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Revascularization procedures in patients with transplant coronary artery disease[1]

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Abstract

Objective: To assess the efficacy of revascularization in cardiac transplant patients who developed de novo coronary artery disease. **Methods:** Eighteen patients underwent one or more of four methods of revascularization: percutaneous transluminal coronary angioplasty (PTCA), percutaneous transluminal coronary rotational atherectomy (PTCRA), coronary artery bypass grafting (CABG), and transmyocardial laser revacularization (TMLR). Eleven PTCA procedures were performed in 10 patients 55.3 ± 6.6 months after transplantation. Six patients underwent PTCRA 83.3 ± 11.2 months after transplantation. Five patients underwent CABG 54.0 ± 12.6 months after transplantation; the mean left ventricular ejection fraction was 49.6 ± 16.9 (20–65%); hypertrophy was present in two of these patients. One patient with distal coronary artery disease and New York Heart Association class IV symptoms underwent TMLR only. One patient underwent both CABG and TMLR because of triple vessel proximal disease, diffuse distal disease, and New York Heart Association class IV symptoms. **Results:** PTCA was successful in 10 procedures with decrease in mean stenosis from 87.7 ± 2.7 to 24.3 ± 6.0%. Follow-up, at 16.9 ± 4.0 months, showed restenosis in two patients. PTCRA was successful in all patients with a decrease in mean stenosis from 83.4 ± 4.4 to 11.7 ± 1.9%. Short-term follow-up did not reveal reocclusion. Two CABG patients who had hypertrophy died of heart failure 2 and 9 days after their operations. One CABG patient with excellent cardiac function died after 15 days because of pulmonary failure. In one patient, left ventricular ejection fraction improved from 35 to 50%, and he is alive 64 months later. Six months after TMLR, the New York Heart Association class in one patient improved from IV to II, and his left ventricular ejection fraction improved from 29 to 42%. The ejection fraction in the patient who underwent both CABG and TMLR improved from 20 to 56%, but the patient expired 7 weeks later. **Conclusions:** It appears that revascularization procedures can be effective in patients with coronary artery disease after cardiac transplantation and that coronary angioplasty or atherectomy would be a therapy of choice for single proximal lesions. CABG should be used cautiously and only reserved for patients with multi-vessel disease without hypertrophy. Laser revascularization with or without bypass grafting has potential to become the therapy of choice for transplant coronary artery disease. © 1997 Elsevier Science B.V.

Keywords: Angioplasty; Atherectomy; Balloon; Coronary artery bypass grafting; Heart transplantation

1. Introduction

Survival of patients with end-stage cardiac disease who undergo cardiac transplantation is significantly better today than in the early period of transplanta-

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tion. During the first postoperative year, early mortality occurs because of acute rejection, acute allograft failure or infectious complications. However, the early mortality rate has declined substantially with improved immunosuppressive protocols and postoperative management. Accelerated coronary artery vasculopathy appears to be the leading cause of patient death in heart transplant patients who survive the first postoperative year [3,14,16,20]. Currently, the pathophysiology of this rapidly progressive cardiac allograft atherosclerosis remains undefined, and it appears to have several causes. There is no known medical therapy to prevent, curtail, or reverse allograft vasculopathy; the only available therapy is retransplantation, and it is suitable for only a few candidates. However, with an ever growing list of patients waiting for transplantation, a small donor pool, and shortened allograft survival following retransplantation [9], alternative therapies must be considered to reduce long-term mortality and hence prolong survival. Coronary angiographic findings in transplant allograft vasculopathy are a mixture of both typical atherosclerotic disease and features consisting of diffuse concentric narrowing with distal vessel narrowing [7]. Conventional therapy with percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery to reduce morbidity and mortality in these patients is not widely practiced because of the nature of the coronary vascular disease. At our institution, several patients have undergone various revascularization procedures, including percutaneous transluminal coronary angioplasty (PTCA), percutaneous transluminal coronary rotational atherectomy (PTCRA), coronary artery bypass graft (CABG) surgery, with and without transmyocardial laser revascularization (TMLR), and TMLR only. We reviewed our experience to assess the efficacy of revascularization in cardiac transplant patients who developed de novo coronary artery disease (CAD).

