Post-transplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices

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Abstract

Objective: We have previously shown that fixed pulmonary hypertension in cardiac transplant candidates can be lowered using left ventricular assist devices (LVADs). The post-transplant survival of these patients is uncertain as pulmonary hypertension may reappear, possibly affecting post-transplant survival. Materials and methods: Between 01/2000 and 01/2005 a total of 26 cardiac transplant candidates (92% male; mean age 56.2 years) in whom fixed pulmonary hypertension was lowered by LVAD implantation (pulmonary vascular resistance (PVR) before implantation: 5.1 ± 2.8 wood units (WU); PVR before cardiac transplantation: 2.0 ± 0.9 WU) underwent cardiac transplantation at our institution. These patients were age and sex matched with 52 cardiac transplant candidates without pulmonary hypertension undergoing cardiac transplantation during the same time period. Study endpoints were peri-transplant complications and long-term survival. Mean follow-up was 36 ± 14 months. Results: Peri-transplant mortality was 5% in patients after LVAD therapy and 7% in patients without prior LVAD therapy (p = .089). We observed 2 cases (4%) of acute right heart failure requiring mechanical support in patients without prior LVAD therapy. None of the patients with LVAD therapy developed peri-transplant right heart failure requiring mechanical support. Incidence of other peri-transplant complications was comparable between the two groups. Log-rank (p = .124) revealed comparable long-term survival between patients with (1 year: 85%, 2 year: 85%, 3 year: 85%) and without (1 year: 90%, 2 year: 82%, 3 year prior 79%) prior LVAD therapy. Conclusion: LVAD therapy lowers fixed pulmonary hypertension in cardiac transplant candidates with fixed pulmonary hypertension. Thereafter, long-term post-transplant survival is comparable to cardiac transplant recipients without pulmonary hypertension.

Keywords: Heart disease; Heart failure; Heart assist devices; Pulmonary hypertension; Transplantation

1. Introduction

Pulmonary hypertension unresponsive to vasodilator treatment is considered a contraindication for orthotopic cardiac transplantation. The reason for this is the unacceptable high risk of fatal right heart failure [1]. In the past early mortality rates of up to 40% have been reported in cardiac transplant candidates with pulmonary hypertension unresponsive to vasodilator treatment [1,2].

Up to date there is no generally accepted treatment for cardiac transplant candidates with pulmonary hypertension unresponsive to maximum vasodilator treatment. Heterotopic cardiac transplantation and reversing of fixed pulmonary hypertension using ventricular assist devices prior to cardiac transplantation have been reported to be successful treatment options in these patients [3–7]. However, heterotopic cardiac transplantation is associated with a variety of adverse effects in the long run (arrhythmias, thromboembolism) [3,8,9]. So far, the long-term post-transplant survival after lowering fixed pulmonary hypertension with ventricular assist devices has not been reported.

We have previously reported our experience with reversal of fixed pulmonary hypertension in cardiac transplant candidates using ventricular assist devices [7].

We now report on the long-term survival of cardiac transplant candidates in whom fixed pulmonary hypertension was successfully reversed by left ventricular assist device implantation.

2. Materials and methods

2.1. Patients

Between January 2000 and 2005 a total of 193 cardiac transplant candidates were treated at our department. Out
of those 35 consecutive patients presented with fixed pulmonary hypertension unresponsive to maximum vasodilator treatment. Those patients received a left ventricular assist device prior to cardiac transplantation. To qualify, all patients had to fulfill institutional inclusion criteria for terminal heart failure and had to have fixed PH unresponsive to maximum medical treatment. With the exception of fixed pulmonary hypertension patients had to be suitable for cardiac transplantation.

A total of consecutive 52 patients without pulmonary hypertension undergoing elective cardiac transplantation at our institution during the same time period served as age and sex matched controls. To qualify patients had to fulfill institutional inclusion criteria for terminal heart failure and had to be free from pulmonary hypertension. Furthermore, patients had to be suitable for matching according to age, sex and primary disease.

