HeartMate II left ventricular assist device; early European experience

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Abstract

Objective: The novel axial flow left ventricular assist device HeartMate II was introduced into clinical practice in Europe as part of the pilot study and after CE approval in November 2005. In order to get an overview of the use and performance of the device in Europe a group of investigators was founded to compare the initial results. Methods: In a retrospective analysis of the first 101 consecutive cases in Europe, data were collected with regard to postoperative outcome and severe adverse events and anticoagulation protocols. Results were stratified by intention to treat as a bridge to transplant or as chronic support therapy in heart failure (destination therapy). Results: In 70% of patients, the HeartMate II was intended as a bridge to transplant therapy, in 30%, it was used as a destination therapy device. The perioperative mortality post implant was 20% in the bridge to transplant patients and 7% in the destination therapy arm. However, after 1 year a comparable survival was observed in both groups (69% destination therapy, 63% bridge to transplant). Main causes of death were multiple organ failure (n = 12) and cerebrovascular accidents (n = 5). All, but one cerebrovascular accident occurred in the first 9 days after surgery. Only one other death was reported thereafter and there was no mechanical failure of the device. Conclusions: Even in the early experience the HeartMate II was used as a chronic support device in a substantial number of patients in Europe. Although the total experience is still limited, the incidence of cerebrovascular accidents is very low and the survival beyond the perioperative period is excellent.

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1. Introduction

The axial flow left ventricular assist device HeartMate II (Thoratec, Pleasenton, CA, USA) was redesigned on the basis of the first clinical trial in Europe and introduced again into clinical practice in Europe first in a pilot study in March 2004 for the CE mark and for FDA approval [1]. After successful CE approval in November 2005, it became available to all centers for cardiac surgery in Europe as a bridge to transplantation or as destination therapy in patients with end stage heart failure. Most European centers agreed to collect data of their initial experience with this device in this retrospective survey, so as to be able to report on the early experience in Europe with this newly designed left ventricular assist device (LVAD).

2. Patients and methods

In a retrospective survey all patients receiving a HeartMate II in the participating centers from March 2004 until January 2007 were included. Data of 101 HeartMate II patients out of 12 centers in 7 European countries were available (Table 1). Most patients had ischemic (n = 61) and dilative (n = 30) cardiomyopathy, 10 patients had other...
severe heart failure including myocarditis, postpartum cardiomyopathy and postcardiotomy failure.

The age ranged from 14 to 72 years (mean $48 \pm 13$ years), the body surface area from 1.4 to 2.5 m$^2$. Days on device ranged from 1 to 972 days with a mean follow-up of $166 \pm 175$ days and a total experience of 16,227 patient days. Intention to treat was bridge to transplant in 69 patients, destination therapy 31 patients and one unknown (postcardiotomy failure). At the time of implantation 89% of patients were NYHA class IV, 6% IIIb and 3% IIIa. One patient was supported by a failing HeartMate I LVAD (NYHA class II). In this patient the corresponding data on preimplantation status is missing. Inotropes were continuously administered in 75% of all patients and two or more inotropic agents were administered in 35% of cases. No patient was mechanically ventilated or on extracorporeal support prior to implantation. Intention to treatment was bridge to transplant (BTT) in 69 patients, destination therapy (DT) in 31 patients and one case of postcardiotomy failure. Among the DT and BTT group two major differences were observed: the mean age in the BTT group was $44.4 \pm 13$ years versus $52.5 \pm 14$ years in the DT group. In terms of diagnosis dilated cardiomyopathy was more frequently seen in the BTT group. In the DT patients ischemic heart disease was more common.

Implantation of the device was carried out as a standard procedure: in all patients a pocket for extrapericardial device placement was created. The pump was connected to the LV apex and the ascending aorta in all cases. In terms of anticoagulation a full dose of protamine was used to antagonize heparin after weaning from the ECC. Heparin infusion was restarted to achieve PTT levels of 50–70 s or an activated clotting time (ACT) of $180 \pm 20$ s. Change of heparin infusion to maintain anticoagulation was carried out on an individual basis. Otherwise, the perioperative management was carried out at the institutions algorithm and is not part of this report.

