# Recurrent Carotid Artery Stenosis Following Endarterectomy

MARTIN THOMAS, M.S., F.R.C.S.,* SHIRLEY M. OTIS, M.D., MICHAEL RUSH, R.V.T., JACK ZYROFF, M.D., RALPH B. DILLEY, M.D., EUGENE F. BERNSTEIN, M.D., PH.D.

**Spectral analysis was used to examine 257 carotid arteries in 227 patients who had undergone carotid endarterectomy at 1, 3, 6, and 12 months after surgery and annually thereafter. Routine intraoperative completion angiography ensured that the operations were technically satisfactory. Postoperative restenoses were identified in 38 patients (15%). In 23 arteries (9%), the restenosis exceeded a 50% diameter reduction while in 15 arteries (6%) the stenosis was less than 50% of the diameter. Restenosis developed in 24/96 women (25%) and 14/161 men (9%). Twenty-nine (70%) stenotic lesions occurred within 12 months. In three patients early lesions regressed. Reoperation with patch angioplasty was required in six patients. When the 219 carotid arteries that remained widely patent were compared to the 38 that restenosed, no differences were noted for age, diabetes mellitus, hypertension, smoking, or degree of preoperative stenosis. Early stenotic lesions appear to be due to myointimal hyperplasia, which is probably platelet mediated. The predominant female sex distribution may be explained by differences in platelet responsiveness in men and women.**

*From the Division of Vascular and Thoracic Surgery, Division of Neurology, and Department of Radiology, Scripps Clinic and Research Foundation, La Jolla, California*

EXTRACRANIAL CAROTID DISEASE causes ischemic cerebral symptoms and stroke by the release of emboli and by decreasing the perfusion to the brain.[1] Carotid endarterectomy has been shown to reduce morbidity and mortality in such patients, particularly after transient ischemic attacks from a flow-limiting carotid stenosis.[2,3] In selected cases the operation also has been recommended for patients with asymptomatic carotid bruits to prevent subsequent stroke.[4] Several reports of recurrent stenosis following carotid surgery have appeared recently, although the frequency, timing, and other correlations of such stenoses remain unclear.[5-11] Initially, restenosis was detected by clinical events with an incidence of 1% to 4%. The first large series (1654 patients) reported showed only a 1.5% symptomatic restenosis rate,[5] while more recently Cossman reported a 3.4% rate.[6] Two additional angiographic studies, while incomplete, suggest a recurrent carotid stenosis rate of about 7% after 5 years or more.[7,8] The introduction of sensitive noninvasive methods for the assessment of carotid arteries has enabled a more routine and complete follow-up of patients after surgery. Such noninvasive methods have revealed restenosis rates from 9%[9,10] to as high as 19%.[11,12] Should other studies confirm these high rates of recurrent carotid stenosis, and should they be associated with the development of clinically significant symptoms, then we may have to revise the current indications for and techniques of carotid surgery. The purpose of this study was to ascertain the incidence and timing of stenosis following carotid endarterectomy in one clinic where all the operations were performed in a similar technical fashion by two vascular surgeons.

## Methods

The Vascular Laboratory records and charts of 249 patients who had undergone carotid endarterectomy at the Scripps Clinic and Research Foundation between January 1979 and June 1983 were reviewed. Twenty-two patients had no postoperative vascular laboratory data and were excluded from this analysis. Of the 227 patients with adequate data, 30 had undergone bilateral endarterectomies so that 257 postoperative carotid arteries were available for study. One hundred sixty-two arteries were in men and 95 in women. Mean follow-up was 20 months and ranged from 1 to 54 months.

Indications for operation included amaurosis fugax, transient ischemic attacks, completed strokes with minor residual neurologic deficit, and asymptomatic bruits associated with significant carotid stenosis (Table 1). All of the operations were performed under normocarbic general anesthesia. Shunts were inserted selectively only in those patients (18%) in whom the stump pressure could not be maintained over 50 mmHg using Neosynephrine if necessary. In addition, shunts were used routinely in patients with prior strokes or with contralateral internal carotid artery occlusion. Carotid endarterectomy was performed with a standard surgical technique with particular attention paid to a smooth distal end point. Distal tacking

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Correspondence to: Dr. Eugene Bernstein, Division of Vascular and Thoracic Surgery, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, CA 92037.

