Can cardiac re-transplantation be performed with an acceptable survival after primary graft failure?

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Received 9 September 2004; accepted 9 September 2004

Summary

A best Evidence topic in Cardiothoracic surgery was written according to a structured protocol. The question addressed was whether cardiac re-transplantation can be performed with an acceptable survival in patients who suffer primary graft failure? Altogether 458 papers were found using the reported search, of which 18 presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are tabulated. We conclude that while re-transplantation for graft coronary disease has a similar survival to patients undergoing primary transplantation, acute graft failure or rejection should be treated with a mechanical assist device, as acute re-transplantation is associated with an unacceptably high mortality.

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Keywords: Evidence-based medicine; Re-transplantation; Heart transplantation; Acute graft failure

1. Introduction

A Best Evidence Topic was constructed according to a structured protocol. The protocol is fully described in the ICTVS [1]

2. Clinical scenario

You are performing a heart transplant on a 34-year-old lady who had a diagnosis of dilated cardiomyopathy. The Donor heart was harvested by another unit. The harvesting surgeon stated that the heart was good quality but in his clinical notes that came with the donor heart he reported a short period of ventricular dilatation prior to explantation.

The transplant is proceeding without complication until you reperfuse the heart and prepare to wean the patient off bypass. No activity returns to the heart and even after 2 h of reperfusion the donor heart shows no sign of myocardial contraction or electrical activity.

The patient remains on bypass for a further 6 h, during which time your hospital receives another offer of a heart, which would be entirely suitable for this lady. However, there is also a 56-year-old man on your list for which it would also be suitable.

After much discussion with your colleagues it is decided that an acute re-transplantation would be too high risk and the man should get the heart. Your patient has a Left and Right Impella Recover device in order to allow this first donor heart more time to recover.

Unfortunately on the Intensive Care, the patient’s clinical condition quickly deteriorates and she dies 24 h later. You are still unsure as to the success rate of acute re-transplantation and also whether the long-term survival is as good with acute re-transplantation and therefore you resolve to look up the literature on this subject.

3. Three part question

In patients with [acute heart transplant failure] is [re-transplantation] a valid treatment option in terms of an acceptable [operative and long term mortality]

4. Search strategy


5. Search outcome

Four hundred and fifty-eight papers were identified by the above search of which 11 papers were deemed to be relevant. In addition to the ISHLT registry, two relevant case reports and four papers identified by cross-checking reference lists were also identified (Table 1).

6. Comments

Radovancevic et al. [2] searched the Cardiac Transplant Research Database from the USA and Canada from 1990 to
Table 1

<table>
<thead>
<tr>
<th>Author, date, country</th>
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<th>Outcomes</th>
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| Radovancevic, J Heart Lung Transplant, USA [2] | 106 patients undergoing re-transplantation from a database of 7290 primary heart transplants from 42 USA and Canadian centres (1990–1999). | Cohort study (level 2b) | Survival if re-transplantation <1 year after first operation | Re-transplant 54% 1-year survival Primary transplant 85% 1-year survival | Patients undergoing re-transplantation for coronary allograft failure after 1996 had same survival to primary heart transplant patients. 
Results poor for patients undergoing re-transplant <6 months after first surgery and for acute graft failure or acute rejection |
| Srivastava, for ISHLT/UNOS registry, 2000, Transplant, USA [3] | 514 adult patients who underwent cardiac retransplantation in the United States between October 1987 and August 1998. Data obtained from Joint ISHLT and UNOS registries. | Cohort study (level 2b) | Survival after 1993 when patients with primary graft failure or acute rejection <6 months post-surgery were refused re-transplantation | Survival after 3 years 70% 1-year survival | One year follow up data available in only 234 patients (45.5%) 
90% of patients on inotropes, 27% had a VAD, 31% on an ventilator, 23% IABP |
| Schnetzler, 1998, Ann Thorac Surg, France [5] | 24 re-transplantations from 1973 to 1996, compared to 47 first transplants in patients matched for date of transplantation. | Case control study (level 3b) | Survival if re-transplantation <1 year after first operation | Survival if re-transplantation <1 year after first operation | The cohort has four patients with primary graft failure who were re-transplanted at day 1, 3, 9 and 30, respectively and only the last patient was alive in 1999 after 9 years after the graft while the others died at day 1, 3 and 13. |
| Smith, 1995, J Heart Lung Transplant, USA [6] | 63 patients undergoing re-transplantation at a single institution since 1968. Causes nine primary allograft failure 17 acute rejection 37 graft atherosclerosis three constrictive disease | Cohort study (level 3b) | Survival for primary transplantation | Survival for primary transplantation | (Compared to 81% 1 year and 44% 5 year survival in primary transplants) |
| John, 1999, J Thorac Cardiovasc Surg, USA [7] | 43 patients undergoing re-transplantation from 1977 to 1999 at a single Centre. Cause 33 graft coronary disease seven acute rejection two primary graft failure | Cohort study (level 2b) | Survival in re-transplantation | Survival in re-transplantation | Five patients had re-transplantation within 1 month, all died |

