Early and long-term results of heart transplantation after previous cardiac surgery

Tarek Aziz*, Malcolm Burgess, Ali Rahman, Colin Campbell, Abdul Deiraniya, Nizar Yonan

Cardiac Transplant Unit, Wythenshawe Hospital, Southmoor Road, Manchester, UK

Received 4 October 1999; received in revised form 12 January 2000; accepted 26 January 2000

Abstract

Objectives: The aim of this study was to evaluate the preoperative management and long-term survival of patients undergoing heart transplantation as a redo-operation and compare the results with those obtained in patients undergoing transplantation as their first cardiac surgical procedure.

Methods: Between 1990 and 1997, 49 heart transplantation procedures were performed in patients who had undergone previous cardiac surgery (group A). This subgroup of patients was compared to 109 control patients who underwent cardiac transplantation as the primary cardiac procedure (group B). Patient groups were analysed regarding their preoperative, intra-operative, and postoperative variables in addition to survival.

Results: Pre-operative events were comparable in both groups but the duration of the operation was longer for group A (311 ± 68 min) compared to group B (202 ± 34 min); P = 0.02. Post-operative exploration for bleeding was 6/49 patients in group A compared to 2/107 patients in group B (P = 0.02). Post-operative blood loss and intensive care stay were greater for group A (1302 ± 360 ml and 6 ± 1 days, respectively) compared to group B (763 ± 126 ml and 4 ± 1 days, respectively); P = 0.02. There was no difference in hospital mortality (group A 12.5%, group B 13% P = 0.9) and the 5-year survival rates were 68 and 71% for group A and B, respectively (P = 0.9).

Conclusions: Heart transplantation after previous open cardiac surgery is entirely justified in terms of outcome and graft function even in time of profound organ scarcity. Long-term events in these recipients are similar to patients in whom transplantation is the primary procedure. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Heart transplantation; Previous cardiac surgery; Early and long-term results

1. Introduction

In recent years orthotopic heart transplantation has become an effective therapy for patients with end stage heart failure. The advances in transplantation have increased the indications for this form of therapy. Because the supply of donor hearts is limited, analysis of perioperative morbidity and mortality and identification of various recipient risk factors for early and late complications after heart transplantation is important in identifying those recipients most likely to benefit from surgery. Previous studies have suggested that previous cardiac surgery may contribute to a poor outcome following heart transplantation [1,2]. Distorted anatomy and dense adhesions may prolong operative and subsequently ischaemic times. In addition, prolonged cardiopulmonary bypass may potentate inflammatory mechanisms resulting in increased blood loss for operative and haemostatic response. Furthermore, previous blood or blood product transfusion can stimulate antibody formation which may result in severe and early acute allograft rejection. In this study we aimed to assess the early and medium-term post-operative outcome of orthotopic heart transplant recipients who had undergone previous cardiac surgery and compare this to patients undergoing this type of surgery as their primary cardiac procedure.

2. Patients and methods

2.1. Patients

All patients underwent orthotopic heart transplantation at Wythenshawe hospital between 1990 and 1997. The study group consisted of 49 patients who had undergone previous cardiac surgery (group A, age 45 ± 6.5 years, 83% male). Fourteen patients had a dilated cardiomyopathy or progressive myocardial dysfunction after valve replacement, 34 patients had ischaemic heart disease, and one patient had previous septal defect repaired. Previous cardiac operations in this subgroup included isolated CABG in 29 patients,
CABG and left ventricular aneursmectomy in three patients, CABG and valve replacement in two patients. Of the patients who had prior myocardial revascularization, 22/34 received at least one internal thoracic artery. Initial open cardiac procedure was performed on elective basis in 42 patients and as an urgent intervention in seven patients. Average time between the initial open-heart surgery to transplantation was 34 ± 11 months. Poor left ventricular ejection fraction (> 20%) was reported in 11 patients (nine patients had CABG and two patients had valve replacement) of group A prior to their initial procedure.

