Cardiac retransplantation: is it justified in times of critical donor organ shortage? Long-term single-center experience

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Abstract

Objective: Survival after heart transplantation has improved significantly over the last decades. There are a growing number of patients that require cardiac retransplantation because of chronic allograft dysfunction. With regard to the critical shortage of cardiac allograft donors the decision to offer repeat heart transplantation must be carefully considered. Methods: Since 1983 a total of 807 heart transplantations have been performed at our institution. Among them 41 patients received cardiac retransplantation, 18 patients because of acute graft failure and 23 because of chronic graft failure. Data were analyzed for demographics, morbidity and risk factors for mortality. The acute and chronic retransplant group was compared to those patients undergoing primary transplantation. Results: The mean interval between primary transplantation and retransplantation was 1.9 days in the acute and 6.7 years in the chronic retransplant group. Mean follow-up was 6.9 years. Baseline characteristics were similar in the primary and retransplant group. Actuarial survival rates at 1, 3, 5 and 7 years after primary cardiac transplantation compared to retransplantation were 83, 78, 72 and 64% vs 53, 50, 47 and 36%, respectively (\( p < 0.001 \)). Early mortality after acute retransplantation was significantly higher compared to late retransplantation (10/18, 55.6% vs 4/23, 17.4%, \( p = 0.011 \)). Major causes of death were acute and chronic rejection, infection and sepsis. Conclusions: Cardiac retransplantation is associated with lower survival rates compared to primary transplantation. However, results after retransplantation in chronic graft failure are significantly better compared to acute graft failure. Therefore, we consider cardiac retransplantation in chronic graft failure a justified therapeutic option. In contrast, patients with acute graft failure seem to be inappropriate candidates for cardiac retransplantation.

Keywords: Heart transplantation; Heart retransplantation; Graft failure; Cardiac allograft vasculopathy

1. Introduction

Survival after heart transplantation has improved significantly over the last decades. As a consequence there are an increasing number of patients that require cardiac retransplantation because of chronic allograft dysfunction. Despite the growing knowledge about the pathogenesis of cardiac allograft vasculopathy (CAV), treatment options are limited. Thus, it remains the major cause of late allograft failure, and cardiac retransplantation remains the only definitive therapy \([1–5]\). On the other hand, about 20% of patients die on the waiting list for heart transplantation according to the Annual Report of Eurotransplant \([6]\). There are more than 900 patients waiting for one of the 550 heart transplants performed annually and the percentage of high urgency transplantations is constantly increasing.

Since its first clinical application in 1977, the discussion about the justification of repeat heart transplantation is still ongoing \([7]\). Previous studies reported lower survival rates after retransplantation compared to primary transplantation. With regard to the critical shortage of cardiac allograft donors the decision to offer repeat heart transplantation must be carefully considered \([1–5,8]\). For validation of our institutional policy of cardiac retransplantation including selection criteria for appropriate candidates we retrospectively analyzed the outcome of all patients who underwent cardiac transplantation at our institution, among them 41 patients that received cardiac retransplantation.

2. Patients and methods

2.1. Patients

Between July 1983 and July 2006 a total of 807 heart transplantations have been performed at Hannover Medical
School, among them 723 primary transplantations and 41 retransplantations. The primary transplantations of those 41 patients that underwent retransplantation were excluded from this analysis. Two patients who received their third heart transplant were excluded as well. There were 18 early and 23 late retransplantations. Early retransplantation was defined as transplantation (TX) ≤30 days after the first TX. Since 2000 retransplantation for acute graft failure has been abolished at our institution because of its disappointing results and the revision of organ allocation (criteria for high urgency transplantation).

Patients presenting for repeat cardiac transplantation were thoroughly evaluated. Exclusion criteria were severe end-organ dysfunction such as renal, liver and pulmonary failure (unless combined organ transplantation was considered), evidence of patient non-compliance, and others such as malignancies and severe osteoporosis. A screening for cytotoxic anti-HLA antibodies was performed in all patients. Before listing, a CT scan was performed in all patients in order to define the distance between heart and sternum. In the majority of patients cardiopulmonary bypass was installed via femoral access.

