Use of centrifugal left ventricular assist device as a bridge to candidacy in severe heart failure with secondary pulmonary hypertension†

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Abstract

OBJECTIVES: Raised pulmonary artery pressure (PAP), trans-pulmonary gradient (TPG) and pulmonary vascular resistance (PVR) are risk factors for poor outcomes after heart transplant in patients with secondary pulmonary hypertension (PH) and may contraindicate transplant. Unloading of the left ventricle with an implantable left ventricular assist device (LVAD) may reverse these pulmonary vascular changes. We studied the effect of implanting centrifugal LVADs in a cohort of patients with secondary PH as a bridge to candidacy.

METHODS: Pulmonary haemodynamics on patients implanted with centrifugal LVADs at a single unit between May 2005 and December 2010 were retrospectively reviewed.

RESULTS: Twenty-nine patients were implanted with centrifugal LVADs (eight HeartWare ventricular assist device (HVAD), HeartWare International, USA and 21 VentrAssist, Ventracor Ltd., Australia). Seventeen were ineligible for transplant by virtue of high TPG/PVR. All the patients were optimized with inotrope/balloon pump followed by LVAD insertion. Four required temporary right VAD support. Thirty-day mortality post-LVAD was 3.4% (1 of 29) with a 1-year survival of 85.7% (24 of 28). Thirteen patients have been transplanted to date: 30-day mortality was 7.7% (1 of 13) and 1-year survival was 91% (10 of 11). Baseline and post-VAD pulmonary haemodynamics were significantly improved: systolic PAP (mmHg), mean PAP, TPG (mmHg) of 57 ± 9.5, 42 ± 4.4 and 14 ± 3.9 reduced to 32 ± 7.5, 18 ± 5.5 and 9 ± 3.3, respectively. PVR reduced from 5 ± 1.5 to 2.1 ± 0.5 Wood units (P < 0.05).

CONCLUSIONS: In selected heart failure patients with secondary PH, use of centrifugal LVAD results in significant reductions in PAP, TPG and PVR, which are observed within 1 month, reaching a nadir by 3 months. Such patients bridged to candidacy have post-transplant survival comparable with those having a heart transplant as primary treatment.

Keywords: Ventricular assist device • Pulmonary hypertension • Centrifugal • Bridge to candidacy • Heart transplant

INTRODUCTION

Heart transplantation is an established treatment for patients with end-stage heart failure [1]. One contraindication that potentially prevents patients from being considered for heart transplantation is fixed pulmonary hypertension (PH) with elevated pulmonary vascular resistance (PVR). In the past, such patients would be turned down for heart transplantation. Medically refractory PH responding to treatment with a left ventricular assist device (LVAD), with implanted patients meeting criteria for transplantation, has been successfully reported [2–5]. Reversal of secondary PH by pulsatile flow and axial flow mechanical support has been demonstrated [6]. Continuous flow devices are now considered the standard of care [7]. The objective of this study was to evaluate the effect and outcome of implanting centrifugal LVADs as a bridge to candidacy for heart transplantation in a cohort of patients with heart failure and secondary pulmonary hypertension.

MATERIALS AND METHODS

Patient cohort

Retrospective data on patients implanted with a centrifugal LVAD between 1 May 2005 and 31 December 2010 were collected. Of the 29 such patients, 17 had trans-pulmonary gradient (TPG) ≥12 mmHg and PVR ≥4 Wood units (WU) preoperatively. These patients were considered for LVAD as a bridge to candidacy for transplantation. During this period, we were using a range of LVADs for bridge to transplant, including Thoratec.
implantable ventricular assist device (IVAD), Thoratec paracorporal ventricular assist device (PVAD) and Thoratec HeartMate XVE (Thoratec Corporation, USA).

Levitronix CentriMag pumps were used in candidates with profound haemodynamic instability as bridging to decision. These patients have not been included in this analysis. Strategically, we would not use temporary devices in patients with PH. Patients with PH that precluded transplantation would not be candidates for temporary mechanical circulatory support.