Group A patients were compared to group B patients. Group B patients were the patients preceding and that following each group A patient within a period of 30 days. Any patient from group B who reported to have had a history of blood transfusion (two patients) before transplantation was excluded from this analysis.

Group B consisted of 107 control patients who underwent orthotopic heart transplantation as a primary procedure during the same period using similar surgical and myocardial protection techniques. In this control group, the cause of end stage heart failure was ischaemic heart disease in 67 cases, idiopathic or valvular cardiomyopathy in 40 patients. Follow-up was completed on December 1998, or at time of recipient’s death, thus giving a minimum follow-up of 12 months for all surviving patients.

The study was retrospective and investigated the perioperative risk factors and survival of the two groups.

2.2. Pre-operative assessment

Right and left heart catheterizations were performed in every patient. Right heart catheterization determined the right atrial, pulmonary artery and pulmonary capillary wedge pressures in addition to cardiac output. Pulmonary and systemic vascular resistance were calculated according to standard formulae. Left heart catheterization was performed to determine left ventricular ejection fraction, segmental wall motion and the presence and distribution of coronary artery disease. All patients underwent routine haematological and biochemical assessment. Measuring of plasma levels of urea and creatinine and measuring creatinine clearance assessed renal function. All patients were screened for CMV, HIV, herpes virus and hepatitis A and B. Patient sera were screened for cytotoxic antibodies and the serum reactivity was tested against non-specific panel of different donor sera. Cross match results were achieved by testing donor specific lymphocytes against recipient serum after transplantation. Preoperative cross-match was defined as positive when serum reactivity panel of more than 10% were present.

2.3. Operative technique

The donor hearts were excised with an intact right atrium and long cavae. Donor hearts were arrested with cold St. Thomas cardioplegic solution and stored in 4°C cold saline solution. The donor left atrium was sutured to the recipient left atrium in the usual fashion prior to suturing of the IVC and SVC to the recipient cavo-atrial cuff. Aorta and pulmonary arteries were sutured in a standard fashion. The standard technique was performed as described by Lower and Shumway [3]. The bicaval technique was performed as previously described by Sarsam et al. [4]. The latter involves the preservation of a 2–3 cm cuff left around each cava (cavoatrial cuff) during excision of the right atrium of the recipient. The left atrial incision is carried to the base of the left atrial appendage, which is removed leaving a small margin of the atrial cuff around four pulmonary veins. In 60% (29/49) of group A patients and 63% (67/107) of group B patients heart transplantation was performed by the standard technique. The remaining patients in both groups (20 in group A and 40 in group B) underwent surgery by the bicaval technique. Cold blood cardioplegia was infused through the aortic root every 20–25 min during recipient’s heart implantation procedure.

2.4. Post-operative management

All patients received isoprenaline intravenously for a minimum of 3 post-operative days as part of a routine protocol. Other cardiac inotropes or mechanical supports (intra-aortic balloon pump or right-sided ventricular assist device) were used whenever clinically indicated in both groups. In all patients, post-operative blood loss was measured and the requirement for re-operation for bleeding or other causes was determined. Bacterial cultures were performed according to standard procedures. Infective complications with respect to the respiratory urinary, cardiovascular, and gastrointestinal systems requiring anti-microbial therapy were noted. Multi-organ failure was defined as failure of at least two organs systems with refractoriness to therapeutic intervention. Respiratory insufficiency was defined as ventilatory failure requiring re-intubation after extubation, which was performed according to common extubation criteria. Cerebrovascular complications were defined as changes in neurological signs. The diagnosis was supported by an abnormal computed tomographic scan in most cases.

