Single-centre experience of 85 patients with a continuous-flow left ventricular assist device: clinical practice and outcome after extended support


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Abstract

OBJECTIVES: We evaluated our single-centre clinical experience with the HeartMate II (HM II) left ventricular assist device (LVAD) as a bridge to transplantation (BTT) in end-stage heart failure (HF) patients.

METHODS: Survival rates, echocardiographic parameters, laboratory values and adverse events of 85 consecutive patients supported with a HM II were evaluated.

RESULTS: Overall, mean age was 45 ± 13 years, 62 (73%) were male and non-ischaemic dilated cardiomyopathy was present in 60 (71%) patients. The median duration of mechanical support was 387 days (IQR 150–600), with a range of 1–1835 days. The 6-month, 1-, 2-, 3- and 4-year survival rates during HM II LVAD support were 85, 81, 76, 76 and 68%, respectively. Echocardiographic parameters demonstrated effective left ventricular unloading, while laboratory results reflected adequate organ perfusion. However, HM II support was associated with adverse events, such as infections in 42 patients (49%; 0.67 events/patient-year), cardiac arrhythmia in 44 (52%; 0.86 events/patient-year), bleeding complications in 32 (38%; 0.43 events/patient-year) and neurological dysfunction in 17 (20%; 0.19 events/patient-year).

CONCLUSIONS: In view of the increasing shortage of donor hearts, HM II LVAD support may be considered a life-saving treatment in end-stage HF patients, with good survival. However, it is still associated with some serious adverse events, of which neurological complications are the most critical.

Keywords: Continuous-flow LVAD • HeartMate II • Survival • Adverse events

INTRODUCTION

Heart transplantation (HTx) has been the most successful treatment for end-stage heart failure (HF); however, its use is hampered by a progressive shortage of donor hearts. The use of left ventricular assist devices (LVADs) as a bridge to transplantation (BTT) has shown favourable long-term results. The first generation of LVADs consisted of large pulsatile flow LVADs (pf-LVADs) with limited mechanical durability. The second generation, continuous-flow LVADs (cf-LVAD), have demonstrated improved durability, long-term survival and exercise capacity [1–4]. More recently, cf-LVADs have also been considered as an alternative for HTx, the so-called destination therapy (DT). While results with cf-LVADs have consistently improved over time, several questions remain with regard to timing of device implantation, patient selection, management and timing of HTx and DT. Adverse events, including bleeding, infection and stroke, also continue to pose challenges. This study describes a single-centre experience with the HeartMate II (HM II; Thoratec, Pleasanton, CA, USA) LVAD support as BTT over a 5-year period.

MATERIALS AND METHODS

Patient selection

From March 2006 until December 2011, 85 patients received a HM II as a BTT at the University Medical Center in Utrecht in the
Netherlands. Throughout this study period, much experience was obtained with long-term support using cf-LVADs in our centre. Patients were categorized according to the Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which is based on the severity of illness at the time of device implantation [5].

HeartMate II LVAD

The HM II, a cf-LVAD, has a titanium axial-flow pump with an inlet cannula that is placed in the left ventricular apex and an outlet cannula in the ascending aorta. It has a percutaneous lead that connects the pump to an external system driver and power source. The pump generates up to 10 l/min of flow at a mean pressure difference of 100 mm Hg [6]. Implantation is done through a median sternotomy using extracorporeal circulation on the beating heart and the device is placed in a small preperitoneal pocket.

Anticoagulation therapy

The postoperative anticoagulation regimen included warfarin, ascal and heparin. Assuming no bleeding, heparin was started 24 h after surgery. A heparin ratio of 2 was intended, which means that the APTT value was targeted twice as normal. Heparin was only considered if: (i) Total drain production during the first 3 consecutive hours postimplant did not exceed 100 ml, (ii) prothrombin time was <18 s and (iii) activated partial thromboplastin time was <40 s. Heparin was stopped when INR >1.5.

