Natural History of Stenosis From Intracranial Atherosclerosis by Serial Angiography

Paul T. Akins, MD, PhD; Thomas K. Pilgram, PhD; DeWitte T. Cross III, MD; Christopher J. Moran, MD

Background and Purpose—Knowledge of the natural history of stenoses due to intracranial atherosclerosis may be useful for evaluating possible treatments such as angioplasty.

Methods—We retrospectively reviewed records over a 7-year period to identify patients with intracranial atherosclerotic stenoses and serial angiograms. Quantitative measurements of stenoses were made in a blinded manner, and clinical outcomes were reviewed.

Results—We identified 21 patients with 45 intracranial stenoses who underwent repeat angiography at an average interval of 26.7 months. The average stenosis for all intracranial lesions was 43.9% initially and 51.8% on follow-up ($P=0.032$). The average stenosis in the intracranial internal carotid artery (ICA) was stable (51.2% versus 52.6%). The average stenosis in the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) progressed from 32.4% to 49.7% ($P=0.037$). Based on a minimum 10% change, 20% of intracranial ICA lesions progressed compared with 61% of ACA, MCA, and PCA lesions. Regression occurred in 14% of the intracranial ICA group and 28% of the ACA-MCA-PCA group. Cerebrovascular events were infrequent during this period, with 4 transient ischemic attacks and 1 intracerebral hemorrhage.

Conclusions—Intracranial atherosclerotic stenoses are dynamic lesions demonstrating both progression and regression.

Key Words: angioplasty n atherosclerosis n cerebral angiography n cerebral ischemia n cerebral ischemia, transient

Patients with intracranial atherosclerotic disease are at increased risk of stroke and heart disease. Atherosclerosis of the intracranial vessels frequently occurs in the setting of widespread vascular disease. Atherosclerosis may also develop selectively in intracranial vessels, particularly in blacks and Asians. In addition to race, other risk factors for intracranial atherosclerosis include age, hypertension, smoking, diabetes, and lipid disorders.

The increased risk in patients with intracranial atherosclerosis for stroke, heart disease, and death has been consistently observed. For example, in patients with stenosis of the intracranial ICA, mortality as high as 50% over an average 3.9-year period has been reported. A retrospective, multicenter study has reported clinical outcomes of symptomatic patients with angiographically defined stenoses of 50% to 99% in an intracranial artery and ischemic events involving the territory of the stenotic vessel. Over a median follow-up of 19.3 months in patients treated with aspirin, 24% had a stroke, and 17% had myocardial infarction or sudden death. In this study, patients treated with warfarin had fewer ischemic strokes and myocardial infarctions but more intracerebral hemorrhages. In the medically managed arm of a trial of EC/IC bypass surgery, 36% of patients with high-grade distal ICA stenoses and 24% of patients with MCA stenoses treated with aspirin had strokes (overall average follow-up for study was 55.8 months).

The management of these high-risk patients is controversial. Based on retrospective data, warfarin may be superior to antiplatelet therapy, but these two treatments have not been compared prospectively. EC/IC bypass surgery for patients with high-grade ICA or MCA stenosis did not reduce the risk of stroke over aspirin treatment alone.

Cerebral percutaneous transluminal angioplasty has been performed in patients refractory to medical treatment. Compared with extracranial vessels, angioplasty of intracranial vessels has a higher complication rate, with strokes occurring in 12% to 33% of cases. Complications have been attributed to vessel dissection, thromboembolism, occlusion of small perforating vessels, and selection bias for high-risk patients in whom anticoagulation treatment has failed. Clinical and angiographic follow-up is limited but encouraging.

The long-term angiographic behavior of intracranial atherosclerotic stenoses has not received much attention. Bauer et al reported the results of serial cerebral angiography in 49 patients with strokes or TIA with an average follow-up interval of 25 months. They reported progression of atherosclerotic stenoses...
by location, including extracranial and intracranial sites. Overall, 35.3% of intracranial sites progressed. Craig et al. reported that intracranial ICA stenoses progressed in 5 of 5 patients on follow-up angiography. In the setting of EC/IC bypass, 9 of 18 stenoses showed significant angiographic changes on follow-up studies: 4 sites occluded and 5 sites improved. For example, an 80% stenosis of the carotid siphon completely resolved, but the bypass occluded. We conducted a retrospective study of patients with intracranial atherosclerotic stenoses who had undergone repeat angiography at our institution to learn more about the natural history of these lesions.

