Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance?☆

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Abstract

Objective: Pulmonary hypertension (PH), defined as a pulmonary vascular resistance (PVR) >2.5 Wood units (WU) and (or) a transpulmonary gradient (TPG) >12 mmHg, is an established risk factor for mortality in heart transplantation. Elevated PVR in heart transplant candidates can be reduced using a left ventricular assist device (LVAD), and LVAD is proposed to be the treatment of choice for candidates with PH. We analyzed the effect on PVR of pretransplant LVAD therapy in patients with PH and compared posttransplant outcome with matched controls. Long-term survival was compared between heart transplant recipients with mild, moderate or severe PH and patients with no PH. Methods: Heart transplant recipients 1988—2007 (n = 405) were reviewed and divided into two groups with respect to pretransplant PVR: <2.5 WU (n = 148) and >2.5 WU (n = 158). From the group with PH, patients subjected to pretransplant LVAD therapy (n = 11) were analyzed with respect to PVR at implant and at transplant and, with respect to outcome, compared to matched historical controls (n = 22). Patients with PH without LVAD treatment (n = 147) were stratified into three subgroups: mild, moderate and severe PH and survival according to Kaplan—Meier was analyzed and compared to patients with no PH. Results: LVAD therapy reduced PVR from 4.3 ± 1.6 to 2.0 ± 0.6 WU, p < 0.05. Three cases of perioperative heart failure required mechanical support whereas one control patient developed perioperative right heart failure requiring mechanical support. The incidence of other perioperative complications was comparable between groups. There was no difference in survival between LVAD patients and controls, 30-day survival was 82% and 91%, respectively and 4-year survival was 64% and 82%, respectively. Conclusions: Pretransplant LVAD therapy reduces an elevated PVR in heart transplant recipients, but there was no statistically significant difference in posttransplant survival in patients with PH with, or without LVAD therapy. The study revealed no differences in survival in patients regardless of the severity of the PH.

Keywords: Pulmonary hypertension; LVAD; Heart transplantation; PVR

1. Introduction

Orthotopic heart transplantation is the 'gold standard' treatment for patients with end-stage heart failure. However, transplant candidate eligibility is highly determined by the severity of pretransplant pulmonary hypertension (PH) and elevated pulmonary vascular resistance (PVR). The donor heart right ventricle (RV) has limited adaptive mechanisms to increased outflow impedance [1] and additional impairment may be associated with organ preservation, effects of cardiopulmonary bypass and RV dysfunction attributable to donor brain death [2,3]. After the first report in 1971 by Grieppe et al. [4] numerous studies have confirmed PVR as an incremental risk factor for early and late death after heart transplantation [5,6]. Furthermore, PH and increased PVR have not only been associated with posttransplant morbidity from acute RV failure and all-cause perioperative mortality but they have also been associated with other causes of postoperative morbidity, including infections and arrhythmias [7,8]. Current consensus implicates PVR > 2.5 Wood units (WU), resistant to pharmacologically induced vasodilatation, as an increased risk whereas PH > 5 WU is commonly regarded as a contraindication for heart transplantation, however, an absolute cut-off value of PVR does not exist.

Despite this, it has been shown that in patients with elevated PVR, the majority of survivors will normalize their PVR after heart transplantation, which indeed questions the term 'irreversible' or 'fixed' PVR in this setting [9]. It is also important to recognize that PH may occur with or without reversible elevation of PVR since the two terms PH and PVR are often used interchangeably in the literature; PVR is, by some authors, considered the more important measurement.
to assess transplant prognosis as compared to mean pulmonary artery pressure (MPAP) or transpulmonary gradient (TPG) [10].

Recently, it has been shown that circulatory support with a left ventricular assist device (LVAD) can reduce the resistance in the pulmonary vasculature [11,12]. Furthermore, equivalent survival rates have been demonstrated in transplanted patients with elevated PVR, pretreated with LVAD, as compared to patients with normal PVR [13]. After those important findings, it is now considered that pretransplant LVAD implantation is indicated, rather than contraindicated, in patients with elevated PVR.

The objective of this study was to compare outcome after heart transplantation between two groups of patients with elevated PVR, transplant candidates managed according to standard clinical practice and patients subjected to pretransplant treatment with LVAD.

