Improved Survival and Decreasing Incidence of Adverse Events With the HeartMate II Left Ventricular Assist Device as Bridge-to-Transplant Therapy

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Background. **Pulsatile left ventricular assist devices (LVADs) are effective as bridge-to-transplant therapy, but they are limited by their large size and lack of durability. Smaller, more durable, continuous flow devices such as the HeartMate II LVAD are increasingly being used. The aim of this study is to report our single-center experience with this device as bridge-to-transplant therapy.**

Methods. **Overall, 47 patients received HeartMate II LVADs at our center from June 2005 to July 2007; 32 as bridge to transplant, 7 as destination therapy, and 8 as exchange therapy for a failed HeartMate XVE. We reviewed our experience with the device as bridge-to-transplant therapy and report on patient survival and adverse events.**

Results. **The mean age of the bridge-to-transplant patients was 50.75 ± 13.78 years; 10 (31.3%) were female. The cause of the underlying disease was ischemic in 18 patients (56.3%), idiopathic in 11 (34.4%), myocarditis in 1 (3.1%), postpartum cardiomyopathy in 1 (3.1%), and congenital heart disease in 1 (3.1%). The mean duration of HeartMate II support was 193.2 ± 139.9 days. At 30 days after HeartMate II placement, the patient survival was 96.9% by Kaplan-Meier analysis; at 6 months (alive or transplanted), 86.9%. Major adverse events included bleeding requiring reexploration in 5 patients (15.6%), right ventricular failure requiring right ventricular assist device support in 2 (6.3%), LVAD-related infections in 4 (12.5%), neurologic or thromboembolic events in 2 (6.3%), and gastrointestinal bleeding in 5 (15.6%). We noted one serious device malfunction (3.1%) resulting in the patient's death; in addition, 2 patients experienced pump thrombosis (6.3%).**

Conclusions. **Despite morbidity, use of the HeartMate II LVAD as bridge-to-transplant therapy is associated with excellent survival and low mortality rates. We found a marked decrease in morbidity related to right ventricular failure, to device-related infections, and to thromboembolic events. However, the requirements for anticoagulation therapy may be associated with increased mediastinal and gastrointestinal bleeding. Strategies to optimize anticoagulation therapy may further improve results for these critically ill patients.**

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Left ventricular assist device (LVAD) placement is an accepted treatment for patients with end-stage heart failure [1]. The increased applicability and excellent results with LVADs has revolutionized the treatment options available for the patient with end-stage heart failure. Most patients who have undergone LVAD implantation as bridge-to-transplant (BTT) therapy have been supported by pulsatile, volume-displacement devices such as the HeartMate XVE (Thoratec, Pleasanton, California), the Novacor LVAD (WorldHeart, Oakland, California), or the Thoratec VAD (Thoratec) [2–6]. Success with those devices for BTT therapy has led to their successful use as an alternative altogether to a transplant, namely, as destination therapy [7]. While tremendous success has been achieved with these devices, their use is associated with significant comorbidity, which may be related to several factors including the need for extensive surgical dissection, a large pump, and a large-diameter percutaneous lead. Even more important, their long-term durability is limited, frequently requiring reoperations for device exchange, which often result in significant morbidity and mortality.

The new HeartMate II LVAD, which incorporates continuous flow, rotary pump technology, represents the

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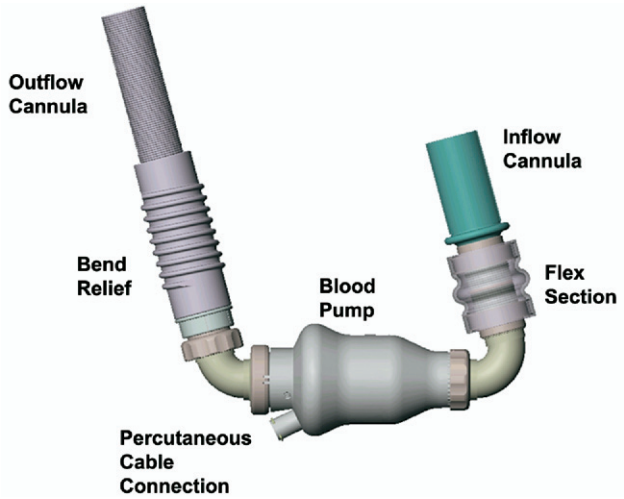

