Between-Method Correlation in Quantifying Internal Carotid Stenosis

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Background and Purpose: The degree of internal carotid stenosis has emerged as the most important predictor of ischemic stroke in extracranial carotid artery disease. The purpose of this study was to assess the validity of the noninvasive techniques for quantifying internal carotid stenosis with respect to the accepted standard of intra-arterial angiography.

Methods: We measured the maximum percentage reduction in luminal diameter on the intra-arterial digital subtraction angiograms of 56 symptomatic patients with extracranial internal carotid stenosis (n=77) or occlusion (n=20). These data were compared with independent measurements based on continuous-wave Doppler ultrasonography, pulsed-wave Doppler spectrum analysis, color Doppler-assisted duplex imaging, and magnetic resonance angiography.

Results: Correlations with intra-arterial angiography were equally strong (r>.90) for magnetic resonance angiography, continuous-wave Doppler, and color duplex analysis. Positive and negative predictive values for (therapeutically relevant) 70% to 99% stenosis were higher for continuous-wave Doppler (.82, .97) and color duplex (.84, .98) than for magnetic resonance angiography (.79, .81). Also, accuracy in quantifying high-grade stenosis was better for both of these ultrasonographic techniques, mainly due to the frequent occurrence of a “flow gap” on the magnetic resonance angiograms. Continuous-wave Doppler and magnetic resonance angiography, but not color duplex, failed to detect slow residual arterial flow in one and two cases of symptomatic “pseudo-occlusion” of the internal carotid, respectively.

Conclusions: (1) Several noninvasive methods compare well with intra-arterial angiography in identifying and quantifying high-grade internal carotid stenosis; (2) the use of these noninvasive methods may suffice for treatment decisions; and (3) because residual between-method disagreement is partly explained by principles of physics, the validity of continuous-wave Doppler and color duplex in quantifying 60% to 99% stenosis is likely to be underestimated by correlation with intra-arterial angiography. (Stroke. 1993;24:1513-1518.)

KEY WORDS • angiography, digital subtraction • angiography, magnetic resonance • carotid artery diseases • cerebrovascular disorders • ultrasonics

In contrast to more subtle angiographic or ultrasonographic features of internal carotid artery (ICA) atherosclerotic lesions, such as “ulcerated surface,”1-3 calcification, or other echomorphologic findings,3 the severity of ICA luminal narrowing has been shown to be prognostically and therapeutically relevant, at least in symptomatic patients.4,5 Both of these ongoing trials4,5 are using intra-arterial angiography as the only method to quantify ICA stenosis.4,7 This raises the question of to what extent clinical decision-making for patients with presumed symptoms from ICA disease may be reliably based on noninvasive tests.

Since the late seventies, a variety of ultrasonographic methods have been proposed for the quantification of extracranial ICA stenosis. Among the most widely used are the auditory interpretation of the continuous-wave (CW) Doppler signal8-13 and the determination of the maximum systolic flow velocity by means of CW or pulsed-wave Doppler spectral analysis.14-18 More recently, color Doppler-assisted duplex imaging3,19-22 (CDDI) and magnetic resonance angiography23-27 (MRA) have been added to the spectrum of noninvasive tests. Faced with this proliferation of methods, the present study was designed to answer the following question: Which noninvasive technique most accurately predicts the degree of ICA luminal narrowing as determined by the accepted standard of intra-arterial angiography?

Subjects and Methods

Patients

We prospectively examined 60 consecutive patients admitted for presurgical evaluation after retinal or cerebral transient ischemic attack or minor ischemic stroke within the last 120 days attributable to a ≥70% extracranial ICA stenosis or ICA occlusion as assessed with CW Doppler sonography, which serves as a screening method in our neurovascular laboratory (see below).
All of these patients (43 men and 17 women; aged 39 to 80 [median, 60] years) were enlisted to also undergo intra-arterial angiography, CDDI, measurements of systolic peak flow velocity, and MRA of both ICAs. Informed consent was obtained before each examination, and the intervals between the first and last of them ranged from 2 to 43 (median, 9.5) days for each patient.

**Interobserver Reliabilities**

Parallel to the multimodal correlation analyses, multiple interobserver reliabilities for quantifying the degree of ICA stenosis were determined for CW Doppler sonography, CDDI, MRA, and intra-arterial angiography using an independent sample of 30 ICAs with 50% to 99% stenosis for each method. Linear correlation coefficients for each method are provided in each of the following sections, respectively.

