Asymptomatic Carotid Artery Disease

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THE RISK OF STROKE in asymptomatic internal carotid artery disease may not exceed the combined morbidity and mortality of surgical therapy. That concern is the subject of an article in this issue of Stroke by Durward et al. The authors encountered but 2 examples of stroke among 73 patients followed for a mean of 4 years after the angiographic demonstration of asymptomatic internal carotid stenosis of > 50% and/or ulcerative disease, and have found roughly similar data in their review of the available literature. On balancing the relative risks, they advise against surgery in asymptomatic patients, unless there is a high-degree (> 90%) stenosis.

Few would argue for a therapy that carries more risk than the untreated disease, and all would applaud the clear demonstration of the relative risks. Accomplishing this goal may prove difficult for several reasons: first, few centers have a large enough population to determine the natural history for all the many variants of carotid disease (i.e., hemodynamically significant stenosis, > 50% stenosis, stenosis with ulceration, ulcers of various types) or the restraint to do so if they are a referral center; second, the risk of the surgical therapy is heavily dependent on the experience of the professional team and should not exceed a combined morbidity-mortality of 3% lest it fail to improve on the best medical therapy of the decade-old Cooperative Study; third, the surgical methods in use are undergoing enough changes that current risk factors may be rendered moot in the near future; and fourth, newer medical therapies may be exerting a separate impact on the course of the disease. The chaotic interactions of these variables will undoubtedly keep the risk-benefit ratio for conservative versus aggressive management subject to lively arguments for some time to come.

Of first importance is the need to clarify the risk for stroke in the asymptomatic population with various forms of carotid disease. Should it be low enough for all forms, it would prove extremely difficult for any innovations in diagnostic radiology or surgery to improve on it. Unfortunately, the available literature remains blurred enough to permit arguments for the existence of a subgroup whose risk is just high enough to warrant surgery but who lie buried in the larger numbers with milder disease. However, even this point is a welcome step forward, indicating as it does that many have little risk for stroke from the lesion. Studies on asymptomatic bruit, presumed but not documented to reflect internal carotid artery stenosis, indicate the entity is common, and present in as many as 4% of the population aged over age 50. The risk of stroke seems to vary widely: at one end of the spectrum are 2 reports, one by Thompson, in which 17.4% of 138 patients developed mild to profound stroke between 1 week and 12 months after documentation of asymptomatic bruit. In the other report, by Cooperman et al., a stroke rate of 15% over 2 to 7 years contrasted with that of 5% without bruit. A somewhat lower rate (6.6%) of stroke was reported by Busuttil et al. in a study only carried to 2.5 years in patients whose bruit was associated with evidence from non-invasive laboratory tests suggesting hemodynamically significant stenosis. No strokes occurred in those whose bruit was not judged hemodynamically significant. In two publications, the issue of the type and location of the stroke is addressed in detail, and the findings contribute further to a skeptical attitude toward the danger posed by a bruit: although each documented a stroke rate approximately twice that of the control population during a period of 5 to 8 years, few of the strokes occurred in the brain ipsilateral to the bruit in the neck, and were of a wide variety of type (including ruptured aneurysm).

The few reports of patients with internal carotid artery disease documented by angiography suffer from a non-uniform method of describing the stenosis, and from a paucity of information on the location of the stroke and its occurrence alone or preceded by TIAs. Further, none of the studies represent controlled clinical trials. Credit is due Javid et al. for their early studies documenting the poor outcome in patients over age 65 who undergo operation for asymptomatic carotid stenosis: over an average period of three years, the stroke occurred in almost 4% (2 strokes among 56 patients), 12 patients died of myocardial disease, and 3 others died from non-cerebrovascular causes. Given these results, the authors advised against prophylactic surgery in the elderly asymptomatic patient. Then Humphries et al. reported an incidence of stroke of < 1% (1 among 168) in patients with > 50% stenosis of the internal carotid artery who were followed over an average period of 32 months. However, these figures contrast with the recent series of 50 cases by Podore et al., who reviewed the course over a 5 year period for initially asymptomatic patients with > 50% stenosis of an internal carotid artery: stroke without TIAs developed in 3 (4.5%). Yet Levin et al. reported the natural course of 137 patients operated for symptomatic carotid stenosis, whose contralateral asymptomatic carotid artery stenosis was < 50% in 12, 50–90% in 125, and > 90% in 7: 16 developed TIA and were operated, 60 died (all from non-cerebrovascular cause), and none of the 137 experienced a stroke during a period of follow-up over a period as long as 20 years. Considering the importance attached to the degree of stenosis, there is disappointingly little information on the natural history of documented internal carotid atheroma, possibly because such lesions are rarely left untreated. In a major early study, Javid et al. followed 93 among 140 patients whose untreated stenotic lesions of the internal carotid artery were < 60%, reangiogramming them over a period of time ranging from 1 to 9 years (averaging 3 years). Thirty-five of 93 showed no change in the severity or configuration of the atheroma; 19 had increased their atheroma size by < 25% per year, while 32 had changed > 25% per year; and 7 had developed recurrent stenosis or throm-
bosis. Increasing stenosis was more frequently encountered among patients with hypertension, bruit, and an initial angiogram showing > 25% narrowing. Data on the fate of lesions already hemodynamically significant when discovered is only anecdotal and widely scattered throughout the literature: some severely stenotic arteries maintain themselves essentially unchanged for at least several years, while in others, a dramatic worsening is observed over periods of weeks to months, this latter often attributed to subintimal hemorrhage. The exact risks for stroke in any of these variants remain unknown, although many investigators share the concern expressed by Durward et al. that severely stenotic arteries might warrant prophylactic therapy.

