Contrast-Enhanced Magnetic Resonance Angiography of Carotid Arteries

Utility in Routine Clinical Practice

Dean C.C. Johnston, MD, MHSc; James D. Eastwood, MD; Thanh Nguyen, MD; Larry B. Goldstein, MD

Background and Purpose—Contrast-enhanced magnetic resonance angiography (CEMRA) is among the newer noninvasive tests used for the evaluation of patients with carotid artery disease. Evidence supporting its utility in routine clinical practice is lacking.

Methods—The results of CEMRA were compared with those of catheter angiography in 50 consecutive patients being evaluated for carotid endarterectomy (CEA) at a community hospital. Using indications for CEA based on published guidelines, we determined the rate of misclassification for surgery, sensitivity, specificity, and positive and negative predictive values. In addition, the interrater agreement (κ score) of CEMRA was compared with that of catheter angiography in the studied population and with interpretations provided by 2 blinded radiologists.

Results—Compared with catheter angiography, 24% (95% CI, 12% to 36%) of patients would have been misclassified for CEA on the basis of CEMRA results alone. CEMRA was associated with sensitivity of 92%, specificity of 62%, positive predictive value of 78%, and negative predictive value of 89%. When both CEMRA and duplex Doppler ultrasound were performed and the results were concordant, the misclassification rate decreased to 17% (95% CI, 2% to 32%). κ scores were similar for CEMRA and catheter angiography (0.72 and 0.75, respectively).

Conclusions—CEMRA was found to be highly sensitive for detection of surgically amenable carotid stenosis. κ scores for the interpretation of CEMRA and catheter angiography were similar. However, clinicians should be cautious when using CEMRA alone for surgical decision making in CEA candidates because a significant number of patients may be misclassified. The rate of misclassification is reduced when the results of CEMRA and duplex Doppler ultrasound are concordant. (Stroke. 2002;33:2834-2838.)

Key Words: carotid stenosis ■ diagnosis ■ evaluation studies ■ magnetic resonance angiography

Noninvasive imaging techniques are increasingly used in place of catheter angiography for the preoperative evaluation of the carotid arteries in patients being considered for carotid endarterectomy (CEA). Although debate continues regarding the appropriate use of catheter angiography, particularly in asymptomatic patients, this study remains the putative “gold standard” test for the evaluation of the cerebral vasculature because it was the test used in the major clinical trials demonstrating the efficacy of CEA. However, catheter angiography is uncomfortable, costly, carries a small but significant risk of stroke, and requires several hours of supervised recovery after the procedure. The increasing reliance on noninvasive methods, such as duplex Doppler ultrasound, magnetic resonance angiography (MRA), and CT angiography, is based largely on clinicians’ concerns over the perceived rate of complications and costs associated with catheter angiography.1 It should be noted that much of the literature reporting the performance of noninvasive tests is methodologically limited. In addition, some of the commonly used noninvasive tests may be associated with a significant error rate when relied on as the sole means of selecting patients for CEA in routine clinical practice.2–4

Contrast-enhanced magnetic resonance angiography (CEMRA) is an emerging technique for evaluating the carotid arteries; however, the diagnostic utility of the test in routine clinical practice is uncertain. The purpose of the present study was to determine the operating characteristics of CEMRA used alone in comparison with catheter angiography in routine clinical practice for detection of surgically amenable carotid artery stenosis.

Subjects and Methods

From the angiography logbooks at a community hospital, 50 consecutive patients were identified who underwent both CEMRA and
catheter angiography as part of a presurgical evaluation for CEA over a 1-year period. A community hospital rather than an academic medical center was chosen to better reflect the performance of these tests in the routine clinical setting.

