How Accurate Is CT Angiography in Evaluating Intracranial Atherosclerotic Disease?

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Background and Purpose—Digital subtraction angiography (DSA) is regarded as the gold standard in assessing degree of stenosis in intracranial vessels. However, it is invasive and can only be carried out at specialized centers. We sought to compare CT angiography (CTA) to DSA for detection and measurement of stenosis in large intracranial arteries.

Methods—We identified all subjects admitted with ischemic stroke or transient ischemic attack and with CTA and DSA studies of good quality completed within 30 days of each other between April 2000 and May 2006 at a single medical center. Two readers blinded to clinical information reviewed each CTA and DSA independently. Each reader located and measured stenosis of 15 prespecified large intracranial arterial segments per study at the same level of magnification. These stenotic lesions were most likely atherosclerotic in etiology. All measurements were made with Wiha digiMax 6” digital calipers. The degree of stenosis was calculated using the published method for the Warfarin-Aspirin Symptomatic Intracranial Disease study. All disagreements of greater than 10% were reviewed by a third reader who decided between the 2 prior measurements. Segments were excluded from analyses if they were judged to be congenitally hypoplastic or seen only through collaterals or cross-filling. Intraclass correlation, sensitivity, and specificity were calculated using DSA as the reference standard.

Results—Forty-one pairs of CTA and DSAs from 41 patients were reviewed. CTAs were completed within 28 days before 13 days after DSA, with a median of 1 day. A total of 475 pairs of major intracranial arterial segment were analyzed. Intraclass correlation between degree of stenosis based on CTA and DSA for all segments was 0.98 (P=0.001). CTA detected large arterial occlusion with 100% sensitivity and specificity. For detection of ≥50% stenosis, CTA had 97.1% sensitivity and 99.5% specificity. To detect all lesions ≥50% as determined by DSA, the cut off point on CTA appeared to be at ≥30%, with a false-positive rate of 2.4%.

Conclusions—Compared to DSA, CTA has high sensitivity and specificity for detecting ≥50% stenosis of large intracranial arterial segments. CTA is minimally invasive and may be a useful screening tool for intracranial arterial disease and occlusion. (Stroke. 2008;39:1184-1188.)

Key Words: digital subtraction angiography ■ CT angiography ■ intracranial arteriosclerosis ■ neuroradiology

Atherosclerotic disease in large intracranial arteries is an important and often under-recognized cause of stroke. It is estimated that intracranial arterial disease (ICAD) is responsible for approximately 5% to 10% of ischemic strokes in the United States. However, ICAD is a much more important cause of stroke in Asia, where it can account for 33% to 67% of stroke cases. Furthermore, the overall risk of recurrent ischemic events may be as high as 15% to 38% per year among persons with ICAD.

ICAD may be identified by transcranial Doppler ultrasound (TCD), MR angiography (MRA), digital subtraction angiography (CTA). TCD is the least invasive and expensive test, but is highly operator-dependent and not technically possible in every patient. In addition, it is not possible to image every vessel, with reliable insonation of the posterior circulation particularly difficult. MRA provides a better projection of the maximum degree of stenosis, but is not readily available and tends to overestimate high-grade stenoses attributable to turbulent flow. DSA is considered the gold standard, but it is the most expensive, most invasive, most time consuming, and carries the most risks of all the techniques, making it the least desirable as a screening tool.

Recently, CTA has emerged as an efficient and accurate noninvasive modality in evaluation of the etiology of acute stroke. Intracranially, with the proper examination and postprocessing techniques, it is possible to use CTA to assess the petrous and cavernous portions of the internal carotid artery. CTA has several advantages: it is (1) minimally invasive; (2) performed quickly; (3) less susceptible to
motion artifacts than MRA; (4) less dependent on hemodynamic effects compared to MRA; and (5) more widely available in the general community than MRA and DSA. Few studies have examined the accuracy of CTA to detect and quantify intracranial arterial stenosis. We sought to examine the accuracy of CTA in evaluating ICAD as compared with DSA as the gold standard.

Methods

Cases

All patients admitted to a single academic medical center for evaluation of suspected acute cerebral ischemia underwent a stroke CT protocol that includes a noncontrast head CT, CTA head and neck, and CT perfusion study. We retrospectively reviewed the admission database with 1477 subjects with stroke or TIA and selected consecutive cases between April 1, 2000 and May 30, 2006 who had both CTA and DSA within 30 days of each other. The stenotic lesions seen in these cases were presumed to be atherosclerotic in nature. Because no cases with subarachnoid hemorrhage or intracerebral hemorrhage were included, vasospasm was unlikely the cause of these stenoses. None of the cases included in this study carried the diagnosis of acute arterial dissection. We could not rule out underlying vasculitis as the cause of some of these stenoses. However, none of the cases carried a final diagnosis of vasculitis.