The study was approved by the institutional review board and all patients gave their written and informed consent prior to LVAD implantation, as well as subsequent cardiac transplantation.

Study endpoints were peri-transplant complications and long-term survival.

2.2. Left ventricular assist devices used

Three different systems of LVADs were used to reverse fixed pulmonary hypertension in the present study. Technical details as well as implantation procedures of the Micromed™ DeBakey (Micromed Technology Inc., Houston, USA) and Dura Heart™ (Terumo Heart Inc., Michigan, USA) (continuous blood flow), as well as the Novacor™ LVAD (World Heart Inc., Oakland, USA) (pulsatile blood flow) have previously been described [10—12].

2.3. Testing for reversibility of pulmonary hypertension

Right heart catheterization was performed according to the guidelines published by the ACC/AHA using a Swan-Ganz thermodilution catheter in all patients [13]. PH was defined as PVR > 3.5 wood units. In those patients with pulmonary hypertension, reversibility of PH was assessed by nitroglycerine, prostaglandin (PGI2), nitric oxide and levosimendan (only available in the last 10 patients). Nitroglycerine was applied intravenously at increasing doses of 2—6 mg/h with dose increments every 10 min. PGI2 was given intravenously at increasing doses of 10—200 ng/kg/min with dose increments every 5 min. Nitric oxide was administered in doses of 40, 60 and 80 ppm via a tight-fitting facemask. In the last 10 patients, levosimendan was additionally used for testing for reversibility of PH. If PH was not reversible to this treatment (below 3.5 wood units) it was considered as fixed. All the mentioned substances were tested in all pulmonary hypertension patients. In those patients with fixed pulmonary hypertension, right heart catheterization was repeated 3 days and 6 weeks after left ventricular assist device implantation.

2.4. Statistical analysis

Data are presented as frequency distributions and percentages. Values of continuous variables are expressed as mean ± standard deviation (SD). Continuous variable were compared using analysis of variance (ANOVA-Bonferroni). Categorical variables were compared by means of chi-square or Fishers exact test as appropriate. Kaplan-Meier analysis was used to calculate long-term survival along with al log-rank p-value when comparing groups. p-values < .05 were considered significant two-sided. The study was analysed using SPSS 11.5 (SPSS Inc., Chicago, Ill).

3. Results

3.1. Demographics

Patient characteristics of cardiac transplant candidates with and without fixed pulmonary hypertension are given in Table 1. All patients receiving an LVAD prior to cardiac transplantation were elective patients, free from inotropic or mechanical support. All patients received maximum standard heart failure therapy. With the exception of PVR patients were completely comparable with regard to patient characteristics.

3.2. Bridge to transplant success and reversal of pulmonary hypertension

Twenty-six patients (74%) were successfully bridged to cardiac transplantation. A total of 51.3% of patients experienced a complication while on LVAD support. Cerebrovascular events occurred in 31% of patients and infections in 25.7%. Cerebrovascular events were the most common cause of death present in 45.4% of patients followed by multi organ failure (36.3%) and infections (18.3%). Pulmonary vascular resistance (prior to LVAD implantation 5.1 ± 2.6 vs 6 weeks after LVAD implantation 2.0 ± .8, p < .0001) and mean pulmonary artery pressure (prior to LVAD implantation 44.0 ± 6.2 vs 6 weeks after LVAD implantation, p < .0001) normalized in all patients 6 weeks after LVAD implantation.