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<td>Interval: 10 h to 11 years</td>
<td>46 patients in the Eurotransplant programme undergoing re-transplant after acute graft failure and high urgent listing.</td>
<td>Cohort study (level 2b)</td>
<td>Survival</td>
<td>1-year survival was 36% compared to 81% for primary transplant</td>
<td>23 cases re-transplanted within 30 days</td>
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<td>De Boer, 1991, Lancet, Holland [16, 17]</td>
<td>13 patients had an LVAD and five patients had an IABP</td>
<td>Survival</td>
<td>Patients on LVAD support had a 21% 1 year survival 1–213 days, 17 within 1 week</td>
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<td>Mullins, 1991, Lancet UK [8]</td>
<td>12 patients undergoing acute re-transplantation at Papworth hospital</td>
<td>Case series (level 4)</td>
<td>Survival</td>
<td>All four patients re-operated within 11 days died.</td>
<td>This is a letter only</td>
</tr>
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<td>Kanter, 2004, Ann Throac Surg, USA [13]</td>
<td>17 children undergoing 20 re-transplantations</td>
<td>Cohort study (level 3b)</td>
<td>Survival at 1 and 3 years</td>
<td>Re-transplantation 94% 1-year survival 78% 3-year survival</td>
<td>Only 2 children had re-transplantation due to acute graft failure, one died.</td>
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<td>Dearani, 2001, Ann Thorac Surg, USA [14]</td>
<td>22 children undergoing re-transplantation from 1985 to 1999 Causes five primary graft failure one acute rejection 16 allograft vasculopathy</td>
<td>Cohort study (level 2b)</td>
<td>Survival</td>
<td>Re-transplantation 82% 3-year survival Primary transplant 77% 3-year survival</td>
<td>Both children who required ECMO and the child who required iv inotropes died within 30 days</td>
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<td>Taylor et al. for ISHLT, 2004, J Heart Lung Transplant [15]</td>
<td>ISHLT registry from 1982 to 2003, of which 2% are re-transplantations. 19% of patients transplanted in 2003 are on LVAD support 13 523 patients from 1995 to 1998 7067 patients from 1999 to June 2002 (roughly 140 re-transplants)</td>
<td>Cohort study (level 2b)</td>
<td>Survival of re-transplantation when 12 months after first transplant Risk of re-transplantation on mortality</td>
<td>Re-transplantation 82% 1 year survival Primary transplant 83% 1 year survival 1995–1998 re-transplant odd ratio for increased risk 1.76 P&lt;0.0001 1999–June 2002 re-transplant odds ratio for increased risk 1.08 P=0.7</td>
<td>LVAD implantation is no longer a risk factor for mortality.</td>
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1999, specifically looking at the results of 106 patients undergoing re-transplantation. They found that patients who had suffered early graft failure or acute rejection performed particularly poorly as did any patients re-operated within 6 months of the first transplant with a 1-year survival of less than 50%. They did report that in the last 4 years of the database figures were improving and that coronary allograft vasculopathy patients were now surviving as successfully as primary heart transplant patients. It is not clear from this paper how acutely the 36 patients who had re-transplantation less than 1 month post-op had their second operation.