Haemodynamic evaluation

Right heart catheter measurements at heart failure assessment and subsequent follow-up along with perioperative pulmonary artery catheterization provided systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was determined by both the Fick method and thermodilution. TPG was calculated as the difference between the mPAP and the PCWP, and PVR was calculated by dividing the TPG by CO. Pulmonary artery catheterization was used primarily to guide therapy. These catheters were removed after all inotropes are weaned with the exception of ‘renal dose’ dopamine. The measurement listed as less than 1-month post-LVAD implantation was the final measurement prior to pulmonary artery catheter removal. Further single measurements were taken at 3 and 6 months at planned catheter laboratory sessions.

Preoperative optimization

Oxygen therapy, nebulized iloprost and optimal fluid management using diuresis or haemofiltration were implemented. Selective patients received inotropic support, including dopamine and enoximone, along with intra-aortic balloon pump placement prior to LVAD implantation.

Statistical analysis

Categorical variables were reported as proportions, and continuous variables were reported as mean ± standard deviation of mean. The paired t-test was used to compare pulmonary haemodynamic measurements before and after LVAD implantation. $P < 0.05$ was considered statistically significant.

RESULTS

Between May 2005 and December 2010, 29 patients were implanted with centrifugal LVADs (eight HeartWare ventricular assist devices (HVAD), HeartWare International, USA and 21 VentrAssist, Ventracor Ltd., Australia).

The mean age was 45 years (18–65 years) and 25 (86%) were male. Fifteen patients were diagnosed with idiopathic cardiomyopathy followed by ischaemic ($n = 9$), hypertrophic ($n = 3$) and familial cardiomyopathy ($n = 2$). The length of treatment for heart failure ranged from diagnosis at admission to a maximum of 70 months (mean 10.9 months and median 6.5 months). Ten patients had biventricular pacemakers. Two patients had functional mitral regurgitation.

According to INTERMACS stratification of LVAD patients into levels of clinical acuity, 8 patients were defined at level 2, 17 met the level 3 criteria and the remainder met the level 4 criteria.

Seventeen had been deemed ineligible for transplant by virtue of high TPG/PVR. All the patients were optimized followed by LVAD insertion. The mean duration of optimization on the intensive care unit was 4.7 (median 4 days and range 0–10 days). Dopamine at 3 μg/kg/min was used in 14 patients, intra-aortic balloon pump support in 11 and enoximone in 5. The demographic data are displayed in Table 1.

Pulmonary haemodynamics were measured using right heart catheterization with the data collected at initial assessment (baseline), early (after LVAD implant), at 3 and 6 months following LVAD implantation and following heart transplantation. The median preoperative cardiac index measured was 1.5 ± 0.5 l/min/m². The measurements during the course of VAD support in both the groups are displayed in Tables 2 and 3 and Figs 1 and 2.

Four patients required temporary right VAD support. The mean duration of right ventricular assist device (RVAD) use was 8.7 (range 4–14 days). Thirty-day mortality post-LVAD implant was 3.4% (1 of 29) with a 1-year survival of 85.7% (24 of 28).

In patients not transplantable by virtue of high TPG/PVR, baseline sPAP decreased from 56.5 ± 9.5 to 29 ± 7.9 mmHg (P < 0.05), mPAP decreased from 42 ± 4.4 to 19.5 ± 5.5 mmHg (P < 0.05), TPG decreased from 14 ± 3.9 to 8 ± 2.9 mmHg (P < 0.05) and PVR decreased from 5.1 ± 1.5 to 2.1 ± 0.5 WU (P < 0.05). The most significant fall in pressures was noted within 1 week of LVAD insertion (Figs 1 and 2). The PCWP pre-LVAD was 28 ± 5.5 (range 15–39 mmHg) lowered to 11 ± 3.8 (range 6–20 mmHg) 6 months post-LVAD. However, there was a continued fall in all parameters with TPG and PVR reaching a nadir at 3 months post-implantation (Table 4). All the LVAD recipients with high TPG/PVR were successfully bridged to candidacy with listing for transplantation.