Subjects and Methods

Approval from the Human Studies Committee was obtained for this retrospective study. We conducted a computer search of the Mallinckrodt Institute of Radiology files and identified 855 patients who had undergone two or more cerebral angiograms during the period of July 1990 to June 1997. The most common reason for repeat angiography was for management of aneurysms, arteriovenous malformations, and vasospasm. These patients were excluded. We reviewed the dictated reports of 183 patients whose follow-up angiogram was performed at least 6 months after the initial study. We identified 28 patients with moderate or severe atherosclerosis in an intracranial vessel that was noted in the report. The angiograms from 5 patients were incomplete or missing.

Cerebral angiograms from 23 patients were initially reviewed in an unblinded manner. We routinely assessed the following vessels for atherosclerotic stenoses of 50% or greater: the intracranial portion of the ICA; the ACA, MCA, and PCA; the distal vertebral and basilar arteries; and the origins of the posterior inferior cerebellar and superior cerebellar arteries. When available, the carotid bifurcations were also reviewed, and the side without interval endarterectomy was identified. The indication for repeat angiography was recorded. Two patients were excluded: one for stenosis of less than 50%, and one for large subarachnoid hemorrhage. Clinical information regarding the indication for repeat angiography, atherosclerotic disease risk factors, secondary stroke prevention measures, functional status, and strokes or transient ischemic attacks were obtained by chart review and phone contact with the patient or immediate relative.

A total of 45 stenoses suitable for serial measurement were identified in 21 patients. Initial and follow-up films were simultaneously viewed. These lesions were well-visualized in the same projection and at a similar arterial phase. Intracranial stenoses that constituted the distal half of tandem lesions were excluded. The maximum stenosis and a nearby adjacent “normal” segment were outlined with a sharp, soft lead pencil on the initial and follow-up studies. The “normal” segment was either proximal or distal to the lesion. For a given stenosis, the same control segment was used. The angiograms were randomly coded A or B, and the identifying data were obscured with a black film mask. On a different day, measurements of stenoses and the “normal” segment were performed by a single observer using a 10× loupe to the nearest 0.1 mm. The percentage of stenosis was calculated by the following formula: \( \frac{1 - \text{stenosis/normal segment}) \times 100}{} \).

The measurement reproducibility was evaluated with use of test-retest analysis by repeating the measurements at 30 randomly selected stenoses from this patient series. Both the stenosis and denominator were remeasured, and the percent stenosis was recalculated. The level of agreement was very high. The repeat values were unbiased, as the 95% confidence interval for the mean difference between original and repeat measures included zero. The standard deviations of the differences between the measures were 0.18 mm for stenosis, 0.39 mm for denominator, and 4.25% for percent stenosis. Simple linear regression was used to fit lines describing the relation between the original and repeat measures. The relation appears to be one-to-one, as a slope of one was included in all the 95% confidence intervals for slope and zero was included in all the 95% confidence intervals for intercept. In all cases, \( r \) was at least 0.96. Consequently, a 10% change in percent stenosis was chosen as a threshold for determining whether an individual lesion had progressed or regressed; this difference is greater than 2 SDs for percent stenosis remeasurement, which eliminates the possibility that the difference could arise from measurement error.

Results

Clinical features of patients are provided in the Table. These diagnoses were based on chart review, using the most current information available. In many cases, diagnoses of coronary and peripheral vascular disease were supported by angiography. Indications for repeat angiography were variable: carotid bifurcation stenosis or occlusion by carotid ultrasound (62%); TIA (19%); evaluation for possible arteriovenous malformation (14%); and to rule out carotid-cavernous fistula (5%). Widespread atherosclerotic disease involving the carotid bifurcation, coronary arteries, and peripheral vessels was present in many patients. The functional status of this group was high, with 81% of patients receiving a Modified Rankin Score of 0 (no symptoms) or 1 (able to resume all previous activities despite symptoms). Many patients had suffered either ischemic (48%) or hemorrhagic (10%) strokes around the time of the initial cerebral angiogram. During the period between the first and second angiograms, 4 patients had TIA and 1 had an intracerebral hemorrhage. The sample size was too small to investigate clinical features associated with TIA or intracerebral hemorrhage. We note that 2 of the 4 patients with TIAs had progression of the intracranial stenoses. Only one patient died