Shrivastava in 2000 [3] reported results from 514 patients who had undergone re-transplantation. They found only a 50% 1-year survival in patients having re-transplantation within 6 months of their first operation, and only a 65% 1-year survival overall. This was a very ill cohort of patients with 90% on iv inotropes, 27% on a ventricular assist device and 31% ventilated, although there was no subset analysis of patients having a re-transplantation within days of first operation. Of note this study had 1 year follow up data on only 45% of their patients.

Schlechter [4] briefly reported the Vienna experience of 31 cases. They had a 48% 1-year survival and a 37% 5-year survival although they did not report any breakdowns of the clinical status of the patients or the time to re-transplantation.

Schnetzler [5] reported 24 cases of re-transplantation. Four patients had early re-operation, at days 1, 3, 9 and 30 and only the patient having the re-operation at 30 days survived. Overall results showed a 46% 1-year survival.

Smith et al. [6] reported the results of 63 patients who underwent re-transplantation. They achieved an overall 55% 1 year survival and a 33% 5 year survival which was

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<td>Loire, 1991, Arch Mal Coeur</td>
<td>38 patients undergoing re-transplants</td>
<td>Cohort study (level 2b)</td>
<td>Survival</td>
<td>Re-transplantation for graft coronary disease similar to primary transplantation</td>
<td>In acute re-transplantation group nine out of 12 patients died</td>
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<td>Vaiss, France [9]</td>
<td>26 cases of graft coronary disease and rejection (50% re-operated within 12 days)</td>
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<td>Michler, 1993, J Thorac Cardiovasc Surg, USA [10]</td>
<td>14 patients undergoing re-transplantation</td>
<td>Cohort study (level 2b)</td>
<td>Survival</td>
<td>Re-transplantation 71% 1-year survival 60% 2-year survival</td>
<td>Primary transplant 75% 1-year survival 71% 2-year survival</td>
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<td>Marelli, 2000, Clin Transplants, USA [18]</td>
<td>47 patients undergoing re-transplantation at UCLA, California, from 1988. Nine patients had re-transplantation for acute graft failure.</td>
<td>Cohort study (level 2b)</td>
<td>Survival</td>
<td>Re-transplantation 43% 5-year survival Primary transplantation 75% 5-year survival</td>
<td>Report on 47 re-transplantations is a short report of their full experience of 1000 transplants in this paper</td>
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<td>Ensley, 1992, J Heart Lung Transplant, USA [19]</td>
<td>449 patients undergoing re-transplantation, reported to the registry of The International Society for Heart and Lung Transplantation from 1968 to 1991, and a matched group of 421 primary heart transplants.</td>
<td>Cohort study (level 2b)</td>
<td>1 year survival</td>
<td>Re-transplantation 48% 1-year survival Primary Transplant 79% 1-year survival P&lt;0.001</td>
<td>Re-transplantation patients had a 15% 24 h mortality. These are data from a very old database. 'Ideal' patients undergoing re-transplantation 68% 1-year survival</td>
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significantly poorer than their 81% 1 year survival in primary heart transplant patients.

John et al. [7] reported a dismal survival in patients with acute graft failure with death occurring in all five patients being re-transplanted within 1 month of primary transplant. However, after they instituted new guidelines for re-transplantation, namely excluding patients with acute graft failure, acute rejection within 6 months, end-organ dysfunction or pulmonary hypertension, their 4-year survival was 94%. Also the overall results of the 43 patients undergoing re-transplantation were not significantly different to their cohort of primary transplants.

