Clinical Differences Between Continuous Flow Ventricular Assist Devices: A Comparison Between HeartMate II and HeartWare HVAD

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ABSTRACT

Background: The HeartWare ventricular assist device (HVAD) is a new generation centrifugal flow VAD recently introduced in Canada. The objective of this study was to compare the HVAD device to the HeartMate II (HMII) axial flow device. Very few studies have compared clinical outcomes between newer generation VADs.

Methods: All perioperative and follow-up data on LVAD recipients were collected prospectively in our institutional database. Between January 2006 and April 2012, 46 consecutive patients underwent implantation of either an HVAD (n = 13) or a HMII (n = 33) device. Pre-implant demographics, perioperative and postoperative clinical outcomes were reviewed between groups.

Results: Overall, the baseline characteristics, demographics, co-morbidities and laboratory values were comparable between the two groups. The majority of the patients were Interagency Registry for Mechanical Assisted Circulatory Support 3–4 (92% in both groups) and most of the patients were bridge to transplant (75% in HMII vs. 79% in HVAD). Survival and the incidence of perioperative bleeding, renal dysfunction, liver dysfunction, and infection were similar between the groups. However, HVAD devices had a significantly higher incidence of gastrointestinal (GI) bleeding (31% vs. 0% in HMII patients, p < 0.01) and stroke (44% vs. 10% in HMII patients, at one year p = 0.04). Hemorrhagic strokes were more frequent in patients with HVAD (three of the five episodes vs. one of the three episodes in HMII patients, p = 0.06). Conclusion: While device complications were comparable, patients with HVAD experienced a significantly higher incidence of stroke and GI bleeding and therefore refinement in patients' management may decrease incidence of these complications.


Recent advancements in device technology have led to a reevaluation of the role of ventricular assist devices (VADs). Devices are now being used as a bridge to transplant (BTT) candidacy,¹ for negative virtual cross-match and for long-term indefinite support (destination therapy).²,³

Comparisons between first- and second-generation VADs have shown that second-generation VADs have improved outcomes in terms of survival and decreased incidence of adverse events such as infection and device malfunction.⁴–⁶ However, second-generation VADs have an increased risk of gastrointestinal (GI) bleeding, thromboembolism, and ventricular arrhythmias.⁷ Despite increasing experience with newer generation devices, there has been little research comparing second- and third-generation VADs. To date, only two reports have directly compared third-generation VADs to other generations. The first report compared 140 HVAD devices to 400 other BTT VADs. The study reported a comparable one-year survival (91% in HVAD vs. 86% in the control group, p = 0.4) and that patients with HVAD experienced fewer...
surgically related bleeding events. However, patients with HVAD also had a significantly higher incidence of stroke. The report was a multicenter unmatched study, which used an Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) control group consisting of different types of BTT VADs. Based on INTERMACS level, the control group was sicker ($p < 0.002$). Recently, preliminary data from the ENDURANCE randomized controlled trial also reported that HVADs had a higher incidence of stroke compared to HeartMate II (HMII) devices. This paper aims to compare outcomes between second-generation HMII devices and third-generation HVADs within a single institution.

METHODS

Study population

The study was a retrospective cohort study consisting of 46 consecutive ventricular assist device patients implanted at Toronto General Hospital between January 1, 2006 and April 30, 2012. Of the 46 VAD patients, 33 had an HMII device while 13 had an HVAD device. The population consisted of 35 patients receiving the device as a BTT, nine as a bridge to candidacy and two as destination therapy. The institutional research ethics board reviewed and approved the study. Device selection was based on patient characteristics and surgeons’ preference. In general, patients who had a lower body surface area (BSA), were female, or were slated for destination therapy preferentially received an HVAD. The patients with HVAD were anticoagulated with 325 mg of aspirin and Coumadin to a target International Normalized Ratio (INR) of 2–2.5 while HMII patients also received 325 mg of aspirin and had a target INR of 1.5–2. No additional anti-platelet agents were used and platelet function was measured in the operating room but not after discharge. Patients with HVAD had a higher target INR since the first two patients experienced transient ischemic attacks and the preliminary ADVANCE trial data reported a higher incidence of strokes in patients with HVAD. Some patients who experienced bleeding events were placed on clopidogrel for less intense anticoagulation than Coumadin. Patients received routine antibiotic prophylaxis which consisted of fluconazole and cefazolin. At our institution, the pump speed of both devices was intentionally decreased, using echocardiographic guidance, to ensure the aortic valve opened intermittently to generate pulsatility where possible. This was done by ramp study echocardiograms at hospital discharge and at monthly intervals in the outpatient clinic. Intensive care unit (ICU) stay was dependent on floor nurse availability while hospital length of stay was dependent upon adequate performance of the device. Outpatient blood pressure was targeted for a MAP between 65 and 75 mmHg.