2.2. Donors

Mean donor age was comparable in the primary transplant group and the retransplant group (31 ± 12 years; range 1–60 years vs 34 ± 16 years; range 21–54 years). Male to female ratio was the same in both groups (male 72%; female 28%) (Table 1).

2.3. Organ preservation and surgical procedures

For cardioplegia St. Thomas solution, University of Wisconsin (UW) solution and histidine-tryptophan-ketoglutarate (HTK) solution were used according to the era of transplantation. Mean ischemic time was 162 ± 41 min (range 47–332) in the primary transplant group and 192 ± 17 min (range 162–204) in the retransplant group (p = 0.111) (Table 1).
Orthotopic transplantation was performed by the technique described by Lower and Shumway [John] until 2000. Since then bicaval anastomosis was the preferred technique.

2.4. Previous surgical procedures

Previous cardiac surgery has been performed in 185 patients (24.2%) in the primary transplant group. Among them 28 patients underwent ventricular assist device implantation prior to transplantation. The devices were explanted at the time of heart transplantation (Table 1).

2.5. Combined organ transplantation

Combined heart and renal transplantation was performed in 11 patients in the primary transplant group and one patient of the retransplant group. Two patients underwent renal transplantation late after heart transplantation (5 and 7 years). Combined liver transplantation was performed in one patient of the primary TX group because of hemochromatosis. One patient underwent liver transplantation because of amyloidosis late after heart transplantation (at 6 years postop) (Table 1).

2.6. Immunosuppression and postoperative management

Postoperative immunosuppression consisted of an induction therapy with anti-thymocyte globulin (ATG) followed by a triple maintenance therapy based on cyclosporine or tacrolimus in combination with azathioprine or mycophenolate mofetil and steroids. In the retransplant group ATG was administered only if it has not been used after primary TX. All patients after cardiac retransplantation received tacrolimus instead of cyclosporine. For the last 10 years mycophenolate mofetil was preferred to azathioprine. All patients received steroids for life. More recently introduced immunosuppressive drugs like everolimus and sirolimus were administered only in selected patients either within a study protocol or for special indications, such as recurrent rejections. All patients were followed up in our transplant outpatient department.

2.7. Statistical methods

Data were prospectively recorded and retrospectively analyzed. Continuous variables were presented as mean ± standard deviation and compared using the independent sample t-test. Categoric variables were presented as proportions and compared by Chi-square analysis. Actuarial survival was estimated with the Kaplan–Meier method and analyzed using the log rank test. A two-sided p value of less than 0.05 was considered statistically significant. For multivariate analysis of risk factors for survival after retransplantation a stepwise regression was performed. All data were analyzed using the Statistical Program of Social Sciences (SPSS, version 15.0, SPSS, Inc., Chicago, Ill.).

3. Results

3.1. Patient population

In the primary transplant group 598 (82.7%) patients were male and 125 (17.3%) female with a mean age of 46 ± 13 years (range 1–71 years). In the retransplant group 35 (85.4%) patients were male and 6 (14.6%) female with a mean age of 49 ± 11 years (range 13–68 years). Mean follow-up was 6.9 ± 5.8 years (range 0–21 years) with a cumulative follow-up of 5248 patient years. Patient characteristics are listed in Table 1.

3.2. Underlying diagnoses and indications

Underlying diagnoses for heart transplantation in the primary transplant group were dilative cardiomyopathy (n = 417, 57.7%), ischemic cardiomyopathy (CAD) (n = 239, 33.1%), congenital heart disease (n = 22, 3.0%), valvular heart disease (n = 18, 2.5%), hypertrophic heart disease (n = 12, 1.7%) and others (n = 15, 2.1%) (Table 1). Diagnoses for primary transplantation in the retransplant group were dilative cardiomyopathy (n = 23, 56.1%), ischemic cardiomyopathy (CAD) (n = 15, 36.6%), valvular heart disease (n = 2, 4.9%), and others (n = 1, 2.4%).

