Background and Purpose—The North American and the European Carotid Endarterectomy Trials demonstrated a significant benefit of surgery in preventing stroke for patients with symptomatic hemodynamically significant internal carotid artery (ICA) stenosis. Because the 3 angiographic methods of measuring carotid stenosis provide discrepant results, the indication for surgery depends on the method used for the evaluation of the angiogram. The goal of this study was to verify whether color duplex scanning of the ophthalmic artery alone might be reliable for detection of the extracranial hemodynamically significant ICA stenosis.

Methods—Three groups of patients (351 total patients) with transient ischemic attack or minor stroke referred for possible carotid endarterectomy were examined by means of color duplex scanning of the ICA, transcranial Doppler, color duplex scanning of the ophthalmic artery, and angiography of the ICA.

Results—in the first group (n = 31) the comparison of findings from each method and the direct measurement of the residual lumen of plaque removed “en bloc” showed that the findings of the ophthalmic artery color duplex scanning, subdivided into 5 categories—NP (normal positive), LP (low positive), NF (no flow), REV (reverse flow), PP (pathological positive)—were associated with the best overall agreement (96.7%). The accuracy of the various categories of the ophthalmic artery color duplex scanning signals was studied in the second group of patients (n = 200). The results pointed out that all but low positive categories were associated with high diagnostic accuracy. Finally, the results obtained in the third group (n = 120) showed that a significant increase in the specificity of the low positive signal could be obtained by processing this signal in terms of pulsatility index and of transmission of pulsatility index.

Conclusions—Our results suggest that the diagnostic capacity of color duplex scanning for the detection of ICA critical stenosis can be appropriately increased if it is performed also at the level of the ophthalmic artery and if the Doppler signals are processed on the basis of criteria we applied. (Stroke. 1999;30:821-826.)

Key Words: Doppler, duplex ■ ophthalmic artery ■ stenosis ■ ultrasonography
The ophthalmic artery (OA) appears very suitable for study because of the following characteristics: (1) OA is the first branch of the ICA and therefore the nearest to the carotid bulb in which the stenosis is located; (2) according to its distribution, OA performs like a catheter that transfers straight away the values of the perfusion pressure gradient from downstream of the ICA stenosis toward the eyelids; (3) the easy insonation with color duplex scanning of the OA (OA CDS) allows us, without interference from the bony skull, to overcome the frequent limitations (5% to 19%) of transcranial Doppler ultrasonography (TCD) in the exploration of the middle cerebral artery and of the anterior cerebral artery because of the temporal bone thickness; and (4) finally, OA is placed at the watershed between the ICA and the external carotid artery (ECA) territories, therefore it is particularly liable to ischemias for hemodynamic reasons.

Previously, Spencer and Whisler\(^2\) applied duplex scanning of the OA for the detection of intracranial ICA stenosis, and Schneider et al\(^2\) used duplex scanning for the assessment of OA as a source of collateral cerebral blood supply. Finally, Wilterdink et al\(^2\) found that to reliably ascertain the hemodynamically significant ICA stenosis, OA duplex scanning should be associated with TCD. The aim of this study was to verify whether the OA CDS examination alone may be a reliable approach for the detection of the extracranial hemodynamically significant ICA stenosis.

### Subjects and Methods

We studied 3 groups of patients \((n=351)\) with transient ischemic attack or minor stroke referred for possible carotid endarterectomy, by means of ICA CDS, TCD, color duplex scanning of the OA, and arteriography. Patients with severe contralateral stenosis or intracranial artery stenosis were excluded from this study.

Our protocol included the following. Before carotid endarterectomy all patients underwent ICA CDS with an Acuson 128 XP ultrasound device with 7.0- and 5.0-MHz linear array transducers. The peak systolic velocity and the end-diastolic velocity at the stenotic area were evaluated, and the findings were classified, according to the method of Bluth et al\(^2\) as critical ICA stenosis when the peak systolic velocity was \(\geq250\) cm/s, and the end-diastolic velocity was \(\geq100\) cm/s.

TCD was performed with a hand-held system that used a 2-MHz Doppier probe (Multidop X4, DWL Elektronische Systeme GmbH) as described by Aaslid.\(^3\) The findings were classified as pathological when there was a reversal of flow in the ipsilateral anterior cerebral artery associated with appropriate effects of the ipsilateral and contralateral common carotid compression (CCC). This maneuver was always carried out at the farthest place from the carotid bulb only when, as shown by ICA CDS, any severe atherosclerotic changes were lacking.