2. Material and methods

2.1. Patients

The study population was derived from reviewing medical records of all heart transplant recipients during the time period 1988—2007 (n = 405) with or without PH prior to transplant at Sahlgrenska University Hospital (Fig. 1). The study was approved by the ethical committee at the University of Göteborg. These patients underwent routine right heart catheterizations, including thermodilution cardiac output measurement and PH was defined as PVR > 2.5 Wood units and (or) TPG > 12 mmHg. Excluded from this analysis were patients undergoing a second heart transplantation (n = 9), combined heart + kidney transplantation (n = 9), children younger than 16 years (n = 33) or patients who did not have pretransplantation hemodynamic measurements available for analysis (n = 48). The total study consisted of 148 patients without PH and 158 patients with PH. Patients with PH were divided into two groups, one group included 147 patients with pretransplant elevated PVR (>2.5 WU) and one group included 11 patients who were pretreated with LVAD. The patients with PH without pretreatment with LVAD were then stratified into three subgroups; mild PH, 2.5—3.0 WU (n = 41); moderate PH, 3.1—4.5 WU (n = 56) and severe PH, >4.5 WU (n = 50).

Furthermore, historical controls were selected from the group of patients with PH in order to match patients pretreated with LVAD in a 2:1 fashion according to the following criteria: age ±10 years, sex, era ±10 years, underlying diagnosis, PVR within subgroup, body surface area (BSA) ±0.2 m², body mass index (BSA) <30 or >30, glomerular filtration rate (GFR) <40 or >40 ml/min/1.72 m², diagnosed diabetes mellitus and properties specific for the donor: sex, age and BSA.

2.2. Right heart catheterization

Measurements of central hemodynamics at rest were obtained via routine right heart catheterization according to standard clinical practice. The following variables were measured or calculated: right atrial pressure (RAP), right ventricular pressures, pulmonary artery pressures (systolic, PAS; diastolic; mean, PAM), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was determined as the mean of 3–5 separate measurements with the thermodilution technique. PVR was calculated in Wood units as the TPG, defined as the difference between PAM and PCWP, divided by CO. Systemic pressures (systolic, SAP; diastolic; mean, mean artery pressure (MAP)) were measured using a radial artery catheter. Height and weight were recorded to determine BSA for calculation of cardiac index (CI) and PVR index. If the baseline pulmonary vascular resistance was >3 WU, a maximal dilation test was performed in order to determine reversibility. In the early experience, the use of intravenous nitrates or prostanooids was predominant, however, with the evolving information since the mid-1990s of the pulmonary selective, vasodilatory properties of inhaled agents such as nitric oxide (NO) or aerosolized, inhaled prostacyclin (iPGI₂), these agents were used in an increasing number of heart transplant candidates being evaluated [7,9].

Patients responding with a decrease in their pulmonary resistance to ≤3 WU and a maintained MAP ≥70 mmHg were considered to have an elevated, but reversible PVR. The preoperative values used in all analyses were those obtained closest to the time of heart transplantation.

2.3. Management of right ventricular failure

The policy at Sahlgrenska University Hospital has been the practice of using modestly larger donor hearts for those with significant pretransplant PH. The intra- and postoperative management of RV failure has evolved as a result of new knowledge during the 1990s to a combination of goals: maximizing coronary perfusion through maintenance of
aortic pressure, reducing preload to a distended and ischemic RV, decreasing RV afterload by reducing PVR and thus, optimizing myocardial oxygen delivery and limiting ventricular oxygen consumption. Early strategy was based entirely on classic intravenous (i.v.) nitrate vasodilators and inotropic agents like isoproterenol combined with dopamine, dobutamine and/or epinephrine and/or norepinephrine. Since the mid-1990s the predominantly used agents are the inodilator milrinone, low dose isoproterenol and, in order to counteract systemic vasodilation and hypotension, i.v. norepinephrine. Furthermore, selective vasodilation and optimal ventilation/perfusion matching in the pulmonary circulation, thereby preventing hypoxemia, is obtained with inhaled agents NO, 20–40 parts per million (ppm) and/or aerosolized, PGI2, 10 ug/ml, using standard, commercially available delivery systems and/or nebulizers [14–16]. Controlling heart rhythm and avoiding hypoxemia is, of course, fundamental. Hemodynamic and functional monitoring usually consists of systemic and pulmonary pressure registration and cardiac output measurements with an arterial line and a continuous cardiac output (CCO) pulmonary artery catheter (Baxter Healthcare Corp, Irvine, CA) as well as perioperative transesophageal echocardiography (TEE). Inhalation therapy is initiated when ventilation is reinstalled before separation from cardiopulmonary bypass. Depending on the clinical situation, the patient is either gradually weaned from inhalation therapy with close monitoring of RV hemodynamics or is considered to be temporarily dependent. If NO has been used, therapy is switched to iPGI2 before transportation to the ICU; therapy is then continued with daily evaluation and subsequent weaning attempts. In case of unsatisfying clinical results of the pharmacological treatment, intra-aortic balloon counterpulsation (IABP) and/or mechanical circulatory support is instituted.