Thirteen of the 29 patients implanted with centrifugal LVADs were transplanted prior to January 2011: 30-day mortality post-LVAD explants and heart transplant was 7.7% (1 of 13), and 1-year survival was 91% (10 of 11). Of the 17 patients with PH who were bridged to candidacy, 8 have been transplanted with 1 post-transplant death. This patient’s TPG was reduced from 20 to 8 mmHg, and PVR was reduced from 5 to 2 WU after 127 days of LVAD support (609 days between LVAD implant and transplant). There was primary graft failure of the donor heart, and the patient died despite extracorporeal membrane oxygenator support. Transient right ventricular dysfunction was observed in 2 patients post-transplant and these were treated with

<table>
<thead>
<tr>
<th>Table 1: Demographic data of all the patients</th>
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<tbody>
<tr>
<td>Normal TPG and PVR (n = 12)</td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Male [n (%)]</td>
</tr>
<tr>
<td>Age [year, median (range)]</td>
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<tr>
<td>Type of LVAD [n (%)]</td>
</tr>
<tr>
<td>VentrAssist</td>
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<tr>
<td>HeartWare</td>
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<tr>
<td>Status [n (%)]</td>
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<tr>
<td>Urgent</td>
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<td>Emergent</td>
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TPG: trans-pulmonary gradient; PVR: pulmonary vascular resistance; LVAD: left ventricular assist device.
inotropic support. None of the patients required RVAD support post-transplant. There has been no recurrence of PH post-transplantation. Five patients remain on the active transplant waiting list (Fig. 3).

**DISCUSSION**

As far back as 2005, we thought that continuous flow LVADs were likely to provide extended periods of support compared with first generation devices. Our group started to implant LVADs to reduce PVR and improve renal function in selected patients who we considered were at high risk of heart transplantation but who, from experience, we expected had reversible disease. Candidates could be optimized to reduce the risk of heart transplant by unloading the left ventricle using LVAD support and by reversing the haemodynamic and pulmonary vascular bed changes associated with secondary PH.

In general, our approach in management of the LVAD is to set the revolutions-per-minute (RPM) at the lowest possible setting to achieve flow that relieves heart failure symptoms, optimizes right ventricular function and improves overall haemodynamics. The rationale for this is to provide adequate systemic perfusion and to minimize the risk of suction-related events.

Nitric oxide is used intraoperatively and immediately postoperatively. As nitric oxide is weaned, inhaled iloprost is instituted if there are signs of right ventricular failure or tricuspid regurgitation. Medical treatment thereafter was to maintain mean arterial pressures <90 mmHg. Therapy included vasodilator therapy including hydralazine, angiotensin-converting enzyme

<p>| Table 2: Patients with secondary pulmonary hypertension receiving LVAD as a bridge to candidacy (n = 17) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>&lt;1 month post-LVAD</th>
<th>3 months</th>
<th>6 months</th>
<th>Most recent</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPAP (mmHg)</td>
<td>56.5 ± 9.54</td>
<td>39 ± 6.6</td>
<td>28 ± 6.9</td>
<td>34.5 ± 5.2</td>
<td>29.5 ± 7.88</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>42 ± 4.44</td>
<td>25.5 ± 3.4</td>
<td>18 ± 5.7</td>
<td>24 ± 7.9</td>
<td>19.5 ± 5.48</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>14 ± 3.96</td>
<td>11 ± 4.4</td>
<td>6 ± 3</td>
<td>5.5 ± 1.7</td>
<td>8 ± 2.87</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>5.1 ± 1.54</td>
<td>2.9 ± 0.9</td>
<td>2 ± 0.7</td>
<td>1.7 ± 0.4</td>
<td>2.1 ± 0.54</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

LVAD: left ventricular assist device; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; TPG: trans-pulmonary gradient; PVR: pulmonary vascular resistance; WU: Wood units.