In 1988 the Eurotransplant organ exchange programme initiated a ‘high urgency’ priority for patients undergoing re-transplantation for acute graft failure. Forty-six patients underwent re-transplantation, 13 of whom had a Left ventricular assist device (LVAD) and five with an IABP. The survival was poor with only a 36% 1-year survival. In addition, patients on an LVAD had a 21% 1-year survival and 17 of all 28 deaths occurred within 1 week of retransplantation. These results were disappointing and the High urgency system for re-transplant was stopped. Papworth surgeons [8] replied in a letter to these reports stating that in four patients re-transplanted by themselves within 11 days of acute failure all died, and only eight patients with coronary occlusive disease have so far survived in their experience.

Loire et al. in France [9] performed 42 re-transplantations in 38 patients. While survival was comparable to primary surgery in patients that suffered graft coronary disease, nine out of 12 patients who suffered acute graft failure died after re-transplantation.

Michler [10] reported 14 patients who underwent re-transplantation. Their 71% 1-year survival was similar to primary transplantation, although all but one were performed more than 30 days after first transplant. They conclude that except for acute graft failure, re-transplantation has a good survival.

Two case reports were found that were similar to our own case scenario (not included in the table). Jurmann [11] reported the case of a patient who had immediate graft failure. An IABP was placed and an AVAD to assist the right ventricle and allow weaning from bypass. This patient was then quickly re-transplanted and is NYHA class I, 13 months after re-transplantation. In a second patient reported by Wahlers [12], the donor heart suffered left ventricular distension on harvesting. Immediate graft failure occurred complicated by aortic valve insufficiency. The Aortic valve was replaced, and an IABP inserted, but CPB could not be weaned. After 11 h on CPB another donor heart became available and was successfully re-transplanted, and the patient was well 3 months post-operatively.

Marelli et al. [18] reported their experience with 47 re-transplantations. Six of the nine patients with acute graft failure died and overall the 5-year survival was 43%, which was significantly poorer than their 75% survival in 1000 primary transplantations.

Ensley [19] performed a risk analysis of 449 patients who underwent re-transplantation from the ISHLT database from 1968 to 1991. They found that patients undergoing re-transplantation had a significantly lower survival with a 48% 1-year survival, compared to 79% for primary transplant. Predictive risk factors for mortality were: re-transplant within 6 months of the first operation; presence of a mechanical assist device and acute graft failure.

In contrast to adults, children seem to do better with re-transplantation, although acute graft failure is still associated with a high mortality. Kanter [13] reported a 95% 1-year survival in 17 children, although one of the two children with acute graft failure died. Dearani [14] reported re-transplantation in 22 patients. They report an 81% 3-year survival, which is the same as for their primary transplants, although two patients on ECMO and one patient on iv inotropes died.

The ISHLT is the largest registry of Heart transplants and has provided a yearly report for many years now, including reports on re-transplantation in the past. Here only the 2004 paper is included. This report [15] provides some very interesting data on re-transplantation. In contrast to previous years, re-transplantation is no longer a risk factor for increased mortality, with the odds ratio for increased risk having dropped from 1.76 in 1995–1998 to 1.08 in 1999–2002. This is thought to be due to more stringent guidelines for re-transplantation, and alternative strategies for acute graft failure including mechanical assist devices. It is also interesting to note that the presence of a mechanical assist device no longer contributes to decreased survival. The registry reports that the incidence of re-transplantation remains at approximately 2% with approximately 140 being performed between 1999 and 2002.

Thus in summary, acute re-transplantation due to graft failure has been a much-tested strategy but is associated with a high mortality. Far more successful is re-transplantation for graft coronary disease many months or years after primary surgery. In view of the decreasing availability of donor hearts and the improving success of mechanical assist devices, the management of acute graft failure or acute rejection should now consist entirely of placement of a mechanical assist device.

The ISHLT reports that this strategy allows safe re-transplantation in patients with graft coronary disease or stable patients with mechanical assist devices.

7. Clinical bottom line

While re-transplantation for graft coronary disease has a similar survival to patients undergoing primary transplantation, acute graft failure or rejection should be treated with a mechanical assist device, as acute re-transplantation is associated with an unacceptably high mortality.

References


