both anterior and posterior circulation vessels.

**Table 1. Baseline Characteristics of the Study Population (n=153)**

| Variable                 | Percent (n) |
|--------------------------|-------------|
| Mean age, years (SD)     | 62 (15)     |
| Men                      | 63 (96)     |
| Hypertension             | 70 (107)    |
| Diabetes mellitus        | 30 (46)     |
| Ischemic heart disease   | 26 (40)     |
| Hypercholesterolemia     | 56 (85)     |
| Atrial fibrillation      | 11 (16)     |
| Congestive heart failure | 5 (7)       |

cutoff (1 cm) was used to differentiate focal from diffuse intracranial stenoses.<sup>28</sup>

### Statistical Analyses

Statistical comparisons were performed between patients with diffuse and focal intracranial disease using the  $\chi^2$  test and Fisher exact test. TCD results were compared with contrast angiography. The accuracy parameters (sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy) with their corresponding 95% CIs of the screening test (TCD) against the gold standard of contrast angiography (CTA and/or DSA) were calculated after computation of true-positive, false-positive, true-negative, and false-negative values.

Multivariable analyses were performed with the use of logistic regression to identify predictor variables of diffuse intracranial disease. Initially, univariable analyses of potential predictors (demographic characteristics, stroke risk factors, and TCD findings) were performed. To maximize sensitivity, those variables with a univariable association of  $P < 0.2$  were included as candidates into a multivariable logistic regression model and then removed by backward stepwise selection procedure. To confirm the robustness of multivariable models, we repeated all multivariable analyses using a forward selection procedure. Predictor variables that were significant at  $P < 0.05$  were retained in the multivariable model. Associations are presented as ORs with corresponding 95% CIs. Finally, the ability of TCD to identify diffuse intracranial disease stratified by the number of arteries with abnormal findings (low MFV and high PI) was examined by receiver operating characteristic curve analyses. The Statistical Package for Social Science (SPSS Inc, version 11.5 for Windows) was used for statistical analyses.

### Results

We evaluated 153 patients (96 men, 76% white, mean age  $62 \pm 15$  years) who had previous stroke ( $n=135$ ) or transient ischemic attack ( $n=18$ ). Demographic characteristics and stroke risk factors are presented in Table 1. TCD was normal in 117 patients (77%) and showed high MFV with variable PI in 17 (11%) and low MFV/high PI in 19 (12%) patients (Table 2; Figure 2). DSA was performed in 16 cases (10%). DSA confirmed CTA findings in all patients and demonstrated additional stenoses in the distal A2 anterior cerebral artery segment ( $n=1$ ) and P2 posterior cerebral artery segment ( $n=1$ ). Overall, contrast angiography was normal in 119 (78%) cases, whereas focal and diffuse intracranial disease was identified in 15 (10%) and 19 (12%) cases, respectively (Table 2; Figure 3). Median time elapsed between TCD and contrast angiography was 3 days (interquartile range, 5 days). Overall, TCD accuracy parameters for detecting focal and diffuse intracranial disease compared with contrast angiography were: sensitivity 79.4% (95% CI: 65.8% to 93%),

**Table 2. Neurovascular Findings in the Study Population**

| Variable                                                                      | N   | Percent |
|-------------------------------------------------------------------------------|-----|---------|
| Transcranial Doppler                                                          |     |         |
| Normal findings                                                               | 117 | 77      |
| Normal MFV, normal PI                                                         | 110 | 72      |
| Normal MFV, high PI                                                           | 4   | 3       |
| Low MFV, low PI                                                               | 3   | 2       |
| Abnormal findings                                                             |     |         |
| High MFV, variable PI                                                         | 15  | 10      |
| Low MFV, high PI                                                              | 17  | 11      |
| Mixed findings                                                                | 4   | 3       |
| High MFV/variable PI in $\geq 1$ artery and low MFV/high PI in other arteries |     |         |
| Contrast angiography (CTA/DSA)                                                |     |         |
| Normal                                                                        | 119 | 78      |
| Focal intracranial disease*                                                   | 15  | 10      |
| Diffuse intracranial disease                                                  | 19  | 12      |
| Stenosis in multiple segments of 1 artery                                     | 2   | 1       |
| Long ( $>1$ cm) stenosis in a segment of 1 artery                             | 2   | 1       |
| Stenosis in multiple ( $\geq 2$ ) arteries                                    | 15  | 10      |

\*Segmental ( $\leq 1$  cm long) stenosis in one artery measured by the WASID criteria.

specificity 92.4% (95% CI: 87.7% to 97.2%), positive predictive value 75.0% (95% CI: 60.9% to 89.2%), negative predictive value 94.0% (95% CI: 89.7% to 98.3%), and overall accuracy 89.5% (95% CI: 84.5% to 94.4%).