2.1. Statistical analysis

All centers agreed to submit all their cases in a consecutive fashion and not be selective on the inclusion of the patients. A databank from the Thoratec Company, independent of this survey, served as a control for completeness of cases. A questionnaire was sent to the study centers and data were collected in a central databank using SPSS 14.0, Windows statistical software.

Included in this analysis were patient data at the time of implant and follow-up until the first of January 2007. The focus of data collection was on intention to treat, survival and adverse events. Patient survival was expressed as a Kaplan–Meier analysis. Outcome of patients was displayed as cumulative frequency. ANOVA was used to compare DT and BTT patients in terms of survival and patient characteristics.

3. Results

3.1. Survival

Overall survival of the patient cohort was 67% at 6 months follow-up (68 patients). During follow-up 17 patients were transplanted, 2 recovered and the device was successfully removed. As of January 1st, 2007 data on hospitalization status were available in 69 living patients: nine patients were still hospitalized, 60 were discharged and 53 patients were ongoing with the device (Fig. 1).

A total of 30 patients of the entire cohort expired: 29 on the device and 1 after heart transplantation. The mortality was highest in the perioperative period: 17 patients expired within the first month post implantation, 23 within the first 3 months. Sixteen out of the 17 heart transplant procedures were successful in the entire patient cohort. Transplantation was not carried out as an emergency procedure. The main support time on the device was $4.6 \pm 3$ months prior to

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\begin{figure}
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\includegraphics[width=\textwidth]{fig1.png}
\caption{Outcome of all patients included in the study with respect to survival, transplant and recovery.}
\end{figure}
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transplant (range 0—12 months). This was most likely dependent on the availability of donor organs. In two patients the device was removed after myocardial recovery after 3 and 6 months.

In 33 patients a follow-up of more than 180 days (198—972 days; mean 350 ± 180 days) was completed. In this subgroup the diagnoses leading to heart failure were ischemic cardiomyopathy (55%), dilative cardiomyopathy (33%) and other (12%), including one case with a failing HeartMate I LVAD. There were two deaths after 6 months on the device due to intracerebral bleeding and to an unknown cause (patient was found with a disconnected drive line cable). In three cases of this group successful heart transplantation was carried out. The remaining 28 patients were ongoing with the device. Intention to treat was destination therapy in 33% and bridge to transplant in 67% in this subgroup.

When survival was stratified by intention to treat, a remarkable difference in the initial postoperative mortality was found: in the DT group survival was 93% in the BTT group 80%. However, beyond 4 months after implant comparable survival was seen in both groups (Fig. 2).

3.2. Adverse events (AE)

The most frequent cause of death was multiple organ failure (13 cases). Three occurred within 2 days after implant, the other 10 in a range of 21—124 days after implantation and were in most instances due to septic complications. Right heart failure was reported in five patients, all within 9 days after surgery. In two cases malignant arrhythmias and in the other patients right heart failure was reported. Cerebrovascular accidents (CVAs) were the causes of death in five other patients: two cases were reported for hemorrhagic and three for ischemic stroke. The causes for the remaining 7 deaths were respiratory failure (3), disconnection of drive lines (2), bleeding after ventricular rupture (1), and suffocation after epistaxis (1).

A total of 251 AEs were reported (Table 2). The most frequently observed adverse events were re-thoracotomy due to bleeding (53 events), cardiac arrhythmias (48 events), sepsis (28 events) and local infections (19 events). Approximately one third of adverse events (87 of 251 events) occurred within the first week post implant, mostly bleeding (35 of 53 events), cardiac arrhythmias (18 of 48 events), right heart failure (6 of 10 events) and renal failure (10 of 18 events).

In terms of neurologic complications, a total of four ischemic strokes were found. Three of these patients expired and one is still ongoing with the device. The incidence of ischemic stroke was 0.07 per patient year, the corresponding mortality 0.05.

