Internal Carotid Artery Stenosis Measurement
Comparison of 3D Computed Rotational Angiography and Conventional Digital Subtraction Angiography

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Background and Purpose—Clinical trials have shown that carotid endarterectomy reduces stroke risk in symptomatic individuals with severe internal carotid artery (ICA) stenosis. As a result of these trials, digital subtraction angiography (DSA) became a standard of reference for ICA stenosis diagnosis. Newer 3D techniques provide a larger number of views than DSA, which may influence the estimated degree of stenosis. We evaluate this possibility by directly comparing stenosis grades from 3D computed rotational angiography (CRA) and DSA.

Methods—As a prospective diagnostic study, we performed CRA and DSA on 26 consecutive symptomatic patients. Only 1 angiographic procedure was performed on normal asymptomatic arteries, yielding 42 arteries for comparison. Four neuroradiologists graded the CRA maximum intensity projections (MIPs) and DSA images, according to the North American Symptomatic Carotid Endarterectomy Trial guidelines. CRA studies included a search for the narrowest view by evaluating 60 MIPs generated at 3° intervals and measurement of actual artery diameters. Artery diameters and stenosis grades were analyzed graphically; statistical significance was determined using a paired t test.

Results—The mean difference of 1.2% (CI, −18%, 21%) between CRA and DSA stenosis grades was not statistically significant (P=0.55). Agreement of the optimal CRA viewing angle was limited, with an interobserver variability of 24±13°. The interobserver variability of DSA and CRA stenosis grades, 9.1% (CI, 0%, 21%) and 9.4% (CI, 0%, 22%), respectively, was not significantly different (P=0.79).

Conclusion—CRA provides stenosis grades equivalent to DSA, as well as absolute measurements, providing a comparison for newer 3D techniques. (Stroke. 2004;35:2776-2781.)

Key Words: angiography ▪ carotid endarterectomy ▪ carotid stenosis ▪ computed tomography

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) demonstrated that carotid endarterectomy reduces stroke risk in symptomatic individuals with moderate or severe internal carotid artery (ICA) stenosis.1–3 In both trials, stenosis severity was determined using 2D intra-arterial angiography. These clinical trials required an objective angiographic method of stenosis gradation, which has subsequently become a standard of reference for endarterectomy decision making. It should be noted that carotid endarterectomy is also beneficial for asymptomatic arteries with a severe stenosis.4

Unfortunately, 2D angiography provides a limited number of views that may not accurately reflect stenosis severity. Additionally, intra-arterial contrast injection carries a risk of neurological complications (<1%),5 decreasing the potential benefit of endarterectomy. Thus, noninvasive techniques, such as helical computed tomography (CT) angiography, duplex ultrasound (DUS), and magnetic resonance angiography (MRA), are preferred for diagnosing ICA stenoses. Accurate diagnosis may require a multimodality approach,6 often including 3D imaging techniques.

Two-dimensional digital subtraction angiography (DSA) equipment is currently being replaced in many hospitals by computed rotational angiography (CRA), which allows tomographic reconstruction of rotational angiograms using cone-beam CT7 (often referred to as 3D rotational angiography and 3D DSA). In addition to providing high-quality 3D images of the contrasted vasculature, CRA could provide information regarding juxtaluminal calcification, as well as absolute measurements (millimeters), which could provide a reference for new noninvasive 3D techniques. However, before CRA is used clinically, it is important to know whether the stenosis grades calculated from CRA maximum intensity projections apply to DSA.

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(MIPs) will agree with the current 2D DSA reference standard. We report a comparison of CRA and DSA stenosis measurements performed in patients with symptomatic carotid artery disease.

