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Carotid endarterectomy in heart transplant patients

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Aim. **The aim of this study was to determine the clinical outcome of carotid endarterectomy in heart transplant recipients and morphologic features of atherosclerotic plaques removed during operation.**

Methods. **Between April 1993 and October 2001 5 heart transplant patients with symptomatic carotid stenosis >70% underwent carotid endarterectomy with regional anesthesia, including a staged bilateral procedure in one patient. Cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol were evaluated in each patient. The plaques (n=6) underwent histologic analysis after carotid endarterectomy. Carotid artery duplex imaging was added to the routine postoperative evaluation.**

Results. **Carotid plaques resulted to be echolucent on B-mode ultrasound examination. Cholesterol, triglycerides and LDL-cholesterol levels were found to be increased, while HDL-cholesterol were decreased. All patients underwent successful carotid endarterectomy; there were no perioperative deaths, major neurologic or cardiac events. The mean lenght of stay was 2.2 days. The mean follow-up was 44 months. In 1 case, an asymptomatic restenosis >50% occurred 9 months later and, in 2 other cases, a contralateral mild stenosis was found 12 and 36 months later. One patient had a progressive contralateral stenosis, requiring operation 18 months later. High lipid content and heterogenous cellular infiltration were observed, including macrophages, T-lymphocytes, neutrophils, and also eosinophils in the rapidly progressing plaque.**

Conclusion. **Heart transplant patients receiving immunosuppression may successfully undergo carotid endarterectomy, without increased risk, but progression of atherosclerotic disease in the carotid arteries seems to continue, despite lipid-lowering regimen and antiplatelet therapy.**

KEY WORDS: Atherosclerosis - Carotid stenosis - Heart transplantation - Endarterectomy, carotid - Treatment outcome.

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Interventions for aneurysmal [1-3] or peripheral arterial occlusive disease (PAD) [4] are being increasingly performed in long-term survivors of cardiac transplantation.

Immunosuppression [5] and coexistent risk factors have been implicated in development of progressive atherosclerotic coronary artery disease (CAD) [6] and PAD, affecting 10% of heart transplant recipients within 3 years of transplantation.[7]

Notwithstanding the number of survivors of cardiac transplantation continues to increase, carotid endarterectomy (CEA) has been reported infrequently;[7-9] at present, no studies have been focused on safety and long-term outcome of the procedure in such patients.

We describe a group of heart transplant patients undergoing CEA for symptomatic lipid-rich plaques.

Materials and methods

The records of heart-transplant recipients undergoing CEA at our institution between April 1993 and October 2001 were reviewed.

Indication for transplantation and risk factors for atherosclerosis before and after transplantation were also evaluated.

The risk factors that were recorded included age, gender, hypertension, diabetes, hyperlipidemia, and smoking habits.

Triple-drug immunosuppressive treatment consisted of prednisone, azathioprine and cyclosporin; in addition, antihypertensive and antiplatelet drugs, and statins were commonly used.

All patients had previous ipsilateral hemispheric neurologic symptoms.

Real-time B-mode imaging, with a pulsed-wave Doppler with a 7.5 MHz probe (Advanced Technology Laboratories, Inc, Bothell, Wash, USA) was performed in all cases to identify the grade of stenosis according to the North American Symptomatic Carotid Endarterectomy Trial Collaborators [10] and the characteristics of the plaques.

Plasma cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol were determined by use of enzymatic tests (Boehringer Mannheim, Mannheim, Germany).

All patients underwent cardiologic evaluation, including physical examination, resting ECG and two-dimensional echocardiography Doppler imaging examination on admission.

Conventional CEA technique was performed under regional anesthesia, using intravenous heparin (3500 U) before carotid cross clamping, with repeated neurologic evaluation during the entire procedure.

Immunosuppressive and lipid-lowering regimen was continued and patients received antiplatelet therapy (acetylsalicylic acid 150 mg/day) within 24 hours after surgery.

Carotid artery plaques removed during endarterectomy were analyzed for plaque composition. Fresh specimens were placed in normal saline solution and then fixed in 10% neutral buffered formaldehyde solution for 24 hours.

Specimens were examined macroscopically and cross sections were obtained.

Paraffin 5 mm tick blocks were prepared; successive 4 µm sections from each block were stained with hematoxylin and eosin (HE) and immunostained with monoclonal antibody to inflammatory populations CD4 T-helper (NCL CD4 - 368 , Novocastra, Milan, Italy) and CD8 T-cytotoxic/suppressor (M 710301, Dako, Copenhagen, Denmark). Secondary antibody staining was performed using an avidin-biotin peroxidase complex (Dako) and visualized with diaminobenzidine.