**Continuous-wave Doppler Ultrasonography**

This procedure was performed and evaluated before study entry for all patients (120 ICAs) by using a 4.0-MHz directional CW Doppler device (Delalane D-480K; MDV, Rauenberg, FRG). The following auditory criteria were used to quantify extracranial ICA stenosis, 11-13 (1) 40% to 60%: Stenosis: Slight-to-moderate flow acceleration in the proximal ICA, together with so-called turbulences. (2) 70%: Stenosis: In addition to (1), poststenotic systolic flow deceleration with reflux and audible spectral broadening (but well-preserved pulsatile flow in the submandibular ICA and symmetric flow in the common carotid artery [CCA]). (3) 80% Stenosis: In addition to (2), reduced end-diastolic flow in the ipsilateral CCA compared with the contralateral CCA (but preserved, although reduced, pulsatile pattern in the submandibular ICA). (4) 90% Stenosis: In addition to (3), strongly reduced and distorted (but continuously detectable) poststenotic ICA flow pattern. (5) 95% Stenosis: In addition to (4), partially undetectable poststenotic ICA flow signal. (6) Occlusion: No detectable ICA signal (together with ipsilateral CCA flow reduction). Stenoses judged as lying between two percentage categories were graded as 65%, 75%, or 85%. Because CW Doppler serves as a vascular screening procedure in our laboratory, the results reported in this study were obtained by eight different observers (three experienced nurse-technicians and five experienced residents; four to 17 study patients examined by each of them). Interobserver correlations for quantifying the degree of ICA stenosis with this method ranged between \( r = .79 \) and \( r = .94 \) (median, \( r = .80 \)).

**Color Doppler-Assisted Duplex Imaging**

This procedure was performed on all patients (120 ICAs) by using an Acuson 128 XP/5 sonography device (Acuson, Mountain View, Calif) with a 10.0-MHz linear-array transducer for real-time display of “anatomic” B-mode gray-scale images and a 5.0-MHz pulsed-wave transducer for superimposed simultaneous color-encoded blood flow information. Evaluation of one ICA was impossible because of massive plaque calcification. The CDDI examinations included longitudinal and transverse views of the ICA at the level of the stenosis, allowing delineation of the normal (former) ICA lumen (\( A_N \)) as well as of the minimal residual “flow lumen” \( A_S \). Using transverse views of the narrowest part of the stenosis (Fig 1), the degree of luminal reduction was determined as the percentage of cross-sectional area reduction \( (1 - [A_S/A_N]) \times 100\% \). All CDDI measurements reported here were obtained by one observer (M.S.), who was unaware of the results of the following investigations. Interobserver correlations for quantifying the degree of ICA stenosis with this method ranged between \( r = .76 \) and \( r = .90 \) (median, \( r = .83 \)).

**Systolic Peak Flow Velocity**

Recordings for all patients (120 ICAs) were performed using a pulsed-wave 4.0-MHz Doppler instrumentation (TC2000S, EME, Überlingen, FRG). This device was preferred over that used for CDDI because it offers a more accurate fast-Fourier transform spectrum analysis and the option of off-line calculations. The hand-held Doppler probe was positioned over the CCA bifurcation and directed cephalad so that the maximum ICA peak velocity was recorded and stored. All examinations were carried out and evaluated by one observer (M.S.).

**Magnetic Resonance Angiography**

This examination was performed on 50 patients (100 ICAs) using a 1.5-T whole-body scanner (Magnetom 63SP, Siemens, Erlangen, FRG) and a Helmholtz neck coil as transmitter and receiver. Ten of the 60 study patients could not be examined because of claustrophobia, cardiac pacemaker, or refusal by the patient. We employed a fast-Fourier transform–fast imaging with steady precession (FFT-FISP) MRA sequence, with first-order (velocity-only) flow compensation along the read and section-encoding gradients. Other technical factors were 29-millisecond repetition time, 7-millisecond echo time, 15° flip angle, one excitation, 50-mm slab thickness, 0.781-mm effective slice thickness (64 partitions), 256² image matrix, and 200-mm field of view. Two image volumes overlapping by 20 partitions (15.6 mm) were investigated in each patient. Elimination of venous in-flow signals was achieved by presaturation slabs positioned above and parallel to the image volumes. Angiographic projection images were reconstructed using the maximum-intensity-projection algorithm. Six images obtained in steps of 20° around a vertical axis of rotation were used for final evaluation. The severity of ICA stenosis was determined as the percentage of diameter reduction on the view showing the greatest extent of luminal narrowing. For this purpose, the minimal residual ICA diameter (\( D_N \)) and the normal ICA diameter beyond stenosis and bulb (\( D_B \)) were measured using a precision scale magnifier marked in tenths of a millimeter. The degree of stenosis was calculated as \( (1 - [D_B/D_N]) \times 100\% \). All MRA images were evaluated by one observer (G.F.), who was unaware of individual clinical data and the results of the other examinations. Interobserver correlations for quantifying the degree of ICA stenosis with this method ranged between \( r = .32 \) and \( r = .56 \) (median, \( r = .49 \)).

