The management of post-cardiac transplantation coronary artery disease

Abstract  Objective. Allograft coronary artery disease remains the single greatest limitation to long term survival after cardiac transplantation. It is peculiarly aggressive in its behaviour and diffuse in its nature. The role of conventional approaches to coronary artery revascularisation were studied in a selected group of cardiac transplant recipients.

Methods. Of the 557 patients undergoing cardiac transplantation at our unit between January 1979 and December 1993, all were screened for the development of allograft coronary artery disease routinely after 2 years and yearly thereafter or after 4 years. Twenty patients with allograft coronary artery disease were considered suitable for treatment by conventional means 17 of whom had undergone transplantation for ischaemic cardiomyopathy and the others for dilating cardiomyopathy.

Percutaneous transluminal coronary angioplasty was performed in 18, 25–103 months after transplantation (mean 60 months) all of whom had severe proximal stenoses and reversible defects on perfusion scans. None suffered chest pain. Coronary artery bypass grafting was performed in 5, 95–105 months after transplantation (mean 101 months) 2 of whom had post-infarction unstable angina and 3 had severe triple vessel disease, dyspnoea, and perfusion abnormalities.

Results. The primary success rate for PTCA was 84% (16/19). Two lesions restenosed and 3 patients had progressive disease which necessitated coronary revascularisation. No patient died. Of the 5 patients undergoing coronary artery surgery 2 died perioperatively, one from acute left ventricular failure and one from acute rejection. All 18 survivors have improved perfusion scans. Following surgery, all survivors had improvement in dyspnoea and relief of angina. Five late deaths a mean of 89 months after transplantation were from coronary artery disease (4) and lung malignancy (1).

Conclusions. Revascularisation by PTCA and CABG is feasible and successful in selected cardiac transplant recipients. Further study is required to determine the effect of revascularisation on prognosis.

Key words  Coronary artery disease • Cardiac transplantation • Coronary artery bypass grafting • Percutaneous transluminal coronary angioplasty

Introduction

With increasing survival rates after cardiac transplantation, coronary artery disease in the graft has emerged as the major cause of death in recipients after 1 year post-transplantation [3]. It has previously been documented that up to 40% of patients have some degree of graft coronary artery disease within 3 years of transplantation [8, 27]. With more than 26, 700 patients having received a cardiac transplant...
up to December 1993 [13], there is a growing population who may require further treatment.

The coronary artery disease which cardiac transplant recipients suffer is peculiar in being particularly diffuse and most prominent in the middle and distal epicardial vessels [9]. In addition, the intramyocardial vessels are heavily and diffusely diseased. Hence it is not readily amenable to current techniques of revascularization. However, as the only other approach is to retransplant, shortages in organ availability [29] and worse results for retransplant recipients than first time candidates [13] impel us to persevere with more traditional approaches. This report documents our experience in myocardial revascularization for graft coronary artery disease with both angioplasty and coronary artery bypass grafting (CABG).

**Patients and methods**

Between January 1979 and December 1993, 557 patients underwent cardiac transplantation (CTx) at our unit with 15 of these undergoing retransplantation for end-stage allograft coronary artery disease (ACAD). Following transplantation, patients undergo routine coronary angiography at 2 years, and, if there is evidence of ACAD, yearly angiography thereafter. In patients with no ACAD at the initial angiogram, the procedure is repeated at 4 years and then yearly thereafter. In our practice this has demonstrated a prevalence of ACAD with angiographic evidence of a greater than 25% reduction in intraluminal diameter of 31.6% at 5 years and 46.3% at 7 years.

Cyclosporin A was introduced into our programme in March 1982, being used in double therapy (with either steroids or azathioprine) until April 1986, after which triple therapy was used. Our policy has been to wean the steroids as soon as possible after the first 3 months as tolerated. All patients (until August 1993) received induction immunosuppressant therapy with rabbit anti-thymocyte globulin. Since January 1989, 20 patients who have demonstrated ACAD amenable to revascularization have undergone percutaneous transluminal coronary angioplasty (PTCA) or CABG. All patients demonstrated reversible myocardial ischemia on MIBI perfusion scanning. There were 18 males and 2 females aged 25–62 years (mean 48 years). Thirteen underwent CTx for ischaemic cardiomyopathy and seven for dilating cardiomyopathy. This proportion reflects the original indications for transplantation in our programme. The indications for revascularization are as shown in Table 1. No patient who underwent PTCA experienced chest pain prior to the procedure though seven suffered from breathlessness and all complained of lethargy.