All patients were imaged on a 1.5-T scanner (Signa: GE Medical Systems) with the use of dedicated neurovascular or anterior neck coils and a standard protocol. CEMRA was performed with a 3-dimensional spoiled gradient-echo sequence with repetition time=33 ms; echo time=5 ms; 45-degree flip angle; 20-cm field of view; 10-mm slice thickness; 0-mm interval; and matrix =256×128. Images were obtained after intravenous infusion of 0.1 to 0.2 mmol/kg gadolinium dimeglumine by mechanical power injector (Medred) at a rate of 2 mL/s. Postcontrast imaging delay was determined by an initial timing run after the intravenous administration of 1 mL of contrast material. Scanning was performed in the coronal plane and included both carotid arteries within the volume of imaging. The typical scanning time was <1 minute. Fellowships-trained neuroradiologists using digital subtraction techniques and standard diagnostic catheters performed selective angiography of the common carotid arteries. Duplex ultrasonography was performed by experienced radiologists at an accredited facility. Estimates of the degree of stenosis were made by the radiologist using velocity criteria, and these were corroborated using the gray-scale images. Velocity sampling was performed in the common carotid artery and the internal carotid artery. In addition, the ratio of peak systolic to end-diastolic velocities was calculated. These parameters have been internally validated with the use of contrast angiography.

A neurologist with expertise in cerebrovascular disease reviewed all patient records, including official radiology reports. Carotid Doppler ultrasound reports were also reviewed when available. Patients were classified as eligible or ineligible for CEA on the basis of official radiology reports with the use of prespecified surgical indications as reflected in published guidelines. These included 50% to 99% stenosis in symptomatic patients or 60% to 99% stenosis in asymptomatic patients. In all cases, the original catheter angiogram report was used as the standard for comparison.

To compare the interrater reliabilities of each technique in the same population, 2 academic neuroradiologists, who were unaware of clinical information and the results of other imaging tests, independently reviewed the maximum intensity projection images from the CEMRA studies. The CEMRA studies were reviewed first to limit bias that might be caused by reviewing the catheter angiograms first. The quality of each CEMRA scan was rated adequate or inadequate by the reviewers on the basis of technical adequacy and the presence of significant motion artifacts. Each internal carotid artery studied was then classified as (1) normal, (2) stenosis, (3) occluded. For arteries with stenosis, the percent stenosis was measured as the ratio of the diameter at the point of maximal stenosis to the diameter of the more distal cervical internal carotid artery where the walls were parallel to one another, similar to the method used by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. For cases in which the radiologist was unable to reliably measure the degree of stenosis (eg, because of the presence of a “flow gap” due to high-grade stenosis), the degree of narrowing of the artery was classified simply as severe (70% to 99%), moderate (50% to 69%), or mild (<50%). The reviewers were also asked to determine whether additional areas of stenosis >50% of the arterial luminal diameter were present proximal or distal to the carotid bifurcation, whether the area of arterial stenosis involved a long segment of the vessel (ie, >5 cm), and whether the carotid bifurcation was high in the neck (ie, at or above the level of the second cervical vertebra). The same criteria were used for analysis of catheter angiograms.

Patient characteristics were summarized with the use of univariate statistics. The level of interrater agreement between the original official radiology reports and the 2 subsequent blinded reviewers (categorizing stenosis as not hemodynamically significant, <50%; moderate, 50% to 69%; severe, 70% to 99%; or total occlusion) was measured with standard weighted \( \kappa \) scores (Cicchetti-Allison technique) for both CEMRA and catheter angiography. Misclassification rates for CEA, sensitivity, specificity, and positive and negative predictive values were calculated. Receiver operating characteristic curves were generated to compare the results of Doppler ultrasound, CEMRA, and the combination of the 2 tests when the results were concordant. Statistical analyses were performed with the SAS statistical package version 6.12 (SAS Institute).

The institutional review board approved the study.