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sutures were rarely used. Arteriotomies were closed using a two-needle continuous 6-0 polypropylene suture. Patch closure of the arteriotomy was performed in 8.5%. Completion intraoperative angiography was obtained in all cases to exclude technical errors that might cause stenosis. As a result of these angiograms, arteriotomies were reopened on seven occasions (2.7%). The intraoperative angiograms of those patients who subsequently developed restenosis were subjected to secondary independent review. Most patients were examined in the Vascular Laboratory at 3, 6, and 12 months after surgery and annually thereafter. More recently, patients have also been examined during their postoperative hospital stay and at 1 month. Follow-up was less complete for some patients who lived at a distance from the clinic.

### Instrumentation

The carotid arteries were examined directly with both a Duplex Scanner (ATL Mark V) and a continuous wave-Doppler spectral analyzer (Dopscan 1050, Carolina Medical Electronics). The Duplex Scanner combines real-time B-mode imaging with a pulsed Doppler device. The pulsed Doppler sample volume was 1 $mm^3$ and was superimposed on the B-mode so that signals from the center stream at an angle of 60% could be recorded with accuracy. The Dopscan CW Doppler device contained no real-time imaging facility. The entire vessel lumen was insonated by one 5 MHz crystal and the returning signal received by another. The quadrature outputs from both machines, processed for directionality, were fed into spectrum analyzers. The resultant Doppler spectrum displays all the audiofrequency information contained in the input signal for simple visual perception. It has time as the abscissa, frequency (proportional to red cell velocity) as the ordinate, and spectrum amplitude as intensity variation of the gray scale. A normal Doppler spectrum has a peak frequency up to 4 KHz and a narrow band of frequencies during systole, resulting in a clear area beneath the systolic peak known as the spectral window. With minor degrees of stenosis the first change in the Doppler spectrum is spectral broadening in the deceleration phase of systole. Further stenosis results in increased spectral broadening until the window is obliterated, together with increasing peak frequency and diastolic frequency. The Doppler spectra were interpreted by measuring peak frequency and assessing the amount of spectral broadening. On the basis of spectral analysis each carotid artery was assigned to one of four groups: normal to 19%, 20% to 49%, 50% to 99%, and occlusion.

### Results

Spectral analysis detected 40 lesions in 257 carotid arteries after surgery (15.5%). The secondary review of completion intraoperative angiograms confirmed all but two to be satisfactory (Fig. 1). In retrospect, two cases were considered to have intraoperative angiograms that contained significant residual stenosis and would not be accepted currently. These two patients were therefore considered to have residual rather than recurrent disease. The true incidence of postoperative lesions was therefore 38 of 257 (15%). Three were complete occlusions (1.2%),

TABLE 1. *Relationship of Carotid Restenosis to Indications for Endarterectomy and Operative Factors*

| Indication | Total # | Restenosis | |
|---|---|---|---|
| | | # | % |
| Amaurosis fugax | 39 | 8 | 21 |
| Motor transient inschemic attack | 76 | 12 | 32 |
| Prior stroke | 69 | 7 | 18 |
| Asymptomatic stenosis | 70 | 11 | 29 |
| Other | 1 | 0 | 0 |
| Patch angioplasty | 16 | 0 | 0 |
| Bilateral operation | 30 | 6 | 16 |

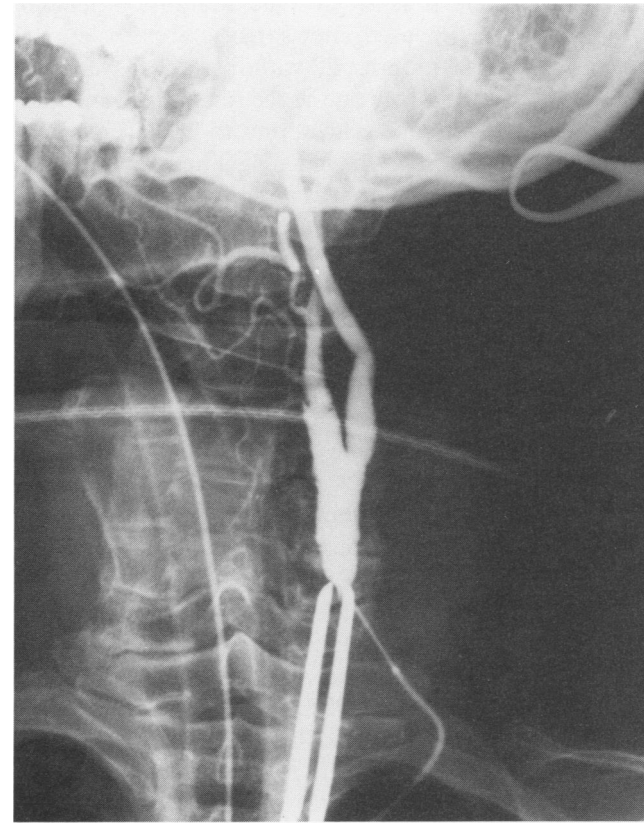

FIG. 1. Completion angiogram following carotid endarterectomy (obtained routinely in all cases) by hemodynamically significant stenosis in the postoperative period. The common carotid artery was clamped while 5 to 7 ml of contrast was hand injected. Immediate reoperation would be undertaken for any demonstrable defect of significance. None of the patients reported with late restenosis had any significant lesions in a retrospective review of their completion angiogram.