2. Subjects and methods

2.1. Patient population

More than 575 cardiac transplant procedures have been performed at our institution. We reviewed and compiled data from the records of all patients who have had revascularization procedures for allograft vasculopathy after cardiac transplantation. The pertinent data collected for each patient included clinical history, primary indication for undergoing a revascularization procedure, angiographic profile, procedural results, and follow-up.

A total of 18 patients underwent one or more of four types of revascularization. Some patients had to repeat the same type of revascularization or had to have a second, different type of revascularization; each procedure was considered a separate treatment. In the PTCA group, 10 patients underwent 11 separate procedures; in the PTCRA group, six patients underwent six procedures; in the CABG group, five patients underwent five procedures; and in the TMLR group, one patient underwent one procedure. In the CABG group, one patient had simultaneous TMLR at the time of the CABG surgery. Maintenance immunosuppression in all patients included cyclosporine and steroid-based pharmacotherapy, with and without azathioprine, as chronic prophylaxis for rejection.

2.2. Statistical analysis

The mean values and standard errors of the means were calculated for group values and reported as mean $\pm$ S.E.M.

3. Results

3.1. Clinical profile

Demographic characteristics for the combined patient population are given in Table 1, and their clinical profile is given in Table 2. Revascularization was indicated in four patients by the presence of congestive heart failure and symptoms of dyspnea and fatigue, in 10 patients by angiographic evidence of CAD on routine follow-up angiograms, and in four patients by a left ventricular ejection fraction of less than 40%. All patients had right heart catheterization including an endomyocardial biopsy before their revascularization procedure, and no episode of acute rejection was evident.

Table 1
Demographic profile of the combined patient population undergoing revascularization procedures

Sex (*n*)	
Male	16
Female	2
Mean patient age (range) (years)	51.3 $\pm$ 3.1 (45–63)
Type of cardiac disease (*n*)	
Idiopathic	7
Ischemic	11
Mean donor age (range) (years)	24.5 $\pm$ 2.5 (15–46)

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Table 2
Clinical profile of patients undergoing revascularization procedures

Variable	Treatment group (%)				
	All groups ($n = 18$)	PTCA ($n = 10$)	PTCRA ($n = 6$)	CABG[a] ($n = 5$)	TMLR ($n = 1$)
Angina	11	10	0	0	0
Myocardial infarction	22	10	0	40	100
Hypertension	100	100	100	100	100
Hyperlipidemia	44.4	50	50	40	0
Obesity	67	90	67	20	0
Diabetes	27.8	20	50	40	0
Renal dysfunction[b]	39	40	17	40	0

PTCA, percutaneous transluminal coronary angioplasty; PTCRA, percutaneous transluminal coronary rotational atherectomy; CABG, coronary artery bypass graft surgery; TMLR, transmyocardial laser revascularization.
[a] Four patients in this group had previously undergone PTCA.
[b] Indicated by a baseline serum creatinine concentration of at least 2.0 mg/dl.

3.2. PTCA and PTCRA groups

The PTCA group ($n = 10$) had a mean age of 52.4 ± 1.6 months (range 45–61 years). The PTCRA group ($n = 6$) had a mean age of 56.5 ± 3.3 months (range 47–63 years). The angiographic locations of the 23 lesions (14 for the PTCA group, nine for the PTCRA group) are shown in Table 3. In a majority of these patients, one- or two-vessel atherosclerosis and discrete proximal lesions were common. The mean number of vessels dilated per procedure was 1.2 in the PTCA group and 1.3 in the PTCRA group. Two patients in each group had two vessels dilated per procedure. All lesions in the PTCRA group and all but one lesion in the PTCA group were successfully dilated, success defined as 50% or greater improvement in luminal diameter. PTCA failed in the one patient because of the inability to cross a totally occluded lesion.