Control carotid duplex scans were performed at 3-month intervals for the first year after surgery and then every 6 months thereafter.

TABLE I.—*Patients characteristics.*

	Pre-transplant	Pre-CEA
Age (y)	55.6	58.8
Current smokers (n)	2	0
Hypertension (n)	2	5
Diabetes (n)	2	4
Plasma cholesterol (mg/dL)	226±12	332±48
Plasma triglycerides (mg/dL)	198±17	448±74
HDL cholesterol (mg/dL)	49±3	32±6
LDL cholesterol (mg/dL)	128±7	186±34

Results

Five heart-transplant patients who underwent CEA were identified during the 8-year period. The patients (2 male and 3 female) had a mean age of 55.6 years (range, 47 to 65 years) (Table I).

Indications for transplantation included ischemic heart disease (3 patients) or idiopathic cardiomyopathy (1 patient), and valvular disease in 1 patient (Table II).

No patient had a pretransplant history of extracranial cerebrovascular disease, and 2 patients had a documented *Cytomegalovirus* infection in post-transplant period.

The patients had a transient hemispheric neurologic deficit (transient ischemic attack [TIA]; n = 3), *amaurosis fugax* (n = 1) or a minor stroke (n = 1).

Carotid stenoses were detected by duplex examination at a mean of 39 months after transplantation (range, 23 to 56 months); all patients had stenoses of the internal carotid artery > 70 %; the lesions were represented by echolucent plaques (Figure 1).

Patients had a significant increase in both cholesterol (332±48 mg/dL) and triglycerides (448±74 mg/dL) levels after transplantation; it was also found an elevation in LDL-cholesterol (186± 34 mg/dL), and a reduction in HDL-cholesterol levels (32 ± 6 mg/dL) (Table I).

A primary closure of the CEA was performed in 1 patient; a CEA with patch closure (CEAP) with bovine pericardium patch angioplasty (Vascu-Guard, Bio-Vascular Inc, Saint Paul, Minn, USA) was used in 4 patients.

No temporary shunt for clamp-induced ischemia was placed during operation, and there was conversion to general anesthesia in none. The patients were observed in the postanesthesia care unit until hemodynamic stability could be ensured. Routine continu-

TABLE II.—*CEA in patients with heart transplants.*

Age (years)/ sex	Heart transplantation on indication	Timing of operation (after heart transplantation) (months)	Symptoms	Procedure	Complication	Outcome
47/F	Valvular heart disease	56	TIA	CEAP	None	67 months, no carotid stenosis
53/M	Ischemic cardiomiopathy	31	Minor stroke	CEAP	Transient superior laryngeal nerve injury	12 months, contralateral mild stenosis
65/F	Idiopathic cardiomiopathy	47	*Amaurosis fugax*	CEA, primary closure	None	9 months, asymptomatic restenosis >50%
58/M	Ischemic cardiomiopathy	38	TIA	CEAP	None	18 months, symptomatic contralateral stenosis >80%; CEAP
55/F	Ischemic cardiomiopathy	23	TIA	CEAP	None	36 months, contralateral mild stenosis

TIA: transient ischemic attack; CEAP, carotid endarterectomy with patch closure

ous cardiac monitoring was maintained on the initial postoperative night.

No perioperative deaths, major neurologic or cardiac events occurred. Discharge on the 2nd postoperative day was the routine; only 1 patient who presented a transient superior laryngeal nerve palsy was observed for an additional day (mean length of stay: 2.2 days).

The mean follow-up time since CEA/CEAP was 44 months (range, 15 to 67 months). One patient (#3) had restenosis > 50% 9 months after surgery, and remained without symptoms.

Another patient (#4) who had rapid progression of contralateral moderate stenosis (from 50% to 80%), with a new TIA, underwent successful contralateral CEAP 18 months after the initial operation.

Two patients, who had not a contralateral stenosis at the time of the initial CEA, were found to have an asymptomatic mild stenosis (≤ 40%) 12 and 36 months later.

Pathologic findings

Histological features were consistent with atherosclerotic unstable plaques with dense inflammatory cellular infiltration, consisting predominantly of macrophages and, to a lesser extent, T-lymphocytes, neutrophils, and high lipid content. A marked foam cell accumulation, with presence of neutrophils and eosinophils, was found in the plaque removed from the patient (# 4) who developed indication for contralateral CEAP 18 months after the first procedure (Figure 2A, 2B).

Discussion

Improvements in the survival of patients with cardiac transplantation have been associated with increase in other atherosclerotic manifestations, including abdominal aortic aneurysm (AAA) [1-3] and PAD.[4, 7-9]

Most patients necessitating heart transplantation, particularly for ischemic cardiomyopathy, also have risk factors for atherosclerotic disease, worsening as the age increases.