3.3. Post-transplant outcome

Peri-transplant mortality was 5% in patients after LVAD therapy and 7% in patients without prior LVAD therapy (p = .089). We observed 2 cases (4%) of acute right heart failure (years) 5.3 .752

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>w fixed PH</th>
<th>w/o PH</th>
<th>p-value</th>
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<tbody>
<tr>
<td>n</td>
<td>35</td>
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<tr>
<td>Age (years)</td>
<td>56.6 ± 7</td>
<td>54.2 ± 5</td>
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<tr>
<td>Male (%)</td>
<td>88.5</td>
<td>92.5</td>
<td>.673</td>
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<tr>
<td>Disease (CAD/ICM, %)</td>
<td>34.5/65.5</td>
<td>37.3/62.7</td>
<td>.543</td>
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<tr>
<td>Ejection fraction (%)</td>
<td>18.2 ± 6.3</td>
<td>17.9 ± 7.3</td>
<td>.676</td>
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<tr>
<td>NYHA class</td>
<td>4 ± 0</td>
<td>3.4 ± 2</td>
<td>.752</td>
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<tr>
<td>Heart failure (years)</td>
<td>5.3</td>
<td>5.5</td>
<td>.873</td>
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<tr>
<td>Pmave (mmHg)</td>
<td>44 ± 6</td>
<td>30 ± 9</td>
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<td>PVR (WU)</td>
<td>5.1 ± 2.6</td>
<td>2.3 ± 0.6</td>
<td>&lt;.001</td>
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</table>

w fixed PH: cardiac transplant candidates with fixed pulmonary hypertension; w/o fixed PH: cardiac transplant candidates without fixed pulmonary hypertension; CAD: ischemic cardiomyopathy; ICM: idiopathic cardiomyopathy; Pmave: mean pulmonary artery pressure; PVR: pulmonary vascular resistance (wood units).
failure requiring mechanical support in patients without prior LVAD therapy. For mechanical support a standard ECMO circuit was used in the two patients. Duration of ECMO support was 3 (patient 1) and 5 (patient 2) days, respectively. None of the patients with LVAD therapy developed peri-transplant right heart failure requiring mechanical support. Incidence of other peri-transplant complications was comparable between the two groups. Operative data and adverse events are given in Table 2.

Log-rank ($p = .124$) revealed comparable long-term survival between patients with (1 year: 85%, 2 year: 85%, 3 year: 85%) and without (1 year: 90%, 2 year 82%, 3 year prior 79%) LVAD therapy. Mean follow-up was 36 ± 14 months. Long-term survival is depicted in Fig. 1.

Causes of death during the period of follow-up were comparable within patient with and without pulmonary hypertension. Causes of death are given in Table 3.

4. Discussion

Long-term post-transplant survival after reversing pulmonary hypertension using ventricular assist devices in cardiac transplant candidates with fixed pulmonary hypertension is comparable to cardiac transplant recipients without pulmonary hypertension.

Pulmonary hypertension is a common complication of severe long-standing heart failure affecting up to 72% of patients with terminal heart failure [3]. Fixed pulmonary hypertension is considered to be present when elevated PVR cannot be significantly lowered (more than 20%) by pharmacological interventions [15]. Depending on the threshold of fixed pulmonary hypertension it eventually becomes a contraindication for orthotopic cardiac transplantation as it poses the patient at great risk for early fatal right heart failure and is furthermore associated with worse long-term outcome [1,2]. Although there is no international consensus, most transplant centres will not offer cardiac transplantation in patients with PVR greater than 3–4 wood units. The cut-off value for fixed pulmonary hypertension in cardiac transplant candidates at our department is 3.5 wood units. The cut-off value is based on our experience with cardiac transplantation.

Treatment options for cardiac transplant candidates with fixed pulmonary hypertension include reversal of pulmonary hypertension prior to cardiac transplantation using left ventricular assist devices and orthotopic cardiac transplantation [4–9,3]. The efficacy of left ventricular assist devices in lowering fixed pulmonary hypertension has been extensively documented by us and others in the past and is evolving as an accepted treatment strategy [4–7]. However, the long-term post-transplant outcome of this approach has not yet been compared to that of orthotopic cardiac transplantation in patients without pulmonary hypertension. In the present study we are the first to show comparable long-term post-transplant outcome after reversal of fixed pulmonary hypertension using left ventricular assist devices with excellent post-transplant outcome of 95% survival at 1 year and 80% survival at 3 year follow-up, respectively. Furthermore, we observed no early right heart failure requiring mechanical right ventricular assistance in cardiac transplant candidates after reversal of pulmonary hypertension using left ventricular assist devices.

