Angiographic Detection of Carotid Plaque Ulceration
Comparison With Surgical Observations in a Multicenter Study

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Background and Purpose
Carotid plaque ulceration is used as one of the determinants in deciding which patients should be submitted to carotid endarterectomy. Uncertainties about its importance persist. Its detection by angiography is an important consideration.

Methods
The detection of ulceration by angiography was compared with observations during endarterectomy in the first 500 patients recruited into the North American Symptomatic Carotid Endarterectomy Trial. This represents the first multicenter compilation of data on this subject and the largest series of patients with both arteriographic and direct surgical observation.

Results
Sensitivity and specificity of detecting ulcerated plaques were 45.9% and 74.1%, respectively. The positive predictive value of identifying an ulcer was 71.8%. These results remained unchanged with differing degrees of carotid stenosis and were confirmed by analyses based on receiver operating characteristic (ROC) methodology. The area under the ROC curve ($A_z$) was estimated to be 0.61 (95% confidence interval, 0.55 to 0.67).

Conclusions
These observations from a multicenter study confirm that little agreement exists between angiography and surgical observation in detecting carotid plaque ulceration.

Key Words
angiography • carotid arteries • carotid endarterectomy • clinical trials

The severity of carotid stenosis and the presence of plaque ulceration are often taken into consideration in making decisions regarding carotid endarterectomy. While the degree of luminal narrowing is largely agreed on, the importance of plaque ulceration has remained a subject of dispute. A major factor contributing to this is the inaccuracy noted in the preoperative diagnosis of plaque ulceration.

One of the factors initially used for stratifying patients at higher risk of stroke in the ongoing North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the presence (or absence) of ulceration of stenotic (30% to 99%) plaque as determined by angiography.

The aim of this study was to assess the agreement between angiography and surgical observation in detecting plaque ulceration.

Subjects and Methods
NASCET is a multicenter study that was designed to determine the role of carotid endarterectomy in symptomatic patients with moderate (30% to 69%) and severe (70% to 99%) stenosis involving the ipsilateral carotid bifurcation. Biplanar (anteroposterior, lateral, and/or oblique) selective carotid angiography was used for the initial (preoperative) assessment of the degree of stenosis and of plaque appearance in all patients. After randomization, half of the patients underwent carotid endarterectomy. Observations during endarterectomy identified or denied the presence of plaque ulceration.

Reports from the first 500 surgical patients have been assessed. All patients had their symptoms (transient ischemic attack or nondisabling stroke relating to the carotid lesion) within 120 days before randomization. Details of the study protocol and baseline characteristics of the patients have been published.

Hard copies of all angiograms were sent to the central office and reviewed by the principal neuroradiologist in a blinded fashion; ie, the neuroradiologist was not aware of any clinical details or the treatment assignment. In each case, the appearance of the plaque was classified into one of three categories: ulcerated, irregular plaque/uncertain ulceration, or smooth/no ulceration. A plaque was classified as ulcerated if it fulfilled radiographic criteria of ulcer niche, seen in profile as a crater penetrating into a stenotic plaque (Figure, panel A) and (when visible) double density on "en face" view (Figure, panel B). These criteria are similar to those used for duodenal ulcers.

The irregular plaque/uncertain ulceration category was used for wall irregularity or multiple small possible craters or when there was difficulty distinguishing a real crater from normal wall between two plaques (Figure, panel C). The smooth/no ulceration category was used for patients with smooth stenosis (Figure, panel D) or when a relatively smooth outpouching between two smooth narrowings was most consistent with the expected position of the carotid bulb wall (Figure, panel E).
Schematic representation of possible appearances of carotid plaque on angiography. A. Definite ulcer niche at the bifurcation; B, definite double density on "en face" view (same patient as in panel A); C, irregular plaque; D, smooth plaque; and E, smooth outpouching between two smooth plaques.

Surgical information was recorded by the participating surgeon on standard forms and then forwarded to the central office with the operative and pathology report. In a few cases, gross photographs were available. All participants were specifically instructed in the protocol to indicate the presence or absence of ulceration at surgery. Ulcerations were diagnosed by the surgeon when there were either pronounced disruptions in the lining of the plaques or pits and depressions in the plaques, often with sharply delineated color differences between the base of the pit and the adjacent luminal surface. The surgical data were centrally reviewed for completeness and accuracy.