Fig 1. External view of HeartMate II left ventricular assist device. (Illustration © Thoratec Corporation. Reproduced with permission.)

next generation of devices [8, 9]. The simpler design of continuous flow, rotary pump technology promises greater long-term mechanical reliability, with a single moving part: the internal rotor (Figs 1 and 2). The HeartMate II LVAD is one seventh the size and one fourth the weight of the previous HeartMate XVE. We report our single-center experience, discussing survival and adverse events with the HeartMate II LVAD as BTT therapy in 32 patients with end-stage heart failure at the University of Minnesota Medical Center.

Material and Methods

Patients

From June 2005 through July 31, 2007, a total of 47 patients underwent HeartMate II placement at the University of Minnesota Medical Center: 32 as BTT therapy, 7 as destination therapy, and 8 as exchange therapy for a failed XVE. The mean duration of HeartMate II support was 193.2 ± 139.9 days.

Our study focuses on the 32 BTT patients. All 32 study patients were part of a prospective, multicenter study evaluating the use of the HeartMate II LVAD as BTT therapy. Patients with end-stage heart failure who were on our transplant waiting list were eligible for study enrollment. The protocol for the study was approved by the Food and Drug Administration and by our own center's Institutional Review Board. Patient consent for data collection and for reporting was obtained by a standard informed consent process. (Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix, available with the referenced article at www.nejm.org [10].)

HeartMate II

The HeartMate II consists of an internal blood pump with a percutaneous lead that connects the pump to an external system driver and power source. The pump has an implant volume of 63 mL and generates up to 10 L/min of flow at a mean pressure of 100 mm Hg. Details of HeartMate II function and the implantation technique have been described elsewhere [8, 9].

The implantation technique at the University of Minnesota is briefly summarized here. To implant the HeartMate II, a median sternotomy is performed. The patient is placed on cardiopulmonary bypass, with aortic and right atrial cannulation. The inflow cannula is inserted into an opening made in the apex of the left ventricle with a coring knife. A circular Teflon (Impra, subsidiary of L.R. Bard, Tempe, Arizona) pledget in the shape of a donut is placed around the ventricular apical core. Then, 2-0 Tevdek mattress sutures are used to secure the inflow cuff to the ventricle using the circular Teflon strip. After a side-biting clamp is placed in the midportion of the ascending aorta, the outflow graft is sewn to a longitudinal aortotomy. The pump is surgically placed in a preperitoneal pocket at the level of the

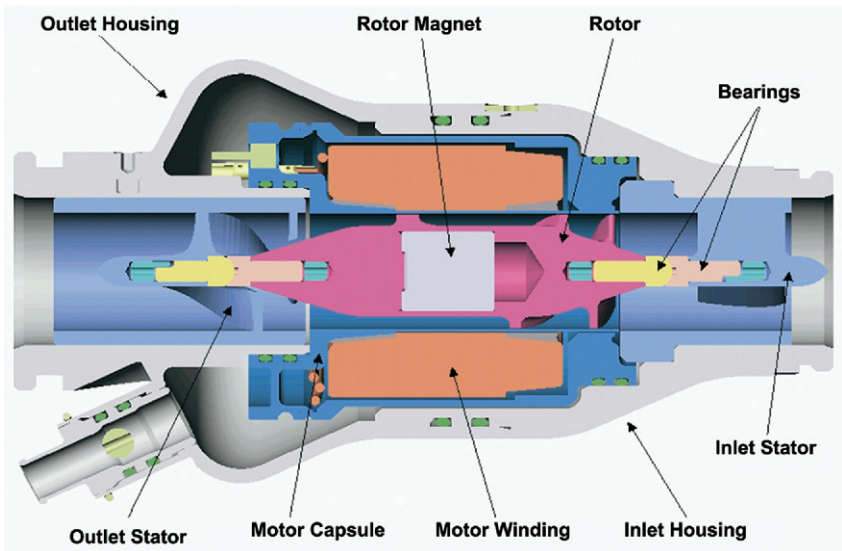

Fig 2. Cross-sectional internal view of HeartMate II left ventricular assist device. (Illustration © Thoratec Corporation. Reproduced with permission.)