The long-term outcome presented in the present study has to be compared to that of heterotopic cardiac transplantation and right ventricle sparing transplant techniques which have been used in cardiac transplant candidates with fixed pulmonary hypertension in the past [8,9,3]. The rationale behind these techniques is that the donor heart acts as a biological assist device to the native left ventricle or both ventricles. However, these techniques are subject of a variety of major limitations, e.g. availability of a suitable

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**Table 2**

<table>
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<tr>
<td>n</td>
<td>26</td>
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</tr>
<tr>
<td>Donor age (years)</td>
<td>33.3 ± 11.1</td>
<td>34.9 ± 12.4</td>
<td>.834</td>
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<tr>
<td>Ischemia time (min)</td>
<td>165 ± 34</td>
<td>170 ± 69</td>
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<tr>
<td>Sex mismatch (%)</td>
<td>25.2</td>
<td>27.4</td>
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<tr>
<td>Bleeding (%)</td>
<td>6.2</td>
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<td>Infection (%)</td>
<td>12.1</td>
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<tr>
<td>Temp. RVAD</td>
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<td>.156</td>
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**Table 3**

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<tr>
<td>n</td>
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<td>10</td>
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<tr>
<td>Cerebrovascular (n)</td>
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<td>4</td>
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</tr>
<tr>
<td>MOV (n)</td>
<td>2</td>
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<tr>
<td>Neoplasm (n)</td>
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<td>.875</td>
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<tr>
<td>Other (n)</td>
<td>0</td>
<td>1</td>
<td>.321</td>
</tr>
</tbody>
</table>

w fixed PH: cardiac transplant candidates with fixed pulmonary hypertension; w/o fixed PH: cardiac transplant candidates without fixed pulmonary hypertension; MOV: multi organ failure.

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Fig. 1. Kaplan-Meier curve displaying long-term post-transplant survival. Black curve: cardiac transplant candidates without pulmonary hypertension; gray curve: cardiac transplant candidates with pulmonary hypertension.
donor, technical difficulties during implantation, and, in particular, late interactions of donor and recipient heart [8]. Survival rates reported at 12-month follow-up range between 83 and 59 percent [8,9,3]. Survival rates at 12-month follow-up in the present study are superior to survival rates reported after orthotopic cardiac transplantation or right ventricular sparing techniques.

Nevertheless, morbidity and mortality while on left ventricular assist device support remain a major concern, significantly limiting the merits of the presented approach of reversal of pulmonary hypertension using left ventricular assist devices and consecutive orthotopic cardiac transplantation. This is underlined by the fact that 51% of cardiac transplant candidates who received a left ventricular assist device prior to cardiac transplantation in the present study exhibited a severe adverse event. Furthermore, mortality during left ventricular assist device support still is 10–30% [16]. Continuous research and improvement of devices as well as careful patient selection are crucial to reduce complications during left ventricular assist device support.

4.1. Limitations

The major limitation of the present study is its nonrandomized design. The reason for this is that we would find it ethically not justifiable to randomize patients with fixed pulmonary hypertension to either orthotopic cardiac transplantation or orthotopic cardiac transplantation after reversal of pulmonary hypertension using left ventricular assist devices. Further limitations include the fact that we do not provide any data on development of pulmonary vasodynamics after cardiac transplantation and that we did not include patients who underwent heterotopic cardiac transplantation for fixed pulmonary hypertension in the present study.

LVAD therapy lowers fixed pulmonary hypertension in cardiac transplant candidates with fixed pulmonary hypertension. Thereafter, long-term post-transplant survival is comparable to cardiac transplant recipients without pulmonary hypertension.

