Outcomes of HeartWare Ventricular Assist System support in 141 patients: a single-centre experience

Long Wu, Yu-Guo Weng, Nian-Guo Dong, Thomas Krabatsch, Alexander Stepanenko, Ewald Hennig and Roland Hetzer

OBJECTIVES: A third-generation ventricular assist device, the HeartWare Ventricular Assist System, has demonstrated its reliability and durability in animal models and clinical experience. However, studies of a large series of applications are still lacking. We evaluate the safety and efficacy of the HeartWare pump in 141 patients with end-stage heart failure at a single centre.

METHODS: A total of 141 patients (116 men and 25 women with a mean age of 52 years) in New York Heart Association (NYHA) Class IV received implantation of the HeartWare Ventricular Assist System between August 2009 and April 2011 at the Deutsches Herzzentrum Berlin. The outcomes were measured in terms of laboratory data, adverse events, NYHA functional class and survival during device support.

RESULTS: The HeartWare system provided an adequate haemodynamic support for patients both inside and outside the hospital. NYHA class improved to I–II. Organ function and pulmonary vascular resistance improved significantly. In this cohort of patients, 14 patients underwent heart transplantation, one had had the device explanted following myocardial recovery, one had changed to another assist device, 81 were on ongoing support and 44 died. The overall actuarial survival rates at 6 and 12 months were 70 and 67%, respectively, and the 3-, 6- and 12-month survival rates on a left ventricular assist device (LV AD) support for bridge to transplantation patients were 82, 81 and 79%, respectively. Infection and bleeding were the main adverse events. Four patients underwent an LV AD exchange for pump thrombosis.

CONCLUSIONS: The HeartWare system provides a safe and effective circulatory support in a population with a wide range of body surface areas, with a satisfactory actuarial survival time and an improved quality of life. It can be used for univentricular or biventricular support, being implanted into the pericardial space with simplified surgical techniques.

Keywords: Ventricular assist device • HeartWare • Heart failure

INTRODUCTION

Cardiac transplantation is the most effective treatment for the failing heart. Due to the shortage of donor organs and since numerous candidates are ineligible for transplantation, mechanical circulatory support (MCS) is an attractive option for end-stage heart failure.

Compared with the first-generation pulsatile pumps, the second-generation axial-flow pumps show encouraging results, with the lower rates of persistent complications and an improved quality of life [1, 2]. MCS has become invaluable as a bridge to heart transplantation or to myocardial recovery and also as a destination therapy (DT).

The third-generation centrifugal HeartWare Ventricular Assist System received CE certification for Europe in 2009. Though its reliability and durability have been proven in animal models and clinical experience [3, 4], studies of large series of patients are still lacking. Here, we present the results of 141 patients with end-stage heart failure treated with the HeartWare system at the Deutsches Herzzentrum Berlin, to evaluate its safety and efficacy in the clinical application.

MATERIALS AND METHODS

Study design

One hundred and forty-one patients received the HeartWare device between August 2009 and April 2011 at the Deutsches Herzzentrum Berlin, in LVAD, RVAD or bi-VAD configuration. At the time of ventricular assist device (VAD) implantation, the majority of patients were in New York Heart Association (NYHA) Class IV and receiving intravenous inotropic agents. The classification of the severity of heart failure and adverse events were defined by the Interagency Registry for Mechanically Assisted Circulatory Support registry (INTERMACS) [5]. The patients were
retrospectively analyzed with regard to INTERMACS level and intention to treat: bridge to transplantation (BTT), bridge to recovery (BTR) and DT. The date of the follow-up was from 26 August 2009 to 1 July 2011. All patients were monitored for pump flow, selected laboratory data, adverse events and device malfunctions. The primary study endpoints were survival to transplant, cardiac recovery with device explantation, change to another device and continuing device support or death.

HeartWare Ventricular Assist System

The HeartWare Ventricular Assist System utilizes a centrifugal blood pump, the HVAD™ pump, which has the following features: 140 g in weight, displacement volume of 50 ml and output capacity of 10 l/min. The pump possesses a hybrid hydraulic-magnetic impeller suspension system that eliminates friction, heat generation and component wear. Its miniature design and the inflow integrated with the pump facilitate intrapericardial implantation. The pump is connected to the external system components by a driveline that is tunneled subcutaneously and exits the patient’s abdominal wall. A controller operates the pump, regulates power, monitors system performance and displays alarm notifications. A carrying case for the controller may be worn on a belt or over the shoulder [6].