In three patients a hemorrhagic stroke occurred (incidence 0.05 per patient year). One of these patients is ongoing with the device, the remaining two deceased (mortality of 0.03 per patient year). A transient ischemic attack (TIA) was seen in one patient after withdrawal of anticoagulation for

| Table 2 |
|---|---|---|---|---|---|---|
| Adverse event | Early post op (<90 days) | Mid term (<6 months) | Long term (>6 months) | Missing data | Total | AE (%) |
| Bleeding | 51 | — | — | 2 | 53 | 21.1 |
| Cardiac arrhythmias | 41 | 1 | 2 | 4 | 48 | 19.1 |
| Sepsis | 21 | 5 | — | 2 | 28 | 11.2 |
| Site infection | 6 | 8 | 12 | 1 | 27 | 10.8 |
| Local infection | 21 | 5 | 1 | — | 19 | 7.6 |
| Renal failure | 17 | 1 | — | — | 18 | 5.9 |
| Pneumonia | 9 | 1 | 1 | — | 10 | 4.8 |
| Hepatic dysfunction | 10 | — | — | 1 | 11 | 4.4 |
| Right heart failure | 10 | — | — | 2 | 12 | 4.0 |
| Hemolysis | 2 | 2 | — | — | 6 | 2.4 |
| Neurologic CVA ischemic | 7 | — | — | 2 | 4 | 1.6 |
| Neurologic other | 3 | — | — | 1 | 4 | 1.6 |
| Neurologic CVA hematologic | 2 | — | 1 | — | 3 | 1.2 |
| Pocket infection | 1 | 3 | — | — | 4 | 1.6 |
| Device thrombosis | — | — | — | 1 | 1 | 0.4 |
| Neurologic metabolic | 1 | — | — | — | 1 | 0.4 |
| Neurologic seizures | 1 | — | — | — | 1 | 0.4 |
| Neurologie TIA | 1 | — | — | — | 1 | 0.4 |
| Thromboembolic event | 1 | — | — | — | 1 | 0.4 |
| Total | 192 | 26 | 21 | 12 | 251 | 100 |

CVA: cerebrovascular accident; TIA: transient ischemic attack.
pleurocentesis. This patient was transplanted thereafter and is still alive.

Isolated driveline infections were present in 21 patients (incidence 0.37 per patient year). In 15 cases the infections were treated successfully locally and with systemic antibiotics. Recurrent driveline infections were found in six patients. Four of these patients were transplanted 30, 53, 78 and 135 days after onset of infection. There was no mortality due to isolated driveline infection.

Pocket infections were reported for three cases. One patient was transplanted, in another patient, the device was successfully removed after myocardial recovery, and a third patient was ongoing with an omental wrap and antibiotic therapy.

In one case pump thrombosis was reported 4 months after implantation in a 40-year-old patient, who was discharged in good clinical conditions after 28 days. Anticoagulation was maintained with warfarin (INR 2.5–3.0) (Coumadin®, Bristol-Myers Squibb GmbH & Co. KGaA, Munich, Germany)/Phenprocoumon (Marcumar®, Roche Pharma AG, Grenzach-Wyhlen, Germany) and aspirin (100 mg/day). He was transplanted successfully locally and with systemic antibiotics.

In one patient driveline infections were present 229 days after LVAD implantation; a thrombus was still present in the device at the time of transplant [2].

### 3.2.1. Anticoagulation protocols

The following drugs were used for maintenance anticoagulation on January 1st, 2007 in this patient cohort: (Table 3).

With growing experience most centers tend to avoid any anticoagulation therapy within the first 24 h after implantation, use full doses of protaminsulfate after the extracorporeal circulation and infuse platelet concentrates at the time of implant.