The outcomes of PTCA and PTCRA procedures are summarized in Table 4. In the PTCA group, the mean pre-PTCA stenosis was reduced by more than 60% after the procedure. Similarly, in the PTCRA group, the mean pre-PTCRA stenosis was reduced by more than 70%. No patient suffered any long-term adverse consequences; renal function returned to baseline in all patients. Late follow-up for the PTCA group was available for only six patients for

Table 3
Angiographic profile of the patients in the PTCA and PTCRA groups

	PTCA ($n = 10$)	PTCRA ($n = 6$)
No. of diseased vessels		
1	3	2
2	4	2
3	1	2
Multiple	2	0
Lesion location		
LAD	8	2
RCA	4	1
CX	1	4
OM	0	1
Ramus	1	1
Site of lesion		
Proximal	8	8
Mid	1	1
Distal	5	0
Nature of atherosclerosis		
Discrete disease	7	3
Discrete and diffuse disease	3	0

LAD, left anterior descending coronary artery; RCA, right coronary artery; CX, circumflex coronary artery; OM, obtuse marginal artery.

Table 4
Outcome of percutaneous transluminal revascularization procedures

	PTCA ($n = 10$)	PTCRA ($n = 6$)
No. of lesions treated successfully	13 (92%)	6 (100%)
Luminal diameter of stenosis (%)		
Pre-procedure		
Range	70–100	60–99
Mean	87.7 ± 2.7	83.4 ± 4.4
Post-procedure		
Range	10–100	0–20
Mean	24.3 ± 6.0	11.7 ± 1.9
Reduction		
Range	0–90	45–97
Mean	63.4 ± 5.7	71.8 ± 5.2
Complications		
No. of patients	2	1
Groin hematoma	1	0
Acute renal failure	1	2
Pneumonia	1	0
Mean no. of days in hospital	4.4 ± 1.0	3.0 ± 0.9

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Table 5
Follow-up for patients who underwent percutaneous transluminal revascularization procedures

	PTCA ($n=10$)	PTCRA ($n=6$)
Follow-up angiography		
No. of patients	6	3
No. of lesions	9	3
Months post-intervention		
Range	6–36	1–6
Mean	16.9 ± 4.0	3.0 ± 1.5
Restenosis (>50% increase in stenosis)		
No. of patients	2	0
Increased stenosis (%)		
Range	0–75	0–10
Mean	22.8 ± 9.1	—
Ejection fraction (%)		
Pre-procedure	50 ± 2.0	—
Post-procedure	51 ± 2.6	—

a mean duration of 16.9 ± 4.0 months after intervention, and restenosis, defined as 50% or greater increase in luminal stenosis, occurred in two patients 10 and 15 months later (Table 5). One patient successfully underwent a repeat PTCA procedure without complications, and late follow-up at 8 months showed no restenosis. The second patient underwent CABG surgery several months later. For the PTCA group, the overall mean increase in luminal stenosis was $22.8 \pm 9.1\%$ (range: 0–75%) (Table 5). The left ventricular function determined by ejection fraction remained unchanged for the patients in the PTCA group during the revascularization procedure (Table 5).

3.3. CABG group

Five patients underwent CABG surgery, and one patient had TMLR at the same time. Four patients were symptomatic and classified as New York Heart Association (NYHA) status II or more, and one patient had nearly complete occlusive disease of the left main coronary (LMC) artery, although he was asymptomatic and in NYHA class I. Angiographic studies in all five patients showed atherosclerotic disease involving all three major vessels, including LMC artery disease in two patients. Three patients had additional disease involving major branches, and diffuse distal disease was most common in the CABG group. The mean time from transplantation to angiographic evidence of CAD was 21.8 ± 7.2 months (range: 10–50 months). The mean time to revascularization following cardiac transplantation was 54.0 ± 12.6 months (range: 24–89 months). The mean time to revascularization surgery following initial evidence of CAD was 31.8 ± 8.9 months (range: 6–52 months). All patients underwent bypass surgery with saphenous vein grafts. Two patients with CABG and significant hypertrophy required perioperative mechanical assistance; these patients died of heart failure 2 and 9 days, respectively, after the operative procedure. One patient with excellent cardiac function and an ejection fraction of 70% died of pulmonary failure after 15 days. CABG surgery improved cardiac function in one patient with hypertrophy and severe left ventricular dysfunction: ejection fraction increased from 20 to 56%. However, the patient died due to mediastinitis and sepsis after 50 days. In one patient, the ejection fraction improved from 35 to 50%, and he is alive after 64 months. Long-term follow-up at 60 months revealed all grafts to be patent. All grafts were patent in three patients who were autopsied. The complications encountered in this group included acute renal failure in one patient, cerebrovascular accident in one patient, infection in one patient, and multiple organ failure in three patients.