**Statistical Analysis**

Receiver operating characteristic (ROC) methodology was used to compare the angiographic review with surgical observation, because this method of analysis has become the standard for qualifying radiological techniques. In simple terms, an ROC analysis is a generalization of sensitivity and specificity. Rather than estimating the sensitivity and specificity for each decision category appearing on a rating scale, the measures are expressed in more global terms as a single figure, namely, the area under the ROC curve (A$_z$). The values of A$_z$ range from 0.5 to 1.0, indicating the lowest to highest degree of accuracy, respectively. A computer program (ROCFIT) developed by Metz$^{21}$ was used to compute the values of A$_z$ and corresponding two-sided 95% confidence intervals.

Surgical observation (ie, macroscopic appearance of the plaque) was used as the comparative standard in this study because this is an accepted approach$^{3-7,9}$ and it was available in all patients. Some prefer the reports of microscopic examinations,$^8$ but the detection of the smallest discontinuity in the endothelium makes this method an impractical standard to be followed.

**Results**

Ulcerated plaques were detected at surgery in 290 (58%) of 500 patients. From among these, seven patients were excluded as a result of a discrepancy between the surgical and pathological reports. Thirteen of the 210 cases in the surgical “no ulceration” group were also excluded as a result of contradiction between the various reports that were examined (disregarding microscopic findings as the only evidence of ulceration).

The results from the radiological classification are shown in the Table. It is observed that the accuracy of detecting ulcer from angiographic film is relatively poor, as measured by the coefficients of sensitivity and specificity and by A$_z$. In particular, the neuroradiologist reported ulcerated plaques in 37.7% (181/480) of the angiograms. Compared with the surgical findings, sensitivity and specificity were 45.9% and 74.1%, respectively. The positive predictive value of identifying an ulcer from angiographic film (71.8%) was also poor. Similar results were obtained when the analysis was stratified by degree of stenosis, namely, moderate (<70%) versus severe (≥70%).

**Discussion**

Our study, the largest and first multicenter study to evaluate angiography in the detection of plaque ulceration, disclosed discouraging results. The rates of false-positive and false-negative results were both high (25.9% and 54.1%, respectively). The degree of stenosis had little or no effect on detectability. Therefore, little agreement exists between biplanar carotid angiography and surgical observation in detecting plaque ulceration.

Review of the literature identified six single-center studies that specifically dealt with assessing ulceration by angiography.$^3-8$ The sensitivity of detecting plaque ulceration ranged from 53% to 86% as reported in these studies. Further comparisons among these studies are complicated by the comparative standard that was used to verify the presence of plaque ulceration and by the variable definitions that were used for the angiographic diagnosis of ulceration. Nevertheless, the results led these observers to the same conclusion: angiography frequently disagrees with direct observation.

Details of the morphology and the extent of ulceration in a plaque necessary to produce emboli and ischemic symptoms remain uncertain. Imaging techniques of the future may help to clarify these persisting problems. Pathological studies using careful macroscopic and detailed microscopic observations are capable of identifying the potential sources of emboli be-
lieved to be responsible for the majority of the cerebral ischemic symptoms associated with ulceration. However, such information cannot be put to use in arriving at preoperative decisions.

Regardless of the disagreement between angiographic review and observations made during endarterectomy, angiography is the only practical preoperative investigative tool currently available in the clinic and at the bedside. Neither magnetic resonance angiography nor ultrasound flow studies provide adequate data regarding ulceration. Furthermore, what is likely to be observed at surgery cannot be anticipated reliably from any available preoperative imaging studies.

Acknowledgments

This study was supported by a grant (R01-NS-24456) from the National Institute of Neurological Disorders and Stroke. We thank B. Sharpe, BScN, and M. Wright, RN, for their technical assistance.

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*Stroke*. 1994;25:1130-1132
doi: 10.1161/01.STR.25.6.1130

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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