2.5. Immunosuppression

An induction dose of anti-thymocyte globulin (2 mg/kg) was used daily for the first 3–5 days post-operatively. Standard triple immunosuppression therapy was commenced in the immediate post-operative period with cyclosporin (3–5 mg/kg), azathioprine (2 mg/kg) and prednisolone (0.75–0.125 mg/kg daily dose). Methylprednisolone 500 mg was given to all patients during surgery and followed by 125 mg daily during the following 3 post-operative days. Cyclosporin was administered to maintain a serum trough level of 180–250 ng/mL. Azathioprine was given in a maximum dose of 2 mg/kg and adjusted to maintain a white cell count greater than 4000/μL. The methylprednisolone dose was tapered after perioperative induction to 0.75–0.125 mg/kg.

within 2–3 weeks post-operatively. In three recipients (one in group A and two in group B) cyclosporin was replaced by tacrolimus (FK 506).

2.6. Endomyocardial biopsy

Surveillance endomyocardial biopsies (EMB) were performed on a scheduled basis – weekly for the first month, every 2 weeks for the next 2 months, monthly up to 6 months, then at 9, 12, and 18 months post-transplantation and annually thereafter. If rejection was suspected on clinical grounds in the interim supplementary biopsies were performed accordingly.

2.7. Haemodynamics evaluation

Right heart catheterization was performed with each biopsy using a multipurpose cordis 7F vascular catheter (Cordis, Miami, FL) connected to an AE 840 (Mikro ElektronikK A/S) pressure transducer. Intracardiac pressures were recorded at the levels of the right atrium, right ventricular body and pulmonary artery. Pulmonary artery occlusion pressure was also recorded.

2.8. Coronary angiography

Coronary artery disease was evaluated by routine coronary angiogram for surviving recipients, or post-mortem examination of dead patients. Surveillance coronary angiogram was performed in every case starting from 18–24 months after transplantation or when clinically indicated. For the purpose of this study, marked allograft vasculopathy was defined as stenosis >70% in one of the main coronary arteries (LAD, Circumflex, dominant right coronary, or left main stem).

2.9. Data analysis

Data are expressed as mean ± standard deviation. Data between the two groups were compared with unpaired t-test (for parametric data only as intra-cardiac pressures and ischaemic time), the Mann–Whitney test, or Fisher’s exact test where applicable. Survival was calculated using the Kaplan–Meier method and compared by log-rank test. A P-value of less than 0.05 was defined as significant.

3. Results

3.1. Pre-operative cardiac catheterization data

No significant differences were found between the two groups in terms of perioperative haemodynamics, serology status or renal function. In group A 19 patients were receiving aspirin and 21 patients were receiving warfarin compared to 25 and 46 patients respectively in group B (Table 1).

3.2. Ischaemic time, implantation time, bypass time and operative time

Mean graft ischaemic time was 237 ± 35 min for group A compared to 201 ± 27 min for group B (P = 0.05). The mean implantation time was 68 ± 13 min for group A vs. 59 ± 11 min for group B (P = 0.09). Mean implantation time was not affected by operative technique regardless of whether the surgical technique was standard or bicaval. In group A mean bypass time was 134 ± 23 min compared to 82 ± 21 minutes group B (P = 0.02). The mean operative time was 311 ± 68 vs. 207 ± 34 minutes in groups A and B respectively (P = 0.02) (Table 2).

3.3. Perioperative complications

The use of intra-operative and early post-operative inotropic support usually started during reperfusion. An intra-aortic balloon pump was necessary in four patients in group A and seven patients group B. A right ventricular assist device was not required in any group A patient but was used successfully in one group B patient. Post-operative bleeding leading to exploration occurred in ten patients (20%) from group A compared to five patients (4%) from group B (P = 0.004). The mean post-operative blood loss within the first 24 h was 1302 ± 360 ml vs. 756 ± 121 ml for groups A and B, respectively (P = 0.02). The requirement for blood transfusion was 4.5 ± 1.6 units in group A compared to 2.6 ± 1.1 units group B (P = 0.3). No significant difference between the two groups was demonstrated in incidence of sternal wound infection (one patient in each group). The incidences of multi-organ failure, cerebrovascular events, respiratory failure, infection, pacemaker implantation, diaphragmatic paralysis are summarised in (Table 3). There was no significant difference between the two groups.