3.4. TMLR group

One patient with NYHA class IV symptoms, anteroapical ischemia on thallium stress test, and a post-infarction left ventricular ejection fraction of 29% underwent TMLR for severe multi-vessel and diffuse distal disease. No post-operative complications occurred and he was discharged following 7 days of hospitalization. After 6 months, he had improved clinically to NYHA class II and is doing well clinically 8 months later. His left ventricular ejection fraction improved to 42%.

4. Discussion

Allograft coronary artery vasculopathy continues to be a major cause of death in cardiac transplant patients after the first postoperative year [3,14–16,20]. The incidence of allograft CAD as determined by angiographic and autopsy studies is between 1 and 18% at 1 year and 40 and 50% at 5 years [2,13,17]. Currently, the pathophysiology of this rapidly progressive disease remains undefined. In most cardiac transplantation recipients, the denervation of the afferent cardiac nervous system prevents the appearance of the classic symptoms of ischemia. Clinical manifestations of transplant CAD include symptoms of congestive heart failure, ventricular arrhythmias, sudden cardiac death, and silent my-

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ocardial infarction [8]. Rarely, some patients may demonstrate typical angina pectoris [19].

Medical management to prevent or retard atherosclerosis in cardiac allografts by use of immunosuppressive modulation, antiplatelet agents, antihyperlipidemic agents, or antihypertensive agents has been ineffective [21]. Cardiac retransplantation was the only alternative until recently for patients who would otherwise have died [7,9,20]. However, cardiac retransplantation is an option only for a selected few patients, and alternative therapies must be considered to prolong patient survival.

Use of conventional therapy with PTCA and CABG has been reported in the literature [1,4–6,10,11,21,22]. These techniques, however, are not used routinely because of the nature of the coronary vasculopathy in cardiac allografts. Coronary atherosclerosis in heart transplant recipients demonstrates unique features of typical discrete obstructive stenoses, similar to atheromatous disease found in non-transplant patients, and in most cardiac allograft vasculopathy, there is diffuse concentric distal vessel obliterative disease without collateral vessel development to affected vessels [7].

Because the rate of progression of CAD in individual transplant patients is difficult to predict, it is unclear when the intervention should be undertaken. The decision when to intervene is often unclear, even when a patient presents with clear evidence, both clinical and objective, demonstrating ischemia and concurrent findings of CAD on angiogram. The role of revascularization procedure in this population is especially unclear for the asymptomatic group. The lack of long-term follow-up data makes it impossible to evaluate the impact of revascularization procedures on preventing sudden cardiac death or progressive heart failure.

PTCA after cardiac transplantation can be successfully applied in suitable patients on the basis of coronary angiographic findings as demonstrated in our study and those reported by Vetrovec et al. [21] and Halle et al. [10]. The low complication rate in our study is comparable to that in routine angioplasty [18] and in reports of its application in transplant patients [10,21]. The results of these studies support the safety and efficacy of this technique in suitable transplant patients with discrete proximal lesions of the major coronary vessels or branch coronary disease, and PTCA may reduce morbidity and mortality in patients with ischemic cardiac dysfunction. PTCRA in the limited number of patients in our study was successful; it had a low incidence of complication not related to the technique.

CABG surgery has been successfully performed in cardiac transplant patients as reported by Copeland et al. [4] and Frazier et al. [5]. As demonstrated in our experience with a limited number of patients, CABG surgery can improve cardiac function significantly in suitable candidates who have myocardial ischemia not amenable to non-surgical revascularization therapy, progressively worsening symptoms, and left ventricular dysfunction.

Patients at high risk for morbidity and mortality, namely those with diffuse distal disease and severe left ventricular hypertrophy, may benefit from CABG and TMLR or possibly TMLR only based on the angiographic findings. Coronary artery vasculopathy in transplant patients invariably involves intramyocardial vessels, and TMLR would appear to offer a viable adjunct or alternative therapy to improve myocardial perfusion [12].