Data collection

Patient demographics, co-morbidities, laboratory values, and complications were retrospectively analyzed using our institutional database. When it was required, additional data were collected retrospectively from the electronic medical record. Baseline information was collected the day before VAD implantation. Patient demographic information and co-morbidities included age, sex, diabetes, implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), etiology of cardiomyopathy, indication for VAD, and INTERMACS patient profile risk score. Height and weight were also collected in order to calculate body mass index (BMI). BSA was calculated statistically. Laboratory data for hemoglobin and creatinine was collected. We also collected left ventricular ejection fraction, cardiac index, mixed venous oxygen saturation, cardiopulmonary bypass time, days of mechanical ventilation, days on inotropic support, duration of hospital stay, and duration of ICU stay.

Outcomes

Patients were followed on VAD support for complications and intraoperative outcomes. We defined perioperative bleeding as a blood loss of over 1 L within the first four postoperative hours in the ICU. Potential device-related complications included: infections, bleeding, liver dysfunction, renal dysfunction, right ventricular failure, stroke, thromboembolism, GI bleeding, VAD malfunction, wound infection, and aortic insufficiency. We defined liver dysfunction as a greater than twofold increase in ALT and AST from pre-VAD values. Renal dysfunction was defined by the presence of at least renal injury according to RIFLE criteria (>2-fold increase in creatinine, >50% decrease in GFR or anuria for 12 hours). We defined right ventricular failure as the need for devices implanted, nitric oxide for longer than 48 hours or inotropes for more than 14 days. We defined GI bleeding by hematemesis, melena or active bleeding at the time of endoscopy or colonoscopy. We also collected the date and number of transplants and deaths. All of the complications were recorded during ICU stay except for infection, device malfunction, GI bleeding, strokes, and death, which were also followed after discharge.

Statistical analysis

Data were analyzed using SPSS 17.0 statistical software. Categorical variables were treated as proportions while continuous variables were reported as means and standard deviations. We compared the groups using independent-sample t-tests for continuous variables and chi-square and Fisher’s exact tests for categorical data. We compared survival, transplant-free survival and strokes using Kaplan–Meier curves and log-rank tests. Complications during VAD support were reported as event rates in events/patient time, which was calculated as the number of events divided by the cumulative time in ICU in early post-VAD complications or by the cumulative support duration in the case of long-term complications. A two-sided p-value $\leq 0.05$ was considered as statistically significant.
RESULTS

Patient characteristics

The mean age of patients in the HMII group was 49 ± 12 years while the mean age in the HVAD group was 53 ± 14 years (p = 0.3). Overall, the groups had statistically comparable clinical characteristics including diabetes, use of ICD/CRT, cause of cardiomyopathy, reason for VAD implantation, and INTERMACS risk score (Table 1). In total, 22 (76%) of the HMII patients were male while only three (23%) of the patients with HVAD were male (p = 0.001). Hemodynamic and laboratory values pre-VAD implantation (Table 2), including cardiac index, left ventricular ejection fraction, creatinine, hemoglobin and mixed venous oxygen saturation, pulmonary arterial pressures, and central venous pressures were comparable between groups. The average pump speeds for the HMII devices were 8837 ± 420 while the average pump speeds for the HW devices were 2564 ± 209. Concomitant procedures during HMII implantations included two aortic valve repairs, two tricuspid valve repairs, three closures of patent foramen ovales (PFO), one right atrium thrombectomy, and one coronary artery bypass graft while 25 patients did not have any other procedure. In the HVAD group, there were two PFO closures, one tricuspid valve repair, one left ventricular thrombectomy, and nine patients who did not have any other procedure.

Survival and transplantation

The survival of patients on HMII and HVAD support was similar (Fig. 1). Survival at six months was 75% for HVAD and 88% for HMII while the one-year survival was 75% for HVAD and 82% for HMII patients (p = 0.91). The groups were similar in terms of probability of receiving a transplant, at one year (50% for the HVAD group and 58% for the HMII patients (p = 0.13) (Fig. 2)).

Intraoperative outcomes

Patients with HMII and HVAD devices experienced similar intra-operative outcomes. Time on cardiopulmonary bypass between the two groups was similar (80 ± 26 min for the HMII devices vs. 81 ± 28 min for the patients with HVAD, p = 0.9). The incidence of perioperative bleeding was also comparable at 13 (39%) for HMII and 3 (23%) for the HVAD group (p = 0.14). The 16 perioperative bleeding events consisted of 12 reoperations for bleeding and four cases of blood transfusions greater than four units of blood.

