Reliability and Validity of Noninvasive Imaging of Internal Carotid Artery Pseudo-Occlusion

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Background and Purpose—Our study evaluated noninvasive tests for the diagnosis of atheromatous internal carotid artery (ICA) pseudo-occlusion.

Methods—Twenty patients (17 men, 3 women; mean age ±SD, 64.3±11.6 years) with angiographically proven atheromatous ICA pseudo-occlusion (20 vessels) were prospectively examined with MR angiography (MRA; 2D and 3D time-of-flight techniques), color Doppler–assisted duplex imaging (CDDI) and power-flow imaging (PFI) with and without an intravenous ultrasonic contrast agent. As a control group, 13 patients (13 men; mean±SD age, 63.0±9.0 years) with angiographically proven ICA occlusion (13 vessels) were studied with the same techniques. For the determination of interobserver agreement (κ statistics), the findings of each diagnostic technique were read by 2 blinded and independent observers who were not involved in patient recruitment and initial data acquisition. Specificity and sensitivity were calculated for all noninvasive techniques (observer consensus) in comparison to the standard of reference (intra-arterial angiography).

Results—Interobserver reliabilities were κ=0.86 for intra-arterial angiography, κ=0.90 for unenhanced CDDI, κ=0.93 for enhanced CDDI, κ=0.93 for unenhanced PFI, κ=1.0 for enhanced PFI, κ=0.93 for 2D MRA, and κ=0.77 for 3D MRA, respectively (P<0.0001). Specificities and sensitivities were 0.92 and 0.70 for unenhanced CDDI, 0.92 and 0.83 for enhanced CDDI, 0.92 and 0.95 for unenhanced PFI, 1.0 and 0.94 for enhanced PFI, 1.0 and 0.65 for 2D MRA, and 0.89 and 0.47 for 3D MRA, respectively.

Conclusions—Advanced ultrasonographic techniques, especially PFI (with only 1 false-positive diagnosis of occlusion in the present series), can provide reliable and valid data to differentiate between ICA pseudo-occlusion and complete occlusion. In contrast, time-of-flight MRA at its present state is not capable of predicting minimal residual flow within a nearly occluded ICA. (Stroke. 1999;30:1444-1449.)

Key Words: angiography, digital subtraction ■ angiography, magnetic resonance ■ carotid artery diseases ■ carotid artery occlusion ■ contrast media ■ ultrasonography

Stroke risk in patients with extracranial atherosclerotic carotid artery disease increases with the degree of luminal narrowing. It ranges up to 14.4% over 3 years in >90% of asymptomatic stenoses and up to 35% over 2 years in >90% of symptomatic lesions.1,2 The risk is believed to be particularly high in patients with so-called atheromatous pseudo-occlusion (APO) of the internal carotid artery (ICA), presumably justifying urgent thromboendarterectomy in such cases.3,5

The standard of reference in distinguishing pseudo-occlusion from occlusion is intra-arterial angiography.6–11 Several retrospective studies have examined the possible validity of ultrasonographic techniques in detecting carotid APO.12–16 They found sensitivities ranging from 78% to 100% for unenhanced color Doppler–assisted duplex imaging (CDDI).13,15 In these series the prevalence of carotid APO varied between 8% and 34% of intra-arterial angiographies performed to verify the diagnosis of ICA occlusion.14,16 These results can be criticized due to possible observer bias, so that the reported sensitivities and specificities may overestimate the diagnostic value of ultrasonographic techniques in clinical practice.

The prospective validity of noninvasive tests for the diagnosis of carotid APO has not been defined. Thus, we performed a prospective between-methods comparison of ultrasonographic and MR techniques versus intra-arterial angiography as the gold standard. We determined interobserver reliability and validity based on blinded readings.
Subjects and Methods

Patients
From February 1996 to August 1998, 713 cerebral angiographies were performed in 713 patients with extracranial carotid artery disease. Among them, 20 (85% men; mean age, 64.3 years; range, 39 to 83 years) fulfilled the angiographic criteria (see below) for carotid APO. All patients included in the study had experienced recent ischemic neurological symptoms (minor strokes, n=3; transient ischemic attacks, n=14; and transient monocular blindness, n=3) within the previous 6 months attributable to the ICA lesion. The control group consisted of 13 patients (100% men; mean age, 63 years; range, 57 to 85 years) randomly selected from 122 patients with angiographically proven complete occlusion of the ICA. All 33 patients underwent echo-enhanced and unenhanced CDDI, power-flow imaging (PFI), and MR angiography (MRA) within a mean time interval of 1.6 days (range, 1 to 5 days) after intra-arterial angiography. In the patients with APO, operative findings confirmed patency of the ICA in all cases.