There were 18 early and 23 late retransplantations. In the early retransplant group the interval between the first and the second transplantation was 1.9 ± 1.7 days (range 0–6 days). Indications for early retransplantation were acute rejection in four patients, right heart failure in six patients, biventricular failure in four patients and acute graft failure of unknown etiology in four patients. In the late retransplant group the interval between both transplantations was 6.4 ± 5.1 years (range 0.2–17.1 years). The main indication for late retransplantation was cardiac allograft vasculopathy (CAV) in 17 patients. Other indications were acute rejection in two patients and progressive graft failure in four patients (Table 2).

3.3. Mortality

Early mortality (≤ day 30) was 10.9% in all patients (83/764). In the primary transplant group early mortality was 9.5% (69/723) compared to 34.1% in the retransplant group (14/41) (p < 0.001). Initial graft failure (n = 29, 34.9%), infection (n = 20, 24.1%) and acute rejection (n = 15, 18.1%)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient characteristics: early vs late retransplantation</th>
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<tr>
<td></td>
<td>Early ReTX (n = 18)</td>
</tr>
<tr>
<td>Interval between the first and second TX</td>
<td>1.9 ± 1.7 days (0–6 days)</td>
</tr>
<tr>
<td>Indications for ReTX</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>Graft failure</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>CAV</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Biventricular failure</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>10 (55.6%)</td>
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ReTX: retransplantation; TX: transplantation.
were the main causes of early death. Major causes of late death included cardiac allograft vasculopathy ($n = 61, 20.6\%$), malignancy ($n = 46, 15.5\%$) and infection ($n = 33, 11.1\%$). Overall causes of death are listed in Table 1.

Early mortality after acute retransplantation was significantly higher compared to late retransplantation ($10/18; 55.6\%$ vs $4/23; 17.4\%; p = 0.011$) (Table 2). Major causes of death after cardiac retransplantation were acute rejection ($n = 5, 17.9\%$), infection ($n = 5, 17.9\%$), initial graft failure ($n = 4, 14.3\%$) and chronic rejection (CAV) ($n = 3, 10.7\%$) (Tables 1 and 3).

Actuarial survival at 1, 3, 5 and 7 years after primary cardiac transplantation was $83\%, 78\%, 72\%$ and $64\%$, respectively. In comparison, survival after retransplantation was $53\%, 50\%, 47\%$ and $36\%$ at 1, 3, 5 and 7 years. Thus, survival rates in retransplant recipients were significantly lower ($p < 0.001$, log rank test). (Fig. 1, Table 4) Survival after early retransplantation was $33\%, 28\%, 28\%$ and $28\%$ at 1, 3, 5 and 7 years vs $68\%, 68\%, 62\%$, and $39\%$ after late retransplantation ($p = 0.118$, log rank test) (Fig. 2, Table 4).

### 3.4. Univariate and multivariate analysis

Univariate analysis revealed recipient female gender ($p = 0.007$) and older age ($p < 0.001$) as well as a shorter interval between both transplants ($p = 0.015$) and an earlier era of transplantation ($p = 0.002$) as statistically significant risk factors for death after retransplantation. Donor specific variables as well as ischemic times were not statistically significant (Table 5). However, multivariate analysis identified only female gender as a statistically significant risk factor (Table 6).
4. Discussion

This study describes our experience with cardiac retransplantation in patients with either acute or chronic graft failure. In times of critical donor organ shortage, when the numbers of heart transplantations are constantly decreasing while the waiting list is increasing, indication and justification for redo heart transplantation has to be thoroughly evaluated.