Complications on support

Overall, complications on support were similar regardless of the device. Patients had comparable lengths of mechanical ventilation, inotropic support, ICU and hospital stay, episodes of infection, perioperative bleeding, need for reoperation, liver dysfunction, renal dysfunction, right ventricular failure, and thromboembolism (Table 3). Out of the four cases of thromboembolism, two were cerebral bleeds and two were strokes which fully recovered. Of the two cerebral bleeds, one died while the other was left with significant neurological dysfunction. Patients had similar rates of ventricular arrhythmias, VAD malfunction,
VAD replacement, aortic insufficiency, and wound infection. VAD malfunction occurred in two (6%) of the HMII patients and two (15%) of the patients with HVAD, $p = 0.56$. The two HMII VAD malfunctions consisted of a controller problem and pump thrombosis resulting in VAD replacement while the two HVAD malfunctions consisted of a controller problem and suspected debris resulting in VAD replacement. VAD replacement occurred in one (3%) HMII patient and one (8%) HVAD patient, $p = 0.99$. However, patients with HVAD had a statistically significant increase in incidence of stroke compared to HMII patients (44% in HVAD vs. 10% in HMII at one year, $p = 0.04$) (Fig. 3). Hemorrhagic stroke showed a trend toward higher incidence in patients with HVAD (three of the five episodes vs. one of the three episodes of stroke in HMII patients, $p = 0.06$). Of the three patients with HVAD with hemorrhagic strokes, none of them had an INR greater than 3.5 within two weeks prior to the event (the highest was 3.26). Furthermore, none of the patients with HVAD suffered a stroke during or shortly after a septic episode.

Patients with HVAD had a higher incidence of GI bleeding compared to the HMII group (31% in HVAD vs. 0% in HMII, $p = 0.004$). Of the four patients who had GI bleeds, three occurred within two to five weeks post-VAD implantation while the fourth occurred after three months. None of the patients had a previous history of GI bleeding. During the events, the patients had a lower target INR to prevent re-bleeding. One patient discontinued clopidogrel while another discontinued aspirin. Three patients had colonic polyps and two had them removed. The fourth patient had recurrent episodes of active duodenal bleeds and was treated with three duodenal clips. None of the GI bleeding events was fatal, although one patient received five units of blood. Of the three patients with polyps, two patients had an INR $< 3.5$ (three and two) and one patient had an INR of

<table>
<thead>
<tr>
<th>Variable</th>
<th>HeartMate II (n = 33)</th>
<th>HeartWare (n = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index ($\text{L/min/m}^2$)$^*$</td>
<td>2.5 ± 0.7</td>
<td>2.4 ± 0.3</td>
<td>0.90</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>19 ± 6</td>
<td>17 ± 5</td>
<td>0.28</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.2 ± 0.4</td>
<td>1.35 ± 0.5</td>
<td>0.43</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>11 ± 1.6</td>
<td>11 ± 1.6</td>
<td>0.32</td>
</tr>
<tr>
<td>MVOS (%)</td>
<td>67 ± 10</td>
<td>73 ± 8</td>
<td>0.50</td>
</tr>
<tr>
<td>CVP</td>
<td>9 ± 6</td>
<td>12.8 ± 6.6</td>
<td>0.15</td>
</tr>
<tr>
<td>SystPAP</td>
<td>51 ± 8.4</td>
<td>59 ± 12.3</td>
<td>0.38</td>
</tr>
<tr>
<td>MeanPAP</td>
<td>32.3 ± 7.1</td>
<td>36 ± 19</td>
<td>0.77</td>
</tr>
<tr>
<td>PCWP</td>
<td>19.6 ± 7</td>
<td>22.2 ± 3.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Pump speed from last day in ICU</td>
<td>8837 ± 420</td>
<td>2564 ± 209</td>
<td>n/a</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; MVOS, mixed venous oxygen saturation; CVP, central venous pressure; SystPAP, systolic pulmonary arterial pressure; MeanPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure.
3.59 within the two weeks prior to the event. The fourth patient who had three episodes of recurrent GI bleeds had an INR of 4.1 in two events and an INR of 1.8 in the third episode prior to the event.

**CONCLUSIONS**

This study showed that overall patients had similar survival, transplantation rates, and intraoperative outcomes regardless of whether they received an HMII or HVAD. These data are supported by the recent ENDURANCE interim analysis of 178 HVAD and 140 control VADs which reported 86% and 87.4% six-month survivals, respectively. In addition, patients had similar rates of many adverse outcomes such as renal dysfunction, liver dysfunction, right ventricular failure, and device malfunction. Patients also had similar intraoperative features such as cardiopulmonary bypass time and perioperative bleeding, which suggests that these devices are comparable in terms of operative risk. However, patients with HVAD did have a significantly greater incidence of stroke and GI bleeding. The differences in overall incidence of stroke were mainly...
attributable to a borderline increase in the incidence of hemorrhagic stroke.

