Risk factors for post-transplant low output syndrome†

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Original Article

INTRODUCTION

Primary graft dysfunction (PGD) is a life-threatening condition that is a major cause of early mortality after cardiac transplantation. As the number of acute rejection cases has reduced, PGD has become the leading cause of death in the first 30 days after transplantation (39% of deaths) and continues to remain prominent throughout the post-transplant period [1]. This condition is defined as severe dysfunction of the cardiac allograft without any obvious anatomic or immunologic cause, and is characterized by low output syndrome (LOS), which requires high-dose inotropic or mechanical support [2]. The incidence of PGD is reported to be greater than 20% [3, 4]. Although veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) has been found to improve outcomes in PGD patients, mortality remains high [5]. Despite the high incidence and high mortality rate, the mechanisms underlying PGD are uncertain. Consequently, donor selection has not been established, because the predicted risk factors are uncharacterized. On the other hand, due to a serious donor shortage in Japan, acceptance of marginal donors is essential. Although extended donor acceptance criteria were recently reported to not compromise clinical outcome, donor-related risk factors for post-transplant PGD remain uncertain [4, 6, 7]. In the present study, we evaluated donor-related factors associated with postoperative LOS and long-term survival.


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Methods

Recipients

Between May 1999 and February 2011, 36 patients underwent heart transplantation at our institution (Table 1). They were comprised of 27 males (75%) and 9 females, with ages ranging from 14 to 60 years old (mean 38 ± 11 years). Causes of refractory heart failure were dilated cardiomyopathy in 32 (89%), dilated phase of hypertrophic cardiomyopathy in 2 (6%), ischaemic cardiomyopathy in 1 (3%) and restrictive cardiomyopathy in 1 (3%). Six recipients (14%) were rated as New York Heart Association (NYHA) class IV, with inotropic support and left ventricular assist devices (LVADs) employed in the remaining 30 recipients (86%), which were comprised of 25 Nipro (previously Toyobo)-extracorporeal LVAD, 2 Heart Mate VE, 1 Novacor, 1 EVAHEART and 1 Jarvik 2000 devices. The support periods ranged from 3 to 57 months (mean 30 ± 13 months).

Donors

According to criteria proposed by Laks et al. [7] and Wittwer and Wahlers [8], we considered marginal donors as those as those who were older than 50 years of age, those requiring high inotropic support (intravenous infusion of more than 10 µg/kg/min of inotropic agents or epinephrine) and those affected by left ventricular hypertrophy (echocardiographic diagnosis of left ventricular septum thickness >13 mm and left posterior wall thickness >13 mm), small left ventricular diameter (echocardiographic diagnosis of left ventricular diameter < 36 mm) or reduced left ventricular contraction [echocardiographic diagnosis of left ventricular ejection fraction (LVEF) less than 55%]. Prolonged ischaemic time (>4 h) and recipient/donor ratio for body weight less than 0.8 were also considered marginal parameters. Informed consent was obtained from all recipients. Donor-recipient matching criteria were based on blood group compatibility, morphological criteria and clinical conditions of the recipients.

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<tr>
<th>Variables</th>
<th>Value</th>
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<tr>
<td>Male/female</td>
<td>27/9 (75% males)</td>
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<td>Age in years</td>
<td>38 ± 11 (14–60)</td>
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<td>Indications for heart transplantation</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>32 (89%)</td>
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<td>Dilated phase of hypertrophic cardiomyopathy</td>
<td>2 (6%)</td>
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<tr>
<td>Ischaemic cardiomyopathy</td>
<td>1 (3%)</td>
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<tr>
<td>Restrictive cardiomyopathy</td>
<td>1 (3%)</td>
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<tr>
<td>Mechanical circulatory support (MCS)</td>
<td>30 (86%)</td>
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<tr>
<td>Nipro (Toyobo)-extracorporeal LVAD</td>
<td>25 (72%)</td>
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<td>HeartMate VE</td>
<td>2 (6%)</td>
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<td>EVAHEART</td>
<td>1 (3%)</td>
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<td>Novacor</td>
<td>1 (3%)</td>
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<td>Jarvik 2000</td>
<td>1 (3%)</td>
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<tr>
<td>Support period of MCS in months</td>
<td>30 ± 13 (3–57)</td>
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<td>Status one</td>
<td>36 (100%)</td>
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LVAD: left ventricular assist device; MCS: mechanical circulatory support.

Cardiopulmonary bypass

After the aorta of the donor heart was cross-clamped, cold cardiopulmonary bypass was established via the aortic root. St Thomas solution was used in the first six cases and Celsior in the subsequent 30 cases [9]. The total amount of Celsior was 2–3 l, based on donor heart size.