diaphragm. After the patient is weaned off cardiopulmonary bypass, support with the HeartMate II pump is initiated. Adequate flows are achieved, both by adjusting pump speed and by ensuring adequate preload and appropriate inotropic support. Protamine is administered to reverse the effects of heparin. After meticulous hemostasis is achieved, the chest is closed with appropriately placed chest tubes.

Device Management

Per our local practice at the University of Minnesota, we set the revolutions per minute (RPM) rate of the HeartMate II to provide adequate cardiac output and achieve optimal left ventricular decompression, while maintaining a pulsatility index greater than 3.5 to 4. In addition, we usually adjust the fixed-rate speed of the HeartMate II to maximize left ventricular decompression and to improve cardiac output, simultaneously allowing for at least a 1:3 ratio of aortic valve opening. We optimize the RPM speed, both hemodynamically and echocardiographically, at the time of LVAD placement, before the patient is discharged from the hospital (ie, after admission for LVAD placement), and if clinical events (eg, new symptoms or suction events) warranted further adjustment.

All 32 study patients were on a standard regimen of heart failure therapy, including antiarrhythmic therapy (our usual practice). Anticoagulation therapy involved a combination of warfarin and aspirin. After LVAD placement, we did not change defibrillator and biventricular pacing settings. All patients underwent a standard postoperative rehabilitation program.

Data Collection

We collected baseline and follow-up data, including patient characteristics, blood chemistry analyses, hematologic findings, neurologic status, and concomitant medication use. After patients were discharged from the hospital to home, they returned to our center for follow-up, device review, and general status assessment—weekly for the first 4 weeks, and then monthly until the study endpoint. We recorded hospital readmissions and patient adverse events (including suspected device malfunctions) throughout the study as they occurred, using standardized definitions [10].

Anticoagulation Therapy

For our study, we agreed on this six-step initial anticoagulation regimen as a guideline: (1) initiation of an intravenous infusion of unfractionated heparin 12 to 24 hours after HeartMate II placement or at the point that thoracostomy tube drainage was less than 50 mL/hour; (2) titration of the heparin infusion to a partial thromboplastin time (PTT) of 45 to 50 s for 24 hours after placement; (3) after 24 hours, titration of the heparin infusion to a PTT goal of 50 to 60 s; (4) after an additional 24 hours, titration of the heparin infusion to a PTT goal of 55 to 65 s; (5) initiation of antiplatelet therapy on postoperative day 2 to 3 (aspirin 81 mg daily); and (6) on postoperative day 3 to 5 and after removal of thoracostomy tubes, initiation of anticoagulation with warfarin, titrating the dose to an international normalized ratio (INR) of 2 to 3 and discontinuing heparin after obtaining a therapeutic INR.

However, as a result of significant gastrointestinal (GI) bleeding in 3 patients and delayed pericardial tamponade in 1 patient (among the first 14 patients), we decided to stop using postoperative heparin in all subsequent patients. Further, we decided to initiate anticoagulation therapy with warfarin (starting on postoperative day 3), titrating the dose to an INR of 1.5 to 2.

Statistical Analysis

We prospectively collected and retrospectively analyzed all data. Results are presented as mean values ± SD. A p value less than 0.05 was considered statistically significant. To calculate survival, we performed Kaplan-Meier analysis. For all data, we used SPSS 11.5 (SPSS, Chicago, Illinois).

Results

Patient Characteristics

Of 47 patients, 32 underwent HeartMate II placement as BTT therapy; 7, as destination therapy; and 8, as exchange therapy for a failed HeartMate XVE. The mean age of the 32 BTT patients was 50.7 ± 13.7 years. Among the BTT patients, the cause of heart failure was ischemic in 56.3% (n = 18) and idiopathic in 33.4% (n = 11); 1 patient had congenital heart disease, 1 had postpartum cardiomyopathy, and 1 had myocarditis. The overall mean duration of HeartMate II support in the BTT group was 193.2 ± 139.9 days.