Other exclusion criteria included intravenous thrombolysis or aortic stenosis. None of the cases included in this study showed evidence of vasculitis. Because no cases with subarachnoid hemorrhage or intracerebral hemorrhage were included, vasospasm was unlikely the cause of these stenoses. None of the cases included in this study carried the diagnosis of acute arterial dissection. We could not rule out underlying vasculitis as the cause of some of these stenoses. However, none of the cases carried a final diagnosis of vasculitis.

Image Acquisition

The CTA data acquisition (lightspeed CT Scanner, GE Healthcare) was performed according to an established protocol that included spiral mode, 0.8-second slices, collimation=8 or 16×1.25 mm, pitch=1.375:1, slice thickness=1.25 mm, reconstruction interval=1.00 mm, acquisition parameters of 120 kVp/240 mA, and FOV for CTA acquisition=22 cm. A caudo-cranial scanning direction was selected, covering the whole brain down to 1 cm below the foramen magnum to encompass the postero-inferior cerebellar arteries in the volume analysis. Seventy cc of iohexol (Omnipaque, Amersham Health; 300 mg/mL of iodine) was administered into an antecubital vein using a power injector at an injection rate of 4 cc per second, followed by a 50-cc saline bolus. Adequate timing of the CTA acquisition was achieved according to a test bolus technique. CTA raw data were reformatted in axial, sagittal, and coronal 3-mm-thick maximal intensity projection images, and occasionally 3-dimensional reformats were also obtained.

Three- or 4-vessel DSA was performed via a transfemoral approach under monitored sedation or general anesthesia. Conventional angiographic views (frontal, lateral, obliques) were obtained, as well as dedicated magnified and focused views.

Image Analysis/Interpretation

Two readers blinded to all subjects’ clinical information independently reviewed all of the CTA images and subsequently all of the DSA images for presence of stenosis and degree of stenosis. Imaging reading was overseen and adjudicated by a neuroradiologist with several years of experience in interpreting CTA and DSA (M.W.). He trained 2 initial readers, both academic physicians with 5 or fewer years of experience in interpreting CTA. All cases were viewed in a random order without correspondence of the CTA and DSA studies. The readers independently identified and characterized the degree of stenosis for each of 15 prespecified large intracranial arterial segments per study at approximately the same level of magnification. Assessed vessel segments included bilateral supraclinoid internal carotid artery, A1, M1, M2, P1, intracranial vertebral, and proximal, mid, and distal basilar artery. For both CTA and DSA, degree of stenosis was calculated using the published method for the Warfarin-Aspirin Symptomatic Intracranial Disease Study: percent stenosis=[(1−{(Dstenosis/Dnormal)})×100]. Dstenosis is the diameter of the diseased segment at its most severe site. Dnormal is the diameter of the proximal normal artery. All disagreements of greater than 10% were reviewed by a third reader who decided between the 2 measurements made.

CTA images including source and reformatted images, as well as 3D image data when available, were viewed on a video display screen (Figure 1). Once an area of stenosis was located, measurements were obtained from the maximal intensity projection images. All measurements were made with Wiha digiMax 6” digital calipers (Switzerland) with a resolution of 0.01 mm ±0.03 mm for 0 to 100 mm. We did not use electronic ruler as a measurement tool, because it was not as exact as the handheld digital caliper.

DSA images were viewed on printed films, with a standard 6 images per page (Figure 1). Stenoses were identified by using all available views. The readers made all measurements on single frame, middle arterial phase views at the same level of magnification, and with the same digital caliper used for CTA. A 6× magnifying glass was available for use by the readers.

Statistical Methods

Arterial segments were excluded from analyses if they were identified by the readers as hypoplastic, poorly reformatted, missing from incomplete DSAs, or seen only through collaterals or cross-fillings. For measurements within 10% difference, the averages of the 2 readers’ measurements were included in the final analyses. For measurements with ≥10% difference, the adjudicator’s values were included for final analyses. For each modality, interoperator agreement rates were determined for measurements within 10% difference. Intraclass correlation, sensitivity, specificity, positive (PPV), and negative predictive values (NPV), 95% confidence interval (CI), and receiver operator curves were calculated using DSA as the gold standard.
reference standard. Standard contingency tables were created for sensitivity, specificity, PPV, and NPV.