Operative technique for implantation

A modified bicaval anastomosis technique was applied, as previously reported [10]. Care was taken to avoid cardiac re-warming, with ice slush generously poured into the pericardial cavity. Before releasing the cross-clamp, terminal blood cardioplegia solution was given for 10 min.

Immune suppression

A conventional triple drug immune-suppressive therapy was administered to the entire population of recipients. Methylprednisolone (0.5 + 0.5 g) was given intra-operatively before aortic cross-clamp removal, followed by three 125-mg pulses during the first postoperative day. Prednisone was commenced orally following extubation. The induction immunotherapy course, when required, was initially muromonab-CD3 (Orthoclone OKT3), while basiliximab was given in more recent years [11, 12]. Cyclosporine A (Neoral®, Novartis International AG, Basel, Switzerland) or tacrolimus hydrate (Prograf®, Astellas) combined with mofetil mycophenolate (Cellcept®, Roche) was commenced on the second postoperative day [12, 13]. Tacrolimus hydrate was given as first-line treatment beginning in 2007.

Follow-up examinations

The entire patient population in this study had immediate postoperative evaluations. Epicardial two-dimensional (2-D) echocardiogram findings were obtained daily for the first week and weekly for the first month. Furthermore, 2-D colour flow Doppler echocardiogram examinations of the four subcostal and apical chambers were performed. Right heart catheterization through a Swan-Ganz catheter was obtained within the first 48 h. A right ventricular flow-directed pulmonary artery catheter was inserted and advanced into the pulmonary artery until wedge pressure was determined. Measurements of pulmonary artery pressure, wedge pressure, central venous pressure, cardiac index and cardiac output were recorded. Graft dysfunction was defined as a cardiac index lower than 2.21/min/m² with adequate medical therapy, or the requirement of intra-aortic balloon pumping (IABP) and/or VA-ECMO.

Pathological examinations

Pathological examinations including rejection surveillance were performed using endomyocardial biopsies, which were carried out after 1, 2, 3, 5, 7 and 11 weeks, then after 4.5, 6, 9 and 12 months. Specimens were stained with Masson’s trichrome and...
haematoxylin–eosin. Diagnosis of acute cardiac rejection was made according to the International Society for Heart and Lung Transplantation (ISHLT) criteria [14]. Perioperative ischaemic myocardial injury (PIMI) was also assessed using PIMI score (0–3), as described by Fyfe et al. [15], with a score of 0 considered to be no evidence of coagulative myocyte necrosis (CMN), 1 showing mild or focal CMN, 2 showing moderate or multifocal CMN and 3 showing severe or confluent CMN (Fig. 1).

Statistical analysis

Data are shown as the mean ± standard deviation. Categorical variables were analysed by a χ²-test when all expected cell frequencies were greater than or equal to 5. Comparisons of values between patients were done using a Mann–Whitney U-test for independent samples. All analyses were performed using the statistical software package JMP 8 (SAS Institute, Inc., Cary, NC, USA). Differences were considered significant with a P-value less than 0.05%. Actuarial survival was estimated using the Kaplan–Meier method.

RESULTS

Survival

No perioperative deaths occurred and only one patient died (sepsis) up to 4 years after transplantation, for an overall 10-year actuarial survival rate of 95% (Fig. 2). There was no haemodynamically compromised antibody-mediated rejection observed.

Primary graft dysfunction

The patient baseline characteristics are shown in Table 2. The age of the donors was 39 ± 11 years, which was not significantly different than the recipient age. Although half of the donors were female and 31% of the cases were female to male transplantation, the donor–recipient weight ratio was 1.2.

Echocardiography revealed cardiac function was maintained with LVEF of 65 ± 10%, which was supported by 8.0 ± 5.2 µg/kg/min of catecholamine. The average ischaemic time was 209 ± 21 min and there was only one case that exceeded 240 min.

PGD was observed in seven patients (19%). Five patients showed a low cardiac index less than 2.2 l/min/m² with adequate postoperative medical treatment. One patient required VA-ECMO and IABP, and one required IABP. The patient who required VA-ECMO showed severely reduced LV contraction soon after transplantation and estimated LVEF assessed by intraoperative transoesophageal echocardiography was 10%. However, weaning from VA-ECMO on day 1 and from IABP on day 4 was successful with maximum inotropic support, including epinephrine, though LVEF was 47% after 1 week and 48% after 1 month. On the other hand, the patient who required IABP was weaned successfully on day 2, and cardiac function recovered quickly to an LVEF of 72% after 1 week. The other five patients had uncomplicated postoperative courses.