The baseline characteristics of the 32 BTT patients are summarized in Table 1. One patient did not meet inclusion criteria for the study and an exemption was obtained from the Institutional Review Board. That patient was a

Table 1. Patient Characteristics at Baseline (n = 32)

Mean age (years)	50.75 ± 13.78 (range, 23–70)
Male:female ratio	2.2:1
Cause of heart failure	
Ischemic	18 (56.3%)
Idiopathic	11 (34.4%)
Postpartum cardiomyopathy	1 (3.1%)
Myocarditis	1 (3.1%)
Congenital	1 (3.1%)
Diabetes mellitus	11 (34.4%)
Hypertension	11 (34.4%)
Coronary artery disease	18 (56.3%)
Myocardial Infarction	18 (56.3%)
PTCA/PCI	12 (37.5%)
CABG	10 (31.3%)
Body mass index	27.3 (range 15.43–44)
Duration of LVAD support (days)	193.17 ± 139.96 (range, 10–644)

CABG = coronary artery bypass graft surgery; LVAD = left ventricular assist device; PTCA = percutaneous transluminal coronary angioplasty; PCI = percutaneous coronary intervention.

Table 2. Hemodynamic Variables at Baseline (n = 31)

Data	Mean ± SD
Systolic arterial pressure (mm Hg)	103.9 ± 14.7
Diastolic arterial pressure (mm Hg)	68.7 ± 10.5
Systolic PAP (mm Hg)	56.52 ± 13.41
Diastolic PAP (mm Hg)	28.19 ± 6.23
Right atrial mean (mm Hg)	14.17 ± 5.27
PCWP (mm Hg)	24.45 ± 5.90
PVR (Woods units)	3.69 ± 1.98
Cardiac output (L/min)	3.96 ± 1.20
Cardiac index	1.99 ± 0.47

PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.

23-year-old male who was transferred from an outside hospital with acute cardiogenic shock with multisystem organ failure and required urgent placement of biventricular support with CentriMag Levitronix devices (Levitronix LLC, Waltham, MA). After failure to be weaned from temporary biventricular support, he underwent placement of a HeartMate II LVAD; he required right ventricular assist device (RVAD) support with the CentriMag device postoperatively.

Hemodynamic Data

Hemodynamic data at baseline for the BTT patients are shown in Table 2 (excluding the hemodynamic data of 1 patient who received biventricular support before HeartMate II placement).

End-Organ Function Data

Serum markers of end-organ function before HeartMate II placement and at 3-month follow-up for the BTT patients are shown in Table 3.

Outcomes

The 30-day operative survival rate by Kaplan-Meier analysis was 95.6% (Fig 3). Of the 32 BTT patients, 1 patient died 10 days after HeartMate II placement from exsanguination related to subclavian vein hemorrhage after central venous line removal. The survival rate at 6 months (alive or transplanted) was 86.9%. After the initial postoperative 1-month period, 2 patients died: 1 was doing well but died at home from sudden unexpected pump malfunction; 1 died in the hospital from septic complications with multisystem organ failure.

Of the 32 BTT patients, 19 (59.4%) have now undergone a heart transplant after an average of 193 ± 93.4 days; another 9 are doing well at home and awaiting a heart transplant. All 19 BTT patients who underwent a transplant were discharged to home. The 1 remaining patient who was alive and discharged to home was not eligible for a transplant because of postoperative paraplegia. Outcomes are detailed in Table 4. Adverse events occurring during HeartMate II support are outlined in Table 5.