**Results**

We identified 41 subjects with CTA and DSA completed within 30 days of each other from April 1, 2000 to May 31, 2006. The mean age of patients was 60 years with a range of 30 to 85 years, and 38.5% were female. CTA was completed within 28 days before 13 days after DSA, with a median of 1 day (IQR: 3 days prior to same day).

All 41 pairs of CTA and DSA were reviewed by both readers. Two pairs were excluded from final analyses because of poor contrast boluses on CTA. Measurements and comments were made on 585 vessel segments. After further exclusions (Figure 2), a final 475 vessel segments were entered for final analyses.

Of the 475 vessel segments measured on DSA, the rate of agreement on percent stenosis (within 10%) between the 2 readers was 93.3%. There were 32 (6.7%) arterial segments that required adjudication by a third reader. For CTA, the rate of agreement between the 2 readers was 90.5% and 45 (9.5%) arterial segments required adjudication. With a cutoff at 50% stenosis, the interrater agreement rate for DSA was 94.3%, and 94.1% for CTA.

No abnormality was seen in any eligible vessel segment in 18 (46.2%) of the DSAs. Of the remaining DSA studies, 10 demonstrated 1 diseased arterial segment and 11 demonstrated ≥2 stenoses. On DSA, 42 (8.8%) of the 475 eligible arterial segments were identified as having disease ranging from 26% to 100% stenosis. Diseased segments were identified in all areas of the intracranial circulation with 57.1% seen in the posterior circulation (Table 1). Occlusions (n=26) were seen equally distributed in the anterior and posterior circulations.

Of the 42 diseased segments seen on DSA, there were 14 disagreements with CTA in stenosis measurements. Half of these intermodality discrepancies had <10% difference in degree of stenosis. The largest discrepancy between DSA and CTA was seen with supraclinoid ICA measurements where the difference in degree of stenosis ranged from 20% to 30%. The higher degree of stenosis was always measured on DSA.

The intraclass correlation for the degree of stenosis based on CTA and DSA for all eligible arterial segments was 0.98 (95% CI: 0.98 to 0.99). After excluding 439 vessel segments with <50% stenosis, the intraclass correlation remained high (0.95; 95% CI: 0.92 to 0.98). CTA was 100% sensitive and specific in detecting complete occlusions seen on DSA. Using DSA as the gold standard, CTA detected ≥50% stenosis with a sensitivity of 97.1% (95% CI: 85 to 99.9%), a specificity of 99.5% (95% CI: 98.4 to 99.9%), and a NPV of 99.8% (95% CI: 98.7% to 100%; Table 2).

We created receiver operating characteristic (ROC) curves including all vessel segments and defining a diseased vessel segment as ≥50% stenosis on DSA (Figure 3). The area under the curve was 0.99. To achieve 100% sensitivity for detecting all intracranial arterial segments ≥50% stenosis as determined by DSA, the cut point on CTA needed to be set at ≥30%. Using this cut point on CTA, the negative predictive value of CTA was 99.7%.

<table>
<thead>
<tr>
<th>Intracranial Artery</th>
<th>No. of Diseased Segments (%)</th>
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<tbody>
<tr>
<td>Internal carotid</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Anterior cerebral</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Basilar</td>
<td>10 (23.8)</td>
</tr>
</tbody>
</table>
As a sensitivity analysis, we eliminated all vessel segments with <30% stenosis by DSA standard and recreated the ROC curve defining a diseased vessel segment as ≥50% stenosis on DSA (Figure 2). The area under the curve was 0.93. Furthermore, the areas under the curve were 0.94 for both anterior and posterior circulations.

**Discussion**

In this series of patients who underwent both CTA and DSA within 1 month at a single academic institution, CTA performed very well compared to DSA for detection of ≥50% intracranial stenosis. This remained true even when arterial vessel segments with no or minimal stenosis (<30%) were removed from analysis. CTA has high sensitivity, specificity, and negative predictive value with narrow 95% confidence intervals.

A prior study of 22 patients with acute strokes in the posterior circulation found that CTA reliably detected lesions in the basilar system, but had difficulty in identifying stenosis in the vertebral system and was not as accurate as DSA for detecting stenosis in the posterior circulation. In our study, many intracranial vertebral segments visualized with CTA were excluded from final analyses because their respective segments were not imaged on DSA. However, there was no difference in CTA accuracy for vessel segments in the anterior versus posterior circulation as seen from the areas under the ROC curves.

