Renal and Hepatic Function Improve in Advanced Heart Failure Patients During Continuous-Flow Support With the HeartMate II Left Ventricular Assist Device

Stuart D. Russell, MD; Joseph G. Rogers, MD; Carmelo A. Milano, MD; David B. Dyke, MD; Francis D. Pagani, MD, PhD; Juan M. Aranda, MD; Charles T. Klodell, Jr, MD; Andrew J. Boyle, MD; Ranjit John, MD; Leway Chen, MD; H. Todd Massey, MD; David J. Farrar, PhD; John V. Conte, MD; for the HeartMate II Clinical Investigators

Background—The effects of continuous blood flow and reduced pulsatility on major organ function have not been studied in detail.

Methods and Results—We evaluated renal (creatinine and blood urea nitrogen) and hepatic (aspartate transaminase, alanine transaminase, and total bilirubin) function in 309 (235 male, 74 female) advanced heart failure patients who had been supported with the HeartMate II continuous-flow left ventricular assist device for bridge to transplantation. To determine whether patients with impaired renal and hepatic function improve over time with continuous-flow left ventricular assist device support or whether there are any detrimental effects in patients with normal organ function, we divided patients into those with above-normal and normal laboratory values before implantation and measured blood chemistry over time during left ventricular assist device support. There were significant improvements over 6 months in all parameters in the above-normal groups, with values in the normal groups remaining in the normal range over time. Mean blood urea nitrogen and serum creatinine in the above-normal groups decreased significantly from 37±14 to 23±10 mg/dL (P<0.0001) and from 1.8±0.4 to 1.4±0.8 mg/dL (P<0.01), respectively. There were decreases in aspartate transaminase and alanine transaminase in the above-normal groups from 121±206 and 171±348 to 36±19 and 31±22 IU (P<0.001), respectively. Total bilirubin for the above-normal group was 2.1±0.9 mg/dL at baseline; after an acute increase at week 1, it decreased to 0.9±0.5 mg/dL by 6 months (P<0.0001). Both renal and liver values from patients in the normal groups remained normal during support with the left ventricular assist device.

Conclusions—The HeartMate II continuous-flow left ventricular assist device improves renal and hepatic function in advanced heart failure patients who are being bridged to transplantation, without evidence of detrimental effects from reduced pulsatility over a 6-month time period.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00121472.

Key Words: heart failure ■ heart-assist devices ■ liver ■ kidney

The HeartMate II is a new continuous-flow left ventricular assist device (LVAD) that has been shown to provide effective hemodynamic support and improve quality of life in patients who are being bridged to cardiac transplantation. Patients who undergo implantation of these pumps have a very low pulse pressure and often have no palpable pulse. There are many potential benefits to continuous-flow devices compared with older pulsatile devices. Chief among these are their smaller size, which enables their implantation in more individuals, and fewer moving parts, which may improve their long-term durability. However, the effects of continuous blood flow and resultant minimal pulse pressure on end-organ function are unclear.

Editorial see p 2313

Clinical Perspective on p 2357

For short-term circulatory support, nonpulsatile flow during cardiopulmonary bypass is common. However, some studies have shown that pulsatile blood flow during cardiopulmonary bypass is associated with reduced systemic vascular resistance, blunted catecholamine response, increased T3, and enhanced splanchnic perfusion and myocardial blood flow.
flow. In a small, single-center series of postcardiotomy support, pulsatile systems had superior pump weaning rates and patient discharge rates compared with nonpulsatile systems, although a difference was not seen in the national registry. Previous experience with pulsatile LVADs has shown improvements in renal and hepatic function during circulatory support. However, the effects of long-term continuous blood flow with reduced pulsatility have not been examined closely. In small cohorts, mechanical circulatory support with axial flow pumps has similar beneficial effects on end-organ function as the pulsatile devices.

The rationale, methods, study design, assessment, and end points of the clinical trial have been described previously. In brief, patients with end-stage heart failure awaiting transplantation with United Network for Organ Sharing status 1a or 1b were eligible for enrollment and underwent implantation of the HeartMate II LVAD. Patients were excluded for severe renal (serum creatinine >3.5 mg/dL or long-term dialysis), hepatic (international normalized ratio >2.5, total bilirubin >5 mg/dL, or transaminases >2000 U/L), or pulmonary (severe chronic obstructive or restrictive disease) dysfunction. Additionally, patients with uncontrolled infections, strokes, mechanical aortic valves, aortic insufficiency, aortic aneurysm >5.0 cm, or other mechanical circulatory support devices (except intra-aortic balloon pumps) were also excluded. The main goals of the present study were to determine whether patients with impaired renal and hepatic function improve over time with continuous-flow LVAD support and whether there are any detrimental effects over time in patients with normal organ function during continuous-flow support.