The causes of PGD were assessed and statistical analysis showed that it was significantly associated with high-dose

![Figure 1: Representative biopsy specimen obtained from right side ventricular septum. Zonal myocardial necrosis with marginal granulation change is shown. The histology was consistent with a PIMI score of 3. Masson’s trichrome stain, original magnification ×100.

Figure 2: Kaplan–Meier survival estimates after transplantation.

Table 2: Donor demographics

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<th>Variables</th>
<th>18/18 (50%)</th>
<th>39 ± 11</th>
<th>22 (61%)</th>
<th>10 (28%)</th>
<th>3 (8%)</th>
<th>1 (3%)</th>
<th>1.2</th>
<th>33 (92%)</th>
<th>8.0 ± 5.2</th>
<th>42 ± 6</th>
<th>27 ± 6</th>
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<th>10 ± 2</th>
<th>65 ± 10</th>
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LVDD: left ventricular diastolic diameter; LVEDs: left ventricular systolic diameter; IVS: interventricular septum; PWth: posterior wall thickness; LVEF: left ventricular ejection fraction.
was lower in patients with PGD (Table 4).

Recipient related factors

- History of stroke
- Exit site infection of LVAD
- Creatinine clearance < 30 ml
- PVR > 4.0 wood unit

Recipient related factors

- Elderly (>50 years old)
- LV hypertrophy
- Exit site infection that required intravenous antibiotics

Histories of stroke, including haemorrhagic stroke, and LVAD exit site infection that required intravenous antibiotics due to LVAD exit site infection.

Recent cardiac arrest indicates patients who required resuscitation. History of stroke indicates patients who suffered from stroke or haemorrhagic stroke during LVAD support. Exit site infection indicates patients who required intra-venous infusion of antibiotics due to LVAD exit site infection.

Postoperative maximum CKMB (U/l) 58 ± 35 75 ± 54 0.51
Days in intensive care unit 6.4 ± 3.7 6.6 ± 4.2 0.97

High dose inotropic support indicates patients who required intravenous infusions of more than 10 µg/kg/min of inotropic agents or epinephrine. Recent cardiac arrest indicates patients who required resuscitation. History of stroke indicates patients who suffered from stroke or haemorrhagic stroke during LVAD support. Exit site infection indicates patients who required intra-venous infusion of antibiotics due to LVAD exit site infection.

Postoperative maximum CKMB was also significantly lower in patients with PGD (Table 4).

Conclusion

- Factors associated with PGD:
  - Elderly (>50 years old)
  - LV hypertrophy
  - Exit site infection

Preservation solution

We also assessed the effects of the preservation solution used for the donor heart after harvesting. The first 6 donor hearts were preserved with St Thomas solution, while Celsior was used in the next 30 cases. There were no significant differences in

- Cardiac index, day 0 (l/min/m²)
- Cardiac index, day 1 (l/min/m²)
- Cardiac index, day 2 (l/min/m²)
- Mean pulmonary pressure, day 0 (mmHg)
- Mean pulmonary pressure, day 1 (mmHg)
- Mean pulmonary pressure, day 2 (mmHg)
- LV Dd, 1 week (mm)
- LV Ds, 1 month (mm)
- LV Dd, 1 month (mm)
- Postoperative maximum CKMB (U/l)
- PIMI score (grades 0–3)
- Days in intensive care unit

Post-transplant cardiac function and ischaemic damage, comparison between preservation with Celsior and St Thomas solutions (Table 5).

Cardiac index, day 0 (l/min/m²) 2.8 ± 0.7 3.3 ± 0.7 <0.0036
Mean pulmonary pressure, day 0 19 ± 4 18 ± 1 0.25
LV EF, 1 week (%) 69 ± 9 65 ± 16 0.72
LV EF, 1 month (%) 71 ± 6 68 ± 9 0.47
Postoperative maximum CKMB (U/l) 58 ± 35 145 ± 58 0.0013
PIMI score (grade 0–3) 1.0 ± 0.8 2.3 ± 0.8 0.0054

Post-transplant cardiac function and ischaemic myocardial injury score.

Current clinical status

All patients were discharged from the hospital with good cardiac function. At the most recent follow-up examination, all except the
one death case, were NYHA class I or II. Furthermore, no recipient had pathological chronic rejection greater than grade 3.

DISCUSSION

The discrepancy between organ supply and demand in the field of heart transplantation has led to an increase in numbers of patients on waiting lists. Recent developments in LVADs and improvements in patient management have been very beneficial for patients with a failing heart, and allow bridging to transplantation. In the present series, the average LVAD support period was 2.5 years. However, patients with an LVAD have elevated risks of stroke, haemorrhagic stroke and infection, which are life-threatening complications.