**Results**

Patient characteristics are given in Table 1. Patients were similar to those traditionally evaluated for CEA. The majority (60%) had symptoms of hemispheric ischemia, with the remaining patients being either asymptomatic or having nonspecific symptoms. Two thirds of the patients had at least 1 factor associated with an increased risk of perioperative complications (coronary artery disease, hypertension, diabetes, chronic obstructive pulmonary disease). Doppler ultrasound (with the use of duplex techniques) reports were available in 36 patients (72%). The number of indeterminate results was low for each of the noninvasive tests (duplex, 4%; CEMRA, 2%). For those patients in whom both CEMRA and duplex studies were performed (n=36), the results of the 2 studies were concordant in 48% (ie, both tests classified the patient as appropriate or inappropriate for CEA on the basis of the prespecified indications for the procedure). The 14 patients who did not receive duplex Doppler ultrasound as part of their evaluation were more commonly asymptomatic (86%) but were otherwise similar to those who had the test with respect to the prevalence of hypertension, congestive heart failure, recent myocardial infarction, chronic obstructive pulmonary disease, and obesity. The presence of at least 1 artery with >50% stenosis was less common (50% versus 72%) in the group not receiving duplex Doppler ultrasound.

Interrater agreement between the blinded reviewers based on category of stenosis for CEMRA and catheter angiography is shown in Figure 1a. Overall agreement for the 2 blinded reviewers was similar for the 2 techniques (\( \kappa =0.72 \) and \( \kappa =0.75 \), respectively). \( \kappa \) scores tended to be higher for detection of occlusion and for detection of stenoses <50% for both tests, but the differences were not statistically significant. When the original, official reports were compared with the interpretations of each of the subsequent reviewers individually, the levels of agreement based on weighted \( \kappa \) scores were similar for CEMRA and catheter angiography.
(Figure 1b) and similar to the levels of agreement between the 2 reviewers (0.72 for CEMRA and 0.75 for catheter angiography).

Figure 2 shows the sensitivity and specificity of CEMRA and Doppler ultrasound performed alone and in combination when the results were concordant, in comparison to catheter angiography (based on the official reports). When performed alone, CEMRA (sensitivity 92%, specificity 62%) was more accurate than Doppler ultrasound (sensitivity 83%, specificity 44%) for the classification of patients as appropriate or inappropriate for CEA. Noninvasive test performance improved when both tests were performed and the results were concordant (sensitivity 100%, specificity 60%); this is reflected in receiver operating characteristic curves (ie, corresponding to a greater area under the curve) for the combination of CEMRA and Doppler ultrasound for patients with concordant results (Figure 3). Similarly, the positive predictive values for Doppler ultrasound, CEMRA, and the combination (60%, 78%, and 78%, respectively) and the negative predictive values (73%, 89%, and 100%, respectively) reflected the superior performance of the combination strategy. When CEMRA and duplex Doppler ultrasound were performed and the results were not concordant (52%), CEMRA correctly identified the degree of stenosis in 72%, and duplex Doppler ultrasound correctly identified the degree of stenosis in 28% of the arteries ($P=0.38$).

CEMRA correctly classified all patients with severe stenosis (defined as $>$70% in symptomatic patients and $>$80% in asymptomatic patients). The rate of misclassification of patients as either appropriate or inappropriate candidates for CEA was 24% for CEMRA, 36% for Doppler ultrasound, and 17% when both tests were performed and the results were concordant (Table 2). The most common reason for misclassification was an overestimation of the degree of stenosis. Failure to detect a complete occlusion of the carotid artery and underestimation of the degree of stenosis occurred infrequently. No tandem lesions, long-segment stenoses, or high carotid bifurcations were detected in this cohort.