Device implantation

After a median sternotomy and a short period of induced ventricular fibrillation during a cardiopulmonary bypass, the LVAD was implanted conventionally into the left ventricular apex, and the outflow graft was connected to the ascending aorta. In patients with a previous median sternotomy, a left lateral thoracotomy was used to implant the pump, the inflow cannula was inserted into the apex, and the outflow graft was connected to the descending aorta [7].

For right ventricular support, to ensure a good orientation of the inflow cannula within the right ventricular or atrial cavity and sufficient space to prevent the inflow cannula from suction to the opposite septum, two 5-mm silicon suture rings were added to the sewing ring to reduce the effective length of the inflow cannula. The pump was inserted at the anterior free wall or the lateral wall of the right atrium. The outflow graft was narrowed before surgery to 5 mm, and was sutured to the pulmonary artery [8].

Anti-coagulation

The anti-coagulation medication was administered according to our established protocol, depending on postoperative studies of activated partial thromboplastin time (aPTT), thrombelastograms and platelet function tests. The protocol consisted of the use of heparin in the early postoperative period to keep the aPTT between 50 and 60 s. After the thoracic tubes were removed and multiorgan dysfunction recovered, coumadin was started to maintain the international normalized ratio at 2.5–3.0. Aspirin and dipyridamol were given according to the results of the thromocyte activation tests and thrombelastogram [9]. In patients with heparin-induced thrombocytopenia, anti-coagulation was switched from heparin to argatroban.

Follow-up after device implantation

Before leaving the hospital, the patient and family members were intensively trained in the care of the device. The local family practitioner was also instructed about the device and performed the routine follow-up examinations once a week or as needed. Patients routinely returned to the hospital for follow-up examinations at intervals of between 2 weeks and 3 months. In addition, a 24-h phone support line for medical and technical problems was introduced [10].

Statistical analysis

SPSS for Windows Release 18.0 (SPSS Inc., Chicago, IL, USA) was used for the calculations. Biochemical and haemodynamic variables are presented as mean values ± standard deviation. Discrete variables are presented as percentages. All statistical comparisons are two-sided. Adverse events are presented both as the percentage of patients and event rates per patient per year. For a comparison between categorical variables, Fisher’s exact test was used. For continuous data, comparisons were performed using a Mann-Whitney U test. The level of statistical significance was set at P < 0.05. Survival probability for patients continuing on mechanical support was performed using the Kaplan-Meier method, and the survival comparison was analysed by the log-rank analysis. Patient survival was calculated from the day of HeartWare implantation until death on mechanical support, and censored at the time of heart transplantation, myocardial recovery or change to another type of device as of 1 July 2011.

RESULTS

Patient population

The pre-implantation demographic characteristics of patients are summarized in Table 1, and preoperative risk factors are listed in Table 2. The group consisted of 116 men (82%) and 25 women (18%) with a mean age of 52 years (range 7–83 years). The HeartWare pump accommodates a large range of body surface areas (BSAs) with a mean of 1.96 m² (0.96–2.60 m²). The primary disease leading to end-stage heart failure was idiopathic cardiomyopathy in 68 cases (dilative cardiomyopathy, 65; restrictive cardiomyopathy, three), ischaemic cardiomyopathy in 63 cases, congenital heart disease in five cases and others in five cases.

Haemodynamic data from the right heart catheter/Swan-Ganz catheter measurements showed the median cardiac index to be 2 l/min/m² (0.90–3.60 l/min/m²). Left ventricular end-diastolic dimension (LVEDD) and left ventricular ejection fraction in echocardiography were 69 mm (30–100 mm) and 17% (5–65%), respectively.

Forty-five (32%, 45/141) patients had a previous sternotomy for coronary artery bypass grafting (CABG), valvular surgery, congenital heart surgery and so on. Two DuraHeart support patients had urgent operations for pump thrombosis in this study.

Outcomes

On 1 July 2011, 14 patients had undergone heart transplantation, one had had the device explanted following myocardial
recovery, one had changed to another assist device, 81 were on ongoing support and 44 had died. The median waiting time for heart transplantation after VAD implantation was 109 days (1–355 days). Ninety (63%) patients were discharged home as part of the release programme during the device support, including biventricular assist device (BVAD) in eight cases. The actuarial survival to heart transplantation, pump explantation for myocardial recovery, change to another device or ongoing support at 1, 3, 6, 12 months was 82, 74, 70 and 67%, respectively (Fig. 1).