### 4. Discussion

Heart transplantation remains the most effective treatment for terminal heart failure. However, the availability of donor organs worldwide is minimal compared to the number of end-stage heart failure patients. Bridging to transplantation with a mechanical assist device has become an established option at many heart transplant centers, thus aggravating the scarcity of donor organs. Since the landmark trial Rematch (randomized evaluation of mechanical assistance for the treatment of congestive heart failure) [3] showed that implantation of a LVAD improves survival superior to any medical treatment and with the emergence of newly designed left ventricular assist devices the question is, whether these new devices are suitable for long term support [4], which is synonymous to destination therapy or chronic support [5]. Since there are plenty of different devices to choose from as bridge to transplantation, an analysis of newly introduced products must focus on the suitability as a possible alternative to heart transplantation for those who were ineligible for transplant or unable to receive a graft in time.

Therefore, a working group of European heart surgeons put their early results of the newly introduced HeartMate II LVAD together to gain broad experience fast. The report of this data is limited in two ways: one is that, although all centers were experienced with LVAD therapy, all were at the beginning of a learning curve with the new device. The other is that most patients included had a follow-up of less than 6 months. Since most AEs were found in the perioperative period, it seems that the risk and mortality per patient year are calculated too high. Also, the conclusion made for the long-term durability of the device is based on 33 patients with a follow-up longer than 6 months.

In addition it must be noted, that availability of donor hearts is very limited everywhere, but there are remarkable differences between centers in different European countries. Therefore indication for implant, which was up to the individual centers, was inhomogeneous too: in some patients LVAD implantation was regarded as a last resort when deteriorating while waiting for a donor heart. In other patients implantation was done more electively, because heart transplantation seemed to be a very unlikely option for the patient. In this respect and in the nature of a retrospective survey, this investigation differs from a prospective multicenter trial.

The frequent use of the HeartMate II for chronic support (DT) was unexpected, but reflects the high demand. When comparing perioperative mortality in BTT and DT patients in this study, the initial period was more favorable for DT patients, possibly reflecting the more elective nature of the implant procedure. However, the survival was comparable after four months of follow-up. It can be speculated that the later mortality in the destination group was due to a higher morbidity in this group since many of these patients were not eligible for heart transplantation due to age or comorbidity.

In a most recent publication, Lietz and co-workers demonstrated in an analysis of 280 LVAD patients receiving a HeartMate I pulsatile LVAD, that 90-day survival was not attributable to the center’s experience, but to preoperative patient characteristics, such as platelet count, right heart function and multiple organ insufficiency [6]. Therefore, it is concluded that the perioperative survival of this survey reflects the preoperative status of the patients in whom the device was used more than specific characteristics of the HeartMate II LVAD. It must be noted that indications for implantation were not study driven and thereby reflected the clinical reality of LVAD implantation in Europe. The initial mortality (seven patients) after implantation of the device was characterized by multiple organ failure (two patients) or the inability to restore hemodynamic function for malignant arrhythmia (two patients) or right heart failure (three patients). In hind sight it can be discussed if LVAD support was too late for this group or that biventricular assist would have been more appropriate.

### Table 3

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonist + ASS</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Vitamin K antagonist + clopidogrel</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Vitamin K antagonist</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Vitamin K antagonist + clopidogrel</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>ASS</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>22%</td>
<td>22%</td>
</tr>
</tbody>
</table>

* Warfarin (Coumadin®, Bristol-Myers Squibb GmbH & Co. KGaA, Munich, Germany)/Phenprocoumon (Marcumar®, Roche Pharma AG, Grenzach-Wyhlen, Germany).
* Plavix®, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany.
Similar to the results in HeartMate I patients of the post Rematch era, sepsis remained the leading cause of death in this survey, both in the perioperative situation and overall. This is consistent with the findings of older reports with other devices used as bridge to transplantation [7,8]. Since infection of the device due to ascending infection of the driveline is rare in the patients in this study, it seems that sepsis following LVAD implantation is attributed to the state of severe malperfusion of some patients prior to implant. This observation is supported by a comparable rate of infections in the experience with a fully implantable device [9].

Two observations are new in this experience. First, absence of a further deterioration of patients beyond 90 days. The survival remains stable even after 6 months resulting in an improved 1-year survival rate. This finding is supported by the most recent data on the experience with the HeartMate II in the United States [10]. In addition the incidence of CVAs seems remarkably low [11], especially beyond the perioperative phase. This and the absence of any mechanical failure in our patient cohort leads to the expectation of supporting patients longer than a year with results superior to the reports on DT so far.