### Percutaneous transluminal coronary angioplasty

Angioplasty was performed in a routine manner by two experienced operators. Continuous intravenous nitrate infusions were started during the procedure and continued postoperatively if there was evidence of ischaemia during instrumentation. A bolus of 10,000 U heparin was administered at the time of angioplasty and subsequently a heparin infusion was continued at 1250 U/h. Both infusions were discontinued on the following morning. The severity of the lesion was assessed before and after the procedure by two independent observers and a primary success was defined as a reduction in the stenosis to less than 50% of the intraluminal diameter of adjacent healthy artery. Recurrence was consequently defined as a reduction in the original luminal diameter gain of more than 50%.

**Table 1** Indications for revascularization in the 20 patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Severe lesion (&gt;75%)</th>
<th>Symptomatic - breathlessness and lethargy</th>
<th>Reversible ischaemia - perfusion scan</th>
<th>Exercise tolerance test</th>
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<tbody>
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<td>PTCA</td>
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<td>CABG</td>
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Coronary artery bypass grafting

Coronary artery bypass grafting was performed using normothermic right atrial-aortic cardiopulmonary bypass. The heart was arrested using 500 ml of cold crystalloid (St. Thomas' II buffered with sodium bicarbonate) cardioplegic solution and this was supplemented by a continuous cold pericardial irrigation system at 4°C. The left internal thoracic artery was used and anastomosed to the left anterior descending coronary artery in all cases. All other grafts were performed using lengths of reversed great saphenous vein.

**Results**

### Percutaneous transluminal coronary angioplasty

Eighteen patients underwent 19 PTCA during a mean of 60 months (range 25–103 months) following transplantation. Eleven patients underwent dilatation of the left anterior descending artery with one undergoing dilatation of a re-stenosis. Two underwent circumflex artery angioplasty and five right coronary artery dilatation. The primary success rate was 84% (16/19). Six of the 19 lesions recurred (31%) and a further PTCA was performed in one of these. At follow-up in two other patients the disease had progressed in the other epicardial vessels and they were therefore referred for CABG. No patient required emergency surgery and there were no procedural-related deaths.

### Coronary artery bypass grafting

Five patients underwent CABG at a mean of 101 months (range 95–105 months) after heart transplantation. Two patients had post-infarction unstable angina whilst three had severe triple vessel disease with dyspnoea or perfusion scan abnormalities. One of this last group of patients was asymptomatic, one had mild angina only and the last had severe dyspnoea. Three had previously undergone PTCA. The number of grafts performed ranged from 3–5 per patient.

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1 Methoxy-isobutyl-isonitrile
Two patients died. The first patient with post-infarction unstable angina had very diffuse distal disease which was not evident on the coronary angiogram, and the heart would not take over the circulation at the end of bypass. Histology of the myocardium showed extensive recent infarction. The other patient had post-infarction unstable angina but otherwise was clinically well with no evidence of cardiac failure. She had a technically uneventful operation but could not be weaned off bypass at the end of the procedure and died despite left ventricular assist device support. Histology of the myocardium showed grade 3A rejection.

Follow-up

All survivors had initial improvement in their perfusion scans. Two of the three survivors of CABG had relief of symptoms, whilst the third was asymptomatic preoperatively. All had relief of dyspnoea and the one patient who had angina prior to surgery had complete relief postoperatively.

Five of the 20 patients died an average of 89 months after transplantation and 21 months after revascularization. There were two operative deaths in the CABG group as detailed above. Two further patients died late due to ACAD, whilst one patient died due to a lung malignancy.

Discussion

Following the first year after transplantation, allograft coronary artery disease (ACAD) is the commonest cause of graft failure [3]. It is estimated that at 3 years between 25% and 40% of patients have developed ACAD [8, 27] and the results from our unit agree with this. Further, it has been calculated that a 40% stenosis or more in one or two epicardial vessels at angiography predicts an overall mortality rate of more than 50% at 2 years after detection [14]. This risk was significantly higher for those with triple vessel disease in whom survival at 2 years was only 13%. Improvements in long-term results therefore depend on improved treatment of, or ideally prevention of, ACAD.

When coronary arteriography of the donor organs has not been performed, there remains a risk that donor organ disease may be the initiating factor, and “ACAD” merely an expression of rapid progression of this disease. Tactile and visual assessment of the donor organ vessels at the time of harvesting is unreliable. Ideally, all donors should undergo arteriography with successful PTCA of suitable lesions and rejection of the organ if the disease is more severe, but often this is impractical. It has therefore been advocated that early post-transplant coronary arteriography be performed, but to date this has been merely for documentation and has not contributed to the clinical management of the patient.