According to the Scientific Registry of Transplant Recipients (SRTR) the percentage of retransplantations among all heart transplants is constantly increasing [1]. The most common indication for retransplantation was cardiac allograft vasculopathy (CAV) in 56% of patients [9]. Despite the growing knowledge about the pathogenesis of CAV, treatment options are still limited and cardiac retransplantation remains the only definitive treatment option [10].

However, short- and long-term outcome after repeat heart transplantation is inferior to primary transplantation [1–5, 11–14]. Therefore, Haddad and other authors conclude that primary transplant candidates should receive priority because they are more likely to benefit from the procedure [8]. Nonetheless, survival after retransplantation has improved over the years, especially after acute retransplantation has widely been abandoned [15]. According to the latest report on Repeat Organ Transplantation in the United States 1996–2005 the 1-, 3- and 5-year graft survival of the retransplant group was 82%, 70% and 58% compared to 86%, 80% and 73% in the first transplant group. The relative risk for graft loss after retransplantation was 1.34 (p = 0.15) at 1 year and decreases to 1.16 (p = 0.43) at 3 years compared to primary transplantation. Survival after retransplantation was significantly affected by the interval between the first and second transplantation [5]. The same results were reported by the International Society for Heart and Lung Transplantation. They found that patients undergoing retransplantation during 2002 to 2005 who were >12 months from the initial transplant procedure experienced a 1-year survival rate of approximately 85%, the same as primary transplants performed during the same period. Moreover, a significant survival benefit was shown for those patients who underwent cardiac retransplantation after an interval of more than 12 months after the initial transplantation compared to those with shorter intervals [9].

Concerning retransplantation in children, an analysis of the United Network for Organ Sharing (UNOS) data found survival following retransplantation that did not differ from that following primary transplantation if early retransplants (<6 months) were excluded [1]. These results were supported by other large single center reports [16, 17].

Because of the ongoing discussion about the justification of repeat heart transplantation in the context of donor organ shortage the Working Group on Heart Retransplantation has released a consensus paper on the indications for this therapeutic option. According to the authors heart retransplantation should be considered in patients with chronic allograft dysfunction. Patients with acute rejection are considered inappropriate retransplant candidates. The authors also suggest that patients with short-term mechanical cardiorespiratory support as well as older patients and patients with post-transplant lymphoproliferative disorder deserve careful consideration on an individual basis. The role of combined kidney transplantation has to be determined. The guidelines are based on available data and personal experience of the authors [1]. As described above our results support the findings of the Working Group.

The individual decision about retransplantation is also influenced by ethical considerations. According to Haddad, the shortage of donors poses an ethical dilemma for allocation of donors and managing of the waiting list. He suggests that since the earliest days of cardiac transplantation, it became apparent that cardiac retransplantation was going to be an inevitable consideration in a proportion of cardiac transplant recipients [8]. In other words, an institution that performs heart transplantation is inevitably confronted with patients requiring retransplantation. In our opinion, this therapeutic option should not be withheld from these patients despite the higher operative and postoperative risk. According to our experience, the option of retransplantation is already a major concern of patients presenting for primary transplantation especially if they are younger. The question after long-term patient survival cannot be answered without consideration of long-term graft survival. The Working Group believes that whether considering primary transplant or retransplantation, an important factor in defining candidacy is the likelihood of success following transplantation. Thus, carefully selected candidates for retransplantation may have a better chance at a successful outcome than some patients undergoing primary transplantation today [1].