Methods

Imaging Technique
This study used a prototype CRA system (Multistar; Siemens Medical Solutions) comprising an x-ray image intensifier mounted on a clinical C-arm, which rotates 45°s⁻¹ while acquiring images at 30 frames • s⁻¹. This system collects 2D projections while rotating around the patient, enabling 3D CT reconstruction.⁷

A common carotid injection of nonionic iodinated contrast (200 mg/ml H²H⁹ Iohexol/Heparinized saline) solution was typically used for CRA and DSA, allowing successive acquisition of both modalities for direct comparison. An injection rate of 10 ml s⁻¹ for 1.2 s was used for DSA. Posteroanterior and lateral projections (880x880 pixels) were obtained for each ICA, with typical x-ray parameters of 75 kVp and 15 mAs. Additional double oblique views were acquired if the carotid bifurcation was superimposed in 1 of the views. Consequently, an average DSA necessitated a total of 6.2±1.6 g of iodine.

CRA images were obtained with a nominal 28-cm field of view (FOV), acquiring 134 exposures (440X440 pixel; 90 kVp; 1.6 mAs average) over 4.4 seconds during a 6-second contrast injection. Typically, 24 mL of diluted iodinated contrast medium was injected, totaling an average of 4.8±0.9 g of iodine. In addition to the contrast-enhanced images, 134 anatomical mask projections (of nonenhanced background anatomy) were also acquired. These image sets were independently acquired and reconstructed to form 2 volumes with 0.38-mm isotropic voxels. The anatomical mask volume was subtracted, voxel by voxel, from the contrast-enhanced volume, eliminating bone and artifacts from the CRA. MIPs of the volume were produced with trilinear interpolation and perspective ray-driven algorithms using VTK (Visualization Toolkit; Kitware Inc.).

Image Quality
The vessel-to-background signal difference-to-noise ratio (SDNR) was used as an objective measure of the CRA-MIP image quality. Vessel signal in the MIP was measured from the center of the common carotid artery, directly proximal to the bifurcation. Background signal was measured from an area adjacent to the stenosis (200 pixels total). Any background intensity variation that could interfere with measurement of the ICA stenosis was considered to be noise. This included the system noise as well as the residual background anatomy. Noise was quantified as the SD of the background signal.

Dose Calculation
The entrance exposure was measured at the table with an electrometer and 15-cm³ ion chamber (Keithley Instruments Inc.). The exposure-to-dose conversion factor was approximated as 1 Gy/R⁻¹.⁸ Total entrance dose was calculated by multiplying the dose per projection by the total number of projections. The dose-area product was calculated, assuming the patient’s head and neck covered the entire 28-cm FOV. Effective dose was determined using the effective dose per entrance dose-area product of 6.75 μSv/Gy cm⁻² for a lateral radiograph of an adult male’s cervical spine.⁹ This is an overestimate because the patient does not cover the entire FOV, and the sensitive thyroid and mandible will receive a lower dose for the posterior-to-anterior views (that than of a lateral radiograph).

Angiographic Stenosis Grading
The NASCET stenosis grades were derived from the angiographic view showing the greatest vessel narrowing.⁹ The narrowest diameter of the stenosis (N) is compared with the ICA diameter distal to the carotid bulb (D), where the artery walls are parallel: (1) stenosis percentage = (1 – N/D) x 100%.

Arteries were only measured if there were no signs of near occlusion, which occurs when flow and pressure reduction reduces the distal ICA diameter.¹⁰ In this case, Equation 1 would underestimate stenosis severity, so the NASCET trialists assigned a 95% grade.

Patient Study
The inclusion criterion was a symptomatic, ambulatory patient referred for catheter angiography because of a stenosis diagnosed with DUS. Patients were consecutively recruited weekly; informed consent was obtained and DSA and CRA images were acquired, as approved by the hospital and university ethics review board. All asymptomatic arteries received at least 1 angiographic examination. If they were diagnosed as clearly normal and not clinically relevant, the second angiographic procedure was not performed. This yielded a total of 42 arteries from 26 patients (16 male, 10 female), aged 47 to 79 years (63±10).

Four neuroradiologists blinded to symptomatology side and other interpretations of stenosis severity separately assessed CRA-MIP and DSA images in random order according to NASCET guidelines. Stenoses were graded using a digital image display and analysis tool developed using VTK. CRA studies included selection of the narrowest view from 60 CRA-MIPs. In accordance with clinical practice, observers adjusted image contrast (window/level) and magnification to optimize the image. Stenosis and distal-ICA measurements were performed with digital calipers and recorded in pixel units. Calculated NASCET grades were not presented at the time of measurement, reducing potential bias. Artery diameters were subsequently converted from pixels to absolute dimensions, and the NASCET grade was calculated.