Previous studies have shown ACAD to differ from atherosclerotic coronary artery disease in being a very diffuse disease of epicardial and myocardial vessels [9] with intimal proliferative lesions and atherosclerotic plaques [8] causing concentric narrowing of all vessels (arteries and veins [22]) and only occasionally presenting with focal stenoses. Conventional coronary arteriographic techniques are therefore inadequate and misleading. The recently developed intravascular ultrasound (IVUS) however shows the diffuse nature of the disease with a true assessment of its severity [12, 28] and therefore demonstrates why conventional approaches to revascularization are limited; only those few patients with focal lesions of proximal epicardial vessels may benefit.

The key to treatment must be prevention, and though the aetiology is poorly understood, in our programme we pay great attention to controlling the known risk factors for conventional atherosclerosis. Obesity, smoking, and hypertension are all rigorously dealt with. However, it is not our practice to try and control blood lipid levels early post-transplantation unless the patient was being treated previously. It is our policy to attempt to wean the steroids and then, if hyperlipidaemia persists, to institute treatment at that time.

Previously when ACAD developed the only option was considered to be retransplantation. However, the results of retransplantation have been very disappointing with mortality rates of 45% at 1 year, 75% at 2 years and 90% at 5 years being published [13]. Further, considering the current shortage of suitable donor organs these poor results from retransplantation have forced us to evaluate conventional methods of treatment for ACAD. Previous reports of surgical revascularization in transplant patients have been few and all reports to date have been case reports of successful interventions which give a misleading impression of the gravity of the problem [4, 5, 7]. This is consequently unhelpful when trying to decide the best way in which to treat a specific patient.

Our results confirm previous reports [18, 25] that PTCA can be safely and successfully performed in patients following CTX for single vessel ACAD. In this series, patients had both angiographically demonstrated disease and objective evidence of reversible ischaemia. The primary success rate of 84% is similar to primary success rates quoted for atherosclerotic coronary artery disease whilst the restenosis rate of 33% is also similar to results quoted for atherosclerotic disease [16]. No patient died, none required emergency surgery, and in 89% the perfusion scan was improved after the procedure. It may therefore be concluded that PTCA is a valuable tool for postponing retransplantation for ACAD.

Similarly, for patients with severe triple vessel disease CABB is feasible, though with an operative mortality of 40% in this small series the risk is significant. However, as one death was due to acute rejection, a potentially avoidable cause, the mortality in this series could be reduced by
preoperative cardiac biopsy. This change has since been incorporated into our preoperative protocol. There have been no further deaths in this group on long-term follow-up. Further, all patients showed improvement in their perfusion scans and all had symptomatic improvement, with complete relief of angina in the one who was symptomatic and reduction of dyspnoea in all. However, CABG cannot be advocated as readily as PTCA for postponing the need of later retransplantation for two reasons: first, there is a significant mortality and second the damaging effects of cardiopulmonary bypass on renal function in this group of patients may preclude retransplantation.

It has long been considered that patients following transplantation will not experience angina as the heart has been denervated. However, classic angina with appropriate electrocardiographic changes may occur, as happened in two of our patients. This only occurs in a small proportion of all patients however in whom there has been sufficient sympathetic regrowth into the appropriately ischaemic area to allow afferent neuronal stimulation [24]. Though known to occur in most animal models, this has only recently been shown to occur also in man. However, in most patients post-transplantation this regrowth is absent or at best only partial. Thus the initial presentation of ACAD is frequently with heart failure following myocardial infarction, and routine angiographic screening of patients is therefore essential. Our policy is for angiography at 2 years after transplantation then yearly if ACAD is detected or after a further 2 years if it is not.

We do not as yet have sufficient evidence from our own patients to conclude whether revascularization alters the prognosis of patients with ACAD. However, if it is accepted that the 2-year survival following identification for patients with a 40% or more stenosis of one or more primary or secondary epicardial arteries is less than 50% [14], our results of 75% survival at 21 months after revascularization indicate a definite benefit from intervention. Further follow-up within our programme should elucidate this problem.