During the operation, thirty-eight (27%, 38/141) patients underwent concomitant cardiac surgery, including a patent foramen ovale closure in 11 cases, tricuspid valve plasty in 10 cases and CABG in five cases. In 19 patients with ischaemic cardiomyopathy, who had previous CABG, a left lateral thoracotomy was used to place the device; in one of these cases, cardiopulmonary bypass was on standby.

Before HeartWare implantation, four patients had extracorporeal membrane oxygenation (ECMO) and two patients had a Levitronix CentriMag support for the left ventricle. They had the opportunity to switch to the HeartWare assist device, but the mortality was 50% (3/6).

The serial laboratory data for the hepatic and renal functions from baseline to 1 and 3 months are given in Table 3. Renal and hepatic functions improved significantly after VAD implantation. The values of total bilirubin, aspartate aminotransaminase and lactate dehydrogenase continued to decline from baseline to the 1- and 3-month follow-up. The levels of blood urea nitrogen and creatinine significantly fell between the baseline and 1-month follow-up. Patients’ general condition, manifested by the levels of albumin and C-reactive protein, deteriorated in the first month, but both had improved at the 3-month follow-up.
Table 3: Laboratory values from baseline to 1 and 3 months after HeartWare implantation

<table>
<thead>
<tr>
<th>Laboratory values</th>
<th>Baseline</th>
<th>1 month</th>
<th>P-value Base vs 1 m</th>
<th>3 months</th>
<th>P-value Base vs 3 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.66 ± 1.39</td>
<td>1.00 ± 1.86</td>
<td>&lt;0.0001</td>
<td>0.75 ± 0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>320.98 ± 1374.15</td>
<td>36.22 ± 43.76</td>
<td>&lt;0.0001</td>
<td>31.10 ± 12.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td>610.34 ± 1686.81</td>
<td>276.42 ± 105.37</td>
<td>0.001</td>
<td>41.61 ± 144.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>74.88 ± 51.79</td>
<td>38.68 ± 25.65</td>
<td>&lt;0.0001</td>
<td>49.04 ± 29.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.40 ± 0.84</td>
<td>0.98 ± 0.50</td>
<td>&lt;0.0001</td>
<td>1.15 ± 0.85</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.81 ± 0.79</td>
<td>2.34 ± 0.82</td>
<td>0.008</td>
<td>3.54 ± 0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>4.05 ± 4.14</td>
<td>5.84 ± 5.78</td>
<td>0.001</td>
<td>2.34 ± 3.98</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransaminase; BUN: blood urea nitrogen; CRP: C-reactive protein; LDH: lactate dehydrogenase.

Base vs 1 m denotes baseline vs 1 month; Base vs 3 m denotes 3 months.

Table 4 shows pulmonary vascular resistance (PVR) to be markedly decreased after VAD implantation. Pulmonary capillary wedge pressure fell from 26.46 to 13.05 mmHg (P = <0.0001), mean pulmonary artery pressure fell from 35.84 to 21.50 mmHg (P = <0.0001), and PVR fell from 9.31 to 3.61 Wood units (P = <0.0001).

Table 4: Pulmonary resistance changes after HeartWare implantation

<table>
<thead>
<tr>
<th>Pulmonary resistance</th>
<th>Baseline</th>
<th>After VAD support</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCWP (Hg)</td>
<td>26.46 ± 6.98</td>
<td>13.05 ± 7.18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSP (mmHg)</td>
<td>53.53 ± 13.80</td>
<td>33.19 ± 15.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PDP (mmHg)</td>
<td>26.44 ± 7.40</td>
<td>15.00 ± 9.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>35.84 ± 8.74</td>
<td>21.50 ± 10.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>14.11 ± 6.23</td>
<td>8.47 ± 4.94</td>
<td>0.002</td>
</tr>
<tr>
<td>PVR (Wood)</td>
<td>9.31 ± 3.81</td>
<td>3.61 ± 1.74</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; PCWP: pulmonary capillary wedge pressure; PDP: pulmonary diastolic pressure; PSP: pulmonary systolic pressure; PVR: pulmonary vascular resistance.

**Subgroup analysis of survival**

**Age.** In this study, the average age was 52 (7–83) years. The majority of patients, 108 (76%), were 18–64 years old, 25 (18%) were 65–83 years old and 8 (6%) were under 18 years old. There were no statistically significant differences in the actuarial survival rates between the three groups (P = 0.307), and there were no statistically significant differences between the two adult groups (P = 0.597). In the youngest age group, seven patients underwent heart transplantation; the median waiting time was 58 days (1–111 days). The youngest patient (7 years old) was still waiting for heart transplantation with the support time >320 days.