Data Analysis
DSA stenosis grades were considered to be the reference standard for endarterectomy decision making. The sensitivity and specificity were calculated for the subset of 26 symptomatic arteries, as well as all 42 arteries, for clinically relevant stenosis thresholds of 60% and 70%.¹⁰ CIs were calculated using the Wilson score with continuity correction.

The mean of the 4 observers’ stenosis grades from the CRA and DSA techniques was compared graphically using linear regression analysis. The resulting slope, intercept, and 95% CIs provided a potential means of converting CRA grades to the DSA reference standard. Although the DSA stenosis grades were treated as the reference standard, they may not represent the true stenosis grade; the best estimate may actually be the mean of the 2 techniques. To investigate the differences between CRA and DSA grades, their differences were plotted against their mean.¹¹ Repeatability coefficients, directly comparable to the 95% CI, were calculated by multiplying the SD by 1.96.¹² Data were tested for normality and the paired t test was used to determine statistical significance.

The interobserver variability of the CRA and DSA techniques was quantified using the SD of the stenosis grades assigned by the 4 observers for each ICA. This variability was plotted against the mean stenosis grade to examine the dependence on stenosis severity. The paired t test was used to determine statistical significance. The CRA viewing angle selected by each observer depicting the narrowest residual lumen was recorded. The SD of the 4 selected viewing angles determined the view-angle-selection variability for each CRA. The overall view-angle variability was determined from the mean variability of all of the CRA volumes. The view-angle variability was plotted against the mean stenosis diameter to assess any potential trends.

The mean distal-ICA diameter was plotted against the mean stenosis diameter. If an average distal-ICA diameter could be determined for this patient population, this diameter could be substituted into Equation 1, allowing estimation of a NASCET grade using only the stenosis diameter.
Results

Image Quality and Dose

Typical DSA and CRA-MIP images are shown in Figure 1. The CRA-MIPs of the 42 arteries had a mean SDNR of 23:1. The mean CRA x-ray tube output was 1.6 mAs. The entrance exposure of 0.012 R(mAs)^{-1} yields a 0.19 mGy entrance dose per CRA projection. The 50 mGy total CRA entrance dose resulted in a 0.21 mSv effective dose for the subtracted 3D image. A similar estimate for DSA (60 exposures, 15 mA) produced a 110 mGy total entrance dose, yielding an effective dose of 0.45 mSv.

Angiographic Stenosis Grading

DSA and CRA stenosis grades are categorized in Table 1. The classification by each technique agreed for 33 of the 42 arteries. CRA classified 4 stenoses as 1 category higher, and 5 stenoses as 1 category lower. For the 26 symptomatic arteries, CRA agreed with the DSA categorization of a severe stenosis in 85% of the patients. At the time of image acquisition, 6 symptomatic arteries were diagnosed as nearly occluded. Observers in this study were not presented with cine or rotational angiograms. Consequently, individuals missed signs of near-occlusion without images of late arrival to the head and measured these stenoses for 12.5% of assessments (3 × for each technique). In concordance with the majority of observers, these stenoses were categorized as near-occlusions. One other artery was diagnosed as a near-occlusion during image acquisition, but all the observers measured it during this study, and these grades were included.

Data Analysis

Analysis of the 60% and 70% stenosis thresholds for endarterectomy is shown in Table 2. CRA agreed with DSA categorization of a severe stenosis in 88% of the 42 arteries.

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Stenosis (%)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>60</td>
<td>0.94 (CI, 0.80, 1.00)</td>
<td>0.88 (CI, 0.55, 0.99)</td>
</tr>
<tr>
<td>All</td>
<td>60</td>
<td>0.95 (CI, 0.82, 1.00)</td>
<td>0.95 (CI, 0.80, 1.00)</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>0.83 (CI, 0.65, 0.92)</td>
<td>0.92 (CI, 0.78, 0.98)</td>
</tr>
</tbody>
</table>

Endarterectomy decision analysis at relevant stenosis thresholds for the 26 symptomatic arteries, and then including the 16 asymptomatic arteries as well.