Intra-Arterial Angiography
Intra-arterial digital subtraction angiography (CG 200: General Electric/CGR) of the carotid system with a minimum of 2 projections was carried out in all patients. The angiographic technique used was similar to that first described by Countee and Vijayanathan. It was performed in the following fashion: (1) selective catheterization of the common carotid artery, (2) prolonged injection of 12-mL non-ionic x-ray contrast agent, (3) prolonged filming with 2 frames/s for 15 seconds followed by 1 frame/s for 10 seconds. ICA-APO was diagnosed when a thin, markedly delayed antegrade trickle of contrast medium without discernible washout on later films was visible in the ICA distal to the extreme stenosis in at least 1 projection (Figures 1 and 2). A time interval of >4 seconds between administration of the contrast agent into the common carotid artery and its arrival at the base of the skull was used as an additional criterion. Based on this definition, the interobserver agreement on the presence of APO between 2 experienced neuroradiologists (M.C. and J.M.) who were not involved in patient recruitment and initial data acquisition was $\kappa = 0.86$ (Table 1). The prevalence of angiographic ICA-APO reported in the following is based on the consensus achieved by the 2 neuroradiologists at joint reevaluation of their data previously obtained independently.

Magnetic Resonance Angiography
All examinations were performed using a 1.5-T whole-body scanner (Vision, Siemens) and a linearly polarized transmit-receive neck coil. To obtain 2D time-of-flight (TOF) MRAs, transverse slices were acquired with a fast, low-angle shot (FLASH), 25-ms TR, 9-ms TE, 40° delta, 4-mm slice thickness, 1 excitation, with velocity compensation in the slice and frequency-encoding directions. Image matrix and field of view were 160 × 256 pixels and 150 × 200-mm, respectively. For 3D TOF MRA, a fast imaging with steady precession (FISP) MRI sequence with the following parameters was used: 30-ms TR, 6.4-ms TE, 10° delta, 73-mm slab thickness (64 partitions), 1 excitation, with velocity compensation in the slice and frequency-encoding directions. Image matrix and field of view were 160 × 512 and 150 × 200 mm, respectively. Two image volumes overlapping by 20 partitions (15.6 mm) were investigated in each patient. Elimination of venous flow was achieved by presaturation bands positioned above and parallel to the image volume. Angiographic projection images were reconstructed using a maximum-intensity projection algorithm. Twelve images in steps of 10° around a vertical axis of rotation were used for final evaluation. The ICA was classified as being patent if a minimal residual flow signal was continuously visible on at least 1 projection (Figure 1). If no flow was visualized on MRA projection angiograms, the transverse source images of the 2D and 3D data sets were also analyzed. Based on this definition, the interobserver agreement between 2 experienced neuroradiologists (A.A. and P.W.) who were not involved in patient recruitment and initial data acquisition was $\kappa = 0.93$ for 2D and $\kappa = 0.77$ for 3D MRA, respectively (Table 1). For MRA techniques, the prevalence of ICA-APO reported in the following is based on the consensus achieved by the 2 neuroradiologists at joint reevaluation of their data previously obtained independently.