<p>| Table 1 |
|---------------------------------|-----------------|-----------------|
| Pre-operative variables for study and control groups* |</p>
<table>
<thead>
<tr>
<th>Pre-operative variables</th>
<th>Group A (n = 49)</th>
<th>Group B (n = 107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart</td>
<td>34</td>
<td>67</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>14</td>
<td>40</td>
<td>0.4</td>
</tr>
<tr>
<td>Age</td>
<td>49 ± 6.5</td>
<td>41 ± 6.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>40/49 (83%)</td>
<td>88/107 (82%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>19 ± 8.5</td>
<td>22 ± 9.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Heart index L/M²</td>
<td>2.0 ± 0.7</td>
<td>1.8 ± 1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>PVR (wood unit)</td>
<td>2.5 ± 1.1</td>
<td>2.2 ± 1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>8.6 ± 1.6</td>
<td>8.7 ± 1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Pre-operative creatinine (mmol/l)</td>
<td>145 ± 23</td>
<td>136 ± 25</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean follow-up range (months)</td>
<td>49 ± 30 (0–81)</td>
<td>52 ± 20 (0–79)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* PVR, pulmonary vascular resistance (wood units); TPG, transpulmonary gradient (mmHg).
3.6. Graft vasculopathy and long-term survival up to 24 months after transplantation (Table 4).

The incidence of acute rejection episodes was similar between both groups in acute rejection in none of the study patients. The incidence of cross-match compared to one patient in group B. Hyper-

3.5. Immunology status

Two patients in group A showed a positive lymphocyte cross-match compared to one patient in group B. Hyper-

3.4. Hospital mortality, duration of intensive care unit and overall hospital stay

Hospital mortality was similar in the two groups (12.5% for group A vs. 13% for group B, P = 0.9). The mean ITU and hospital stay were longer for group A than for group B (6.1 ± 3.1 and 24 ± 11 days, respectively, vs. 4.1 ± 1.7 (P = 0.04) and 17 ± 4.8 (P = 0.04) days, respectively).

3.6. Graft vasculopathy and long-term survival

After a mean follow up period of 50 ± 26 months for both groups 13 patients in the group A had developed marked graft atherosclerosis compared to 28 patients in group B (P = 0.9). The survival at 1-, 3- and 5-year intervals were, 83, 75, and 68% for group A vs. 83, 76 and 71% for group B (P = 0.9) (Fig. 1, Table 5).

4. Discussion

Cardiac transplantation is currently an accepted treatment for end stage heart disease. The annual registry of the International Society for Heart and Lung Transplantation [5]

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group A (n = 49)</th>
<th>Group B (n = 107)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi organs failure</td>
<td>2</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>Cerebro-vascular</td>
<td>3</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Infection</td>
<td>9</td>
<td>16</td>
<td>0.8</td>
</tr>
<tr>
<td>Re-exploration</td>
<td>6</td>
<td>2</td>
<td>0.02</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>2</td>
<td>5</td>
<td>0.8</td>
</tr>
<tr>
<td>Death</td>
<td>5</td>
<td>9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

shows an increase in the recipient pool in the context of decreasing donor organ availability. Because of limited supply of donor hearts the analysis of perioperative morbidity and mortality and identification of recipient risk factors for early and late death after transplantation may play an important role in identifying patients who are most likely to benefit from this type of therapy. In our institution the great majority of transplant candidates are presently between 45 and 60 years of age and this group constitutes a considerable proportion of potential recipients who have had previous cardiac surgery.

Our study has demonstrated the significantly increased operating time and blood loss in addition to the relatively prolonged intensive care unit and hospital stay in patients in whom cardiac transplantation is not their primary cardiac surgical procedure. The recipient procedure in our patients with a previous sternotomy is timed somewhat early to avoid a rushed dissection under difficult conditions and this minimises an unnecessary long donor ischaemic time in this group. A previous report [6] has suggested that pre-operative coumarin therapy is associated with increase in the blood product requirement but has no influence on bleeding-associated with post-operative complications. Despite the perioperative use of aprotinin in 70% of patients’ blood loss was significantly higher than in patients in whom transplantation was the primary cardiac surgery. It is unlikely that this increased propensity to post-operative bleeding was due to differences in pre-operative anti-coagulation as the level of anti-coagulation was similar in both groups.