**Intra-arterial Angiography**

Selective arterial digital subtraction angiography (CG 200, General Electric/CGR, Monza, Italy) of the carotid system with a minimum of two projections was carried out on 56 patients (111 carotid arteries). One carotid artery was inaccessible transfemorally and was not...
investigated. Four of the 60 study patients refused intra-arterial angiography. The severity of ICA stenosis was determined as the percentage of diameter reduction on the view showing the greatest extent of luminal narrowing. For this purpose, the minimal residual ICA diameter (D_r) and the normal ICA diameter beyond stenosis and bulb (D_N) were measured using a precision scale magnifier marked in tenths of a millimeter.\(^5,^6,^28\) The degree of stenosis was calculated as \(1 - \frac{D_r}{D_N}\) * 100%.\(^5,^6,^28\) All angiograms were evaluated by one observer (H.F.), who was unaware of individual clinical data and the results of the other examinations. Interobserver correlations for quantifying the degree of ICA stenosis with this method ranged between \(r = .71\) and \(r = .89\) (median, \(r = .79\)).

Data Analysis

For each method described above, comparisons of left and right ICA measurements supported the assumption of data independence \((P = .47\) to \(P = .93\) for each method by paired Student’s \(t\) test). Pooling the bilateral data, the correlation with intra-arterial angiography was then determined for each noninvasive modality. For this purpose, linear or best-fitting nonlinear regression curves were calculated and drawn (SIGMA- PLOT software package, Jandel Scientific, Corte Madera, Calif). In addition, the sensitivity, specificity, and predictive values for detecting or excluding \(\geq 70\%\) ICA stenosis (as defined by intra-arterial angiography) were determined for each noninvasive technique to assess its utility in identifying those patients known to benefit from carotid endarterectomy.\(^5,^5\)

Results

Intra-arterial digital subtraction angiography performed on 56 patients revealed 14 normal ICAs, 33 ICA stenoses of 1% to 69%, 44 ICA stenoses of 70% to 99%, and 20 ICA occlusions. Correlations between the degree of ICA stenosis measured on these angiograms and the corresponding data obtained noninvasively were determined (Fig 2). Sensitivities, specificities, and predictive values of CW Doppler analysis, CDDI, and MRA in detecting high-grade (70% to 99%) ICA stenosis or occlusion were high but differed between methods (Tables 1 and 2).

The interpretation of the audible CW Doppler signal as well as the determination of the maximum peak flow velocity using pulsed-wave Doppler spectral analysis failed to reliably detect or exclude <60% ICA stenosis (Fig 2A and 2B). Likewise, CDDI correlated poorly with intra-arterial angiography in this lower percentage range of ICA narrowing (Fig 2C), where MRA corresponded best with invasive angiography (Fig 2D).