Methods

Baseline data were collected on all patients, including demographics, functional capacity, hemodynamics, medications, neurological status, and blood chemistry and hematologic values. This included blood urea nitrogen (BUN), creatinine, total bilirubin, alanine amino transferase (ALT), and aspartate aminotransferase (AST). Values were measured before implantation; on days 1, 3, 5, 7, 11, 14, and 21; and at months 1 through 6.

Statistical Analysis

All values are presented as mean±SD. Discrete variables are presented as percentages. To determine the longitudinal effects of continuous-flow LVAD support in patients with normal and abnormal preoperative end-organ function, we analyzed all patients over 180-day follow-up, as well as subgroups divided into those with baseline values that were normal or above-normal on the basis of clinical thresholds used at Johns Hopkins University Hospital. Linear mixed-effects modeling was performed on all patients and on the normal and above-normal subgroups to determine the impact of time and group on end-organ function. Time and group type were modeled as fixed-effects variables, whereas the intercept was modeled as a random-effects variable. Time was coded at baseline and at 30, 60, 90, 120, 150, and 180 days after implantation. An interaction term between time and group type was included in the model to determine the effect of time on end-organ function in each group. The statistical power for the longitudinal analysis at a significance of α=0.05 for all laboratory values (BUN, creatinine, AST, ALT, and total bilirubin) was >0.9. All 307 patients were included in the linear mixed-effects model. Statistical comparisons were also performed on paired changes in blood chemistry from baseline to 6 months of support or through the last value measured for patients who were supported for <180 days, with a 2-sided paired t test. P<0.05 was considered significant.

Results

The baseline characteristics of the patients are shown in Table 1. The mean age was 54 years, and the majority of the patients were male (76%). There were equal distributions of ischemic and nonischemic causes of heart failure. The patients all had advanced heart failure; only 28% were taking an angiotensin-converting enzyme inhibitor, 5% were taking an angiotensin receptor blocker, and 34% were taking β-blockers. Cardiac resynchronization therapy had been used previously in 47% of patients, and 44% were on intra-aortic balloon pump support.

The mean baseline BUN and creatinine levels were minimally elevated (29±16 and 1.4±0.5 mg/dL, respectively) in the entire cohort, which reflects the selection of transplant candidates with limited end-organ dysfunction (Table 2). However, there was a wide range in renal function parameters. The mean BUN and creatinine levels for the above-normal groups were 37±14 and 1.8±0.4 mg/dL, respectively, compared with 15±4 and 1.0±0.2 mg/dL, respectively, for the normal groups.

Similar to renal function, there was evidence of hepatic dysfunction due to right ventricular volume overload and hepatic congestion. The AST and ALT were both elevated at 80±214 and 95±230 U/L, respectively, and values for

### Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>309</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>235 (76)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>74 (24)</td>
</tr>
<tr>
<td>Age, y</td>
<td>50±14; Median 54 (range 15–73)</td>
</tr>
<tr>
<td>Ischemic origin, %</td>
<td>43</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.0±0.3; Median 2.0 (range 1.33–2.81)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>16.5±6.6</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>70±13</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>98±14</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>2.1±0.7</td>
</tr>
<tr>
<td>RA pressure, mm Hg</td>
<td>12.3±6.4</td>
</tr>
<tr>
<td>PA mean pressure, mm Hg</td>
<td>36±9</td>
</tr>
<tr>
<td>PCW pressure, mm Hg</td>
<td>25±8</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs, n (%)</td>
<td>28/5</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>34</td>
</tr>
<tr>
<td>CRT, %</td>
<td>47</td>
</tr>
<tr>
<td>Intravenous inotropes, %</td>
<td>89</td>
</tr>
<tr>
<td>IABP, %</td>
<td>44</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; LVEF, left ventricular ejection fraction; BP, blood pressure; CI, cardiac index; RA, right atrial; PCW, pulmonary capillary wedge; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CRT, cardiac resynchronization therapy; and IABP, intra-aortic balloon pump.
above-normal patients were further elevated. Total bilirubin was mildly elevated in the entire cohort (1.3±0.9 mg/dL) and was 2.1±0.9 mg/dL for the above-normal group. There was also evidence of reduced hepatic synthetic function, with a mean international normalized ratio of 1.3±0.3.