2.4. Cardiac assist devices

During the study period four different mechanical assist devices were used. Early in our experience HeartMate VE (Thoratec Corporation, Pleasanton, CA) were used and five patients in the present study received HeartMate. Since the year 2000 axial-flow pumps were used and four patients received MicroMed DeBakey LVAD (Houston, TX), one patient received Jarvik 2000 (Jarvik Inc., NY) and one patient received VentrAssist (Ventracor, Ltd. Sydney, Australia) according to our actual pump program. The implantation technique for different pumps has previously been described [17–20].

HeartMate VE is a replacement pump, which is implanted into the abdomen with the outflow conduit, connected to the ascending aorta through a sternotomy.

The electromagnetically actuated MicroMed DeBakey LVAD is a miniaturized, titanium axial-flow blood pump. The outflow conduit connects the pump to the ascending aorta. An ultrasonic flow probe is placed around the outflow conduit to provide exact measurement of pump flow.

The Jarvik 2000 VAD was implanted through a left thoracotomy incision, where the outflow graft was connected to the descending aorta using a partial occlusion clamp.

The VentrAssist pump was implanted via a sternotomy in the posterior rectus sheath. The inflow cannula was connected to the left ventricular apex and the outflow cannula to the ascending aorta.

2.5. Follow-up

Patient data were collected retrospectively from the medical charts. Follow-up was 100% complete. Conditions, such as posttransplant renal failure requiring renal replacement therapy (RRT), days in intensive care unit (ICU), total length of stay, need for posttransplant mechanical support, 30-day, intermediate- and long-term survival following transplant were analyzed.

2.6. Statistical analysis

The continuous variables are reported as mean ± standard deviation. To test for statistical significance of differences between the groups LVAD treatment or not, the Mann–Whitney test was used, except for categorical data for which Fisher’s exact test or chi-square was used. The correlation between PVR before implantation of pretransplant LVAD and PVR during the time on support before transplantation was calculated according to Wilcoxon’s signed ranked test. Patient survival was calculated according to the Kaplan–Meier method and the log-rank test was used to test the two groups. A p value <0.05 was considered statistically significant.

3. Results

The mean age of the patients with PH was 49 years (16–68 years). There were 29 females and 128 males. Seventy-two patients had dilated cardiomyopathy, 68 had ischemic heart disease and 17 patients had miscellaneous underlying conditions. The MPAP was 37.2 ± 7.3 mmHg, PCWP was 24 ± 6.4 mmHg and TPG was 13.4 ± 4.9 mmHg. Cardiac index was 1.7 ± 0.41/min m³ and the mean PVR was 4.3 ± 1.7 WU. The donor hearts used for recipients with pretransplant PH were not significantly larger as compared to donor hearts to recipients with normal PVR. It is notable that in our series with pulmonary hypertensive patients, 27 male recipients received female donor hearts.

3.1. Pretreatment with LVAD

The mean age for patients with PH without LVAD prior to the transplant was 49 ± 11 years and 46 ± 10 years in the LVAD group. Thirty-two percent were female in the non-LVAD group and 18% in the LVAD group. There were no statistical differences between groups regarding preoperative data as diagnoses, hemodynamic measurements, data on the donors and ischemic time (Table 1). PVR measured at the time of pretransplant evaluation was 4.3 ± 1.7 WU in patients who were transplanted without pretreatment with LVAD. In patients who were treated with LVAD, the PVR measured before the implantation of LVAD was 4.3 ± 1.6 WU. PVR was significantly reduced to 2.0 ± 0.6 WU after implantation but before transplantation, p < 0.05 (Fig. 2). Duration of LVAD treatment was 239 (24–1002) days. One patient, not pretreated with LVAD, developed acute right heart failure
after transplantation requiring mechanical support whereas three patients treated with LVAD required biventricular mechanical support, none attributable to acute RV failure. One patient developed an acute humoral rejection, one patient had an immediate, massive myocardial infarction and one patient suffered from primary graft failure, all three cases with fatal consequences.