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, years</td>
<td>62</td>
</tr>
<tr>
<td>Male</td>
<td>62</td>
</tr>
<tr>
<td>White</td>
<td>81</td>
</tr>
<tr>
<td>Black</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33</td>
</tr>
<tr>
<td>Smoking</td>
<td>71</td>
</tr>
<tr>
<td>Peripher al vascular disease</td>
<td>48</td>
</tr>
<tr>
<td>Carotid bifurcation disease</td>
<td>86</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>48</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>19</td>
</tr>
<tr>
<td>Chronic ethanol use</td>
<td>10</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>48</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>10</td>
</tr>
<tr>
<td>Antiplatelet treatment</td>
<td>76</td>
</tr>
<tr>
<td>Warfarin treatment</td>
<td>19</td>
</tr>
<tr>
<td>Modified Rankin Scale score 0–1</td>
<td>81</td>
</tr>
</tbody>
</table>
during the follow-up period (of gastrointestinal hemorrhage). This represents a 5% mortality for this group over an average follow-up time of 26.7 months.

Quantitative measurements of the carotid bifurcation and intracranial stenoses were performed in a blinded manner following an initial, unblinded screening of films. Examples of stenoses are provided (Figs 1 through 7). The most common location for an intracranial stenosis of 50% or greater was the intracranial portion of the ICA (Fig 2; 49% of lesions), followed by the MCA (Fig 4; 20%), PCA (Fig 5; 11%), distal vertebral and basilar arteries (Figs 6 and 7; 11%), and ACA (Figs 3 and 7; 9%).

The average stenosis for all intracranial sites worsened from 43.9% (range, 0% to 100%; SD, 22.3%) to 51.8% (range, 0% to 100%; SD, 15.9%) (Fig 8; \( P = 0.032 \) by one-sided \( t \) test). Bivariate analysis with ANOVA and \( t \) test was performed for potential risk factors for disease progression. The following factors were evaluated: age, sex, race, interval between angiograms, diabetes, hypertension, tobacco use, hypercholesterolemia, chronic ethanol use, and carotid bifurcation disease (>50% stenosis). Patients without carotid bifurcation disease were more likely to progress (\( n=9 \); average change, +24.7%) than those with extracranial disease (\( n=36 \); average change, +3.8%; \( P = 0.045 \) by paired \( t \) test). The average stenosis of the carotid bifurcation did not change significantly; however, we did not measure the stenosis if the patient underwent interval endarterectomy.

The intracranial lesions were divided into three groups: (1) intracranial ICA segment (petrous to supraclinoid portion); (2) ACA, MCA, and PCA; and (3) distal vertebral and basilar arteries and their branches. The mean stenosis for lesions of the ACA, MCA, and PCA progressed (\( P = 0.037 \) by one-sided \( t \) test), whereas the mean stenosis for the intracranial ICA was stable (Fig 8). The number of lesions studied in the intracranial vertebrobasilar system was small. Lesions were categorized into stabilization, progression, or regression, if a change of 10% or greater was observed (Fig 9). Based on test-retest analysis, a 10% difference was reliably detected using our measurement technique. Overall, 40% of intracranial stenoses were stable, 20% regressed, and 40% progressed. Lesions in the intracranial ICA were less likely to progress compared with those in other sites. Only two occlusions were studied. Both occurred in the same patient and were asymptomatic. The anterior cerebral artery spontaneously reperfused, demonstrating several diseased segments (Fig 7), and the right vertebral artery, with an initial 70% distal stenosis, occluded. In three sites, striking regression occurred with a residual stenosis of less than 20% (Fig 7), suggesting that a significant component of the stenosis was thrombus.