The OA CDS signal was obtained by applying the 7.0-MHz Acuson probe on the closed eyelid with the patient in the supine position. The OA is easily located by aiming the Doppler beam near the optic nerve at a depth of 4 to 6 cm. Acuson 128 XP provides an ocular program that forsees \(<17\) mW/cm² of ultrasound emission at the transducer surface according to the FDA rules.\(^2\) The patient was invited to turn the eyes toward the contralateral side to avoid the refractive power of the ocular lenses.

Under normal conditions the perfusion pressure in the territory of the OA is higher than in the ipsilateral ECA territory. The direction of flow is toward the ECA territory and, therefore, the Doppler signal of the OA is anterograde.

Under pathological conditions, as long as the OA perfusion pressure decreases, the amplitude of the anterograde Doppler signal progressively decreases, reaching the basal line when the pressure gradient at the border between the 2 territories becomes equal to 0. When the perfusion pressure becomes higher in the ECA territory, the direction of the OA flow reverses. Finally, if the ICA stenosis is associated with stenosis or occlusion of the ipsilateral ECA, the perfusion pressure in the ECA territory may become very low. In that case the OA signal may still stand anterograde.

According to Figure 1, the OA CDS findings were classified as normal positive (NP) when the signal obtained was anterograde. In that case the systolic blood velocity of OA was \(48.5\pm7.8\) cm/s on both eyes. Moreover the ipsilateral CCC was associated with a significant reduction of the ipsilateral OA systolic velocity. The signal was classified low positive (LP) when the amplitude of the Doppler signal on the stenotic side was \(<25\%\) of that found on the contralateral eye and the ipsilateral CCC was associated with the disappearance of the OA flow. This parameter was \(12\pm4.6\) cm/s. The signal was classified no flow (NF) when no Doppler signal was detected on the stenotic side and reverse (REV) when the signal on the stenotic side was backward. Finally, it was classified pathological positive (PP) when the signal disappeared during the contralateral CCC and it did not change during the ipsilateral CCC. The detection of the OA CDS signals was performed 3 times on each eye. NF, REV, and PP signals were assessed qualitatively, whereas the NP and LP signals were quantified according to the average of the 3 values of the systolic velocity.

Arteriography was performed using the intra-arterial digital subtraction technique via the femoral artery with the injection of contrast medium at the level of the first part of the aortic arch. Biplar images were obtained for each ICA. The measurements of ICA diameter reduction were performed by the NASCET method and by visual estimation by 2 independent angiographers. All measurements were blindly assessed. Three experienced examiners (D.R., I.N., and F.B.) performed ICA CDS, TCD, and OA CDS examinations without knowledge of the degree and side of the stenosis or occlusion. Table 2 shows the criteria used for discrimination between hemodynamically and nonhemodynamically significant ICA stenosis.

Statistical analysis was performed with the Student’s (2-tailed) \(t\) test, and the results are given as mean\(\pm\)SD. All subjects gave informed consent to participate in the study, which was approved by the Ethics Committee of the University of Florence.

### Results

In the first group of 31 patients (24 men and 7 women; mean age, 64 years; age range, 52 to 73 years) we compared the findings of ICA angiography, color duplex sonography of ICA, TCD, and (4) OA CDS versus the residual lumen of ICA...
TABLE 1. Accuracy of the 4 Diagnostic Methods Used Versus the Direct Measure of Residual ICA Lumen

<table>
<thead>
<tr>
<th>Direct Measure</th>
<th>AGF</th>
<th>ICA CDS</th>
<th>TCD</th>
<th>OA CDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamic ICA stenosis: residual lumen &lt;1.5 mm</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (FP)</td>
<td>0 (FP)</td>
<td>0 (FP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (ND)</td>
<td>3 (ND)</td>
<td>2 (ND)</td>
</tr>
<tr>
<td>Nonhemodynamic ICA stenosis: residual lumen &gt;1.5 mm</td>
<td>18</td>
<td>12</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (FN)</td>
<td>0 (FN)</td>
<td>1 (FN)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (ND)</td>
<td>1 (ND)</td>
<td>1 (ND)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>91.6%</td>
<td>100%</td>
<td>91.0%</td>
<td>92.3%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>74.2%</td>
<td>87.0%</td>
<td>87.0%</td>
<td>96.7%</td>
</tr>
<tr>
<td>Specificity</td>
<td>75.0%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

AGF indicates arteriography; FP, false positives; FN, false negatives; and ND, nondiagnostic tests.

