Carotid Artery Stent Restenosis

A challenging problem in patients with previous endarterectomy or radiation.

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Percutaneous carotid artery stenting (CAS) has become increasingly accepted as an alternative to carotid endarterectomy (CEA) in the management of carotid artery stenosis. Much of the initial experience with this procedure has been with patients in high-risk subgroups, including significant medical comorbid conditions, history of previous CEA, and cervical radiation-induced stenosis. Recent clinical trials have revealed that surgical treatment in this group of patients has offered inferior results to CAS.[1] One of the enduring concerns about CAS, however, is the development of restenosis. In-stent restenosis has been reported to occur in 3% to 8% of large published series.[2] However, higher restenosis rates have been reported in patients with a history of prior CEA or cervical radiation. The purpose of this study was to review our experience with CAS to determine the incidence and predictors of restenosis. Our intention was also to identify the patients with the highest incidence of restenosis and to review the therapeutic alternatives and outcomes of these interventions.

PROCEDURES

From January 1996 until February 2004, a total of 279 successful CAS procedures were identified, with at least 6 months of follow-up. The mean duration of follow-up was 17 months. The majority of the patients (63%) were male, with a mean age of 70±11 years (range, 32-92 years). Indications for stenting included *de novo* atherosclerotic lesions in 200 patients, history of cervical radiation in 30 patients, history of ipsilateral CEA in 48 patients, history of

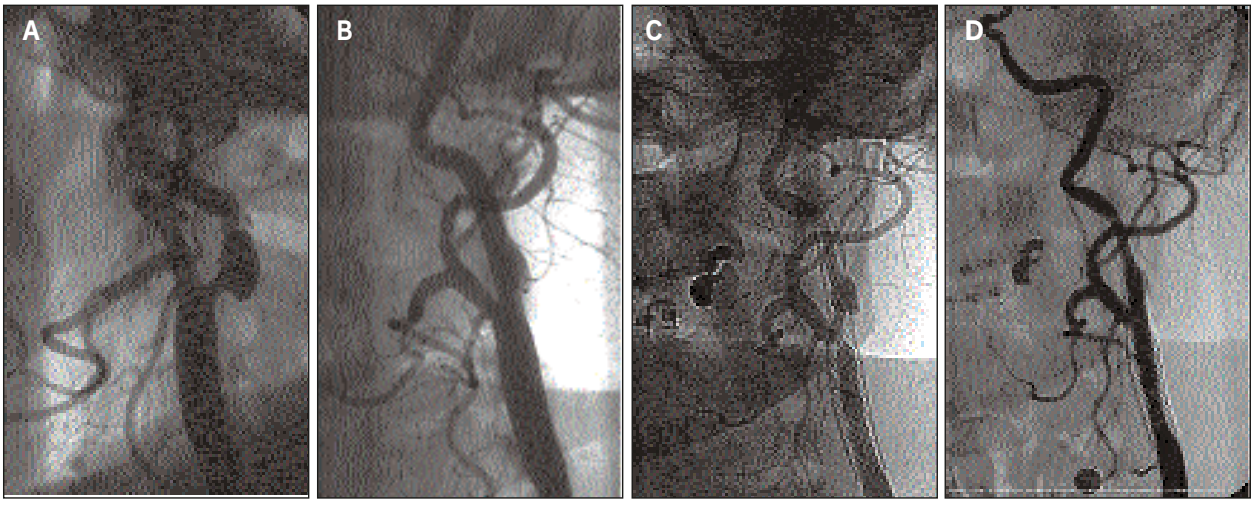

Figure 1. A 61-year-old woman with a history of diabetes, coronary artery disease, hypertension, and hyperlipidemia presented with carotid bruit. Angiography shows 85% ulcerated proximal left internal carotid artery stenosis and a 50% to 60% ostial stenosis (A). After balloon angioplasty and placement of a 10-mm X 31-mm Wallstent and postdilation with a 5-mm X 20-mm balloon (B). One-year follow-up duplex ultrasound revealed evidence of restenosis with increased velocities within the stented area. Angiography confirms that there is at least 80% in-stent stenosis (C). After predilation with a 5-mm X 20-mm Cutting Balloon (Boston Scientific Corporation, Natick, MA) and placement of an 8-mm X 40-mm Precise (Cordis Corporation, a Johnson & Johnson company, Miami, FL) stent. Postdilation was performed with a 5-mm X 40-mm balloon (D).

both ipsilateral CEA and radiation in six patients, and Takayasu arteritis in one patient. The study was initiated prior to the availability of cerebral protection; therefore, 69 patients underwent stenting without cerebral protection, whereas 210 underwent stenting with cerebral protection. Transient ischemic attack or stroke within 48 hours of the procedure occurred in nine of the 69 patients treated without cerebral protection and 19 of the 210 patients treated with cerebral protection.