One hundred sixty patients had data at 180 days after implantation. A total of 115 patients underwent transplantation before 180 days, and 34 patients died before 180 days.

**Renal Function**

As shown in Figure 1, after a slight rise in values in the early postoperative period, renal function showed improvements in the above-normal groups for both BUN and creatinine, stabilizing by approximately 1 to 2 months of LVAD support with no further change afterward. Linear mixed-effects analysis revealed that group type (above-normal or normal baseline values) and time had statistically significant impacts on BUN and creatinine levels. There were significant (P<0.0001) reductions in BUN and creatinine levels over the period of support for the above-normal groups and no significant changes for the normal groups. When we assessed the paired change from baseline to 6 months (Figure 2), there was a statistically significant improvement in mean BUN for the overall group (from 28±15 to 21±10 mg/dL, P<0.001) and the above-normal group (from 37±14 to 23±10 mg/dL, P<0.0001), whereas values in the normal group remained in the normal range. Similarly, the above-normal group experienced significant reductions in creatinine from 1.8±0.4 to 1.4±0.8 mg/dL at 6 months (P<0.001), with the normal group remaining in the normal range. Patients who received heart transplants before 180 days of support also showed improvements in BUN and creatinine, whereas there was no change in patients who died before 180 days (Figure 2).

**Hepatic Function**

Figure 1 shows the values for hepatic function over time, and paired changes are shown in Figure 2. Similar to renal function, after the early postoperative period, there was an improvement in hepatic function that was sustained over time. Linear mixed-effects analysis revealed that group type (above-normal or normal) and time had statistically significant impacts on AST, ALT, and total bilirubin values (P<0.0001). Furthermore, there was much more of a significant drop in values in the above-normal groups than in the normal groups (P<0.001). For AST and ALT, the baseline values of 67±144 and 85±234 U/L, respectively, improved to 38±23 and 33±32 U/L, respectively, by 1 month. This normalization of values was sustained, and at 6 months, the AST was 35±17 U/L, and the ALT was 29±16 U/L. For the above-normal group, similar
reductions in transaminases occurred. At baseline, the AST and ALT were 121/11006 206 and 171/11006 348 U/L, respectively. By 1 month, these values normalized to 46/11006 27 and 40/11006 26 U/L, respectively, and this improvement was sustained at 6 months. For the group with normal baseline values, there were statistically significant but clinically negligible increases in ALT (from 24/11006 9 to 27/11006 11 U/L) and AST (from 25/11006 6 to 33/11006 15 U/L).

In contrast to the transaminases or renal function, mean total bilirubin increased by day 7 before improving to baseline in both groups (Figure 1). Importantly, the group with above-normal baseline values experienced the highest increase, to >5 mg/dL at day 7. However, by 2 months, the bilirubin level for all groups decreased to the normal range and remained there through month 6. Patients who underwent heart transplantation before 180 days of support also showed improvements in hepatic function in AST, ALT, and total bilirubin. Patients who died before 180 days showed an increase in total bilirubin but no changes in transaminases.

Discussion
This observational analysis from a large multicenter trial evaluating the effects of continuous, minimally pulsatile blood flow with the HeartMate II LVAD shows that both renal and hepatic function are restored to normal values in patients awaiting heart transplantation. For both the overall population and those with abnormal renal and hepatic function, laboratory values returned to normal within 1 to 2 months of device implantation and remained normal through month 6. Patients with normal values at baseline remained normal at month 6. Two important implications arise from these observations. First, similar to pulsatile LVADs, normalization of hepatic and renal function occurs with minimally pulsatile, continuous-flow devices. Second, continuous blood flow with reduced pulsatility does not appear to have any intermediate-term deleterious effects on renal or hepatic function.

One indication for placement of an LVAD is inadequate end-organ perfusion. This can be manifested by elevated BUN and creatinine, elevated liver enzymes, hyponatremia, and altered mental status. Poor renal function is a marker of mortality in patients with heart failure in both the inpatient and outpatient setting.9–11 The true cause of this cardiorenal syndrome is unclear, but to some extent, it reflects a lack of cardiac output to the kidney. Similar studies have not shown that abnormal liver function tests are markers of poor outcomes; however, poor baseline liver function has been shown to be a marker of poor outcomes after LVAD implantation.12,13

Previous studies with pulsatile LVADs have shown improved renal and hepatic function with device support.4,5 Frazier et al4 reported 280 patients who underwent implantation of a pulsatile assist device as a bridge to transplantation. The baseline values in their trial (mean creatinine 1.7 mg/dL, BUN 39 mg/dL, and total bilirubin 2.1 mg/dL) were similar to those in the group with abnormal baseline values in the present study, and all values returned to baseline by the time of transplantation, which was on average 112 days. Similar values and improvements were also shown in the Thoratec VAD (ventricular assist device) trial.5 Improvements in function have also been demonstrated with continuous-flow assist devices in 3 small reports.6–8 The present study confirms these findings in a larger patient population with carefully and prospectively obtained data. By 1 month, in both the overall population and the abnormal-value group, the patients had improvement and normalization of both renal and hepatic function.