### 3.2. LVAD-treatment vs matched controls

There were no statistical differences between patients pretreated with LVAD and matched controls regarding transplant era ±10 years, underlying diagnosis, PVR within subgroup, sex, age ±10 years, BSA, BMI, GFR, diagnosed diabetes mellitus and properties specific for the donor: sex, age and BSA (Table 2). The need for postoperative RRT was 27% in patients not treated with LVAD and 64% in patients treated with LVAD prior to the transplantation, p = 0.04 (Table 3). The stay in ICU was 11 days (2–84) in patients without pretreatment with LVAD compared to 8 days (1–30 days) in patients treated with LVAD, p = 0.56. The total length of stay at hospital was comparable between the two groups.

| Table 2 Demographics in patients pretreated with LVAD prior to transplantation and matched controls. |
|---|---|---|---|
| Variable | LVAD (n = 11) | No LVAD (n = 22) | p value |
| PVR pre tx (WU) | 4.3 ± 1.6 | 4.5 ± 1.8 | 0.9 |
|Recipient age (years) | 46 ± 10 | 50 ± 10 | 0.2 |
|Recipient BSA (m²) | 2.1 ± 0.2 | 2.0 ± 0.2 | 0.2 |
|Ischemia (min) | 198 ± 50 | 188 ± 57 | 0.6 |
|Donor age (years) | 41 ± 13 | 39 ± 14 | 0.8 |
|Donor BSA (m²) | 2.0 ± 0.2 | 1.9 ± 0.2 | 0.5 |
|CI (l/min m²) | 1.5 ± 0.4 | 1.5 ± 0.3 | 0.6 |
|PCWP (mmHg) | 24 ± 8 | 27 ± 6 | 0.1 |
|MPAP (mmHg) | 37 ± 10 | 41 ± 6 | 0.2 |
|GFR (ml/min/1.73 m²) | 59 ± 20 | 63 ± 16 | 0.5 |

LVAD: left ventricular assist device; WU: wood units; PVR: pulmonary vascular resistance; BSA: body surface area; CI: cardiac index; PCWP: pulmonary capillary wedge pressure; MPAP: mean pulmonary artery pressure; GFR: glomerular filtration rate.

| Table 3 Outcome in patients pretreated with LVAD prior to transplantation and matched controls. |
|---|---|---|---|
| Variable | LVAD (n = 11) | No LVAD (n = 22) | p value |
| Post tx RRT | 7/11 (64%) | 6/22 (27%) | 0.04 |
| Days in ICU post tx | 8 ± 9 (1–30) | 11 ± 18 (2–84) | 0.7 |
| In hospital mortality | 4/11 (36%) | 2/22 (9%) | 0.8 |
| Total length of stay | 30 ± 21 | 43 ± 44 | 0.7 |
| Post tx mechanical support | 3/11 (27%) | 1/22 (5%) | 0.1 |

LVAD: left ventricular assist device; tx: transplantation; RRT: renal replacement therapy; ICU: intensive care unit.

### 3.3. All-cause mortality

In patients with PH, there was no significant difference between mild, moderate and severe PH in 10-year actuarial survival, p = 0.12. The 5-year survival was 88%, 63% and 78%, respectively (Fig. 3).

#### 3.3.1. Matched LVAD vs non-LVAD patients

Thirty-day survival for patients in the matched non-LVAD group was 91% compared to 82% in patients in the LVAD group.
The implantation of LVAD becomes a high-risk procedure with patients though all had elevated PVR. Candidates with PH may present with rapid deterioration in organ function and survival is comparable to patients with normal PVR [13]. The normalization of PVR with LVAD treatment in this group of patients with PH may have important implications. Patients with non-reversible PH, not eligible for heart transplantation due to unacceptably high risk for fatal RV failure and poor long-term outcome may be converted to candidates with the same transplant prognosis as patients with normal PVR. On the other hand, the data analysis in this study did not reveal any impact of elevated PVR on long-term survival posttransplant, regardless of classified severity, which is quite inconsistent with other reports. Furthermore, in our institution there is the practice of using modestly larger donor hearts for those with significant pretransplant PH but data analysis in this study revealed that this strategy has not been possible to apply.

Our definition of PH was dependent on a calculated value, PVR, assessed in a setting where medical therapy was not being actively adjusted. Baseline measurements and calculated PVR reflect the patient's true clinical state at a given time understanding that the hemodynamic state can easily fluctuate with and without medication adjustment. At our institution, once the candidate has been accepted for transplantation, medical management of the patients clinical condition is continued in a sometimes more multidisciplinary manner which may, theoretically, optimize the patient resulting in reclassification of mildly elevated PVR into the normal range due to pharmacological adjustments. However, associated with time on the waiting list, re-evaluation of patients with right heart catheterization is not always necessary and improvements with respect to an elevated PVR might pass undetected. On the other hand, given the fact that there is a prevailing shortage of donor organs, time awaiting transplant might obliterate initial improvement. In this study, the analyzed data were those obtained closest to the time of heart transplantation. Nevertheless, more than 50% of included patients had PH and the stratifying with regard to severity of PH resulted in more than 60% classified as patients with moderate to severe PH (35% and 30%, respectively) concluding that included patients were those with more advanced heart failure than other studies [10], consistent with previous reports from this institution [9]. Given this perspective, the impact of elevated...
PVR on transplant prognosis may need to be revisited. However, this has to be studied further.