Our policy of the selection of retransplant candidates is based on the individual evaluation of every patient. Exclusion criteria for cardiac retransplantation based on our institutional experience are comparable to those reported by other groups: any kind of malignancy, severe pulmonary hypertension, concomitant end-organ failure (renal, hepatic or pulmonary), and evidence of patient non-compliance [3]. Other relative contraindications are severe peripheral vascular disease, severe osteoporosis as well as severe deterioration of the patients’ general physical status. In case of renal failure combined transplantation is a feasible option in selected patients. As described above, combined renal and repeat heart transplantation was performed only once at our institution, whereas 11 patients of the primary transplant group received combined transplantation. According to our results survival after retransplantation was influenced by recipient gender and age as well as the era of transplantation and the interval between both transplants. A mortality rate of more than 50% after acute retransplantation led to a change of our policy. We have learned to accept acute graft failure as a contraindication for repeat heart transplantation although there is no alternative therapeutic approach for these patients.

### Table 6
Multivariate analysis of risk factors affecting retransplant survival

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>p value</th>
<th>Odds ratio</th>
<th>95% Confidence Interval</th>
</tr>
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<tbody>
<tr>
<td>Recipient female gender</td>
<td>1.215</td>
<td>0.013</td>
<td>3.37</td>
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5. Conclusion

Cardiac retransplantation is associated with lower survival rates compared to primary transplantation. However, results after retransplantation in chronic graft failure are significantly better compared to acute graft failure. Therefore, we consider cardiac retransplantation in chronic graft failure a justified therapeutic option in a growing number of patients. In contrast, patients with acute graft failure seem to be inappropriate candidates for cardiac retransplantation.

References


Appendix A. Conference discussion

Dr C. McGregor (Rochester, Minnesota, USA): This was a very clean, helpful paper; but it illustrates a number of issues. What we have been discussing in the previous papers about the quality of donors, of course, leads to early problems after transplantation. And so what we have is a series of decisions, both in terms of donor selection and management, leading into transplantation and then early transplant failure. My own belief is in patients who have early graft failure is to make an early decision for either right ventricular assist or biventricular assist, and I think that the outcomes in our experience are much better than immediate retransplantation.

We’re running into tremendous programmatic bias and high selection bias that is not in the manuscript. The average age of the retransplanted patient is still under 50. So could I ask you, my impression is that the patients that you’re retransplanting for coronary artery disease are highly selective; is that correct?

Dr Goerler: That’s correct. We exclude patients with severe comorbidities such as renal failure. Moreover advanced age is another exclusion criterion. That is why results of cardiac retransplantation are relatively good.

Dr D. Loaisis (Creteil, France): Are you accepting patients with late deterioration of the graft because of coronary disease associated to chronic renal insufficiency? Are you doing them?

Dr Goerler: You mean if we accept patients with renal disease for retransplantation? In case of the first transplantation we accept those patients for combined heart and kidney transplantation. But in retransplantation, we are really reluctant to perform retransplantation in patients with associated renal disease.

Dr Loaisis: But we do have now plenty of patients with a 15-year history of cardiac transplantation who, unfortunately, 15 years ago were receiving a high dose of cyclosporine which killed the renal function. What are you doing with these patients 15 years after their transplantation? Usually they are on dialysis for at least 5–6 years, are you accepting them or do you refuse them?

Dr Goerler: We would, as I said, be very reluctant. The problem is that there is no real alternative for those patients. Assist device implantation is no good option for those patients as well if they are on dialysis. But I think for some patients we don’t have any further therapeutic options.

Dr A. Simon (Hannover, Germany): Simon from Hannover from the same program.

We are very, very reluctant to accept anybody for retransplantation who has associated comorbidities. These patients are highly screened. And we are very lucky that we do not have an extremely high pressure for retransplantation in patients with associated renal disease. We had a very excellent postoperative management by our cardiologists; so we don’t have a lot of renal failure in our patients. However, we would probably not accept the patient if he has significant renal disease and may have to undergo dialysis after the retransplant. So if you would consider doing a combined organ, we wouldn’t do it. We are very, very reluctant to have associated risks, because of the data. If you want to do that, you really have to choose your recipient.

Dr Loaisis: But when you look at the data through combined cardiac and renal retransplantation, there is no difference.

Dr Simon: Yes. But in our hands, we haven’t been there yet.