No studies have evaluated the histological effects of continuous minimally pulsatile blood flow in humans. Kihara et al14 studied continuous-flow LVADs in 29 calves. Nearly 80% of the animals developed smooth muscle cell hypertrophy in the renal cortical arteries compared with 0 of 7 control animals. There also was a trend toward increased hypertrophy with lower flow rates. In contrast, Saito et al15 implanted pumps into 9 sheep (6
controls) and found that the histology of the kidney, liver, and brain were unchanged compared with controls. They did find that the thickness of the medial layer of the ascending aorta was diminished. Similar to the study by Kihara et al,14 there were no differences in BUN, creatinine, total bilirubin, or liver transaminases between the 2 groups.15 Finally, in a similar study with a different device, Saito et al16 found no change in liver and renal function in 6 sheep.

The results of the present analysis extend these findings to humans. After 6 months of continuous blood flow, there was no evidence of any decline in renal or liver function. Although histological changes might have occurred, there was no impact on organ function. It is interesting that Kihara et al14 noted more histological abnormalities in animals with lower ventricular assist device flows.14 For humans, lower flow rates are associated with increased pulsatility and more blood ejected across the aortic valve but a lower cardiac output.17 Perhaps the chronic changes seen by Kihara were related to low blood flow rather than a lack of pulsatility. Unfortunately, cardiac output was not routinely acquired in the present study, and therefore such an analysis cannot be performed in our study population.

Study Limitations

One of the benefits of the HeartMate II LVAD is its small size and durability due to fewer moving parts. Clinically, it is quite reassuring that at 6 months, there was no evidence of end-organ dysfunction with continuous blood flow. However, once one moves from a bridge-to-transplantation situation, with a required pump durability of 1 to 2 years, to long-term support in nontransplant candidate patients who require support for 5 to 10 years, it is unclear whether organ function will be maintained. Further studies of longer duration will be required to determine whether these effects are sustained for longer periods of time. Second, we studied patients with reduced pulsatility, and the results do not resolve questions that remain about the effects of true nonpulsatile blood flow over time.

Third, as in all studies in patients who are being bridged to transplantation, the sickest patients with the worst renal and liver function were excluded in the present trial, and it is impossible to determine whether there is a cutoff level at which organ function will not improve. However, among the patients with abnormal function at baseline, there was improved function by 1 month.

Conclusions

In a bridge-to-transplantation patient population with mildly abnormal renal or hepatic function, the use of a continuous-flow LVAD improved renal and hepatic function in patients with abnormal baseline parameters and did not worsen function in patients with normal baseline renal and hepatic values. Furthermore, this function was maintained through 6 months. There was no evidence that blood flow with reduced pulsatility was detrimental to end-organ function in patients with heart failure. Further studies should be performed in patients with severe renal or hepatic dysfunction, because the results of the present study might not apply to a more advanced population or over longer durations of follow-up.

Sources of Funding

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Disclosures

Drs Russell, Boyle, and Rogers are consultants to Thoratec. Drs Russell and Conte have received research grants from Thoratec. Dr Farrar is an employee and stockholder of Thoratec. The remaining authors report no conflicts.

References

The HeartMate II left ventricular assist device (LVAD) is a small continuous-flow device that has been shown to provide effective hemodynamic support and improve quality of life in patients being bridged to cardiac transplantation. However, because of the continuous flow of blood with this device, these patients often have no palpable pulse and a very low pulse pressure, and the subsequent effects of continuous flow on end-organ function are unclear. In patients who underwent placement of the HeartMate II as a bridge to transplantation and who were followed up for 6 months of support with the left ventricular assist device, we demonstrated that both hepatic and renal function in patients with abnormal baseline function improved to normal levels by month 1 to 2 and that they remained normal. Additionally, in patients with normal baseline function, we found that renal and hepatic function remained normal during continuous-flow support. In summary, despite low pulsatility, the HeartMate II continuous-flow left ventricular assist device improved both hepatic and renal function in advanced heart failure patients awaiting transplantation.
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for the HeartMate II Clinical Investigators

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