From March 2006 until August 2009, warfarin was titrated to an INR of 2–2.5, 7 days after implantation. With this anticoagulation regimen, the reported incidence of bleeding events in the literature was substantial, leading to a recommended reduction in the INR range [7]. Therefore, our INR target was adapted to a range of 1.5–2 from August 2009 until December 2011. In case of major bleeding, all anticoagulation was temporarily stopped and continued on an individual basis after the bleeding episode.

Patient and device management

All patients were seen on scheduled visits 1 week after discharge and 1, 3, 6 and 12 months in our out-patient department, every 3 months thereafter, and more often when indicated. Echocardiographic analyses were performed at 3, 6 and 12 months after implantation. Baseline and follow-up data were collected prospectively, including patient characteristics, blood chemistry analysis, haematological findings and neurological status.

Definition of adverse events

Each event was scored and defined according to the INTERMACS definitions [5] with the following adjustments:

Major infection was characterized as a clinical infection accompanied by pain, fever, drainage and/or leucocytosis with a positive culture from the infected site or organ, which was treated by antimicrobial agents. The general categories of infections were sepsis, pocket, driveline and non-device-related infections. Haemolysis was defined as elevated levels of LDH (>1500 U/l) and bilirubin (>21 μmol/l), low haptoglobin (<30 mg/dl) in combination with increased fatigue, muscle ache and dark urine, occurring after the first 72 h postimplant.

Right HF was classified as symptoms and signs of persistent right ventricular dysfunction requiring right ventricular assist device (RVAD) implantation and/or inhaled nitric oxide ≥48 h and/or inotropic therapy for a duration of more than 14 days at any time after LVAD implantation or LVAD replacement [8].

Statistical analysis

Categorical data are presented by number (%) and continuous data by median (interquartile range; IQR, i.e. 25th–75th percentile) or by estimated mean ± standard error, where appropriate. The laboratory and echocardiography parameters were analysed with linear mixed models, where data were checked for normality using histograms and log-transformed if data were positively skewed. The estimated means and confidence interval were presented on the original scale. Survival was analysed based on Kaplan–Meier, with patients censored for device explantation (recovery), or HTx. Adverse events are presented both as percentages of all patients as well as events/patient-year (e/pt-y). A P-value <0.05 was considered as statistically significant. All analyses were done with SPSS 20.0 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

Baseline characteristics are presented in Table 1. Prior to HM II implantation, 21 patients (25%) were in critical cardiogenic shock (INTERMACS profile-I) and 64 (75%) experienced progressive haemodynamic deterioration despite inotropic treatment (INTERMACS profile-II). The mean age was 45 ± 13 years (range 17–69 years). Sixty-two patients (73%) were male. The aetiology of HF was non-ischaemic dilated cardiomyopathy in 60 patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on HeartMate II LVAD (n = 85)</td>
<td></td>
</tr>
<tr>
<td>Inclusion period</td>
<td>March 2006 to December 2011</td>
</tr>
<tr>
<td>Mean age (years) ± SD</td>
<td>45 ± 13 (range 17–69)</td>
</tr>
<tr>
<td>Male/female</td>
<td>62 (73%)/23 (27%)</td>
</tr>
<tr>
<td>INTERMACS level</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (25%)</td>
</tr>
<tr>
<td>II</td>
<td>64 (75%)</td>
</tr>
<tr>
<td>Heart failure duration (days)</td>
<td>1413 ± 1790 (range 1–7386)</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>24 (28%)</td>
</tr>
<tr>
<td>Non-ischaemic DCM</td>
<td>60 (71%)</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Intracardiac defibrillator</td>
<td>49 (58%)</td>
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</tbody>
</table>

DCM: dilated cardiomyopathy.
(71%), ischaemic cardiomyopathy in 24 (28%) and hypertrophic cardiomyopathy in 1 (1%). The median duration of support was 387 days (IQR 150–600), with a range of 1–1835 days.

Outcome

On 31 December 2011, 17 patients (20%) had died, 32 (38%) were still ongoing (LVAD duration 543 ± 411 days; range 33–1835), 3 (4%) had recovered with subsequent device explantation and 33 (39%) were transplanted (LVAD duration 566 ± 386 days; range 85–1393).