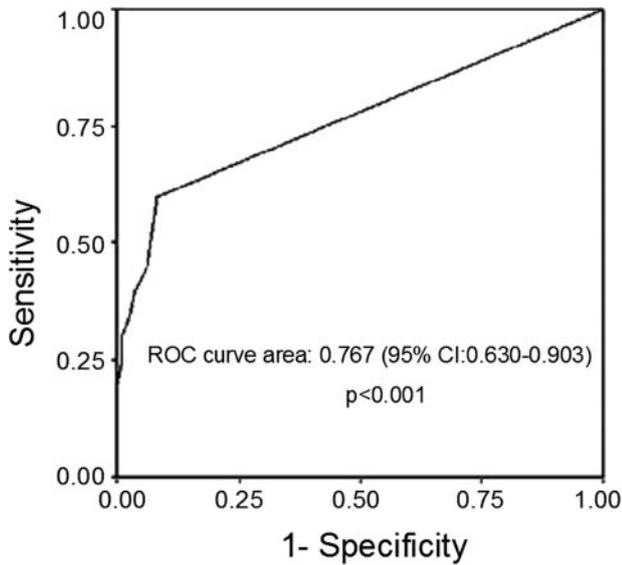
TCD findings in patients with angiographically proven focal intracranial disease ( $n=15$ ) were different from patients with diffuse intracranial disease ( $n=19$ ) (high MFV/variable PI 67% versus 21%, low MFV/high PI 13% versus 58%, and normal MFV/normal PI in 20% versus 21%, respectively;  $P=0.014$  Fisher exact test; Table 3). More specifically, the pattern of low MFV and high PI was documented in 100% (2 cases) of patients with stenosis in 2 or more segments of one artery, in 50% of patients with long ( $>1$  cm) stenosis (one case), and in 53% (8 cases) of patients with stenoses in multiple arteries. In the remaining 7 patients with angiographically proven multivessel intracranial stenotic disease (total of 15 individuals), TCD showed high MFV with variable PI in 4 cases (27%), whereas it disclosed no abnormal findings in 3 patients (20%).

After adjustment for stroke risk factors, TCD findings of low MFV and high PI in a single vessel were independently associated with angiographically demonstrated diffuse single

**Table 3. TCD Findings in Patients With Angiographically Demonstrated Focal and Diffuse Intracranial Disease**

| TCD Findings         | Contrast Angiography |                 |
|----------------------|----------------------|-----------------|
|                      | Focal Disease        | Diffuse Disease |
| High MFV/variable PI | 67%                  | 21%             |
| Low MFV/high PI      | 13%                  | 58%             |
| Normal MFV and PI    | 20%                  | 21%             |

Fisher exact test=8.593,  $df=2$ ,  $P=0.014$ .



**Figure 4.** Receiver operating characteristic curve analysis of the ability of TCD to identify diffuse intracranial disease stratified by the number of arteries with abnormal spectral Doppler findings (low MFV and high PI).

vessel intracranial disease, whereas low MFV/high PI in multiple vessels were related to multivessel intracranial disease (OR: 19.7, 95% CI:4.8 to 81.2,  $P<0.001$ ). The exclusion of patients with long (>1 cm) stenoses in a single vessel from the group of patients with diffuse intracranial disease slightly attenuated the former relationship, which retained its statistical significance (OR: 15.7, 95% CI: 4.1 to 59.7,  $P<0.001$ ). After the exclusion of patients with mixed TCD findings (high MFV/variable PI in  $\geq 1$  artery and low MFV/high PI in other arteries;  $n=4$ ) from the multivariable analyses, TCD findings of low MFV and high PI were independently related to diffuse intracranial disease (OR: 10.0; 95% CI: 3.1 to 32.6,  $P<0.001$ ). In addition, after adjustment for stroke risk factors, the ultrasound pattern of high MFV/variable PI correlated more strongly to focal (OR: 17.68, 95% CI: 4.10 to 76.34,  $P<0.0001$ , Wald statistic=14.819) intracranial disease than with diffuse intracranial atherosclerosis (OR: 8.40, 95% CI: 2.15 to 32.83,  $P=0.002$ , Wald statistic=9.362).

The ability of abnormal TCD findings (low MFV and high PI) to identify diffuse intracranial disease stratified by the number of affected arteries was further tested using receiver operating characteristic curve analyses. The area under the curve was 0.767 (95% CI: 0.630 to 0.903,  $P<0.001$ , Figure 4). TCD showing low MFV in the presence of high PI in 2 or more arteries was able to predict diffuse intracranial disease with sensitivity of 58%, specificity of 95%, positive predictive value of 61%, negative predictive value 94%, and overall accuracy of 90%. The pattern of low MFV and high PI was present in a single vessel (the affected artery) in patients with stenosis in 2 or more segments of one artery (2 cases) and in patients with long (>1 cm) stenosis (one case). In contrast, the pattern of low MFV with high PI was present in 2 or more vessels in the subgroup of patients with multiple arterial stenoses.