All patients were enrolled in various Institutional Review Board-approved clinical trials. The patients were accepted into the trials following strict inclusion and exclusion criteria. The severity of carotid artery stenosis was assessed with carotid duplex study and quantitative angiography. Symptomatic patients were required to have ≥60% stenosis, and asymptomatic patients were required to have ≥80% stenosis. All patients were seen prior to and within 24 hours of the procedure by an independent neurologist. Follow-up evaluation was obtained at 1 month, 6 months, and annually thereafter. The follow-up evaluation included a neurological evaluation and duplex study. If the duplex study indicated restenosis, defined as ≥60% stenosis of the stented carotid artery, or if a patient experienced neurological symptoms related to cerebrovascular disease, quantitative carotid angiography was also performed.

RESULTS

Among 279 patients, the overall incidence of restenosis was 4.7% over a 17-month mean follow-up period. Background characteristics of the patient population are listed in Table 1. There was no statistical association between restenosis and the patient's age, presence of hypertension, diabetes, tobacco abuse, renal insufficiency, coronary disease, hyperlipidemia, or peripheral vascular disease. However, there was a significantly higher incidence of restenosis in those patients with a history of ipsilateral CEA or cervical radiation. Among the 48 patients with previous CEA, six (12.5%) had restenosis. Among the 30 patients with previous neck radiation, seven (23%) had restenosis. Of six patients who had both previous CEA and radiation, two (33%) had restenosis. In contrast, among the 200 patients with *de novo* atherosclerotic carotid artery disease, one (0.5%) had restenosis.

Angiographic analysis revealed similar pre- and postprocedure percent stenoses in the restenosis and nonrestenosis cases (Table 2). There was, however, a trend toward smaller reference vessel diameters in the restenosis group (4.1 mm) compared to the nonrestenosis group (5.2 mm), although this did not reach statistical significance due the small number of restenosis cases.

In addition, angiographic analysis revealed slightly smaller reference vessel diameters in postradiation patients compared to those with CEA and *de novo* atherosclerosis (Table 3). The pre- and postprocedure percent stenoses, lesion lengths, and stent diameters were similar.

The majority of patients received a self-expanding Wallstent (Boston Scientific Corporation), Smart (Cordis Corporation), or Precise (Cordis Corporation) stent. There was no significant impact between the type of stent used on the incidence of restenosis for the entire cohort and the subgroup of patients with a history of CEA or radiation (Table 4). There were 12 patients that required placement of

TABLE 1. PATIENT CHARACTERISTICS

	Total (n=279)	Restenosis (n=13)	Nonrestenosis (n=266)	*P* Value
Mean Age	70	62	71	N/A
Male	176 (63%)	6 (46%)	170 (64%)	.11
Hypertension	273 (98.1%)	12 (92.3%)	261 (98.1%)	.23
Diabetes Mellitus	74 (26.5%)	4 (30.7%)	70 (26.3%)	.58
Tobacco	246 (88.1%)	11(84.6%)	235 (88.3%)	.63
Renal Insufficiency	82 (29.4%)	3 (23%)	79 (29.7%)	1.0
CAD	225 (80.6%)	7 (53%)	219 (82.3%)	.025
Hyperlipidemia	268 (96.1%)	11 (84.6%)	257 (96.6%)	.075
Peripheral Vascular Disease	230 (82.4%)	8 (61.5%)	222 (83.3%)	.040
De Novo Atherosclerosis	200	1 (0.7%)	199 (74%)	N/A
Previous XRT	30	7 (54%)	23 (8%)	<.0001
Previous CEA	48	6 (46%)	42 (16%)	.01
Previous CEA + XRT	6	2 (15.3%)	4 (1.5%)	.017

TABLE 2. ANGIOGRAPHIC FEATURES IN PATIENTS WITH AND WITHOUT RESTENOSIS

	Restenosis (n=13)	Nonrestenosis (n=266)	Total (n=279)
Pre %	88%	83%	84%
Post %	3%	6%	6%
Reference Vessel Diameter (mm)	4.1	5.2	5.2
Lesion Length (mm)	18.5	20.8	20.7

TABLE 3. LESION CHARACTERISTICS: *DE NOVO*, RADIATION, AND CEA PATIENTS

	Radiation (n=30)	CEA (n=48)	Atherosclerosis (n=200)	Total (n=278)
Pre %	80%	86%	83%	84%
Post %	7.5%	4.4%	6.3%	6.1%
Reference Vessel Diameter (mm)	4.9	5.2	5.2	5.2
Lesion Length (mm)	19.8	20	20.8	20.7
Stent Diameter (mm)	8.1	7.5	7.9	7.8

two stents in the same artery. Of these, one patient had restenosis in both stents (common carotid and internal carotid).