**Discussion**

The evaluation of the performance of noninvasive tests for measuring carotid artery stenosis in routine clinical practice is important given that these technologies are frequently relied on when patients are selected for CEA. CEMRA is a

| Table 2. Reasons for Misclassification for DU, CEMRA, and the Combination of CEMRA and DU When the Results of Both Tests Were Concordant |
|-----------------|--------|--------|
| Overall misclassification rate | DU 13 (36) | CEMRA 12 (24) | COMBO 4 (17) |
| Overestimate of degree of stenosis | DU 9 (25) | CEMRA 9 (18) | COMBO 3 (13) |
| Underestimate of degree of stenosis | DU 3 (8) | CEMRA 2 (4) | COMBO 0 |
| Undetected occlusion | DU 1 (3) | CEMRA 1 (2) | COMBO 1 (4) |

DU indicates duplex Doppler ultrasound; CEMRA, contrast-enhanced magnetic resonance angiography; COMBO, both tests were concordant.
relatively new technique used for this purpose and has shown considerable promise as a test for evaluating the degree of arterial narrowing in patients being considered for CEA.\textsuperscript{9–13} Traditional MRA sequences frequently require long acquisition times, resulting in patient movement artifact. Contrast-enhanced techniques have shown promise, in part because of more rapid acquisition speeds.\textsuperscript{14} However, much of the current literature has not consistently compared the performance of this test to the current gold standard (catheter angiography), a methodological requirement for the adequate evaluation of a new diagnostic test.\textsuperscript{2,15,16} Furthermore, the published literature on diagnostic tests of the carotid arteries is usually based on data from academic centers acquired under “ideal” circumstances that may not be representative of their performance under the varied conditions characteristic of routine clinical practice. This study represents 1 of the largest series of patients in whom the performance of CEMRA has been evaluated in comparison with catheter angiography and is, to our knowledge, the only study evaluating this test in routine clinical practice at a nonacademic center.

Previous work has shown that Doppler ultrasound and non–contrast-enhanced MRA are both associated with clinically important error rates in comparison with catheter angiography when used alone to select patients for CEA and that this error rate can be reduced when both tests are performed and the results are concordant.\textsuperscript{4} The present study shows that important errors also occur when CEMRA is used alone to select patients for CEA (24%), and it shows similarly that this rate is reduced when both CEMRA and Doppler ultrasound tests are performed and the results are concordant (17%). Earlier work in this area using smaller numbers of patients also showed that a combination of Doppler ultrasound and gadolinium-enhanced MRA was associated with higher sensitivity and specificity than either test alone, but that non–contrast-enhanced 3-dimensional MRA was superior to contrast-enhanced methods.\textsuperscript{17} This may be related in part to relative inexperience with the new technology when that study was performed.

The reasons for the improved performance of a combination of noninvasive tests may be due, at least in part, to the use of complementary methods for determining the degree of arterial narrowing, thus reducing characteristic errors associated with an individual technique. Duplex Doppler ultrasound uses the velocity of flowing blood to estimate the amount of arterial narrowing as well as providing an “anatomic” image of the vessel. CEMRA provides the internal diameter of the artery with a contrast agent and creates a 3-dimensional image of the vessel using computerized postimaging processing.

In routine clinical practice, clinicians frequently rely on official radiology reports to make decisions regarding CEA in individual patients. Therefore, we used these reports as the basis for determining whether a clinician would have correctly classified an individual patient as appropriate for CEA on the basis of the information available in the report. We also assessed the accuracy of the official report by having each study independently reviewed by 2 neuroradiologists and found similar moderate to significant agreement between blinded reviewers and the original reports for both CEMRA and catheter angiography. In fact, agreement was similar between the original reports and each of the blinded reviewers compared with the levels of agreement between the blinded reviewers.

The level of interrater agreement for the gold standard (catheter angiography) is important to highlight. The $k$ scores between the original official reports and each of the reviewers for catheter angiography were 0.81 and 0.82, respectively. This compared favorably with the level of agreement for catheter angiography between the reviewers ($k=0.75$). These levels of agreement were similar for the comparison of CEMRA and catheter angiography, which suggests similar levels of reliability in routine clinical practice for the 2 imaging modalities. These data also suggest that some of the misclassification between CEMRA and catheter angiography observed in this study may be related to the inherent variability associated with the interpretations of the studies. However, investigators in the clinical trials on which CEA decisions are based used catheter angiography as the determinant of whether a patient should receive the operation. Therefore, the observed misclassification rates for CEMRA alone (24%) and for CEMRA in combination with a concordant duplex ultrasound (17%) compared with clinically generated catheter angiography reports must be considered because these tests are used in routine practice. Whether this level of misclassification is clinically significant can only be addressed though a prospective study directly comparing the imaging modalities as they affect the outcome of CEA.