Ultrasoundographic Examinations
In all patients the extracranial carotid system was insonated by means of a 5.0- or 10.0-MHz linear-array transducer for real-time display of high-resolution B-mode gray-scale images combined with a 6.0- or 5.14-MHz pulsed-wave Doppler probe for superimposed simultaneous color-encoded blood flow information (ATL HDI 3000 or Siemens Sonoline Elegra). Each examination cycle included sequential longitudinal (antero-oblique/postero-oblique/lateral) and transverse views of the entire extracranial carotid system using CDDI- and PFI-modalities. Controlled parameters for each examination were lowest pulse repetition frequency without aliasing, angle of insolation $\leq 60^\circ$, and beam focusing at the level of the vessel being investigated. For optimal gain adjustment, the color gain was increased until color noise occurred at the region of interest in the image background. The resulting color Doppler gains ranged from 45 to 63 dB (mean ± SD, 56.8 ± 6.9 dB) for CDDI and from 60 to 74 dB (mean ± SD, 66 ± 17.5 dB) for PFI, respectively. According to the examination protocol, transmission power and gain adjustment were maximized and pulse repetition frequency and wall filter were minimized (150 to 200 Hz) if no residual flow was detected within the ICA under standard conditions. Transpulmonary stable ultrasonographic contrast agents can enhance reflected ultrasonographic energy and may increase the sensitivity of CDDI in detecting minimal residual flow in the highly stenosed ICA. Based on these findings, both CDDI and PFI examinations were performed under echo-enhanced and unenhanced conditions in each patient. The contrast agent (16 mL: 200 mg/mL: Levovist, Schering) was continuously administered (0.5 mL/s) through a cubital vein. Under echo-enhanced conditions, the resulting gains ranged from 32 to 60 dB (mean ± SD, 48 ± 17.5 dB) for CDDI and 47 to 63 dB (mean ± SD, 56 ± 7.5 dB) for PFI, respectively. For all patients, the entire examination cycle was recorded on a S-VHS video system for offline analyses (see below). All examinations were performed by 1 sonographer. The ICA was classified as being patent if an antegrade flow signal could be detected within the nearly occluded vessel in at least 1 orientation (Figures 1 and 2). Interobserver reliabilities were determined both for echo-enhanced and unenhanced CDDI and PFI examinations, respectively. For this purpose, typical video sequences for each examination modality were randomly matched and presented to 2 experienced neurosonographers (M. Schroeter and T.N.-H.) who were not involved in patient recruitment and initial data acquisition. Based on the above mentioned definition, interobserver agreement was $\kappa = 0.90$ for unenhanced CDDI, $\kappa = 0.93$ for both echo-enhanced CDDI and unenhanced PFI, and $\kappa = 1.0$ for echo-enhanced PFI (Table 1). The prevalence of ultrasonic ICA-APO reported in the following is based on the consensus achieved by the 2 neurosonographers at joint reevaluation of the video sequences previously classified independently.

Data Analysis
Interobserver reliabilities for each diagnostic test were based on $\kappa$ statistics. Cross tabulation correlations between intra-arterial angiography as the gold standard and the different noninvasive modalities were calculated using Fishers exact test. The Wilcoxon test was used for intermethod comparisons.

Results
For intra-arterial angiography, there was interrater disagreement in 2 cases due to a very weak poststenotic flow signal within the ICA, which made it difficult to decide whether poststenotic flow was antegrade. In 5 of 33 patients MRA was not available because of claustrophobia (2 patients), cardiac pacemaker (1 patient), and patient refusal (2 patients). Two MRAs had to be excluded from evaluation because of motion.
artifacts. Across the remaining 26 patients, 2D TOF MRA misdiagnosed 6 of 17 (36%) carotid APOs as complete occlusions and 3D TOF MRA misdiagnosed 9 of 17 (53%), respectively (Table 2, Figure 2). In 1 patient (11%), a completely occluded ICA was incorrectly diagnosed as being patent with 3D TOF MRA.

In 2 of 33 patients enhanced CDDI and enhanced PFI video sequences, and in 1 patient unenhanced PFI video sequences, were not available for offline analysis. Unenhanced CDDI misdiagnosed 6 of 20 (30%), echo-enhanced CDDI 3 of 18 (17%), unenhanced PFI 1 of 19 (5%), and echo-enhanced PFI 1 of 18 (6%) carotid APOs as complete occlusions (Table 2, Figure 1). In 1 patient (8%) a completely occluded ICA was misinterpreted as being patent with unenhanced and echo-enhanced CDDI and unenhanced PFI. Sensitivity could not be increased to 100% combining ultrasonographic and magnetic resonance techniques.

Intermethod comparisons revealed significant differences in sensitivity between CDDI versus PFI under unenhanced conditions, unenhanced and echo-enhanced PFI and CDDI.