Notably, seven of 13 (54%) restenoses occurred among the first 58 patients (12%) treated at our institution with CAS. There were only six restenosis cases among the following 221 patients (2.7%), suggesting that the learning curve of the operators and/or the refinement in procedural equipment and techniques may portend an even lower restenosis rate in future analyses.

PRESENTATION AND TREATMENT OF RESTENOSIS

Of the 13 patients with restenosis, three presented with neurological symptoms, and the remaining 10 were detected on a routine follow-up evaluation by carotid duplex study. The mean time to restenosis was 25 months (range, 5-90 months). Treatment of restenosis included balloon angioplasty in three (Figure 1); five were restented; two are awaiting treatment; and two remain asymptomatic and totally occluded.

DISCUSSION

The surgical literature suggests that patients with a history of CEA or cervical neck irradiation are at risk for accelerated carotid stenosis.[3,4] Postendarterectomy restenosis is generally attributed to myointimal hyperplasia from collagenous proliferation of the medial layer of the arterial wall during the early postoperative period (within 36 months) and recurrent atherosclerosis thereafter. Although the incidence of restenosis averages 6% (range, 0%-37%), the risk of restenosis is highest in the first few years after endarterectomy, and much lower thereafter. Risk factors for restenosis after endarterectomy include age <65 years, hypertension, hyperlipidemia, smoking, and female gender.[5,6] "Redo" carotid surgery for recurrent stenosis is technically challenging and carries an increased risk of cranial nerve palsies over surgery for primary disease. Cranial nerve injury rates as high as 10% have been reported.[7] Accordingly, CAS has been suggested as an alternative in this subset of patients. We performed stenting on 48 post-CEA arteries with technical success, but subsequent restenosis has occurred in six patients.

The incidence of stenotic carotid artery lesions in patients who receive neck radiation has been reported to be as high as 30%.[8,9] Radiation-induced carotid disease is often extensive and may involve long segments of the common and internal carotid arteries. Histologically, these lesions have been associated with destruction of the internal elastic lamina and replacement of the normal intima and media with fibrous tissue. This is accompanied by severe fibrosis and atrophy of the cutaneous tissues overlying the stenotic segment. Surgical treatment in this setting is difficult because of radiation-induced arterial, periarterial, and cutaneous sclerosis. In addition to increased risk of cranial nerve palsies, there is increased risk of poor cutaneous healing, anastomotic rupture, and arterial infection. Accordingly, CAS is preferred in postradiation stenosis as well. We performed stenting in 30 post-CEA arteries, with subsequent restenosis in seven of these patients.

Our review suggests that because myointimal hyperplasia with smooth muscle cell proliferation is the predominant mechanism leading to in-stent restenosis, stent deployment in a pre-existent hyperplastic (post-CEA) or fibrotic (postradiation) process may be associated with a higher incidence of in-stent restenosis than after CAS for *de novo* atherosclerotic disease. Perhaps the application of drug-eluting stents in the future may help attenuate the existing hyperplastic or fibrotic response and decrease the incidence of restenosis in this subgroup. Alternatively, because carotid lesions in the post-CEA or postradiation setting are typically more

TABLE 4. STENT TYPES DEPLOYED BETWEEN THE THREE GROUPS OF PATIENTS

	Wallstent	Precise Stent	Smart Stent
CEA or Radiation Patients	25	35	11
Restenosis Occurrence	3 (12%)	4 (11%)	3 (27%)
P Value	.371	.275	.111
Total Cohort	83	166	24
Restenosis	6 (7%)	4 (2%)	3 (13%)
P Value	.115	.015	.045

resilient to angioplasty and may require higher balloon inflation pressures to achieve a satisfactory angiographic result, perhaps the use of more aggressive dilatation technique or oversized stents in these patients would increase poststenting luminal diameter and affect the incidence of restenosis.

The optimal management strategy for carotid stent restenosis is not well defined. Operative management may be technically challenging due to the presence and position of the carotid stent, which may make distal exposure quite difficult. Also, operative reconstruction of a previously stented carotid artery is more complex than primary endarterectomy. Still, initial success has been reported with both endartectomy[10] and carotid artery bypass.[11] This study confirms previous observations that carotid stent restenosis can be treated safely with further percutaneous interventions.

SUMMARY

This was a retrospective, noncontrolled, single-center experience in CAS and may not reflect the experience of all centers. The study was initiated before the advent of supraaortic equipment and techniques, particularly with regard to cerebral protection devices. In addition, this study is limited by a small number of patients in the restenosis subgroup. Clearly, larger studies are needed to more conclusively evaluate factors that are predictive of carotid stent restenosis as well as to determine whether different stent designs, stent sizes, or deployment techniques might affect the incidence of restenosis in post-CEA and postradiation patients. Until more clinical data are available regarding restenosis in this high-risk subgroup, closer surveillance is required. ■

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