TABLE 2. *Incidence of Restenosis Following Carotid Endarterectomy*

| | Total # | Restenosis # | Restenosis % |
|---|---|---|---|
| Number of arteries studied | 257 | 38 | 15 |
| Hemodynamic significance (>50%) | 257 | 23 | 9 |
| Number arteries in men | 161 | 14 | 9 |
| Number arteries in women | 96 | 24 | 25 |
| Diabetes mellitus | 28 | 4 | 11 |
| Smoking history | 208 | 25 | 66 |
| Hypertension | 136 | 16 | 42 |

two of which occurred within 2 months. Twenty were stenoses from 50% to 99% so that the frequency of hemodynamically significant lesions was 23/257 (9%). Fifteen (6%) other stenoses were classified as 20% to 49% of the internal carotid artery diameter. A further 25 carotid arteries exhibited Doppler velocity patterns compatible with minor degrees of stenosis less than 20%. These spectra are of doubtful significance after surgery and have not been included in analysis.

Fourteen recurrent lesions were documented in men and 24 in women; thus 9% of male and 25% of female carotid arteries restenosed after surgery. Sixteen lesions developed within 3 months, 22 within 6 months, and 29 (76%) within 1 year. Only one of the remaining nine had been examined within 1 year, found to be normal, and subsequently restenosed. The other eight had not attended the clinic in the first 12 months and presented later with stenotic lesions. It is therefore possible that some or all of these eight restenosed in the first year. Regression of lesions was documented in three patients. The 22 arteries followed for 1 year or more have had the stenosis confirmed an average of 2.5 times by Vascular Laboratory examination indicating reproducibility of the technique. Eight arteries were also examined by conventional or digital subtraction angiography and the recurrent stenosis confirmed in every case.

Other than the sex distribution, there did not appear to be any difference in preoperative status between the 219 nonstenosed and the 38 stenosed carotid arteries (Table 2). Clinical indications for surgery and preoperative degree of stenosis were proportionately similar among those patients who developed restenosis and those who did not. Neither was any difference noted between the two groups for diabetes mellitus, hypertension, or smoking habits. Of the 38 cases of carotid restenosis, six underwent reoperation, four within 1 year. All six had developed lesions of greater than 50%, and clinical symptoms were present in four: transient ischemic attacks in three and a bruit audible to the patient in the fourth. Subocclusions of less than 95% diameter reduction were seen in the other two. Thus, in the relatively short average follow-up period of 20 months, 16% of patients with restenosis and 30% of those with a hemodynamically significant restenosis (>50%) required reoperation.

## Discussion

This study confirms that recurrent stenosis of the carotid artery is a problem of significant concern to the vascular surgeon. Noninvasive tests reveal a larger number of postoperative recurrent stenoses than have been suggested by clinical criteria alone. Spectral analysis has proved a reliable noninvasive method for assessing the carotid artery and can detect stenoses that do not limit flow, as well as those over 50%.[11,12] It is less invasive than digital subtraction angiography and probably as accurate. In a separate review of 258 carotid arteries that were examined by spectral analysis and subsequently underwent angiography at this clinic, the overall accuracy of spectral analysis was 86%, and the sensitivity for a stenosis of less than 50% was 90%. The present study could only be undertaken with a noninvasive method and these figures justify the use of spectral analysis for such screening surveys.

Kremen detected 9.8% hemodynamically significant stenoses using the ocular pneumoplethysmograph (OPPG), although the time after surgery that the patients were studied is not clear.[15] Using oculoplethysmography and carotid phonoangiography (OPG/CPA), supplemented in some later patients by Doppler imaging, Cantelmo found 9% significant stenoses,[9] while Turnipseed found 8.9% Doppler imaging alone.[10] These figures are remarkably consistent with our own 9% for stenoses equal to or greater than 50%. Zierler reported an initial incidence of 36% flow-limiting stenoses in the first year following operation, although only 19% persisted.[12] This high figure has not been confirmed by other studies. Available long-term studies suggest that disease progression on the operated side occurs at the same rate as on the unoperated side.[16] After 10 years, a quarter or more arteries may have developed restenosis.[16] It should be emphasized that in very few of these prior studies was intraoperative angiography employed routinely and none mention a secondary independent review of completion angiographic films as described in this report.