In comparison with previous work with non–contrast-enhanced MRA and duplex Doppler ultrasound, we found similar though less dramatic differences when concordant results from CEMRA and duplex Doppler ultrasound were compared with either test alone. It is important to remember that this was a study of how CEMRA, duplex Doppler ultrasound, and catheter angiography performed in clinical practice, and which patients received which tests was likely not random. If a clinician was confident that the initial test was accurate, further confirmatory investigations would likely not have been obtained. Catheter angiography may have been used in patients in whom there was some degree of uncertainty about the results of CEMRA, leading to some degree of bias. However, only a small number of the studies were judged to be suboptimal when independently reviewed.

It should be noted that the criteria used to select patients for CEA were based on hard cut points for degree of stenosis that were based on the results of several clinical trials. This is necessary for statistical purposes and may not be indicative of the actual decision an individual clinician might make under similar circumstances. Although we could not ensure blinding to clinical information of the radiologists providing the official study reports, the sequence in which the tests were performed virtually ensured that the CEMRA and Doppler ultrasound were interpreted without knowledge of the catheter angiography results. It has been suggested that the degree of interobserver agreement varies with the degree of carotid stenosis and that this rate of disagreement may account for much of the difference in performance between the various modalities.\textsuperscript{18} Although not statistically significant, we found
that the \( \kappa \) scores among the blinded reviewers were relatively lower for the arteries with stenosis in the 50\% to 99\% range, suggesting that it may be more difficult for radiologists to accurately determine discrete degrees of clinically significant carotid narrowing compared with determining whether an artery is completely occluded or has <50\% or 60\% stenosis. Furthermore, determination of the degree of stenosis may be more variable for ranges of stenosis that are close to hard cut points (eg, for a “true” stenosis of 70\%, one reviewer might report 65\% and another 75\%). However, the aim of this study was to critically evaluate the information available to clinicians in routine practice when they may be making a decision regarding surgery in an individual patient.

In summary, CEMRA is associated with a high sensitivity for detecting surgically amenable carotid stenosis in routine clinical practice. Furthermore, these results also show similar levels of agreement for the interpretation of CEMRA and catheter angiography. However, a significant misclassification rate may occur when CEMRA is used alone to select patients for CEA compared with the results of catheter angiography. This error rate is reduced when duplex Doppler ultrasound and CEMRA are used in conjunction and the results are concordant. Clinicians should understand the potential misclassification rates for CEMRA used alone or with carotid duplex ultrasonography in comparison with catheter angiography when evaluating patients for CEA. Knowledge of the accuracy of noninvasive tests as performed in local laboratories is important for clinicians when relying on these studies for the preoperative evaluation of patients with carotid stenosis.

Acknowledgments

This study was supported by a grant from the Heart and Stroke Foundation of Canada (Dr Johnston) and by the National Institutes of Health (K-24 NS 01265) (Dr Goldstein). The authors would like to acknowledge the assistance of Robert Mitchell, MD, Joanie Messler, RN, Vernon Byrd, MD, Doug Sheafor, MD, and Ryan Woods, MSc.

References
Contrast-Enhanced Magnetic Resonance Angiography of Carotid Arteries: Utility in Routine Clinical Practice

Dean C.C. Johnston, James D. Eastwood, Thanh Nguyen and Larry B. Goldstein

Stroke. 2002;33:2834-2838; originally published online December 2, 2002;
doi: 10.1161/01.STR.0000043632.51378.24

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/33/12/2834