In the 60% to 99% range of stenosis, CW Doppler, CDDI, and MRA correlated strongly with intra-arterial angiography, as illustrated by Fig 2A, 2C, and 2D. In contrast, maximum systolic peak flow velocity was highly variable throughout this range and did not predict the severity of moderate or severe ICA narrowing (Fig 2B). (It deserves mentioning that the curve fit shown in Fig
FIG 2. Correlations between four noninvasive methods (Y axes in A-D) and intra-arterial digital subtraction angiography (i.a.−DSA) (X axes in A-D) in determining degree of internal carotid artery (ICA) stenosis. Correlations obtained for first-order regressions (R1) (dotted lines in A and C, solid line in D) or best-fitting higher-order regressions (Ri) (solid curves in A through C) were as follows: A, R1 = .92, R1 = .94; B, R1 = .85; C, R1 = .94, R1 = .96; and D, R1 = .95 (P < .0001 for A, C, and D). In addition, the following first-order regressions (R1') were calculated for the 50% to 99% range of angiographic stenosis (regression lines not shown in figure): panel A, R1' = .72; C, R1' = .71; and D, R1' = .73 (P < .0005 for A, C, and D). Note that 17 ICAs showing a flow gap on MRA (corresponding to 75% to 99% stenosis on i.a.−DSA) are not included in D or corresponding regression analyses. CWD indicates continuous-wave Doppler ultrasonography; peak-v, peak systolic flow velocity; CDDI, color Doppler-assisted duplex imaging; and MRA, magnetic resonance angiography.

2B closely resembles a model prediction of Spencer and Reid.15)

Continuous-wave Doppler and CDDI slightly overestimated the degree of angiographic stenosis in the 60% to 99% range of ICA narrowing, as illustrated in Fig 2A and 2C, and by the higher negative than positive predictive values in Table 1. There was no systematic overestimation or underestimation with MRA (Fig 2D, Table 1). A zone of signal intensity loss demonstrated on MRA (“flow gap”) occurred in 17 ICA stenoses (17% of ICAs examined with MRA) and corresponded to 75% to 99% luminal narrowing on intra-arterial angiography (Fig 1). Within this range, occurrence of a flow gap did not predict higher degrees of stenosis. Vessels displaying a flow gap on MRA have been excluded from the regression analysis shown in Fig 2D because precise measurements of luminal narrowing were not possible in these cases.

Two false-positive diagnoses of ICA occlusion occurred with MRA, one of them corroborated by CW Doppler ultrasonography. In both instances, CDDI identified tight residual lumina (graded as 97% ICA stenoses), confirmed by intra-arterial angiography (99% ICA stenoses), and successfully desobliterated thereafter.

Discussion

In the present study, the accepted standard of quantifying ICA stenosis (ie, assessment of maximal lumen diameter reduction using invasive angiography) correlated strongly with methodologically diverse noninvasive measurements provided by CW Doppler (audible signal interpretation), CDDI (cross-sectional luminal area reduction), and MRA (luminal diameter reduction) (Fig 2). More importantly, the predictive values of two of these noninvasive tests, CW Doppler and CDDI, were particularly high with respect to angiographic 70% to 99% stenosis, which could be predicted with 82% or 84% certainty and excluded with 97% or 98% certainty (Table 1). Studies using intra-arterial angiography have shown that the identification of 70% to 99% ICA stenosis is important for secondary prevention of stroke with carotid endarterectomy.4,5 The question arises of

| Table 1. Specificities, Sensitivities, and Positive and Negative Predictive Values of CWD, CDDI, and MRA in Detecting High-Grade (70% to 99%) ICA Stenosis As Defined by Intra-arterial Angiography |
|-----------------|-----------------|-----------------|
|                  | CWD             | CDDI            | MRA             |
| Specificity      | .86 (58/67)     | .87 (58/66)     | .86 (50/58)     |
| Sensitivity      | .95 (42/44)     | .97 (43/44)     | .73 (31/42)     |
| Positive predictive value | .82 (42/51) | .84 (43/51) | .79 (31/39) |
| Negative predictive value | .97 (58/60) | .98 (58/59) | .81 (50/61) |
| Prevalence       | .39 (44/111)    | .40 (44/110)    | .42 (42/100)    |

CWD indicates continuous-wave Doppler ultrasonography; CDDI, color Doppler-assisted duplex imaging; MRA, magnetic resonance angiography; and ICA, internal carotid artery. Numbers in parentheses are numbers of vessels.

| Table 2. Specificities, Sensitivities, and Positive and Negative Predictive Values of CWD, CDDI, and MRA in Detecting ICA Occlusion As Defined by Intra-arterial Angiography |
|-----------------|-----------------|-----------------|
|                  | CWD             | CDDI            | MRA             |
| Specificity      | .99 (90/91)     | 1.00 (90/90)    | .97 (83/85)     |
| Sensitivity      | 1.00 (20/20)    | 1.00 (20/20)    | 1.00 (15/15)    |
| Positive predictive value | .95 (20/21) | 1.00 (20/20) | .88 (15/17) |
| Negative predictive value | 1.00 (90/90) | 1.00 (90/90) | 1.00 (83/83) |
| Prevalence       | .18 (20/111)    | .18 (20/110)    | .15 (15/100)    |