**Interagency Registry for Mechanically Assisted Circulatory Support profiles.** The actuarial survival at 1, 3, 6 and 12 months was 67, 58, 55 and 52% for INTERMACS level 1; 84, 73, 71 and 68% for level 2; 93, 88, 86 and 86% for level 3 and 67, 67, 67 and 67% for level 4, separately. The level 1 group had higher mortality than the other groups (P = 0.033).

**Left ventricular assist device and biventricular assist device.** In this study, 19 (13%) patients received a BVAD, 121 (86%) patients a LVAD and 1 (1%) patient a right ventricular assist device (RVAD). The right atrium was chosen to place the RVAD pump in two patients. The actuarial survival at 1, 3, 6 and 12 months was 74, 53, 47 and 47% for BVAD and 84, 78, 76 and 74% for LVAD, respectively. A support with an LVAD shows a better survival than with a BVAD (P = 0.021). One patient had undergone heart transplantation and seven patients were still on support, with five cases of support >500 days.

There are 87 cases for BTT and 32 cases for DT among 121 LVAD support patients. The 1-, 3-, 6- and 12-month actuarial survival rates were 88, 75; 82, 69; 81, 65 and 79, 59%, respectively. There were significant differences between the two groups (P = 0.048) (Fig. 2).

**Adverse events**

Bleeding and infection were the main adverse events; the incidence of these complications was 30% (43/141), 0.97 events/patient-year and 35% (50/141), 1.04 events/patient-year, respectively.

Infection occurred in 50 patients with 66 events. Sepsis developed in 18 patients. None of the septic events were related to the pump. Eighteen cases of local driveline exit site infection were recorded in 12 patients.

Bleeding needing surgical intervention occurred in 33 patients with 45 events, including re-thoracotomy in 38 events and laparotomy in seven events.

There were 18 cases of implanted Levitronix CentriMag RVAD for right ventricular failure (RVF) during LVAD implantation. The four CentriMag pumps were switched to HeartWare HVAD. Six patients underwent explanation for right ventricular recovery, one patient had cardiac transplantation and seven patients died. The results for unexpected RVF needing temporary RVAD were poor, with a mortality of 39% (7/18). Compared with delayed LVAD implantation of Levitronix CentriMag, concomitant implantation during the operation showed a trend towards better survival (P = 0.141).

Device failure occurred in 12 patients, including haemolysis, thrombosis, cable break and controller dysfunction. The four left ventricular assist pumps were exchanged due to thrombosis. Of these four patients, three (75%, 3/4) cases were positive for heparin-induced thrombocytopenia (HIT).
Causes of death

One-third of supported patients (31%, 44/141) died during support. Of these deaths, nearly two-thirds (59%, 26/44) occurred in the early postoperative period (device support ≤30 days). The primary causes of death for patients receiving primary VAD implants are given in Table 5. The major cause was RVF representing the proportion of one-fourth (23%, 10/44).

DISCUSSION

The ultimate goal in developing VADs is to allow the patient to lead a normal, active life while receiving MCS.

The HeartWare Ventricular Assist System is a representative of the third-generation of devices. It may be possible to increase its availability to a broader patient population, simplify implant procedures, reduce the risk of device-related complications such as bleeding and infection, eliminate the probability of pump thrombosis and haemolysis and improve the quality of life in outpatients.

In the present study, the HeartWare system provides adequate haemodynamic support for patients with end-stage heart failure. This benefit can be attributed to the recovery to NYHA functional Class I–II and improvement of organ function in the majority of patients. The data indicate the hepatic and renal functions to be significantly improved, patients’ general condition was ameliorated effectively and pulmonary vascular resistance declined progressively. The HeartWare pump has acceptable long-term blood compatibility with low levels of plasma free haemoglobin.

The surgery and cardiopulmonary bypass may cause further injury to the VAD patients, who always have hepatic and renal dysfunction or beginning multi-organ failure before device implantation. The less invasive implantation techniques available for the HeartWare system will bring great benefits to these patients. The left lateral thoracotomy is an alternative approach to the conventional median sternotomy to implant the pump with femoral cardiopulmonary bypass, ECMO support or off-pump techniques, especially for DT in patients with previous sternotomy. This approach minimizes the complications associated with a repeat sternotomy and simplifies the implant procedure [7].

One patient with dilative cardiomyopathy was successfully weaned from an LVAD support when it was demonstrated that the heart had completely recovered in the size and function. A special plug for the apex suture ring was used to facilitate pump removal by left lateral thoracotomy without cardiopulmonary bypass [9]. This technique may conserve the myocardial structure and preserve the function of the left ventricle.