TABLE 2. Criteria Used for Discrimination between Hemodynamically and Nonhemodynamically Significant ICA Stenosis

<table>
<thead>
<tr>
<th>AGF</th>
<th>ICA CDS</th>
<th>TCD</th>
<th>OA CDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral ICA stenosis: &lt;70%</td>
<td>Systolic velocity of the ipsilateral ICA ≥250 cm/s, End-diastolic velocity ≥100 cm/s</td>
<td>Reversal of the ipsilateral ACA flow associated with increase of velocity on the ipsilateral CCC</td>
<td>LP: OA systolic velocity of the stenotic side at least 25% lower than that of the contralateral side, associated with a significant decrease or disappearance on the ipsilateral CCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NF: No Doppler signal was detected at the stenotic side</td>
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<td></td>
<td></td>
<td></td>
<td>REV: Backward flow at the stenotic side</td>
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<td></td>
<td></td>
<td></td>
<td>PP: When the anterograde Doppler signal disappeared during contralateral CCC and did not change during ipsilateral CCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NP: Anterograde Doppler signal of OA with systolic velocity of 48.5±7.8 cm/s, associated with significant reduction of velocity on the ipsilateral CCC</td>
</tr>
<tr>
<td>Ipsilateral ICA stenosis: &gt;70%</td>
<td>Systolic velocity of the ipsilateral ICA &lt;250 cm/s. End-diastolic velocity &lt;100 cm/s</td>
<td>Normal direction of flow in the ipsilateral ACA associated with decrease of flow velocity on the ipsilateral CCC</td>
<td></td>
</tr>
</tbody>
</table>

LAGF indicates arteriography; ACA, anterior cerebral artery. See text for definition of ratings for OA CDS.

obtained by the whole plaque removed en bloc at the time of carotid endarterectomy.

The 31 plaques consisted of short portions of the common carotid artery and of the ECA with the diseased segment of the ICA, which always included the point of maximum lumen encroachment. They were primarily placed in 10% formalin and decalcified with EDTA for 3 hours. The specimens were then sectioned horizontally at 0.2-cm intervals with a razor blade and laid in series so that slides of each section could be obtained. A slide scanner scanned the slide of the section with the smallest residual lumen, and the images were stored on floppy diskettes. The luminal area of each stored image was measured digitally, and the minimal residual diameter was calculated from this area measurement with a Corel computer program (Corel Corp, Ltd). The residual lumen diameter measurements were rounded to the nearest 0.1 mm, ie, 0.15 mm was recorded as 0.2 mm. If the vessel had 2 largely different diameters (ie, it was asymmetrical), the value we chose was the mathematical mean of the 2 values. We therefore, were considered hemodynamically significant stenosis; 18 plaques showed a residual lumen >1.5 mm and were considered as nonhemodynamically significant stenosis.

In the first group of plaques (hemodynamic ICA stenosis) arteriography gave appropriate answers versus the gold standard in 11 and nonappropriate answers in 4 (false-positives), with specificity equal to 75.0%. In the second group of plaques (nonhemodynamic ICA stenosis), arteriography gave appropriate answers in 12 and nonappropriate answers in 1 (false-negative), with sensitivity equal to 91.6%. In 3 cases, the answers were considered nondiagnostic. The overall agreement between the gold standard and arteriography (accuracy) was equal to 74.2%.

ICA CDS in the first group of plaques gave appropriate answers versus the gold standard in 10 and nonappropriate answers in 0 (specificity = 100%). In the second group of plaques, this method gave appropriate answers in 17 and nonappropriate answers in 0 (sensitivity, 100%). In 4 cases, the answers were nondiagnostic because of the presence of heavy calcification of the plaque. The overall agreement between the gold standard and color duplex scanning was 87.0%.

The TCD in the first group of plaques gave appropriate answers in 10 cases and nonappropriate answers in 0 (specificity, 100%), and in the second group of plaques this
method gave appropriate answers in 17 cases and nonappropriate answers in 1 (sensitivity, 91.0%). In 3 cases the test was nondiagnostic because the temporal windows were closed. The overall agreement between the gold standard and TCD was 87.0%.