TABLE 2. Estimated Sensitivity and Specificity for CRA Using DSA as the Standard of Reference

![Figure 2. a, CRA vs DSA stenosis percentage; line of identity (thin), linear fit (thick) with slope=0.90; intercept=7%. b, Technique variability: Difference between CRA and DSA plotted against mean stenosis (slope=-0.018; intercept=2%).](image-url)
The mean of the 4 observers’ stenosis grades from the CRA and DSA techniques was plotted in Figure 2a. Linear regression yielded a slope of 0.90 (CI, 0.73, 1.07), with an intercept of 7% (CI, 4%, 17%). The difference between the CRA and DSA grades was plotted against their mean in Figure 2b, illustrating their agreement across the range of stenoses. Although there is variability in individual measurements, the mean difference for all arteries is relatively small. Linear regression produced an intercept of 2% (CI, 9%, 13%) and a slope of 0.016 (CI, 0.19, 0.16), which was not significantly different from zero (P=0.86). The mean difference between the techniques of 1.2% (CI, 18%, 21%) was not statistically significant (paired t test; P=0.55). Nearly and completely occluded arteries were not included in the numerical analysis because of the fact that these were not actual measurements; if included, their strong agreement would reduce the mean difference between the techniques to 0.86% (CI, 17%, 19%).

Interobserver variability is plotted against stenosis severity in Figure 3a. The variability of CRA follows the same trend as DSA. The range of disagreement decreased with increased stenosis severity, as illustrated by the linear fits. The mean interobserver variability for DSA and CRA, 9.1% (CI, 0%, 21%) and 9.4% (CI, 0%, 22%), respectively, was not significantly different (paired t test; P=0.79). The view angle variability is plotted against stenosis severity in Figure 3b. The view angle variability was not correlated with stenosis severity (P=0.58). The mean view angle variability was 24±13°.

Each stenosis and distal-ICA diameter was calculated from the digital measurements of the CRA-MIPs. The nearly occluded arteries were omitted from the analysis of absolute measurements. The interobserver variability of the artery diameter measurements was 0.37 (CI, 0, 0.92) mm, which is comparable to the 0.38-mm isotropic voxel spacing. The distal-ICA diameter is plotted against the stenosis diameter in Figure 4a. Linear regression analysis produced a slope of 0.22 (CI, −0.02, 0.45) and an intercept of 3.42 (CI, 3.0, 3.9) mm. As the stenosis diameter decreased, the distal-ICA diameter tended to decrease, although the slope was not significantly different than zero (P=0.07). Thus, the mean distal-ICA diameter of 3.8 (CI, 2.5, 5.0) mm could be used in Equation 1, yielding: (2) stenosis percentage = (1−N/3.8 mm)×100%.

DSA stenosis grades were plotted against the absolute stenosis diameters measured from the CRA-MIPs (Figure 4b). Linear regression resulted in a slope of −23 (CI, −28, −17) % mm⁻¹ and an intercept of 92% (CI, 81, 103). The line produced by Equation 2 (Figure 4b, thin line) is within the CIs (slope = −26.4 % mm⁻¹; intercept=100%) of the DSA fit. Therefore, a NASCET grade could be estimated using and the stenosis measurement (millimeters) and a 3.8-mm distal-ICA diameter.
diameter. The resulting interobserver variability of 10.6% was not significantly different from the variability produced using the actual distal diameter (paired t test; \( P = 0.19 \)).