CWD indicates continuous-wave Doppler ultrasonography; CDDI, color Doppler-assisted duplex imaging; MRA, magnetic resonance angiography; and ICA, internal carotid artery. Numbers in parentheses are numbers of vessels.
whether the invasive method is still needed for quantifying ICA obstruction or for planning surgery. In contrast to the angiographic evaluation of ICA stenosis, hemodynamic measurements using Doppler ultrasound correspond more closely with diminished cross-sectional area than with reduced diameter of the diseased vessel. Expected area-diameter relations for different types of stenoses are shown in Fig 3, which has been modified after Spencer and Reid. It becomes evident that incongruence between angiographic and ultrasonographic measurements as used in our study must occur on physical grounds. A comparison of Fig 3 with the spread of data points in Fig 2A and 2C shows that most of the spread observed for 60% to 99% stenoses indeed fell within a range shaded in Fig 3, illustrating a trend toward "overestimation" by CW Doppler and CDDI of the angiographic degree of ICA stenosis. This was not explained by hemodynamic effects of contralateral ICA disease because the contralateral degree of stenosis did not differ between patients overestimated or underestimated with ultrasound (P=.28; unpaired Student's t test). This compliance of actual findings (Figs 2A and 2C) with a physical model prediction (Fig 3) suggests a higher validity of CW Doppler and CDDI than revealed by correlation with conventional angiography.

Nevertheless, several arguments may favor the use of intra-arterial angiography for presurgical planning in patients with extracranial ICA disease. First, interobserver reliability is high with this method. On the other hand, the present study did not reveal higher reliabilities of digital subtraction angiography (median, r=.79) than of ultrasonographic measurements using CW Doppler or CDDI (medians, r=.80 and r=.83, respectively; see "Subjects and Methods"). Also, due to our study design, the CW Doppler measurements given in Fig 2A and Tables 1 and 2 were obtained by eight different investigators and thus already reflect a range of disagreement realistic for one department. With respect to CDDI measurements, other authors have also reported very high interobserver reliabilities. Second, conventional angiographies are easy to communicate between medical subspecialties. Increasing image quality of CDDI or MRA, however, may allow "objective" documentation of surgical topography with sufficient detail also (Fig 1). Third, simultaneous assessment of the intracranial circulation is still a particular advantage offered by intra-arterial angiography. Although this may indeed be the strongest argument for its continued use, it deserves mentioning that no intra-arterial angigram of the present study disclosed an "intracranial lesion that was more severe than the surgically accessible lesion," to cite the only angiographic exclusion criterion of the North American Symptomatic Carotid Endarterectomy Trial (NASCET). One of our patients (2%) suffered a minor stroke immediately after ipsilateral carotid angiography, a rate of neurological complications lying within the 2% to 3% range reported for symptomatic cerebrovascular patients in large prospective angiographic studies. Therefore, to us the question appears open and deserves further investigation of whether a possible benefit from improved presurgical planning may outweigh the risk of intra-arterial angiography. The necessity of accurate and precise quantification of ICA stenosis has been clearly demonstrated in the NASCET study, in which benefit from surgery increased with degree of high-grade ICA narrowing. Depending on the results of other ongoing trials, it may become crucial to differentiate between 60%, 70%, 80%, or 90% ICA stenosis in asymptomatic patients as well. This would further enhance the role of noninvasive technology. Our data suggest that both CW Doppler and CDDI can provide valid means of precisely quantifying 60% to 99% extracranial ICA stenosis (Fig 2A and 2C). Although MRA correlated equally strongly with intra-arterial angiography (Fig 2D), the relatively frequent occurrence of a flow gap in 75% to 99% stenoses diminished the utility of MRA in more precise assessment. (Note that 17% of all ICAs examined with MRA showed this phenomenon and therefore have been excluded from the analysis shown in Fig 2D.) This shortcoming is likely to be ameliorated in the near future by even shorter MR echo times and higher spatial image resolution. Nevertheless, cost effectiveness and rapid availability are among the reasons that will probably lead to the continued favor of ultrasonography as the primary diagnostic procedure in centers dealing with and following up large numbers of cerebrovascular patients.

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