Table 3. Serum Indicators of End-Organ Function at Baseline and at 3 Months (n = 32)

Data	Baseline	3 Months	*p* Value
Renal			
Creatinine	1.55 ± 0.56	1.23 ± 0.5	0.031
Blood urea nitrogen	34.81 ± 18.70	22.6 ± 13.1	<0.001
Liver			
Alanine aminotransferase	68.22 ± 100.87	36.2 ± 19.3	0.05
Aspartate aminotransferase	70.38 ± 118.25	53.5 ± 30	0.158
Total bilirubin	1.31 ± 0.83	0.78 ± 0.5	<0.001

Table 4. Outcomes on Left Ventricular Assist Device Support (n = 32)

Outcomes	Number
Transplanted	19
On the transplant waiting list	9
Death	3
Early deaths (<30 days)	
Subclavian vein hemorrhage	1 (day 10)
Late deaths (>30 days)	
Device failure	1 (day 73)
Multisystem organ failure	1 (day 42)

Neurologic or Thromboembolic Events

During the entire period of HeartMate II support, we noted only 1 thromboembolic event (2.2%). This patient subsequently underwent a heart transplant and, as of the end of this study, is doing well. In addition, 1 patient had postoperative paraplegia, without any significant recovery. The cause of her paraplegia is unknown. It may be

Table 5. Adverse Events on Left Ventricular Assist Device Support (n = 32)

Adverse Event	Number
Neurologic or thromboembolic	2 (6.25%)
Stroke	1 (3.12%)
Paraplegia	1 (3.12%)
Hemorrhagic	
Mediastinal bleeding requiring reexploration	5 (15.6%)
Gastrointestinal bleeding	5 (15.6%)
Infectious	
Driveline infection	4 (12.5%)
Pump pocket infection	0
Right ventricular failure	2 (6.25%)
Requiring RVAD support	2 (6.25%)
Requiring prolonged inotropic support	0
Pump thrombosis	2 (6.25%)
Device malfunction	1 (3.12%)
Device replacement	0
Renal failure	1 (3.12%)
Respiratory failure	2 (6.25%)
Hemolysis	1 (3.12%)

RVAD = right ventricular assist device.

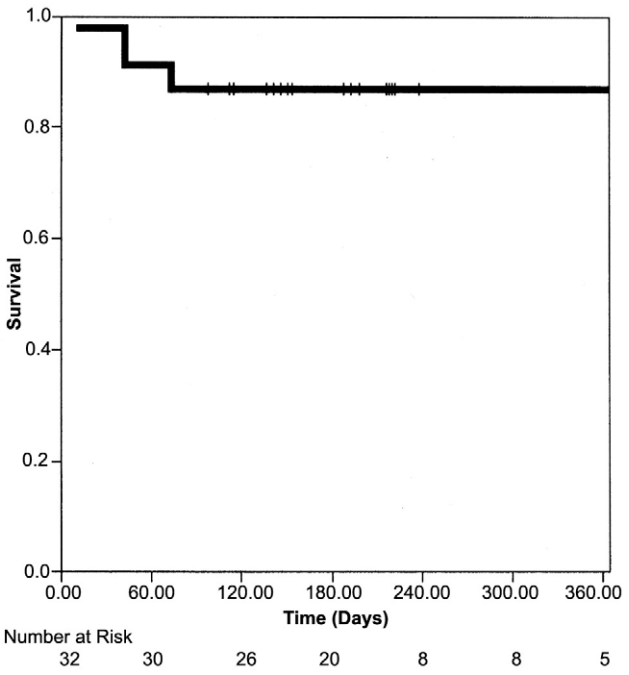

Fig 3. Actuarial survival (Kaplan-Meier analysis) of patients undergoing HeartMate II placement as bridge-to-transplant therapy.

related to the perioperative hypotension that she had. She also had immediate right ventricular failure requiring temporary RVAD support for 1 week after HeartMate II placement with a significant pressor requirement. Thus, the overall incidence of adverse neurologic events was 2 of 32 (6.25%). Note that no transient ischemic attacks occurred in our group of 32 HeartMate II patients. Also, none of the patients who discontinued warfarin experienced any thromboembolic events during HeartMate II support.

Infections

During the entire period of HeartMate II support, 4 patients (12.5%) had driveline infections that required long-term intravenous and oral antibiotic therapy. *Staphylococcus aureus* was identified in 3 patients and *Enterobacter* species in 1 patient. The mean duration to onset of infection was 50.5 days. The infections resolved without any evidence of recurrence in all 4 patients. There were no LVAD-pocket infections in our experience.