Figure 1. Multimodality imaging of symptomatic right ICA-APO. All images were obtained within 1 day. A and B, Intra-arterial angiograms (lateral views) obtained 2 and 6 seconds after contrast application into the common carotid artery. Contrast flow through the severely stenosed ICA (arrows) is antegrade and markedly delayed and has not reached the carotid siphon by the sixth second. The intracranial portion of the ICA is filled via the ophthalmic artery (arrow). C and D, 2D and 3D TOF MR angiograms (lateral views) reveal ICA patency (arrows). 2D TOF MRA (C) provides slightly better contrast. E and F, Unenhanced and echo-enhanced CDDI; G and H, unenhanced and echo-enhanced PFI (longitudinal views). Unenhanced and echo-enhanced PFI (G, H) and echo-enhanced CDDI (F) also reveal ICA patency, whereas unenhanced CDDI failed to identify residual flow through the nearly occluded ICA.
Figure 2. Multimodality imaging of symptomatic left ICA-APO. All images were obtained within 1 day. A and B, Late contrast angiograms obtained 6.5 and 8.5 seconds after application of the contrast agent into the common carotid artery (lateral views). C, 2D TOF MR angiogram (lateral view). D and E, Echo-enhanced CDDI (longitudinal and transverse views). Intra-arterial angiography reveals extremely delayed antegrade flow through the patent ICA (arrows, A and B), whereas 2D TOF MRA fails to identify ICA patency (C). Echo-enhanced CDDI demonstrates patency of the severely stenosed ICA (arrows) on both longitudinal (D) and transverse (E) views.
versus 3D TOF MRA, and echo-enhanced PFI versus 2D TOF MRA ($P<0.05$ for all comparisons; Wilcoxon test). The use of the intravenous contrast agent did not improve sensitivity significantly ($P>0.05$).

**Discussion**

Hemodynamically, carotid APO is characterized by an extreme atherosclerotic stenosis, usually at the ICA bulb, with minimal residual and slow flow through this segment and an extreme decrease of poststenotic perfusion pressure.$^{17,20,21}$ The frequent angiographic appearance of the “slim sign,” mimicking a hypoplastic ICA, may be due to a collapse of the vessel during diastole or contrast layering within the vessel lumen.$^{21}$ The latter may create the radiographic impression of an apparent lumen somewhat narrower than the actual lumen in its collapsed state. This was confirmed by vascular surgeons who found no hypoplastic vessel or wall-adherent thrombotic material in the distal ICA in patients with APO who were undergoing endarterectomy.$^{5,13}$ Such hemodynamic features may explain the difficulties of nonelective contrast angiography, ultrasonography, and MR techniques in diagnosing carotid APO. Indeed, in our sample using selective intra-arterial angiography with prolonged injection of the contrast agent, experienced neuroradiologists disagreed in 2 cases of ICA-APO whether the very weaken poststenotic flow signal was antegrade or reversed, leading only to a substantial but not perfect reliability of $\kappa=0.86$.

In this prospective series we found high sensitivities and specificities for several advanced ultrasonographic techniques. Conventional unenhanced CDDI was compromised by a false-negative rate of 30% and a false-positive rate of 8%, mainly due to the fact that ultrasound emission energy and gain cannot be increased high enough without the appearance of disturbing acoustic noise that diminishes the reliable depiction of orthograde flow signals. This disadvantage could be partially overcome by the intravenous application of an ultrasonic contrast medium which can increase the reflected ultrasonic energy by nearly 20 dB, and, by this, enhance the sensitivity of CDDI in detecting minimal and slow blood flow remaining below the detection threshold under unenhanced conditions.$^{18,19}$ Thus, the use of an ultrasonic contrast agent reduced the false-negative rate of CDDI from 30% to 17%.

In contrast to velocity-based CDDI, ultrasonographic flow visualization based on amplitude analysis (PFI) was not compromised by gain-related “blooming” artifacts. This is because the hue and the brightness of the PFI color signal reflects the pressure amplitude of the Doppler-shifted acoustic signal, which is directly related to the quantity and the acoustic impedance of the flowing blood.$^{22-24}$ As a result the PFI gain could be further enhanced than the CDDI gain (see “Subjects and Methods”) before acoustic noise began to obscure flow imaging. Additionally, PFI is nearly angle independent, which helps especially in the evaluation of minimal residual blood flow of changing directions due to atherosclerotic plaque material or tortuosity of the vessel anatomy (ie, carotid bifurcation).$^{24}$ Physically, PFI maps the parameter directly related to the acoustic quantity that is enhanced by the contrast agent.$^{25}$ Thus, PFI is a natural choice for echo-enhanced ultrasonic flow imaging. In our experience, the combined use of PFI with an ultrasonic contrast medium increased the imaging quality and maximized the