It has been stated that RV dysfunction after cardiac transplantation is primarily related to status of the donor heart [18]. The donor RV is exposed to factors associated with brain death and organ preservation detrimental to its mechanical performance well before facing an increased afterload in the recipient. This single center experience has been subjected to evolving new techniques and strategies for almost 20 years, including change in preservation solution and cardioplegia that may have affected the outcome.

Heart transplantation in patients with fixed, severe PH is contraindicated but sometimes it is difficult to determine the degree of reversibility in PVR. Therefore, a final option to evaluate reversibility could be LVAD therapy and, in case of irreversible PH, heart transplantation is contraindicated.

In conclusion, treatment with LVAD prior to transplantation reduces elevated PVR in heart transplant recipients, and there was no statistically significant difference in short-term or long-term survival between patients with PH managed according to standard clinical practice or pretreated with LVAD. LVAD therapy for elevated PVR in heart transplant candidates emerges as an option but further studies are required and the cut-off value in PVR for LVAD therapy remains to become established. Furthermore, there was no correlation in long-term survival and the severity of PH.

References


Appendix A. Conference discussion

Dr A. Maat (Rotterdam, Netherlands): I want to congratulate you and your team on your results since we know that the pulmonary hypertension patients are not simple patients to manage, and your results on survival are good.

This study population is small, as you said, and you got it in 20 years, and a lot changed in this period. One other item is the hemodynamic state as measured at baseline can easily fluctuate during the waiting time. So at the time of real transplant, we do not know the exact situation of the patients.

Two questions. Implantation of a VAD can turn a patient with pulmonary hypertension into a heart transplant candidate with a normal PVR, so potentially this strategy will increase the number of patients waiting for a donor heart. How do you face this situation in light of an ongoing decrease in the number of suitable heart donors?

The second question is, have you ever treated a patient with a VAD in whom the PVR did not normalize so that they could not be listed for transplant, and if so, what happened in this situation?

Dr Liden: I will start with the second question.

We did not have that situation. We implanted an LVAD in a patient who did not go down in PVR. All the patients either were transplanted before another cath could be done or they indeed lowered their PVR. We did not face the situation of a patient not lowering his PVR.

Regarding the first question I’m not sure I really got it, but I think you asked me did we increase the number of waiting patients? Pittrow DW, Gregoire ID, Khan T, Tamez DW, Conger JL, Macris MP. Research and development of an implantable axial-flow left ventricular assist device: The Jarvik 2000 heart. AnnThorac Surg 2001;71:5125—32.


So if you have a patient with a vascular resistance of, let’s say, 5 Wood units, what do you do with this patient? Do you transplant this patient? We have a clear strategy in Freiburg for the patients who have fixed elevated pulmonary vascular resistance. And we are talking only about fixed pulmonary vascular resistance, because once it can be reduced by medication, that’s a completely different story. But if you have a fixed pulmonary vascular resistance, the only treatment in my view is to implant an assist device.

**Dr Liden:** Yes. I would like to stress that we are looking at different populations from the paper published by Dr Zimpfer and Professor Wieselthaler. We agree that in patients with a fixed PVR of 3.5 or more, an LVAD should be considered. Four of these patients were actually of that kind.

**Dr Beyersdorf:** But why would you implant a VAD in a patient who can be medically reduced?

**Dr Liden:** It was not the only reason for LVAD implantation. Mostly the implantations were on vital indication, arrhythmias, but they also had -

**Dr Beyersdorf:** Okay.

**Dr Liden:** To be able to make a study at all, we had to -

**Dr Beyersdorf:** Okay. But then again, I think that the conclusion is not right because nobody should go out of the room thinking that elevated or fixed PVR cannot be treated with LVADs. They can be treated.

**Dr Liden:** I agree.

**Dr D. Loisance (Creteil, France):** More questions? I think we have to thank Professor Beyersdorf to make a very clear point, and VAD therapy now is a well-established technique to make a patient transplantable when he has a high pulmonary resistance.