References


Appendix A. Conference discussion

Dr M. Pasic (Berlin, Germany): Thank you for a nice presentation and really excellent results. It’s an excellent help for the surgeons who perform heart transplantation to improve the results and to make heart transplantation easier in such a group of patients.

My question to you is how frequently should we check the patients on the waiting list for the increase of pulmonary hypertension? Because we see, when our patients are on the waiting list and the hemodynamic situation is deteriorating, that the pulmonary resistance is increasing, so in some of these patients they should be transferred from the waiting list to surgery for implantation of the left ventricular assist device. So the question is, how frequently do you check the pulmonary vascular resistance of the patients on the waiting list?

Dr Zimpfer: I guess that’s one of the arising problems, because patients are on the waiting list for longer times today and we don’t have an exact algorithm on when to check the patients.

Dr Zimpfer: I guess that’s one’s of the arising problems, because patients are on the waiting list for longer times today and we don’t have an exact algorithm on when to check the patients.

Dr Kassif (Ramat Gan, Israel): What kind of a VAD did you use.

Dr Zimpfer: We used the Novacor system, the DeBakey LVAD in the majority of patients, and in one patient we used the Duromatic.

Dr Kassif: Second question, please. Those 9 that deceased, I mean, those that did not reach transplant, were they all, or can you identify whether the VAD did not reduce the pulmonary hypertension?

Dr Zimpfer: Well, the VAD reduced the pulmonary hypertension in all patients.
Dr Kassif: In all?

Dr Zimpfer: In all patients.

Dr G. Laufer (Innsbruck, Austria): What caused you to select exactly the value of 3.5 wood units as a definition for being a critical candidate for straightforward orthotopic heart transplantation?

Dr Zimpfer: That’s also a difficult question. It was more or less a value that was based on our experience. I think that there should be extensive further research to really define the right cut-off point. But with a certain mortality on the VADs that still exists, we were more reluctant to go to a higher value.

Dr D. Esmore (Melbourne, Australia): I think we all know when we put a VAD in somebody that we are subjecting them to a 30% mortality. In cardiac surgery, we operate with a 2% mortality. So every time we put in a VAD, as was your experience, you took a group of patients that were high risk and you implant them immediately subjecting them to a 30% mortality, and if successfully ‘bridged’ a 30 day post-heart transplant mortality of 6% or 7% with primary cardiac allograft failure as the most common contributing morbidity. With VAD implantation the device costs $100,000, the implant, a significant procedure with an overall 30% failure rate. Hopefully therefore 70% of the implants will proceed to successful transplantation, a second big operation with the attendant risks.

But there is an alternative; to perform ‘straight up’ heterotopic heart transplantation (HHTx) in an LVAD configuration. In this scenario we have taken high-risk patients, a number have been pulmonary hypertensive, and transplant them in the HHTx configuration with quite reasonable results, similar results to those you have presented.

At the Alfred Hospital we have performed 20 cases over a period of about 8 or 9 years with excellent intermediate term outcomes. I just mention this as an alternative therapy. I think they are both comparable therapies, but primary HHTx is one operation utilizing often quite a small donor heart that may not be used by any other program. HHTx as a therapy achieves both salvage and survival, a one stage biological bridge to the "future".

I compliment you on the excellent results you have achieved with LVAD therapy in this application. Could you comment please?

Dr Zimpfer: So you’re not afraid of the complications, of the long-term complications, of the heterotopic heart transplantation? You’re not afraid of thromboembolic events and arrhythmias?

Dr Esmore: Look, I think they do occur. And I just, on the presentation I gave, we showed survival curve, which is not as good, of course, as orthotopic heart transplantation. It’s just another way to potentially treat the same condition. And I think that I mention that to you for your consideration.

But I think it’s one of the areas we didn’t know much about earlier on, that you’ve done large numbers and got this fall in PBI in all patients. So fixed pulmonary hypertension sort of isn’t sort of real in some ways. I think that if you support someone for long enough you can get them down to a transplantable level, which you’ve very well demonstrated.