The true incidence of nonflow limiting restenosis is not known. Most studies have not reported stenoses of less than 50%, usually because the available instrumentation has not been sufficiently accurate. Several of the indirect and plethysmographic methods depend on changes in both pressure and flow to detect a stenosis and are therefore of little use in diagnosing the more moderate lesions. Cantelmo reported 3% nonflow limiting stenoses but since OPG/CPA was used this figure is probably low.[9] The current study demonstrated 15 (6%) stenoses from 20% to 50%. A further 25 carotid arteries

showed minor spectral changes consistent with stenoses less than 20%. While we are confident that the former group represents true restenoses, the significance of the latter group remains less certain. Some degree of spectral broadening can be expected from arterial wall compliance changes after endarterectomy and from turbulence secondary to altered intraluminal geometry. Minor abnormalities in the Doppler spectra are common after endarterectomy and probably do not represent pathological restenosis in most cases. Since no other studies of minimal and moderate restenosis following carotid surgery have been reported, the precise frequency of these lesions remains unknown. The significance of the mild and moderate lesions is also uncertain as is the likelihood that these lesser grades of stenosis progress to a tight stenosis or cause symptoms.

Stenoses were recorded at the first postoperative examination at 1 month in 11 cases. Review of these patients' intraoperative angiograms did not reveal any significant surgically related narrowing. Progression of disease from apparently normal at 1 month to severely stenosed at 3 months was also documented. Twenty-nine of the lesions appeared within 1 year. These figures suggest that restenoses may occur remarkably quickly. The condition did not progress in every case and three patients even showed regression of early stenotic lesions. The phenomenon of regression was also described by Zierler[12] and may be due to remodeling, as has been demonstrated in animals[17] and humans.[7] Thus, the early stenotic lesion occurring in the first few months has the potential to worsen or to improve. Late lesions were seen less often because follow-up was limited to 54 months. A few additional patients seen at this clinic who presented with restenoses up to 19 years after previous surgery elsewhere have been excluded from this analysis as their inclusion would bias the true incidence of restenosis.

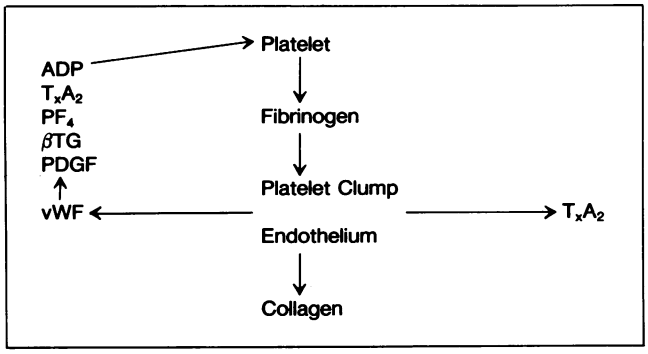


FIG. 2. Scheme of platelet-mediated myointimal hyperplasia. Rapid platelet adherence to exposed subendothelial collagen involves interaction of the collagen with von Willebrand's factor and a platelet membrane glycoprotein. Released adenosine diphosphate (ADP) and thromboxane $A_2T_xA_2$ act synergistically to recruit and, with fibrinogen bridging, to aggregate more platelets. Platelet-derived growth factor (PDGF) released into the subendothelium promotes intimal migration and proliferation of smooth muscle cells. ($PF_4$—platelet factor 4; βTG—β thromboglobulin; vWF—von Willebrand's factor.)

FIG. 3. Specimen removed at reoperation for carotid restenosis 8 months following initial carotid endarterectomy. Myofibroblastic intimal proliferation arising from apparent disruption of internal elastic membrane (arrows). Trichrome stain with original magnification of 125× (top) and 400× (bottom).