In another study, CTA and DSA were performed prospectively in 18 patients with suspected intracranial stenosis based on MRA. Using DSA as the gold standard, the authors found that the addition of CTA to MRA raised the sensitivity of detecting ≥50% stenosis from 92% for MRA alone to 100% with both imaging modalities, and raised the specificity from 91% to 99%. However, this study did not assess the accuracy of CTA to detect lesions independent of MRA.

More recently, Bash et al examined the accuracy of CTA to detect and quantify intracranial stenosis compared with MRA and DSA in 28 subjects. After consensus interpretation by two readers, the authors reported that CTA had a higher sensitivity and positive predictive value than MRA using DSA as the gold standard. In a separate analysis putting CTA and DSA images side by side, the authors found that in cases with possible slow flow in the posterior circulation, CTA was superior to DSA in detecting vessel patency.

Our study has several limitations. One limitation has to do with the spatial resolution of our CTA (1.25 mm z axis resolution) which is shared by all studies using similar technology. In small vessels with a diameter <2 mm, as is typical for ACA and distal MCA branches, a slight difference in measurement could potentially result in a significant difference in the degree of stenosis. We chose a conservative cutoff to adjudicate all disagreements of >10%. In addition, to achieve a more exact measurement of vessel diameter, we chose to use a handheld digital caliper for both CTA and DSA which could carry measurements out to 2 decimal points. Our method of using the digital calipers provides a more exact assessment of vessel segment diameter than using electronic ruler or visual estimation but is generally used less in clinical practice. In addition, the readers were academic physicians who had undergone a training period before the start of the study, specifically focusing on reading CTA and DSA images. Thus, CTA may not be as accurate in clinical practice as reported here. We could not determine the accuracy of CTA for 70% to 99% stenosis because the number of vessel segments with disease in this range was too low. A multi-institutional study is ongoing to investigate the accuracy of CTA for detection of high grade stenosis.

Although prior studies in the United States reported an incidence of ICAD of approximately 8% among patients with ischemic stroke, with higher prevalence likely in Blacks and Asians, these studies did not image intracranial vessels in every patient. A recent autopsy study of 259 consecutive patients with fatal ischemic stroke reported a 42.2% prevalence of intracranial stenosis ≥30%. The stenosis was felt to be responsible for the infarct in 5.6% of cases. Approximately a third of these cases had lesions ranging between 30% to 50% stenoses defined by CTA.

**Table 2. Accuracy of CTA Compared With DSA in Detecting 50% to 100% Stenosis in Large Intracranial Arteries**

<table>
<thead>
<tr>
<th></th>
<th>Seen on CTA</th>
<th>Not Seen on DSA</th>
<th>Total</th>
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<tbody>
<tr>
<td>Seen on DSA</td>
<td>34</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Not seen on CTA</td>
<td>1</td>
<td>438</td>
<td>439</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>440</td>
<td>475</td>
</tr>
</tbody>
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CTA indicates CT angiography; DSA, digital subtraction angiography. Data presented are vessel segments.

Figure 3. Receiver operating characteristic curves for all arterial vessel segments (n=475, AUC 0.998) and for only diseased vessel segments with ≥30% stenosis (n=41, AUC 0.933). The outcome of ≥50% stenosis as seen on DSA was used for both curves, with sensitivity plotted against 1-specificity over a range of stenoses defined by CTA.
75% stenosis. ICAD may be under-recognized cause of ischemic stroke and more widespread use of CTA could reduce under diagnosis.

Despite medical therapy with either aspirin or warfarin, approximately 20% of patients with symptomatic ICAD of 50% or more still suffered recurrent ischemic stroke within 2 years.21 Other studies have reported recurrent stroke rates as high as 25% to 38% per year among patients with ICAD.5,7 Angioplasty and intracranial stenting are quickly emerging as potential therapeutic options, especially for those who have failed medical therapy, although a trial comparing these options to medical therapy has not yet been done. It is crucial to identify an inexpensive, efficient, and accurate neuroimaging method for triaging patients with significant intracranial stenosis (≥50%) for emerging therapies to prevent ischemic stroke recurrence.

DSA is considered the gold standard in evaluation of intracranial stenosis and occlusion. It provides images with high spatial resolution. However, it has a number of limitations including procedural risks, costs, and limited availability that makes it less desirable than CTA for screening for ICAD or following patients with this condition. CTA has relatively fewer risks, costs less, is more readily available and appears to be highly accurate, suggesting that this approach may be preferred for identifying patients with ICAD.

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Disclosures
None.

References
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