While our research supports previous findings that patients with HVAD experience a higher incidence of stroke, our patients had a higher incidence of stroke than previously reported (44% vs. 6.7–15%).8–10 This discrepancy may be due to the relatively small sample of patients with HVAD in our series and the fact that the first two patients who received an HVAD suffered from neurologic events prior to the institution of the revised INR targets. In addition, none of the patients with HVAD suffered a stroke during or shortly after a septic episode which was contrary to the ADVANCE HVAD trial which showed that most of the neurological complications occurred when anticoagulation was low in the setting of sepsis.8 There was a 10% one-year incidence of stroke in our HMII patients which was comparable to a study of 133 HMII patients that reported an incidence of 8%.11

In HMII devices, lower revolutions per minute (rpm) result in a higher pulsatility index which is the flow during systole minus the flow during diastole divided by the mean flow.12 Higher rpm can lead to more dramatic changes in negative left atrial and ventricular pressures (suction events).12 Subsequently, it has been hypothesized that lower rpm VAD devices may have less extreme hemodynamic effects and may result in fewer GI bleeding events.4 Conversely, a very low pulsatility in the flow created by the device may be responsible for GI bleeding due to decreased capillary pressure and ischemia in the GI mucosa. Low pulsatility may also influence the loss of von Willebrand factor multimers which may increase GI bleeding.8 We found that even though the HVAD device had a lower rpm range than the HMII, the HVADs had a higher incidence of GI bleeding. Our patients with HVAD experienced GI bleeding rates of 31% versus past studies which have reported rates between 11% and 13%.4,8–10 The previously reported 13% bleeding rate targeted an INR of 2.5–3, higher than our institutional targets. In this series, patients with HMII had fewer GI bleeding events than previously reported. In fact, none of the patients with HMII experienced a GI bleed while a recent study of 86 patients with HMII with a target INR of 1.5–2.5 reported a GI-bleeding incidence of 22%.13

In our series, although the HVAD group was predominantly female, sex has not been shown to have a significant impact on incidences of upper or lower GI bleeding.14–16 On the contrary, females have been found to have a lower risk of developing colonic polyps than males.17 In addition, one study reported that GI bleeding in continuous flow VAD devices such as HMII is common because the continuous flow of blood results in arteriovenous malformations.16 The article called for less anticoagulation therapy. At our institution, patients with HVAD are anticoagulated with Coumadin to a target INR of 2–2.5 while HMII patients have an INR target of 1.5–2. Although our patients with HVAD were slightly more anticoagulated, previous research has shown that only INRs greater than four have been associated with increased risk of bleeding.18

We speculate that differences in device management may contribute to the dramatic variance in GI bleeding. We initially lowered our support speeds in HMII patients to preserve aortic valve competence and rates of aortic insufficiency. We attempted this in our patients with HVAD but found that lowering speeds to achieve intermittent aortic valve opening was more difficult due to the centrifugal nature of the pump and the offsetting effects of decreased afterload with lower pump speeds. Although our intent is to preserve the aortic valve, in this HMII cohort (and now expanded to almost 40 patients), there have been no GI-bleeding events when the published literature would suggest that we should have observed at least ten cases.

Due to sample size restrictions, we were unable to perform an adjusted analysis. Furthermore, small sample sizes may have limited the study’s ability to detect statistically significant differences in some of the variables compared. In addition, there was a significant difference in sex between HMII and patients with HVAD. This may be due to the smaller size of HVAD devices and that females tended to have a smaller body habitus. Furthermore, von Willebrand factor multimers were not routinely measured. Unlike past papers, this study consisted of only HMII and patients with HVAD and included patients undergoing destination therapy. Finally, although we did not observe high INR before strokes, some GI bleeding events may have been precipitated by high INRs in patients with underlying conditions.

In conclusion, HMII and HVAD devices were comparable in most respects such as survival, intraoperative features, and the majority of complications. However, in our population patients with HVAD have a significantly higher incidence of stroke and GI bleeding. As an institution, we have increased the target INR from 2 to 2.5, but in the setting of sepsis our target is closer to 3.0. While this predisposes us to bleeding complications, as a program we felt that bleeding was easier to manage than pump thrombus and embolic stroke. A better understanding of the differences in device complications secondary to variances in pump management may allow for adjustments to preemptively avoid negative outcomes.

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REFERENCES