**Discussion**

In this series of patients with intracranial atherosclerotic stenoses, repeat angiography demonstrated the dynamic nature of...
these lesions. Angiography is an excellent method for monitoring atherosclerosis, but some limitations should be noted. This method defines the vessel lumen only. The disease process leading to luminal narrowing is inferred. If the patient has widespread atherosclerosis, the stenosis is usually ascribed to this. Based on pathological specimens,\(^1\),\(^3\),\(^4\) the narrowing is generally caused by local atherosclerosis, but associated thrombus may also contribute. Emboli also cause luminal narrowing. In this situation, the follow-up study may show complete resolution of the stenosis due to spontaneous clot lysis. This pattern was encountered in 3 of the 45 sites studied. Physiological variables such as cerebral autoregulation in response to PCO\(_2\) and vessel pulsation from the cardiac cycle can affect vessel diameter. Pathophysiological processes such as vasculitis, vasospasm, and certain malignancies, including glioblastoma multiforme and intravascular lymphoma, can also cause vessel narrowing. None of our patients had clinical features to suggest these other pathologic conditions.

The frequency of lesion progression for intracranial stenoses is consistent with previous angiographic studies.\(^2\),\(^21\),\(^22\) Progression of stenoses has also been reported with use of serial transcranial Doppler measurements.\(^23\) We offer several possible explanations for the relative stability of the intracranial ICA lesions compared with those in other intracranial sites. First, for similar absolute changes in luminal narrowing, the change in percent stenosis will be greater for small vessels compared with large vessels. Consider a stenosis that progresses from 3 mm to 2 mm. If the normal segment is 5 mm, the percent stenosis will progress from 40% to 60% (20% change). If the normal segment is 10 mm, the percent stenosis will progress from 70% to 80% (10% change). Second, the smaller vessels may be more prone to local thrombus formation compared with the intracranial ICA. Third, certain intracranial vessels have a predilection for atherosclerosis.\(^1\),\(^3\),\(^4\),\(^14\) The distribution of lesions in our series is fairly representative of this pattern. It would be reasonable to expect that once focal lesions form in these vulnerable locations, they would advance more quickly compared with other sites. Fourth, the retrospective nature of this study.
distal to the stenosis has been well documented in coronary vessels. It is likely that similar responses occur in cerebral vessels.

When serial quantitative measurements are made, the average scales for change and calculated percent stenosis using an analysis. The significance of this finding is diminished by the small size of the study and the numerous risk factors assessed. Other investigators have noted the low frequency of carotid bifurcation disease in ethnic groups prone to develop intracranial disease. In an angiography–based study, the duration of tobacco use was the most significant predictor of intracranial ICA atherosclerosis, followed by hypertension and diabetes.

While serial angiography has rarely been used to investigate intracranial atherosclerosis, coronary artery disease has been extensively researched using serial angiography. This approach has been very instructive. Angiographic progression of coronary atherosclerosis is associated with an increased risk of a clinical coronary event. For example, in a trial of partial ileal bypass for hyperlipidemia with serial coronary angiography at 0, 3, 5, 7, and 10 years, medically managed patients with qualitative progression in coronary artery disease had a twofold increase in mortality compared with patients with stable or regressing disease.

Strategies to treat hyperlipidemia (eg, lovastatin or colestipol and niacin) have consistently demonstrated that coronary lesions could stabilize and regress. Many trials used qualitative scales for change and calculated percent stenosis using an adjacent “normal” segment. More recent studies have developed computer-assisted quantitative coronary angiography. When serial quantitative measurements are made, the average diameter of coronary vessels without focal narrowing has mild progression in about 25% of patients studied. Compensatory vessel dilation at the initial site of atherosclerosis as well as distal to the stenosis has been well documented in coronary vessels. It is likely that similar responses occur in cerebral vessels (Fig 3).

This study has provided information about the spectrum of changes that can be observed in stenoses associated with intracranial atherosclerosis. Lesion progression occurs frequently in patients with intracranial atherosclerosis, particularly in medium-sized vessels. In this study, intracranial ICA lesions were more stable than other sites. Lesion regression clearly occurs in some patients. The pathological process that leads to this angiographic improvement may be regression of atherosclerosis or resolution of local thrombus or both. These results may be useful when designing studies to investigate potential therapies for this high-risk population. Such studies will need to include a control group, because some patients with intracranial disease can have a benign clinical course and spontaneous regression of intracranial stenoses.

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**References**

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