The 6-month, 1-, 2-, 3- and 4-year actuarial survivals during HM II support were 85, 81, 76, 76 and 68%, respectively (Fig. 1). Of the 17 non-survivors, 10 died peroperatively (±30 days after HM II implantation) due to major bleeding (n = 2), pneumonia (n = 2), ischaemic CVA (n = 1), haemorrhagic CVA (n = 1), sepsis (n = 1), irreversible multiorgan failure (n = 2) and right HF (n = 1). Late mortality (>30 days) occurred in 7 patients due to pump thrombosis (n = 2), right HF (n = 1), recurrent myocarditis (n = 1), ischaemic CVA (n = 2) and severe encephalopathy due to the MELAS syndrome (n = 1). After HM II implantation, 73 patients (86%) were discharged after a mean hospital stay of 40 ± 24 days.

Rehospitalization occurred 84 times in 39 patients. The mean rehospitalization period was 14 days (range 1–177 days).

Echocardiographic data

Echocardiographic data at baseline pump speed are presented in Fig. 2. The left ventricular end-diastolic dimension (LVEDD) and the left ventricular end-systolic dimension (LVESD) decreased significantly after 3 months of mechanical support (overall trend for both P < 0.0001) and the LVESD further decreased significantly after 12 months compared with 3 months (P = 0.037).

Laboratory parameters

Serum markers of end-organ function before HM II implantation and after 3, 6 and 12 months of follow-up are shown in Fig. 3. Mainly, BNP decreased rapidly after implantation. Kidney (creatinine and urea), hepatic (AST, ALT and GGT) and inflammatory markers (leucocytes, CRP) improved for up to 1-year postimplant.

Adverse events

Adverse events of the 85 BTT patients are presented in Table 2. There were 310 adverse events during a cumulative support time of 109.1 years (2.8 events/patient-year; e/pt-y). In total, 73 major infections occurred in 42 patients (49%; 0.67 e/pt-y), 22% of them were non-device-related infections and sepsis. Driveline infections occurred 14 times in 12 patients (0.13 e/pt-y), and 4 pocket infections were diagnosed in 4 patients (0.04 e/pt-y). In particular, 7 patients with driveline and/or pocket infection received permanent antibiotic prophylaxes until HTx.

Cardiac arrhythmias occurred 94 times in 44 patients (52%; 0.86 e/pt-y). In 1 patient, ventricular tachycardia remained untreatable while the patient was haemodynamically compromised, despite HM II support. As a result, the patient had to be rehospitalized for several months and eventually underwent emergency HTx.

A total of 47 major bleeding events were identified in 32 patients (38%; 0.43 e/pt-y), mostly early postoperative and often related to surgery (<30 days after implantation). Gastrointestinal (GI) bleeding, developed five times in 4 patients (5%; 0.05 e/pt-y, onset GI bleeding after HM II implantation 211 ± 180 days).
Figure 3: Change in laboratory parameters during cf-LVAD support. Haemoglobin and sodium levels increased significantly during HM II support. BNP decreased significantly rapidly after HM II implantation and remained stable thereafter. Kidney (creatinine and urea), hepatic (AST, ALT and GGT) and inflammatory markers (leucocytes, CRP) improved for up to 1-year postimplant. Asterisks reflect significant differences with \((P < 0.001)\) between groups indicated by horizontal lines.
Twenty-seven right HF events occurred in 27 patients (32%; 0.25 e/pt-y), of which 25 were within the first 30 days after implanta
tion. In case of right HF, patients were treated with a phosphodiesterase-3 inhibitor and nitric oxide. Yet, 4 patients required a RVAD. Of these, RVAD explantation was possible in 2 patients after 12 and 7 days, respectively. The other 2 patients died during RVAD support, due to right HF and severe encephal-
opathy, respectively.

Furthermore, 21 neurological events (8 TIAs, 9 ischaemic CVAs and 4 haemorrhagic CVAs) occurred in 17 patients (20%; 0.19 e/pt-y). The mean interval until the first neurological event was 213 ± 316 days. Of the 13 CVAs, 4 were fatal, 6 resulted in minor limitations and 3 in major limitations of daily life activities.