## Discussion

Our study shows that diffuse intracranial disease was relatively common (12%) in the select stroke population referred to the neurosonology laboratory of our tertiary care center. Abnormal TCD findings showing low MFV in the presence of high PI were independently associated with the presence of diffuse intracranial disease after adjusting for demographic characteristics and stroke risk factors. Furthermore, the ability of TCD to detect diffuse intracranial disease increased with the number of arteries affected.

Our findings also parallel previous reports<sup>29,30</sup> determining the prevalence of focal intracranial stenoses. However, we documented a substantial proportion of patients with additional diffuse intracranial disease in our study population. In some patients, both focal and diffuse lesions were found on angiography, thus contributing to the possibility of finding both high and low MFVs in the same patient. Recent data suggest an association between the degree of stenosis and recurrent stroke with higher degrees of stenosis and the number of vessels affected predicting worse prognosis.<sup>2</sup> Our study raises the possibility of increasing the yield of screening for intracranial disease and defining a broader spectrum of intracranial lesions for future clinical trials.

Currently, PI is not uniformly used for TCD reporting. Czosnyka et al<sup>31</sup> described the complex relationship between TCD-determined PI and cerebrovascular resistance in animal models. They concluded that although the relationship between PI and cerebrovascular resistance is not linear in all circumstances, changes in PI reflect changes in cerebrovascular resistance if cardiac output and cerebral perfusion pressure remain stable. Thus, PI may provide important information about the hemodynamic status of intracranial blood flow and disease burden.

Low MFV/high PI were documented in multiple vessels by TCD in patients with diffuse intracranial disease on contrast angiography, whereas the presence of low MFV/high PI in 2 or more intracranial arteries was highly specific for angiographically proven diffuse intracranial disease. Recent autopsy-based reports in patients with dementia also demonstrated correlation between low velocity/high resistance flow pattern with degree of cumulative intracranial stenosis due to atheromatous disease.<sup>32,33</sup> Interestingly, the same hemodynamic pattern (low MFV/high PI) was identified in patients with diffusely severe vertebral artery stenosis (>70% lumen stenosis and >1 cm length of plaque or multiple plaques) that were evaluated by transcranial imaging.<sup>28</sup>

Our study has several limitations. Our study is a single tertiary care center experience and thus, there may be a variety of selection biases that could affect disease prevalence. Hence, further validation by independent data sets is required to determine the sensitivity of our proposed criteria for the detection of diffuse intracranial disease. TCD information is limited to flow dynamics and does not provide any imaging to determine pathology of an intracranial vasooclusive lesion. In addition, distal MCA, anterior cerebral artery, and posterior cerebral artery branches are out of reach for the TCD ultrasound beam. The presence of low MFV/high PI in a single or multiple arteries could be transiently induced by hyperventilation or can be present at rest for technical reasons

such as suboptimal angle of insonation, especially in the distal arterial segments. In addition, it is difficult to differentiate between a hypoplastic artery and diffuse atherosclerotic disease, because both can produce low MFV and high PI, and no histopathological correlation was performed in the present study. Also, it needs to be kept in mind that TCD is useful for ruling out intracranial disease (high negative predictive value, 94% in the present cohort) but less reliable for ruling in disease (lower positive predictive value, 75% in the present cohort). Therefore, TCD should ideally be used as the initial screening tool for the detection of diffuse intracranial disease, and other neuroimaging modalities are necessary for the final confirmation of this diagnosis. Of note, however, in certain patients with stroke, TCD can provide real-time flow findings (real-time embolization, collateralization of flow with extracranial internal carotid artery disease, alternating flow signals indicative of steal phenomenon) that are complementary to information provided by CTA.<sup>34</sup>

Moreover, single-vessel stenotic lesions longer than 1 cm were arbitrarily included in the angiographic definition of diffuse intracranial disease. However, it should be noted that even after exclusion of these cases, TCD findings of low MFV and high PI were independently associated with angiographically demonstrated diffuse intracranial disease.

Another potential shortcoming of our study is related to the time interval that elapsed between stroke onset and ultrasonographic evaluation of our patients, because it could be argued that emboli could have actually cleared in certain individuals. Of note, however, we evaluated only patients with subacute (3 to 14 days from ictus) and chronic (>14 days from ictus) cerebral ischemia and thus, it is unlikely that individuals with acute intracranial occlusions may have been included in the present study sample. Finally, it should be acknowledged that the reliability of CTA for the diagnosis of intracranial disease was suboptimal according to the recently presented results of the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Study.<sup>35</sup>

In summary, our findings indicate a higher than expected frequency for diffuse intracranial stenosis in a select tertiary care center stroke population and suggest new potential criteria for its detection with noninvasive ultrasonographic screening. Current TCD criteria are based solely on high-velocity cutoffs and may be too simplistic to accurately reflect the entire spectrum of intracranial stenooclusive disease. Our study introduces novel abnormal TCD findings that, if validated by other independent investigators, may be helpful for the detection of patients with multifocal or diffuse intracranial disease.

### Disclosures

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