Right Ventricular Failure

Severe right ventricular failure requiring placement of an RVAD occurred in 2 (6%) patients. Both patients required CentriMag Levitronix RVAD placement for immediate right ventricular failure (which occurred immediately after HeartMate II placement). In both patients, the RVAD was explanted within 1 week after placement. Both patients survived more than 6 months; 1 is awaiting a heart transplant. The other patient survived almost 2 years after LVAD placement, but was not transplant eligible owing to the development of postoperative paraplegia. It should be noted that no additional patients required prolonged inotropic support. Thus, the overall incidence of right ventricular failure (as defined by RVAD requirement or intropic support $>$ 14 days) was 6%. An additional patient who required temporary RVAD support was not included here as he had right ventricular failure requiring RVAD support even before HeartMate II placement (discussed earlier).

Hemorrhagic Complications

Of the first 14 patients on the HeartMate II in our series who received heparin followed by warfarin, 3 had GI bleeding and 1 suffered delayed pericardial tamponade (4 of 14, 28.5%). Of the remaining 18 patients who received only warfarin and no heparin, 2 had GI bleeding, and none suffered pericardial tamponade (2 of 18, 11.1%). Note that this part of the analysis excluded patients who underwent mediastinal exploration for bleeding on the day of surgery, because that was unrelated to postoperative anticoagulation therapy. In addition, 5 patients (15.6%) had postoperative bleeding requiring mediastinal reexploration, with no resulting mortality.

Device Thrombus

Of our 32 BTT patients, 1 had a suspected pump thrombus that resolved with a high-intensity heparin anticoagulation protocol (the INR was 1.3 at the time of presentation). This patient had gone to an outside hospital with HeartMate II flows in the mid–3 L/min range (in contrast to this patient's usual flows $>$ 4 L/min) and with increased HeartMate II power. After 12 hours of high-intensity anticoagulation heparin therapy (target PTT, 60 s to 80 s), this patient's hemodynamic indicators returned to normal. Heparin therapy was continued for 48 hours. Warfarin therapy was continued to achieve a goal INR of 1.5 to 2.0. No thrombolytic therapy was used. As of the end of this study, this patient is doing well on the heart transplant waiting list, without any further similar episodes 6 months after this suspected pump thrombus. Thus, our overall incidence of device thrombus was 2 of 32 (6 %), including 1 explanted pump that received a thrombus score of 3, as reported in the next section.

Explanted Pump Analysis

Fourteen patients in our study group whose HeartMate II was explanted (at the time of their heart transplant) underwent examination of their explanted pumps for thrombus deposition. All pumps except one received a thrombus score of 0 (none) or 1 (minimal). The one explanted pump that received a high score of 3 ($>$ 50% obstruction with thrombus) had been in the patient who died after prolonged sepsis. He had several days of low pump flow preceding his death, which may have been associated with the development of pump thrombus.

Comment

The discrepancy between the limited availability of donor organs and the ever-increasing number of patients

with heart failure has led to the increasing use of LVADs [11, 12]. Further, the excellent medium-term results with LVADs has led to the use of permanent LVAD support for patients with end-stage heart failure [7]. The findings from our current study extend our and others' previous observations that continuous-flow LVADs such as the HeartMate II can be safely used as BTT therapy in patients with end-stage heart failure [10, 13].

Recently, several single-center and multicenter studies have shown improved outcomes with the newer continuous flow devices [10, 13, 14]. Frazier and colleagues [14] reported a 80% 1-year survival in a series of 43 patients receiving the HeartMate II both as BTT and destination therapy, with markedly improved functional status and quality of life. An actuarial survival of 89% at 1 month and 75% at 6 months was seen in the HeartMate II BTT multicenter study. The incidence of several adverse events in the multicenter study, including LVAD-related infections, need for RVAD support, and pump thrombosis, was similar to that seen in our experience. However, the incidence of other adverse events such as bleeding requiring reexploration and stroke was higher than that reported in this study. It is possible that some of these differences in adverse events could be related to differences in individual management practices among different centers, for example, anticoagulation strategy, as will be discussed later. Nevertheless, an overall improvement in outcomes has been clearly demonstrated both with the HeartMate II as well as with other newer continuous flow devices as compared with that obtained with pulsatile devices. Esmore and coworkers [15] reported a 86.7% 6-month survival in 30 patients receiving the VentrAssist LVAD in an international multicenter trial. These improvements are due primarily to the many advantages of these newer devices as we will discuss later in this article. However, improvement in the results with the newer devices in the current era may also be secondarily related to lessons learned from earlier experiences (with pulsatile devices) that have led to stepwise and systematic improvements in patient selection, better preoperative optimization, improved operative techniques, and better postoperative management such as improved optimization of right ventricular function in the postoperative period.