The stenotic lesion that develops within 1 year does not appear to be due to atheroma. This early lesion apparently is caused by myointimal hyperplasia[5,18] and seems to be platelet mediated (Fig. 2). Platelets adhere rapidly to the exposed collagen surface of the endarterectomized segment of carotid artery (Fig. 3). A collagen-induced platelet aggregation mediated by platelet-dense granule nucleotides and other substances follows. These activated adherent platelets have been shown to release a mitogenic factor that promotes proliferation of arterial wall smooth muscle cells.[19-21] The resultant myointimal hyperplasia has been examined histologically in specimens obtained at the time of operation for restenosis[18] and shown to be different from atherosclerosis (Fig. 3). Stoney and String described myointimal proliferation in 11 specimens removed within 15 months of the initial endarterectomy and typical changes of atherosclerosis in a further 20 lesions removed 2 to 20 years later.[5] The late

recurrent atherosclerotic lesion may be removed by standard techniques while the early myointimal lesion will not separate easily and should be treated by widening the artery with a patch.[6] There also appear to be radiological differences between the two lesions. The stenosis secondary to myointimal hyperplasia is smooth, regular, and occurs at the exact site of endarterectomy. The recurrent atherosclerotic lesion tends to be irregular, ulcerated, and worse at one or the other end of the previous endarterectomy site where the arterial wall was left intact. A similar phenomenon of smooth muscle proliferation has been reported after arterial reconstructions in the leg using vascular grafts.[22]

No difference was found in the incidence of diabetes mellitus, hypertension, clinical indications, preoperative severity of disease, or smoking habits among the patients whose carotid arteries restenosed compared to those in whom they stayed open (Table 1). Clagett described a high incidence of continued smoking in the restenosis group, but was unable to demonstrate any difference in other factors.[23] Neither the current study nor that of Clagett et al. used objective means to monitor tobacco consumption such as carboxyhemoglobin or thiocyanate measurements. Since patients' reporting of their tobacco consumption is notoriously unreliable, no firm conclusions can be drawn on the role of cigarette smoking.

One outstanding feature of these results is the high frequency of restenosis among women. In another clinical study, Cossman found 11 of 14 patients with symptomatic carotid restenosis were female.[6] This finding was also confirmed in a case control study in which the male:female ratio among patients with restenosis was 1.6:1 compared to 2.9:1 for the whole group.[23] Women tend to have higher platelet counts than men and the explanation for the predominance of restenosis among women could be sex differences in platelet behavior. Significant sex differences in platelet aggregation have been demonstrated in rats, guinea pigs,[25] and in humans.[26] All our patients were placed on aspirin with dipyridamole after surgery, although their compliance rate is unknown. Platelet response to aspirin also shows sex differences in animals and humans. Aspirin reduced the thrombosis rate and mortality of testosterone-treated rats with indwelling aortic cannulae[27] and also reduced thrombosis in male rabbits but not in female rabbits.[28] Hirsch showed a differential effect of aspirin on bleeding time between men and women.[29] The Canadian Cooperative Study of aspirin and sulphinpyrazone in patients with threatened stroke reported a risk reduction in stroke or death of 48% for men but none for women.[30] This evidence suggests that the difference between male and female restenosis rates is real and is probably mediated through their platelet response to endarterectomy.

If the early myointimal hyperplasia is platelet mediated then it may be suppressed by antiplatelet agents that have been used to try to improve patency following vascular operations. Promising results with aspirin and dipyridamole have been reported measuring myointimal thickening in rhesus monkeys,[31] canine coronary artery bypass graft thrombosis,[32] and platelet survival in baboons with Dacron aortic grafts.[33] Early human studies using these agents were equivocal.[34] However, the most convincing results have been reported by Chesebro et al. who showed that antiplatelet drugs improved patency rates of coronary artery bypass grafts when started before the operation.[35] Platelet adherence to collagen and subsequent aggregation is so rapid that administration of the drugs prior to surgery seems necessary. We have initiated a trial of antiplatelet agents started before carotid endarterectomy to ascertain their role in reducing recurrent carotid stenosis.

When early postoperative carotid stenosis occurs it appears to be well tolerated by most patients. The lesion should be monitored by noninvasive methods and in some cases will regress. Should symptoms develop, or the lesion progress to subocclusion, then angiography must be considered. The decision to reoperate will depend on symptoms and risk factors in each individual case. Simple patch angioplasty in the early cases and repeat endarterectomy with patch in the late cases is recommended. Whether the patch material (autogenous vein or prosthesis) is important in preventing continued progression of myointimal reaction is not known.

We conclude that restenosis following carotid endarterectomy occurs in 15% of patients at Scripps Clinic and Research Foundation. Nine per cent of the patients developed restenoses severe enough to be flow limiting and 16% of these required reoperation. These recurrent stenoses usually develop early, within 12 months or sooner, are more common in women and are probably due to platelet-induced myointimal hyperplasia. As a result of the high incidence of restenosis in women, the appropriateness of performing carotid endarterectomy for asymptomatic stenoses in women must be reconsidered.

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