**Figure 1:** Reduction in TPG following LVAD implantation in patients with raised TPG compared with patients with normal TPG.

**Figure 2:** Reduction in PVR following LVAD implantation in patients with raised PVR compared with patients with normal PVR.

<p>| Table 3: Patients with normal TPG and PVR prior to LVAD implant (n = 12) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>&lt;1 month post-LVAD</th>
<th>3 months</th>
<th>6 months</th>
<th>Most recent</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>sPAP (mmHg)</td>
<td>47.5 ± 12.1</td>
<td>28.5 ± 8.7</td>
<td>31 ± 8.6</td>
<td>30 ± 4.9</td>
<td>32.5 ± 11</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>34 ± 5.7</td>
<td>16 ± 3.3</td>
<td>21 ± 4.4</td>
<td>22 ± 4</td>
<td>24.5 ± 7.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TPG (mmHg)</td>
<td>7 ± 2.9</td>
<td>9 ± 3.4</td>
<td>9 ± 2.1</td>
<td>7 ± 1.3</td>
<td>8 ± 2.7</td>
<td>0.32</td>
</tr>
<tr>
<td>PVR (WU)</td>
<td>3 ± 0.7</td>
<td>2.4 ± 0.8</td>
<td>1.7 ± 0.5</td>
<td>2 ± 0.5</td>
<td>2.2 ± 0.9</td>
<td>&lt;0.05</td>
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inhibitors and angiotensin II antagonists. We do not routinely use selective pulmonary arterial vasodilators such as oral phosphodiesterase V inhibitors or endothelin antagonists post-LVAD implantation. The RPM is increased if symptoms of congestive heart failure (e.g. fatigue, breathlessness, weight gain) develop or the LVEDP remains elevated, suggesting that there is need to supplement offloading of the LV.

This approach has been shown to provide good results in this cohort of patients following continuous flow LVAD implantation. Furthermore, this study shows that patients who have had prior support with continuous flow devices are not at increased risk of poor post-heart transplant outcomes.

We know that heart transplantation in patients with secondary PH is contraindicated due to an increased risk of right ventricular failure following orthotopic heart transplantation. Reversal of secondary PH by pulsatile flow and axial flow LVADs has been reported [8].

Mechanical unloading of the left ventricle has been noted to be more effective when using pulsatile devices when measured by both echocardiographic parameters and some biochemical markers [9]. There have been concerns that continuous flow LVADs may not offload the LV as well as a volume displacement (pulsatile flow) device [10]. If so, that might also compromise their ability to reduce left atrial pressure and PCWP, thereby affecting their effectiveness in reversing PH secondary to heart failure. However, our results have shown that LVAD therapy with continuous flow devices significantly reduces PH in patients with heart failure, allowing them to safely undergo heart transplantation. In addition, results of transplantation both in the immediate postoperative phase and in the medium term have shown survival rates comparable with those of patients without secondary PH.

Heart transplantation following the use of LVAD has been demonstrated to be a safe and reproducible therapy. In a retrospective study of anaxial-flow LVADs in over 450 patients of whom 250 went onto heart transplantation, John et al. [11] showed a 30-day mortality of 97% and a 1-year post-transplant survival of 87%. A comprehensive systematic review of 31 studies including over 19 500 patients on the effect of VAD on long-term post-transplant outcomes came to the conclusion that
intracorporeal VAD support does not have a deleterious impact on post-transplant outcomes. This is not supported in International Society for Heart & Lung Transplantation (ISHLT) data that report VAD as a risk factor for worse outcomes. Extracorporeal devices were associated with higher mortality, but there is speculation that this could be attributed to this group being a sicker population prior to transplant [12].