Perioperative morbidity in cardiac transplant recipients as reflected by bleeding complications requiring operative intervention was significantly higher in patients who had previous cardiac operation than in control group. This group required more prolonged intensive care and hospital stays. However, the incidence of other major post-operative events (i.e. respiratory failure, renal failure, cerebro-vascular accidents) was comparable between these two groups.

In contrast to the findings of Uthoff [7] and associates increased perioperative bleeding and operative time in our patients undergoing heart transplantation after previous cardiac surgery was not followed by an increased incidence.
of post-operative infection and the incidence of infections was similar in both groups.

Cardiac allograft vasculopathy is the most common cause of morbidity and mortality in patients surviving for more than 2 years after transplantation [5,8]. Cardiac allograft vasculopathy is an accelerated form of coronary artery disease characterised by rapidly progressive vascular myointimal hyperplasia that leads to either diffuse, concentric, homogenous lesions spread uniformly along the length of the epicardial and endocardial arteries or focal stenosis quite similar to native atherosclerotic vessels [9]. It has been postulated that changes in the allograft coronary circulation originate from an interaction between immune and non-immune factors that lead to smooth muscle cellular infiltration and accumulation of expanded neointima. The angiographic evidence of coronary artery disease has been reported to range from 2 to 28% at 1 year after transplantation [10,11], increasing to 40–70% by 5 years [12–14]. An association between allograft rejection, the subsequent development of CAV and rejection episodes (especially those which are mild and untreated) has been previously reported [14,15].

Although previous cardiac surgery has been identified as a risk factor for frequent rejection [1] this was not demonstrated in our study. The trend toward increased morbidity in patients who had undergone previous cardiac surgery was not associated with early or late mortality in our series with no distinguishable difference in survival was noted between the two groups. Cardiac allograft vasculopathy, in particular, the main determinant of long-term outcome following transplantation was comparable in the two groups.

Our experience in heart re-transplantation is limited and was not included in this study. The international society of heart and lung transplantation annual Registry [16] identified re-transplantation as a significant risk factor for 1- and 5-year graft failure. Recent studies [17] concluded poor outcome of cardiac re-transplantation particularly if it is performed for graft failure during the first year after primary heart transplantation. However, comparable outcome between primary and re-transplantation was achieved in

Table 5
Survival analysis in group A (redo recipients) and group B (control group)

<table>
<thead>
<tr>
<th>Survival/year</th>
<th>Group A (redo patients)</th>
<th>Group B (control patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (%) CI (%)</td>
<td>Rate (%) CI (%)</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>83 79–87</td>
<td>83 79–86</td>
<td>0.9</td>
</tr>
<tr>
<td>2 year</td>
<td>75 72–79</td>
<td>76 73–81</td>
<td>0.9</td>
</tr>
<tr>
<td>5 year</td>
<td>68 64–71</td>
<td>71 67–77</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Fig. 1. Survival analysis in group A (redo recipients) and group B (control group).
selected patients with accelerated cardiac allograft vasculopathy [17,18]. In view of persistent lack of donor grafts, we believe that heart re-transplantation should be considered cautiously to ensure optimal use of donor organs.

5. Conclusion

Heart transplantation after previous cardiac surgery is technically demanding requiring a relatively high operative time and early post-operative morbidity than for primary cardiac transplantation. However, the long-term post-operative events in these recipients are similar to patients in whom transplantation is the primary procedure. Our results implicate that in contrast to cardiac re-transplantation, heart transplantation after prior open-heart surgery is an excellent option for patient and good use of the organ even when the ethical dilemma of profound scarcity of donor heart is considered. When cardiac surgery has previously been performed carefully selected candidates for transplantation are not exposed to an increased post-operative risk and this should be considered in pre-operative risk assessment.

References