This optimistic view is supported by experience in some patients and by the low hospitalization rate in ongoing patients.

The second observation is that survival after heart transplantation proved to be excellent in patients of this survey, although the surgical procedure is more invasive following a previous LVAD implantation. The improvement of the patient’s functional status may be beneficial to the outcome after heart transplantation [12]. Another explanation might be a beneficial effect of LVAD therapy on pulmonary vascular resistance. Recently it has been shown that LVAD support effectively reduces fixed pulmonary vascular resistance (PVR) leading to comparable post-transplant survival [13]. In this patient cohort the post-transplant survival seems exceptionally high. Possibly the small size of the device contributed favorably to the less invasiveness of an explantation procedure, when compared to larger devices.

The question of chronic LVAD support with nonpulsatile devices has been discussed in the past. [14] Nonpulsatile flow allows for smaller devices with less mechanical parts, the potential for long term durability and less noisy operation. Comparing patients with HeartMate II [15] to other patients with pulsatile LVAD (HeartMate I), a similar end-organ function [16] and exercise performance has been reported [17]. Possible adverse effects of nonpulsatile flow may be more discrete and a careful analysis of the possible cognitive and psychological effects as well as the risks due to the obstacles in measuring blood pressure in outpatients is required. Temporarily we conclude that LVAD support with a continuous flow device beyond 6 months is possible and has a very low incidence of adverse events and hospitalization beyond the perioperative period.

Bleeding and thrombus formation are common problems after LVAD implantation with possible life threatening implications. Prior to the introduction of the HeartMate II into clinical practice during the Pilot study a very aggressive anticoagulation protocol was chosen to prevent thrombus formation. Prior experience with other axial flow devices led to the assumption that this type of device is prone to thrombus formation [18,19]. After gaining clinical experience with the HeartMate II, however, it seems that the risk of thrombus formation has been grossly overestimated: in our cohort only one device thrombosis was reported accounting for 0.4% of all reported adverse events. In contrast, perioperative bleeding episodes in 53 of 38 patients were the single leading AE (21.1% of all AEs). For this reason most centers modified the original anticoagulation protocol to less aggressive regimens in order to reduce bleeding events.

Thus, there is no uniform anticoagulation strategy amongst European investigators anymore. Different strategies to preserve either platelet function or plasmatic coagulation, or both, are pursued. In general, different vitamin K antagonists are used in combination with a platelet aggregation inhibitor. However, there is no consent on what minimum anticoagulation therapy is required for the device and how to adjust the anticoagulation therapy to the individual patient.

Comparing this data with the experience in BTT patients in the United States [10] the outcome is comparable overall. In the United States more patients were transplanted within 180 days after LVAD implantation, thereby a larger cohort received only short-term support with a HeartMate II LVAD. The spectrum and onset of adverse events indicate the same cumulation of events in the early perioperative period and a stable patient course after discharge. A relatively high incidence of bleeding episodes was also observed in the U.S. study. Overanticoagulation in the early experience may here play a role. In addition the HeartMate II LVAD design includes non-sealed vascular graft. Sealing methods of the inflow graft evolved with clinical experience and may have contributed to the incidence of perioperative bleeding.

In summary, the early experience with the HeartMate II in Europe was favorable and far beyond expectations derived from earlier experiences with pulsatile devices. The perioperative outcome was comparable to the institutions experiences in the past. However, the absence of adverse events beyond the perioperative period, the rare event of a readmission and the mechanical stability of the LVAD seem to indicate the suitability for chronic support. High rates of bleeding events at the time of implantation and low rates of both thrombus formation and ischemic strokes warrant the development of new, safe and less aggressive anticoagulation protocols. With the growing evidence of the safety of the device and the knowledge of the preoperative patient factors impeding a favorable outcome, future implantation at a less advanced stage of heart failure should be discussed.

References