For purely ulcerative disease or for non-hemodynamically significant stenosis, a similar small cluster of reports is available. Plaques and ulcerations have been recognised as potential sources of TIA and stroke since the early years of this century. Some studies, apparently confining the analysis of causes of ischemic stroke to lesions found on the angiogram, have concluded that ulcers are a greater risk factor for stroke than stenosis. The increasing frequency of surgical attack on such lesions has led to a correspondingly higher prevalence of ulcers reported in the specimens. These reports have also demonstrated the difficulty in showing the smaller ulcers angiographically: as many as 40% being missed on routine angiography, and often found at operation in smooth plaques of benign appearance. Despite this surge in interest in ulcer disease, some recent opinion seems to be swinging toward a more conservative approach: a crude annual stroke rate was calculated at only 0.4% for the group with minimal ulceration, in the study of 67 patients with 72 asymptomatic lesions studied by Moore et al., but fully 12.5% for the group with large and compound ulcers. Remarkably, this study is the only one in the entire literature on asymptomatic lesions indicating the occurrence of no TIAs, only strokes. They recommended prophylactic surgery for the large ulcers. Yet in another recent retrospective study by Kroener et al., 76 patients with 87 asymptomatic shallow ulcers or ulcerated plaques followed over a mean of 3 years yielded only 4 TIAs overall, 1 stroke in the 55 patients with 63 small ulcers, and none in the 21 with 24 large ulcers. Based on the stroke rate of 1% over a seven year period, the authors concluded endarterectomy is not justified for asymptomatic carotid bifurcation ulcerations. The published discussion that followed the paper was conducted by Drs. Moore, Machleder, Levin, Javid and Eastcott, whose combined opinions supported the conclusion concerning small ulcers. However, the TIA and stroke risk for complex, deep ulcers remains a subject of disagreement.

In any discussion of this subject, the relevant risk in all these lesions is for stroke without warning, not for TIA. There is general agreement that the risk of stroke (presumably in the relevant vascular territory) rises sharply once a TIA in a given vascular territory has occurred. It also appears there is enough agreement to make it unlikely that the exact risk or impact of medical versus surgical therapy will be reinvestigated in detail in the foreseeable future, despite the criticisms levelled at the results of the original Cooperative Study. This widely accepted difference in prognosis then places the burden on the physician to determine that the patient has been asymptomatic. How often such patients are completely asymptomatic has been openly disputed by many, raising yet again the chronic arguments regarding what symptoms are correlated with carotid disease. This issue may never be fully settled, but available evidence suggests that the less focal and less hemispheric the symptom, the lower its post-operative remission, and if the symptoms are considered to represent brainstem ischemia, little improvement following surgery is expected.

For those with a plan for conservative management of asymptomatic carotid disease, the advent of digital venous angiography and quantitative phonangiography offers new safer methods to follow the course of asymptomatic stenosis over time to document progression or remission on medical therapy. The value of medical therapy in reversing atherosclerosis is still unclear, some data even suggesting that aspirin therapy is less effective in patients with widespread atheromatous disease or more severe stenoses. Recent interest in dietary manipulations featuring foods with platelet inhibiting properties, especially those high in eicosapentaenoic acid (i.e., salt water fish, oysters, fish liver oils) and other agents (garlic, onions) may eventually yield another mode of therapy but its utility is largely undetermined.

Innovations in neuroradiologic techniques offer a different hope, that of lowering the present morbidity of surgical therapy to levels that match or exceed the benefits of benign neglect or of medical treatment. Digital venous angiography has the presumed advantage of demonstrating the lesion with a morbidity much lower than conventional angiography. As to possible innovations in surgery, reports have just begun to appear on the use of percutaneous transluminal angioplasty in brachiocephalic arteries, despite fears of embolic complications. If the risk of intracranial embolization in such procedures proves to be low, or can be made low with modifications in the technique, another mode of therapy will await evaluation.

Calls for a randomized study, however welcome, may be muted somewhat by the calculations recently presented by Norris and D’Alton. Based on a literature review estimating an annual stroke rate of 2.2% per year over a period of 4 years for asymptomatic carotid bruits, the sample size calculations to document 25% reduction in the stroke rate for surgical therapy indicate the study would involve 3958 patients, a large enough requirement to overwhelm the efforts of most countries, let alone any one institution. Failing the organization of such a multicenter trial, the incidental data being collected in the ongoing Extracranial-Intracranial By-Pass trial regarding the fate of the contralateral unrandomized stenosis, may well prove of major value.

For now, the available unrandomized data indicates...
the risk of carotid territory stroke without prior TIA is low enough that the best surgical statistics do not prove superior to medical management. Despite this conclusion, restraint from surgery appears not to be in vogue: data on the incidence of carotid endarterectomies performed over the past decade shows a dramatic upswing from an estimated 7.4/100,000 to > 24/100,000.19 This trend is perhaps understandable since the morbidity/mortality data represents the accumulated group statistics, and as each individual patient presents, the temptations are great to anticipate he will pass safely through the diagnostic tests and the surgery. With the widespread introduction of digital venous angiography, even greater numbers of lesions will be uncovered. Like the rising tide that floats all boats, this effect may set current practices adrift, creating a discouraging tangle of conflicting opinions, each based on the presumed importance of a different uncontrolled variable. The results of a surgical versus medical randomized clinical trial, however large and difficult to carry out, should provide either the welcome opportunity to set sail with the tide or the firm anchor to ride it out.

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