Reduction in secondary PH using pulsatile and axial flow devices has been demonstrated by many groups. Liden et al. [13] demonstrated that 22 patients with PH pretreated with LVAD had a reduction in PH with post-transplant survival similar to those with PH. Zimpfer et al. [14] showed similar results with a range of assist devices. Torre-Amione et al. showed a reduction in TPG from 19 ± 3 to 13 ± 4 mmHg in 8 of 9 patients. Organ procurement and transplantation network data, also presented by the group, identified 1082 patients with PH who received a heart transplant between 2000 and 2005 and had a long-term implantable LVAD at the time of transplant. They identified a trend towards lower 1-year survival post-transplant compared with those that did not have an LVAD implanted [7]. Alba et al. [12] reported that LVAD therapy is successful in decreasing PH, even in patients with ‘fixed’ PH. In their retrospective study of 54 patients between 1999 and 2008, normalization of PH allowed for transplant candidacy in 22 patients with fixed PH. They also noted that the presence of fixed PH did not reduce post-transplant survival [15]. Investigations by John et al. of their patient group identified 50 patients with PH including 18 with fixed PH. Significant fall in PH was noticed in all the patients. Four patients treated with LVAD had persistently raised PVR above recognized limitations for transplantation and were advised to remain on LVAD therapy as destination therapy [16]. In a retrospective study of 120 patients with end-stage heart failure, Mikus et al. [17] demonstrated that mortality after heart transplantation in 63 patients with fixed PH before LVAD implantation is higher than in 36 patients with reversible PH. However, they did hypothesize that fixed PH on LVAD may be a marker of a sicker, high-risk population. They reiterated the importance of TPG and PVR, but not mean PAP, as useful criteria in patient selection for heart transplant vs LVAD implantation.

This paper demonstrates how the Papworth Hospital VAD programme successfully optimizes appropriate candidates both pre- and postoperatively after LVAD implantation resulting in successful bridging to transplantation with emphasis on reducing TPG and PVR.

LIMITATIONS

The limitation of this study is that it is a retrospective review of data with a relatively small number of patients. Well-designed, prospective, large-cohort studies with similar patient groups would help us better understand the processes of reversal of secondary PH. The centrifugal LVAD implanted during the timeframe of this study encompasses two different manufacturers, but both devices provided excellent clinical results at our institution over the period of investigation.

The use of blood products in the perioperative phase following VAD implantation has made obtaining tissue type compatible organs more challenging when the patient is bridged and presented as a candidate for transplantation. This resulted in long waiting times before suitable donor hearts are found for some of the patients bridged to candidacy, and many of those rendered eligible for heart transplant are still waiting for a suitable organ.

CONCLUSIONS

Patients with PH secondary to heart failure previously considered ineligible for orthotopic heart transplantation can now be treated with LVADs, not only for the management of their deteriorating primary disease process but also to reduce their pulmonary haemodynamics, rendering them transplant eligible. Centrifugal devices appear to be as effective as volume displacement/pulsatile and axial flow devices in reducing PH secondary to heart failure. PVR reaches nadir after 3 months of LVAD support allowing patients to be bridged to candidacy for heart transplantation without increases in post-transplant RV failure and excellent outcomes.

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Conflict of interest: Steven Tsui discloses the following affiliations: Advisory Board Member, Thoratec Ltd; Advisory Board Member, Terumo Heart Ltd; Advisory Board Member, Micromed Ltd.

REFERENCES

In patients with advanced heart failure, elevated pulmonary vascular resistance as a consequence of a chronic elevation in left atrial pressure is a significant risk for early mortality after heart transplantation [1]. Heart failure patients with elevated pulmonary vascular resistance can be extremely challenging to manage, and medical options to reduce pulmonary vascular resistance so that the patient becomes an acceptable transplant candidate are limited. In some, intensive therapies including inotropes may be of benefit, though even if successful, they will need to stay on these therapies until the time that a suitable donor heart is available. Heart lung transplantation and heterotopic heart transplantation are alternative transplant options that are now rarely performed. Ventricular assist devices, however, can reduce pulmonary vascular resistance effectively after a period of...