The limitations of our study include the fact that it is a retrospective non-randomized analysis, only a small number of patients were available for the study, and long-term follow-up was incomplete for 11 patients. The impact on survival is difficult to assess because of the limited number of patients and incomplete clinical and angiographic follow-up for some of the patients.

In conclusion, it appears that revascularization procedures in cardiac transplant patients for progressive allograft vasculopathy can be effective. Non-surgical intervention with PTCA and PTCRA would most likely benefit patients with discrete lesions. CABG surgery should be used cautiously and only reserved for patients whose disease involves multiple vessels and who do not have severe hypertrophy. TMLR, with or without CABG surgery, has the potential to become an important therapeutic alternative for transplant CAD.

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Appendix A. Conference discussion

Dr M. Yacoub (*London, UK*): I would like to ask you two questions. One is related to what you have just said, and that is, what were the indications for revascularization? Were they symptoms, deterioration in ventricular function, or just the presence of the disease?

Dr B. Radovancevic: As I showed on one slide, four patients had symptoms, either angina or shortness of breath, and additional decreases in ejection fraction; these were motivating factors. So in eight patients, there were some objective reasons to hope that there would be an improvement. In 10 patients, angiographic findings indicated revascularization. Coronary surgery was indicated for two patients by angiograms that showed left main lesions. Both of these patients died. I am now following two other patients who have 90% left main lesions on whom we did not operate. We have been following them for more than a year, and they are still alive.

Dr M. Yacoub: Do you think a randomized trial would be warranted, particularly when you start using TMLR?

Dr B. Radovancevic: Yes, absolutely, because the prospect of a natural survival with the disease is pretty good, as you have shown in your paper in Nice.

The other interesting finding was that we did serial PET scans in these patients with coronary disease to identify candidates for TMLR, and surprisingly, there were patients who had severe disease with totally normal PET scans. There was no hibernating myocardium. There is no animal data to show that TMLR will be successful in that type of situation when you do not have a hibernating myocardium.

Dr M. Yacoub: What indices did you use in your PET scanning?

Dr B. Radovancevic: There was both perfusion and viability with—

Dr M. Yacoub: Deoxyglucose and water?

Dr B. Radovancevic: Deoxyglucose, yes, both. One more thing, there was one patient that had a hibernating myocardium and a year later had a severe hibernating myocardium with an EF of 25%; a year later, his EF went to 45% with no therapy and the PET scan significantly improved.

Dr M. Yacoub: With no therapy?

Dr B. Radovancevic: No therapy.

Dr S. Large (*Cambridge, UK*): I enjoyed your presentation enormously, mainly because your presentation mirrored precisely what we found. We undertook 19 PTCAs and five coronaries, and the results were very similar to yours. An extra piece of information is that our findings were very much the same as other reports describing anginal symptoms in patients after transplantation. It seems that some 12–15% of patients who have angiographic coronary artery disease describe this syndrome. The issue of revascularization in such patients begs a number of questions: firstly, we do not have a universally recognized and versatile method of describing the severity and extent of coronary artery disease within a vessel and within the coronary tree, making com-

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parison of intervention, for example in PTCA and coronary artery bypass grafting, difficult. A second point in contrast to what we have heard in your paper is the issue of survival with coronary artery disease. Can intervention influence this? Professor Yacoub mentioned the use of transmyocardial revascularization. It may be that the use of TMR in patients with transplant coronary artery disease could meet with a better prognosis for those patients. This would be powerful information to support the role of TMR which is currently undergoing evaluation for those with symptoms from coronary artery disease. I very much look forward to the results of such a study on both those accounts; that is, the improvement in the prognosis of patients with transplant coronary disease, which is currently not good, and a conclusive piece of work showing the value of TMR.

Dr B. Radovancevic: Yes, this is a very fair comment. I do not want anybody to think that we have come to any firm conclusions about TMLR and transplant CAD based on the results of the 2 patients treated with TMLR. However, it does look promising and a prospective randomized trial should be done. There is not much to lose, especially now that retransplantation is a limited option due to the shortage of donors. TMLR is a relatively easy procedure to do, and it is a low-mortality and relatively low-risk procedure.

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