Great efforts have been made to provide alternatives to heart transplantation, such as LVAD destination therapy with less complicated devices or cell transplantation for functional recovery of the damaged heart. Nevertheless, heart transplantation remains the gold standard for a failing heart [16, 17]. Although the regulations have been changed in Japan, resulting in a greater than 5-fold increase in number of donors, the waiting period remains the same, because demand has also increased. As a result, greater acceptance of marginal donors is essential.

In the present study, 28 (78%) donors were considered to be marginal as defined by criteria that included old age, high inotropic support, recent cardiac arrest, left ventricular hypertrophy, reduced left ventricular contraction, prolonged ischaemic time and donor–recipient size mismatch. However, only seven (19%) recipients showed postoperative LOS, of whom five did not require mechanical support. Fortunately, we had no hospital mortality and a 95% survival rate after 10 years. These results may be attributed to not only appropriate preservation methods and post-transplant management, but also donor selection. Since there were fewer chances for heart transplantation when compared with other countries, more attention had been paid to donor–recipient matching, such as donor–recipient weight ratio, dosage of catecholamine and ischaemic time. Moreover, maximum efforts were conferred to decrease these risks, such as replacing catecholamine by vasopressin to maintain systolic blood pressure, or preserving donor hearts with Celsior solution and transferring them mainly by in combination of helicopter and air planes. When the donor heart matched one of these criteria, careful attention was given to not overlap any two of those elements. There were 10 donors (28%) who were considered marginal by two matching criteria, while there was none considered to be marginal by more than three matching criteria. Furthermore, more attention was paid when donor–recipient size mismatch and LV hypertrophy were observed [18–20], which resulted in a limited number of donors who showed donor–recipient size mismatch or LV hypertrophy in our series (Table 3). In our analysis of donor condition, small ventricular size was shown to be a significant factor associated with postoperative LOS, as well as reduced LVEF and high inotropic requirement.

Donor–recipient size mismatch has been identified as a significant risk factor for PGD, as has female to male transplantation, which is likely associated with size mismatch [18, 20]. Small ventricular diastolic diameter is also expected to cause the same condition. Thus, it is important to consider LV size as well as donor–recipient size mismatch for donor selection. However, even with a small heart or a heart from a small donor, once the initial complicated period of LOS has passed, excellent long-term outcomes may be anticipated [21]. Therefore, acceptance of donors with a small left ventricular diameter might be reasonable when there are no other known disadvantages.

It is important to note that high-dose inotropic requirement for the donor heart implies not only impaired LV function, but also the possibility of continuous myocardial damage from increased oxygen demand and depletion of high energy phosphates from the myocardium [8]. Thus, a donor heart with reduced LV contraction that requires high dose inotropic support should be carefully evaluated by determining whether the myocardial damage is permanent. For optimal haemodynamic management to protect organ damage, arginine vasopressin is being used more often to maintain systolic pressure with lower levels of inotropic support, which may be helpful for appropriate evaluation [22].

All of our patients with postoperative LOS recovered cardiac function quickly, then were discharged from the intensive care unit about 6 days later and returned home without major concerns. Echocardiogram findings revealed nearly total recovery of LV contraction after 1 week. Optimal postoperative management, such as appropriate use of NO inhalation and inotropes, and proper indications for mechanical support should result in good outcomes. The present results suggest that cautious donor selection is essential when the donor heart has a small ventricular diameter or requires a high level of inotropic support. However, long-term survival in recipients with marginal donor hearts can be anticipated with adequate treatment.

A long preservation period is another hurdle to overcome for successful heart transplantation. To maximize the cardiac function of the donor heart postoperatively, a low level of ischaemic damage is critical. Preservation with Celsior may be less invasive and decrease ischaemic insult when compared with St Thomas solution. We found that creatine kinase-MB and postoperative PIMI scores were significantly lower in the Celsior group, although cardiac function was not different. Therefore, Celsior may contribute to expand acceptance for marginal donors, especially when a prolonged preservation period is expected.

Fortunately, we experienced only one VA-ECMO case and two IABP cases, but these mechanical supports were always on standby. Based on the excellent results by optimistic introduction of VA-ECMO for PGD, the hurdle for the use of them should be set low [3].