Long-term immunosuppressive regimen of prednisone, cyclosporine and azathioprine can initiate or exacerbate hypertension,[5] diabetes, hypercholesterolemia [11] and hypertriglyceridemia, and promote the development and rapid progression of atherosclerosis, also in patients with transplants for non atherosclerotic cardiomyopathies [8] (2 in our series).

According to the frequent coexistence of CAD and PAD [1] or AAA,[13] carotid artery stenosis also is observed in heart transplant patients; despite these observations, only 8 cases treated with CEA have been reported,[7-9] with no significant differences in the tissue composition of excised plaques from patients who had not undergone transplants.

Echolucent lipid- and macrophage-rich plaques were found in all our patients, who were symptomatic and had increased both plasma cholesterol and triglycerides levels.

This is in accordance with findings of association of hypercholesterolemia and more commonly hypertriglyceridemia, particularly in women,[14] with high lipid and macrophage [15] content, plaque echolucency on B-mode ultrasonography and plaque instability. In addition, hypertension and decreased HDL-cholesterol correlate with a higher risk for worsening carotid stenosis over time.[16]

Of interest is our observation of high lipid accumulation and polymorphic inflammatory cell infiltration, consisting in macrophages, T-lymphocytes, neutrophils and eosinophils in the carotid plaque rapidly evolving in patient 4.

Eosinophil infiltration may be hypothesized, in our opinion, to be expression of an immunologic aberration due to immunosuppressive treatment.

All of our patients had unstable carotid plaques with a poor indication for angioplasty and stenting [17] and, therefore, underwent CEA with regional anesthesia, with no need of an indwelling shunt and without adverse cardiac events.

The choice of anesthetic technique was determined according to the potential advantages including reduction in hemodynamic instability [18, 19] during and after surgery, with less frequently intensive care unit admission and shorter hospitalization than general anesthesia.

Based on our experience, we believe that regional anesthesia is the most appropriate type of anesthesia for heart transplant recipients undergoing CEA, in whom the denervated state causes an altered hemodynamic response to surgical stress.

Furthermore, drug therapy can be administered immediately after surgery at preoperative dosages and intervals.

To prevent severe hypertension and hyperlipidemia following heart transplantation, a program of diet and exercise, antihypertensive therapy, and administration of lipid-lowering drugs [20] is indicated; moreover, long-term treatment with statins,[21] as well as aspirin,[22] has been reported to reduce cardiovascular risk, lowering C-reactive protein and macrophage density, independently from plasma lipid concentrations.

Carotid plaques developed and progressed rapidly in our patients although they were undergoing this therapy.

Our study pointed out that heart transplant patients affected with atherosclerotic carotid lesions have a more aggressive disease.

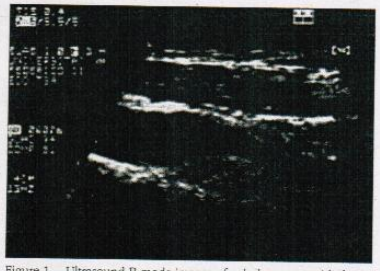

Figure 1.—Ultrasound B-mode images of echolucent carotid plaque with luminal narrowing greater than 80%.

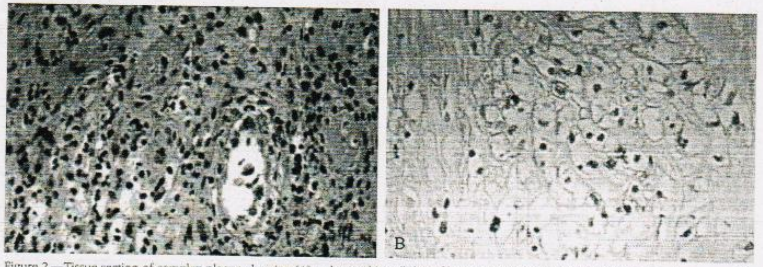

Figure 2.—Tissue section of complex plaque showing (A) polymorphic cellular infiltration, including macrophages, lymphocytes, neutrophils and eosinophils (HE, 400 ×) and (B) dense large extracellular lipid content, foam cell accumulation and T-lymphocytes (CD8, 400 ×).

This seems to be due to a higher prevalence of risk factors and to immunosuppression, and perhaps, also to an increment in the incidence of *Cytomegalovirus* infections,[23] that had occurred in two patients of ours after transplantation.

Altough this series is too small to make any statistically valid correlation, our data seem to demonstrate that CEA can be performed in this patient population safely and with favorable results, with no increase of the surgical risk, but 80% of our patients tend to have a progressive or recurrent carotid disease within 3 years.

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