BVAD and the total artificial heart are the two main methods for patients presenting biventricular failure. The para-corporeal pump Berlin Heart Excor is the most common BVAD for the long-term support at our institute [11]. After some surgical modifications, 19 patients received two HeartWare pumps to support both ventricles, with a 3-month survival of 53% and 5 cases of support >500 days.

Although the BVAD requires two controllers and four batteries of the HeartWare system, it is more compact and more easily portable for outpatients, enabling greater life quality than

Table 5: Causes of death (n = 44)

<table>
<thead>
<tr>
<th>Primary cause of death</th>
<th>N (%)</th>
<th>Indications</th>
<th>INTERMACS level</th>
<th>Phase Early (≤30 days)</th>
<th>Late (&gt;30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BTT</td>
<td>DT</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>10 (22.73)</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8 (18.18)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>CNS event</td>
<td>3 (6.81)</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>8 (18.18)</td>
<td>6</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (4.55)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Device failure</td>
<td>6 (13.64)</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other causes</td>
<td>7 (15.91)</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>24</td>
<td>18</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

CNS: central nervous system; BTT: bridge to transplantation; DT: destination therapy.

Other causes include traumatic cerebral haemorrhage and unknown causes.
pneumatically driven double ventricle support. Long-term BVAD support with the HeartWare pump is feasible and warrants further investigation.

Implantable VAD systems suitable for adults are too large for paediatric patients and para-corporeal pumps are routinely used in children [12]. The application of axial-flow pumps in children is less reported in the literature [13]. In this group, the results are satisfactory. Eight young patients (<18 years) received LVAD support, and seven of them underwent heart transplantation. The youngest child (7 years old) was still waiting for a suitable donor heart.

Advanced age is one of the most common predictive factors of death in patients with MCS [14]. The increase in age from 60 to 70 years conferred more than double the risk of early mortality. Approximately 80% of patients hospitalized with heart failure are >65 years old. We found that there was no difference between the 18–64 age group and the over 65 age group (P = 0.597) in this study. However, this benefit of the HeartWare pump requires more cases before it can be confirmed.

Appropriate patient selection for MCS plays a major role in influencing the development of adverse events and the survival of the patients. Our study once again confirmed the view of the INTERMACS data, which consistently demonstrates that critically ill patients (level 1) have the worst mortality [2].

Our study does not demonstrate better results in terms of the survival time and adverse effects than other HeartWare clinical trials [4]. This may be partly related to patients’ critical history and dismal status before implantation. The purpose of the clinical trial was to evaluate the results of the HeartWare pump for BTT patients with stringent inclusion and exclusion criteria for age, right ventricular function, hepatic and renal functions, prior cardiac surgery and so on, which results in an absence of INTERMACS level 1 patients in the observation [4]. At our institution we offer VAD treatment to almost all patients suffering from end-stage heart failure and who agree to this kind of treatment. Therefore, our “real world” results differ from those obtained in clinical studies. However, a recent INTERMACS report showed comparable results in terms of long-term survival. It should be kept in mind that all these patients would die within weeks or months without VAD support.

Nevertheless, it is the reality that surgical indications continue to be updated and expanded as new devices emerge. It is valuable to apply a new VAD in critically ill patients. The overall actuarial survival rates were lower than those of the HeartWare clinical trial, but we found that the outcomes in BTT patients with HeartWare LVAD support were good compared with the HeartMate-II LVAD for the same purpose. The 6 and 12-month survival rates were 81 and 79% in Pagani’s report [15] and 82 and 73% in Miller’s report [16].

Though device-related bleeding and fatal infection are decreasing [4], bleeding and infection were still the dominating factors in this investigation. Early post-operative RVF is associated with the increased rates of short-term morbidity and mortality during LVAD support [17]. According to a recent report, the incidence of RVF after continuous-flow LVAD implantation for BTT patients was 20% [18].

The present study has some limitations. This is a single-centre, retrospective, non-randomized study with a short follow-up period. Therefore, there is some inherent bias and confounding. However, this study shows a good performance of the HeartWare system as an MCS.

CONCLUSION

In conclusion, we report the first large retrospective study of clinical experience of the HeartWare Ventricular Assist System support in patients with end-stage heart failure. The HeartWare system provides a safe and effective circulatory support in a population with a wide range of BSAs, with a satisfactory actuarial survival time and an improved quality of life. The results show that excellent haemodynamic support and organ function recovery can be achieved with this new device in a short time. It can be used to support one ventricle or both ventricles, being implanted into the pericardial space using simplified surgical techniques.

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