Ultimately it is to be hoped that advances in the understanding of ACAD will allow us to identify the cause and thereby prevent it rather than attempt to treat it by rather inadequate means. Whether it is a representation of chronic vascular rejection [17, 21] or due to viral infection [6, 11], advances in immunosuppression with more accurate targeting of the immunosuppressant drugs may hold the key. It is claimed that other drugs such as diltiazem [23] amiodipine [2] and captopril [15] can reduce the incidence of ACAD in the rat model, but this has not been confirmed in humans. Identification of the “at risk” population will enable accurate targeting of these more aggressive approaches. Recent work has shown endothelial dysfunction to precede detectable endothelial thickening as determined by intravascular ultrasound. In addition, this dysfunction is potentially recoverable in the early stages [1]. Thus the previously reported attenuated vasodilatation to acetylcholine [26] papaverine [19] and Substance P [20] may develop into predictive tests for those at risk of developing ACAD. This will then allow us to manipulate antirejection/vasodilator/other medication to aid recovery and prevent progression to ACAD.

Recent advances in revascularization techniques may broaden the acceptance criteria and permit treatment of patients unsuitable for conventional revascularization techniques. Transmyocardial revascularization (TMR) using laser techniques may be the ideal approach to the problem for two reasons. Firstly, as previously stated, ACAD is a disease of the myocardial as well as the epicardial vessels. Thus conventional revascularization techniques are inevitably inadequate. By creating new intramyocardial channels, this problem may be circumvented. Secondly, TMR can safely be performed without cardiopulmonary bypass. Thus the renal insult is avoided.

In conclusion, PTCA and CABG can both be performed following CTx but only in a small, highly selected population in whom there are severe proximal stenoses; the risk of PTCA is small but that of CABG is significant. However the majority of patients with ACAD will not be amenable to this treatment. Advances in techniques for revascularization and improvements in immunosuppression to prevent the immunological component of the insult may reduce the number of grafts lost to ACAD. Our experience to date has taught us a number of lessons. All patients undergo cardiac biopsy within 48h of re-operation regardless of whether they have subjective or objective evidence of rejection. Appropriate treatment is then instituted if necessary prior to further surgery and the effect monitored by further biopsy. Our experience has also confirmed what has been known for a long time, that angiography underestimates the severity of the disease [10] and does not give a good impression of the state of the distal arteries, which are always severely and diffusely diseased.
References


Discussion

Dr. S. Mattila (Helsinki, Finland): Your Paper deals with one of the major problems after heart transplantation. The invasive methods, revascularization by PTCA or coronary bypass grafts or retransplantation, are the only hope for survival of patients with critical occlusive changes in the coronary arteries. I would like to focus attention on prevention of chronic rejection and to the fact that post-transplant coronary artery disease differs from ordinary artery disease. The Stanford group first showed that prophylactic diltiazem treatment prevented the development of coronary occlusive changes, and yesterday the Hannover group showed that acute rejection periods was the risk factor for post-transplantation coronary artery disease. We in Helsinki have performed 165 heart so far transplants.

In one case we found enormous vasculopathy with gross intimal thickening of the coronary arteries after severe and lethal cytomegalovirus (CMV) infection. Therefore we decided to do a follow-up study on the impact of symptomatic CMV infection on the coronary arteries from the endomyocardial biopsy specimen and coronary angiograms. As shown here, there are diffuse, and also local, changes in the coronary arteries 2 years after transplantation in a patient who had had a symptomatic CMV infection.

And when we gathered together all our information we found that actually CMV infection accelerates the development of occlusive changes in the coronary arteries. The upper curve shows patients without CMV infection, and, as you see, more than 80% of the patients were free from coronary artery disease at 4 years and only about 45% of the patients who had had symptomatic CMV infections were free from the occlusive changes in the coronary arteries.

My question is: did you use diltiazem or other methods to prevent chronic rejection, and did you see any correlation between acute rejection periods or infections and the occlusive changes of the coronary arteries after heart transplantation?

Mr. Parry: We have analysed our data regarding frequency and severity of CMV infection and the occurrence of coronary obliterative disease in transplant patients and found no correlation. We have also looked at the incidence of severe rejection episodes, and we, like the Hanover group, have found that the incidence of coronary obliterative disease does appear to be associated with the number of severe treated rejection episodes.

Young et al. in 1992 presented data showing that there was a direct correlation between the level of soluble IL-2 receptors and the incidence of coronary obliterative disease. Those with levels less than 1000 U/ml had no coronary obliterative disease, whereas those who had levels above 1000 U/ml had severe coronary obliterative disease. I wonder whether this is not the final common pathway; whether it is rejection which triggers the immune response or CMV infection, the mechanism is the same.

As far as prophylaxis is concerned there has also been evidence that captopril can reduce the incidence of post-transplant coronary artery disease, at least in a rat model. We do not routinely use diltiazem but do control the known risk factors for non-transplant coronary artery disease (blood sugar, serum lipids, blood pressure etc.).