Finally, the OA CDS signals in the first group of plaques gave appropriate answers in 12 cases (in 6 the signal was REV, in 1 it was NF, in 1 it was PP, and in 1 it was LP) and nonappropriate answers in 0 (specificity, 100%), whereas in the second group of plaques the OA CDS gave appropriate answers in 18 (in these cases the signals were NP) and nonappropriate answers in 1 (LP signal; sensitivity, 92.3%). The overall agreement between this method and the gold standard was 96.7%.

In a second group of 200 patients (148 men and 52 women; mean age, 68.4 years; 397 ICAs), we verified, on the basis of the results obtained in the first group, the accuracy of each of the 5 categories of the OA signals versus its screening capacity between the hemodynamically and nonhemodynamically significant ICA stenoses. The results obtained in this second group of patients are shown in Figure 2. In this group, 285 ICAs showed a nonhemodynamically significant stenosis, 51 a hemodynamically significant stenosis, and 61 an ICA occlusion.

The NP signal was in any case associated with a nonhemodynamically significant ICA stenosis. The NF signal was constantly associated with hemodynamically significant ICA occlusive disease: 13 ICAs with 80% to 99% luminal narrowing and 16 ICAs with occlusion of the lumen. The REV signal was constantly associated with hemodynamically significant ICA occlusive disease: 18 ICAs with 80% to 99% stenosis of the lumen and 19 ICAs with occlusion of the lumen. The PP signal was constantly associated with hemodynamically significant ICA occlusive disease: 10 ICAs with 80% to 99% stenosis and 10 ICAs with occlusion of the lumen.

The LP Doppler signal was associated with 90 ICAs with <60% nonhemodynamically significant stenosis, 30 ICAs with 60% to 79% nonhemodynamically significant ICA stenosis, 10 ICAs with 80% to 99% hemodynamically significant ICA stenosis, and 16 ICAs with occlusion of the lumen.

Finally we examined a third group of 120 patients (63 men, 57 women; mean age, 69.1 years; age range, 56 to 80 years; 240 ICAs), who showed LP signal at 1 eye. Toward the aim of increasing the specificity of LP signal, we processed this parameter in terms of the pulsatility index (PI): $PI = \frac{\text{systolic velocity} - \text{diastolic velocity}}{\text{mean velocity}}$. We also calculated the transmission of the PI (TPI): $TPI = \frac{\text{PI of the stenotic side}}{\text{PI of nonstenotic side}} \times 100$. Because the reproducibility of PI, as automatically provided by our device, was low, we measured straight away on the display the value of the systolic and diastolic velocities. Then we traced the envelope of each OA CDS signal and received automatically the values of PI. In 5 patients without ICA occlusive disease, we tested the maximum and the mean reproducibilities of PI (5.9% and 4.7%, respectively) and of TPI (6.1% and 4.2%, respectively). We classified the signal as NP if the TPI value was >90% and LP if this value was <80%, whereas the TPI values ranged between 80% and 90% and were classified “uncertain values.” On the basis of arteriography, ICA CDS, and TCD, the ICAs were classified into 3 subgroups: (1) patients with nonhemodynamically significant stenosis (n=55 with <60% ICA stenosis and n=25 with 60% to 79% ICA stenosis); (2) n=15 patients with 80% to 99% ICA stenosis; and (3) n=25 patients with occlusion.

The OA PI value was 1.29±0.54 ipsilateral to an ICA with hemodynamically significant occlusive disease, whereas it was 1.62±0.37 in the presence of noncritical ICA stenosis ($P<0.01$). The average length for a complete measurement of TPI in each patient was 8.1±2.5 minutes.

In the first subgroup, the values of TPI ranged between 89% and 107%, mean±SD 96.9%±5.1 (>60% ICA sten-
(sis), and between 87% and 106%, mean±SD 96.1%±5.9 (60% to 79% ICA stenosis). In the second subgroup, the value of TPI ranged from 48% to 84%, mean±SD 68.2±9.8 (80% to 99% ICA stenosis), and in the third subgroup 43% to 88%, mean±SD 69.8%±12.9 (occlusion of ICA). The difference between the mean value of TPI of the ICAs of the first 2 subgroups (96.6±5.3) and that of the other 2 subgroups (69.2%±11.7) was statistically significant (P<0.01). Figure 3 also shows that in 7 cases the TPI values dropped in the “uncertain area”: 2 cases of the first subgroup, 2 of the second, and 3 of the third subgroup; therefore there were 2 cases of false-positive results and 5 cases of false-negative results.