**Discussion**

Despite the progress of noninvasive alternatives, x-ray angiography is still used for ICA stenosis diagnosis. Ultrasound has been recommended for primary investigation, with follow-up by other modalities if it is not clear that the artery is unobstructed.\(^1\)\(^2\) Unfortunately, noninvasive techniques may not be adequate for all patients. CT angiography (CTA) experiences venous enhancement and artifacts attributable to juxtaluminal calcification and bones, necessitating postprocessing.\(^1\)\(^3\)\(^4\) Time-of-flight (TOF) MRA has limited superior-to-inferior coverage and experiences flow-related limitations, making measurement of severe stenoses difficult.\(^1\)\(^5\) Contrast-enhanced MRA overcomes most limits of TOF but may be contraindicated or inconclusive for some patients.\(^1\)\(^6\) The combination of DUS and MRA may be inconclusive in 6% of patients,\(^1\)\(^7\) and even concordant results produce misclassification rates of 8%;\(^5\) with rates as high as 17% in routine clinical practice.\(^1\)\(^8\) Inconclusive noninvasive examinations may still require either DSA or CRA to make appropriate treatment decisions. CRA is becoming a standard component in neurointerventional radiology departments, primarily for the evaluation of cerebral aneurysms. However, CRA could also be used to resolve discrepancies between DUS and CTA/MRA.

Observer variability of the DSA grading was consistent with previous studies.\(^1\)\(^9\)\(^1\)\(^0\) This variability decreased with stenosis severity (Figure 3a), with the observer variability of the CRA following the same trend. Although virtually any viewing angle of the CRA was possible, the view angles chosen had a mean SD of 24±13° (Figure 3b). This implies that the narrowest stenosis measurements were not generally perceived to be associated with 1 unique view.

The observers in this study were not presented with cine or rotational angiograms. If possible, this dynamic information should be assessed during clinical diagnosis. Consequently, observers may have missed signs of near-occlusion, such as delayed ICA filling. In addition to the 6 arteries categorized as a near-occlusion, 1 of the symptomatic arteries had stenosis and distal-ICA diameters of 0.35 and 1.45 mm, respectively. During image acquisition, this artery was diagnosed as approaching near-occlusion, with a grade >90%. During the study, this artery was measured by all 4 observers and underestimated as 87% and 76% using DSA and CRA, respectively. Measuring the absolute artery diameter (millimeters) could facilitate the essential identification of a nearly occluded artery and avoid calculation of an erroneous ratio.

Three-dimensional images can provide absolute artery diameters. When an artery becomes nearly occluded, the reduced pressure and flow will eventually reduce the distal-ICA diameter. As the distal-ICA becomes narrower, a NASCET ratio will increasingly underestimate the stenosis grade. This error could be avoided with absolute stenosis measurement, which may also be useful when distal-ICA measurements are prohibited by limited superior-inferior coverage, such as with 3D TOF-MRA or DUS. The absolute stenosis diameter could potentially be converted to a stenosis grade using an estimate of the mean distal-ICA diameter (D), which we determined to be 3.8 mm. This diameter is considerably smaller than reported previously for normal vessels (5.5 mm)\(^1\)\(^1\) but comparable to artery diameters from patients referred to MRA (4.6±0.68 mm).\(^2\)\(^2\) As severe stenosis measured with DUS (3.5±0.8 mm),\(^2\)\(^3\) Consequently, this mean distal-ICA diameter should be a reasonable estimate for research investigations of symptomatic patients with carotid stenosis. However, this information should be verified with a larger patient population before it is clinically used for endarterectomy decision-making.

Using Equation 2, stenosis diameters of 1.5 and 1.1 mm would correspond to NASCET grades of 60% and 70%, respectively. Severe stenoses <1.1 mm in diameter require images with high spatial resolution and SDNR, while ensuring there are no signs of a near-occlusion. The CRA technique achieves these criteria with 0.38-mm isotropic resolution, SDNR of 23:1, and dynamic rotational acquisition. Three-dimensional techniques can also provide 2D area measurements (mm\(^2\)) from transaxial views, but spatial resolution may need to be improved to properly resolve severe stenoses, which are currently as small as 1 pixel.

We report the first analysis of the application of CRA to the diagnosis of carotid artery stenosis. For the limited number of arteries studied, the stenosis grades derived from CRA were not significantly different from those of DSA. CRA can provide high-quality images as a 3D reference standard for ICA stenosis during development of noninvasive techniques. Assuming that CRA is equivalent, lumen area and other absolute vessel dimensions could be measured directly from the CRA volume, providing a useful link between state-of-the-art 3D images and the 2D standard for clinical decisions.

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**References**


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