Although the number of patients analysed is small, our 10-year survival rate was 95%. Based on this excellent long-term result, we consider that acceptance of marginal donor hearts can be extended, when the donor is selected based on the donor–recipient matching and mechanical supports such as IABP and VA-ECMO are on standby. Furthermore, to maintain good long-term results in recipients in stable condition and also rescue marginal recipients, development of an alternate recipient list may provide a partial solution, although the concept of ‘marginal donors for marginal recipients’ is not commonly accepted at this time.

Conflict of interest: none declared.

REFERENCES

APPENDIX. CONFERENCE DISCUSSION

Dr A. Pavie (Paris, France): Yours is an unusual series because you performed only three transplantations per year which is quite a different experience from other transplant teams. A lot of the patients were supported on cardiac assist, 30 out of 36 patients, which is quite rare. How many other patients did you have on assist during this same period?

Dr Fujita: As you know, the waiting period for heart transplantation is pretty long, about three years in Japan. We selected to implant LVAD in patients who were mostly candidates for heart transplantation. The survival rate at three years for the patients with LVAD was about 60% and surviving patients undergo heart transplantation.

Dr Pavie: You had only LVAD patients on cardiac assist. Were any of your patients on biventricular support?

Dr Fujita: Only LVAD at the time of cardiac transplant.

Dr Pavie: Perhaps, we would like a better definition of marginal donor. When we look at your criteria, for us in Europe they are clearly not considered marginal donors. The mean level of drugs is low. You said in your series that seven patients had primary graft dysfunction. We have some concern about that. You put a patient on ECMO, and you are able to wean this patient after one day. Generally such patients stay one, two, or three weeks on ECMO before recovering good myocardial function. You wait a long time for a donor, but you have an excellent donor when you carry out the transplantation. It is an excellent paper but with a very particular approach which is difficult to compare with the European experience.

Dr Fujita: I agree with you.

Dr F. Beyerdsorf (Freiburg, Germany): As Dr Pavie has already said, in Europe we have completely different results, unfortunately, worse results. And 10 years ago, the survival of 95% is unknown to me. I know that in Japan you have a long history of resistance to transplantation, so that is the reason why you are not doing so many transplants. But could you give us some idea why the results are so extraordinarily good?

Dr Fujita: I think the major reason is we do not have many ischaemic myocardopathy patients. The idiopathic dilated cardiomyopathy patient is younger, and very few are in the vascular programme. This is the reason for the good long-term results I think. And the other thing is we have a special system called ‘medical consultant system’, in which the cardiac surgeon always goes to the donor side, and gives advice in order to better maintain the patient.

Dr Beyerdsorf: So you think that the treatment of the donor is often suboptimal? For example, in the UK, I heard the system to treat donors is much better than in other countries in Europe. So you think this is one of the main reasons?

Dr Fujita: Yes.

Dr D. Esmore (Victoria, Australia): The previous report by the Italian group suggests they only had 5.9% of their patients on VADs at the time of transplant. The world trend is towards your experience. Norman Shumway made a comment about six or seven years ago that he believed that everyone transplanted down the track will actually be transplanted off a VAD. So what you have is a group of VAD-supported patients who are stable at home, presumably, with a large investment in their wellbeing who will be potentially transplanted with donor organs that are perhaps older, perhaps of lesser quality, i.e. ‘marginal’. And, therefore, the risks perhaps that you are referring to in regards to 30-day mortality are probably only going to increase over time. The data for VAD-supported patients suggests that they do as well post-transplant as a non-VAD patient, but we do know the VAD pathway is more complex.

So actually what you are experiencing is a low organ donation rate, a high VAD implant rate, and still getting good outcomes post-transplant. I think this is something that is going to be a challenge down the track for all of us. The two-and-a-half or three-hour heart transplant that you complete and then go out to lunch, that is the past. Heart transplantation for the future will be in a mechanically-supported waiting list patient, often marginal donor cardiac allografts, with the challenge being to achieve the sort of results that you have presented. And I think that is where heart transplantation really is today. I comment on that and seek your response.

Dr Fujita: I think our experience is very small, so during the waiting period, the very long waiting period, we have automatically selected a good recipient. So the situation in the United States or Europe, where the patient gets worse and then they get their heart transplant in one month, is not realistic for us. Our patient stays in good condition for longer and gets a heart transplant. That is why we get a good result I guess.

Dr Esmore: But as for your mechanical support, I think the majority of patients only had a balloon pump, and two had ECMO and a balloon pump. So your primary graft failure, although present, is not actually associated with a requirement for VAD support, and the potential mortality associated with that and longer term support. With your donor rate being low, you may be pressured to use marginal donors, but they were not perhaps ‘marginal’ in your study given the aforementioned discussion. As the session moderator said, you still achieved very good results, and I think this is where the future of heart transplantation will perhaps be going for all of us.