Haemolysis was noted in 16 patients (21 episodes; 19%; 0.19 e/pt-y), often 30 days after implanta
tion. Device malfunction was the result of driveline fractures in 4 patients (5%; 0.04 e/p-y). One of these fractured drivelines was repaired, while the other three were irreparable and pump replace-
ment was necessary. Pump thrombosis occurred in 7 patients (8%; 0.06 e/p-y). Four of these patients needed a pump replacement, 2 died and 1 died of a recurrent myocarditis with pump thrombosis as secondary finding. Other adverse events were perioperative renal failure requiring continuous veno-venous haemofiltration (CVVH) in 9 patients (11%; 0.08 e/pt-y) and seven venous thrombosis events a result of central venous catheters (including three pulmonary embolisms) in 7 (8%; 0.06 e/pt-y).

## DISCUSSION

The discrepancy between the limited availability of donor hearts and the increasing number of end-stage HF patients has led to an increased use of LVADs as a BTT. Over the last 6 years, there has been a transition from pf-LVADs to cf-LVADs. Compared with our earlier limited experience with pf-LVADs [9], cf-LVADs provide circu
latory support for longer periods of time. This study evaluated the outcome of 85 patients supported with a single type of cf-LVAD. Our 1- and 2-year actuarial survival rates during HM II as BTT were 83 and 76%, respectively, consistent with other recent publications [10-12]. In the present study, the most common adverse events during HM II support were cardiac arrhythmias (mainly ventricular arrhythmias) and perioperative bleeding. The incidence of infections was substantial, with 0.43 e/p-y, but did not lead to mortality and was similar to that reported by other centres [10-12].

In our cohort, thrombo-embolic complications resulted in limi
tations of daily live activities or were a cause of death. Pump thrombosis occurred in 8% of patients (0.06 e/p-y) and required pump exchange. These incidences imply that the anticoagulation regimen remains a challenge, and requires precise evaluation and follow-up to limit associated complications.

Remarkably, GI bleedings were less frequent in our cohort com-
pared with other experiences [13, 14]. It has been suggested that GI bleedings during HM II support are related to the decrease in pulsatility induced by the cf-LVAD with minimal opening of the aortic valve. This may induce angiodysplasia of the GI tract, arterio-venous malformations and eventually cause bleeding, es
dually in combination with anticoagulants, platelet inhibitors and acquired von Willebrand syndrome [13]. Our policy is setting the pump speed to maintain some degree of pulsatility. Our low incidence of GI bleeding may also be generally associated with the younger patient cohort, the possible differences in anticoagula
tion regimens and the use of standard proton-pump inhibitors in this patient cohort.

It is well known that patient selection and timing of implant-
ation remain important issues in optimizing the results after
device implantation. In contrast to reported HM II trials including selected patients, our series present the results of a consecutive cohort of patients referred to our centre. In this study, 25% of the patients who received a device were classified as INTERMACS profile-I and 75% as INTERMACS profile-II, reflecting a population with severe HF. Yet, medium-term survival was comparable with other reported results from cohorts mostly based on less-sick patients (INTERMACS profiles III and IV) [5].

This analysis represents a single-centre experience of 85 end-stage HF patients with long-term HM II support used explicitly as BTT. Despite the fact that HTx remains the only curative therapy for end-stage HF, HM II LVAD therapy provides an off-the-shelf life-saving solution for critically ill patients who have no chance of surviving the increasing waiting periods required for a donor heart to become available. Yet, there is a price to pay in terms of the risk of serious adverse events during support. Therefore, emphasis should be focused on minimizing adverse events while improving survival and quality of life while on HM II support. It is important to explore treatment options to achieve the optimal anticoagulation regimen, improve the management of ventricular arrhythmias and diminish device-related infections and haemolysis.

Conflict of interest: Jaap R. Lahpor is a member of the advisory board of Thoratec.

REFERENCES