### TABLE 1. Interobserver Reliabilities ($\kappa$ Statistics) for Distinguishing ICA Atheromateous Pseudo-Occlusion and Occlusion as Defined by Intra-Arterial Angiography

<table>
<thead>
<tr>
<th>Technique</th>
<th>$\kappa$*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDI, unenhanced</td>
<td>0.90</td>
</tr>
<tr>
<td>CDDI, echo-enhanced</td>
<td>0.93</td>
</tr>
<tr>
<td>PFI, unenhanced</td>
<td>0.93</td>
</tr>
<tr>
<td>PFI, echo-enhanced</td>
<td>1.00</td>
</tr>
<tr>
<td>3D TOF MRA</td>
<td>0.77</td>
</tr>
<tr>
<td>2D TOF MRA</td>
<td>0.93</td>
</tr>
<tr>
<td>Intra-arterial angiography</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*P<0.0001 for all tests.

### TABLE 2. Sensitivities, Specificities, Prevalences, and Pearson Correlation Coefficients for Distinguishing ICA Atheromateous Pseudo-Occlusion From Occlusion as Defined by Contrast Angiography

<table>
<thead>
<tr>
<th>Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Prevalence</th>
<th>Pearson Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unenhanced</td>
<td>0.70 (14/20)</td>
<td>0.92 (12/13)</td>
<td>0.61</td>
<td>12.57</td>
<td>0.0001</td>
</tr>
<tr>
<td>Echo enhanced</td>
<td>0.83 (15/18)</td>
<td>0.92 (12/13)</td>
<td>0.58</td>
<td>18.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unenhanced</td>
<td>0.95 (18/19)</td>
<td>0.92 (12/13)</td>
<td>0.59</td>
<td>22.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Echo enhanced</td>
<td>0.94 (17/18)</td>
<td>1.0 (13/13)</td>
<td>0.58</td>
<td>25.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2D TOF MRA†</td>
<td>0.65 (11/17)</td>
<td>1.0 (9/9)</td>
<td>0.65</td>
<td>9.24</td>
<td>0.003</td>
</tr>
<tr>
<td>3D TOF MRA†</td>
<td>0.47 (8/17)</td>
<td>0.89 (8/9)</td>
<td>0.65</td>
<td>2.82</td>
<td>0.182</td>
</tr>
</tbody>
</table>

*P values are based on Fisher’s exact test; values in parentheses indicate numbers of vessels.

*One unenhanced PFI and 2 enhanced CDDI and enhanced PFI studies could not be evaluated because of severe artifacts.

†Five patients could not be examined with MRA because of claustrophobia, cardiac pacemaker, or refusal; 2 MRAs were severely compromised by motion artifacts and excluded from evaluation.
interobserver agreement but had no significant influence on the overall diagnostic accuracy compared with PFI alone.

We found substantial interobserver reliabilities but only moderate or poor sensitivities in detecting carotid APO for 2D and 3D TOF MRA, respectively. In comparison, 3D TOF MRA was significantly inferior to all ultrasonic techniques tested. In the 3D implementation of TOF MRA, the detection of minimal and slow flow is hampered by the saturation of blood traveling through the entire slab. Principally, the use of the 2D implementation may provide higher sensitivities because the angiograms were acquired as a series of thin transverse slices that are sensitive even to highly compromised flow. This was supported by our findings with a decrease of the false-negative rate from 53% for 3D to 35% for 2D TOF MRA. In this context we found significantly lower sensitivities of 2D TOF MRA against echo-enhanced PFI (P=0.034). However, TOF MRA in its present state is not capable of diagnosing carotid APO because of technical reasons. Currently, it is unclear whether the use of first-pass, gadolinium-enhanced 3D MRA may provide higher accuracy in diagnosing ICA-APO.

Thus, one can conclude that the diagnosis of ICA-APO can be made with a high degree of accuracy using echo-enhanced CDDI or PFI but not with unenhanced CDDI or the current MR-based TOF techniques. These results may help in the selection of the appropriate noninvasive tests before intra-arterial angiography or intervention.

References
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