Discussion

Our results point out that the duplex scanning approach of the OA appears very suitable for the assessment of hemodynamically significant ICA occlusive disease. The comparison of the gold standard and the findings obtained by the other methods of ICA examination has shown that the ones delivered by OA CDS were associated with the overall best agreement: OA CDS, 96.7%; ICA CDS, 87.0%; TCD, 87.0%; and arteriography, 74.2% (Table 1).

Figure 2 shows that not all of the 5 categories of the OA CDS signals have shown the same degree of reliability. NP, NF, REV, and PP parameters showed a very high degree of specificity (100%). The NP parameter was constantly associated with nonhemodynamically significant ICA stenosis, whereas NF and REV signals were, in any case, associated with hemodynamically significant ICA occlusive disease. However, these 2 parameters were not able to discriminate between hemodynamically significant stenosis and occlusion of the ICA: NF and REV signals were found in 13 and 18 patients, respectively, with hemodynamically significant ICA stenosis and in 16 and 19 patients with ICA occlusion. These results are in keeping with those obtained by others.20

The PP OA CDS signal, for which the incidence rate has been equal to 5% of all ICAs studied and which can be easily discriminated by NP and LP signals on the basis of the ipsilateral and contralateral CCCs, was found in 10 patients with hemodynamically significant ICA stenosis and in 10 patients with ICA occlusion. Therefore, this signal also appeared very reliable for the screening of hemodynamically ICA occlusive disease, but it did not discriminate between ICA stenosis and ICA occlusion. LP signal, on the other hand, has shown a very low specificity (18%). This parameter was associated with hemodynamically nonsignificant ICA stenosis in 90 patients and with hemodynamically significant ICA stenosis or occlusion in 26 patients. The very low accuracy of the LP OA CDS signal may be related to the following: (1) the abnormal origin of OA from the middle meningeal artery (branch of ECA) whose frequency ranges between 2% and 5%;28 (2) the tortuous pathway of the OA, associated with eye movement, makes the angle between the ultrasound beam and the artery lumen variable; (3) the absolute value of the velocity measurement is more liable to be wrong primarily when its value is low. These limitations may be reliably overcome if we process the LP signal in terms of PI, which, as the result of a ratio, is less dependent on the ultrasound beam angle of insonation. The results shown in Figure 3 point out that the LP OA CDS signal when processed in terms of PI and TPI can properly discriminate between hemodynamically nonsignificant and significant ICA stenosis. The >90% TPI value (the value with the highest sensitivity) was in all cases associated with hemodynamically nonsignificant ICA stenosis or occlusion. Finally, the TPI values ranged between 80% and 90% and appeared as “uncertain values.”

Because the ICA occlusion cannot be subjected to carotid endarterectomy, the most clinically relevant diagnostic problem concerns the discrimination between hemodynamically
and nonhemodynamically significant ICA stenosis. The results shown in Figure 3 point out that if we set the cutoff point at the TPI value of 90% all the hemodynamically significant ICA stenoses are discriminated, and a few (only 2 ICAs in our group of patients) hemodynamically nonsignificant ICA stenoses may be diagnosed as “false-positives.” However, because for the subgroup of transient ischemic attack patients with severe ICA stenosis the average annual risk of stroke in nonoperated patients was 14% per year and the perioperative risk of any stroke or death was 5.8% (and functional deficit persisting beyond 90 days and death was 2.1%),1 we believe it is better to use a cutoff point that provides the best sensitivity rather then the best specificity.

In conclusion, our results confirm the statement that the exploration of the collateral blood supply in an arterial territory can be a reliable way to ascertain the hemodynamic meaning of the artery stenosis present in that territory. Also, if the advent of duplex ultrasound modality has unfortunately made the periorbital Doppler sonography a procedure that is not routinely performed at present for the extracranial ICA exploration, that approach still is the most cost-effective Doppler approach for the detection of the extracranial critical stenosis of this artery.20 Our results suggest that according to the periorbital Doppler principle if the Duplex ICA examination is performed also at the level of the OA, and if the obtained signals are assessed on the basis of the criteria we applied, its diagnostic capacity in the detection of the critical stenosis and its cost-effectiveness both can be appropriately increased.

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References
Duplex Scanning Exploration of the Ophthalmic Artery for the Detection of the Hemodynamically Significant ICA Stenosis


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