The decreased morbidity associated with the HeartMate II, especially the lower incidence of postoperative bleeding and device-related infections, may be due to its smaller size, the lack of need for a large pocket to house its pump, and its smaller driveline. The absence of a large preperitoneal pocket (which was required with the larger pulsatile devices) has reduced the need for extensive dissection, reduced postoperative bleeding, and reduced LVAD pocket hematomas and the development of pocket infections. Device-related infections still occur with the HeartMate II LVAD, but they are often treatable with antibiotic therapy; they do not result in significantly delayed transplants or in pretransplant or posttransplant morbidity and mortality (unlike with the earlier generation of LVADs). To further reduce and possibly even eliminate LVAD-related infections, we are currently evaluating additional therapeutic modalities, such as the use of routine antibiotic-impregnated beads around the HeartMate II and the use of platelet gel application to its driveline exit site. We have preliminary evidence that this strategy has reduced the incidence of LVAD-related infections [16].

Importantly, the smaller size of the HeartMate II has made it more applicable for women with heart failure. In our study, female patients accounted for more than 30% of our BTT group. In contrast, in several studies in the literature involving the larger pulsatile VE or XVE device, both as BTT and as destination therapy, fewer than 20% of the patients were female [1, 7, 17]. Clearly, the new generation of smaller continuous-flow devices, such as the HeartMate II, will extend this life-saving technology to a previously underserved population of female patients with end-stage heart failure.

Again, the HeartMate II is a continuous flow, rotary LVAD composed of a blood pump, a percutaneous lead, and an external power source and system driver. The inlet and outlet cannulas include woven polyester grafts (Dacron; C.R. Bard, Haverhill, Pennsylvania) that require preclotting. The pump motor and associated blood tube have smooth titanium surfaces; in an effort to duplicate the excellent biocompatibility of the original pulsatile HeartMate XVE, the inlet and outlet elbows and the intraventricular cannula are textured with titanium microsphere coatings [18]. The rationale for using textured materials for the original HeartMate XVE was that they would absorb and entrap elements from the patient's blood to form a stable, densely adherent biologic lining on the inside of the device [19]. The resultant tissue lining, rather than the underlying biomaterials, would then form the long-term blood-contacting interface, thus obviating the need for systemic anticoagulation. The standard strategy to reduce the risk of thromboembolism with continuous-flow LVADs has been systemic anticoagulation therapy. Despite this strategy, the risk of thromboembolism with those earlier LVADs has been reported in other studies to be as high as 30% [20]. The risk of bleeding, even with the HeartMate II, is exacerbated with anticoagulation treatment. With increasing experience in this study, we successfully reduced the intensity of anticoagulation in our HeartMate II patients without any increased risk of thromboembolic events.

Several previous studies identified multiple risk factors for poor heart transplant survival rates, including the need for pretransplant mechanical circulatory support, pulmonary hypertension, a prior heart transplant, immunologic sensitization, and prolonged donor ischemic times [21]. Outcomes after mechanical circulatory support have vastly improved. Better immunomodulatory regimens to treat sensitized patients are now available, yet pulmonary hypertension remains a relative contraindication to a heart transplant. The issue of pulmonary hypertension assumes importance when evaluating the efficacy of continuous-flow devices. Previous studies showed a lesser degree of left ventricular unloading with continuous-flow (versus pulsatile) devices but a similar degree of pressure unloading under resting conditions

[22, 23]. Other endpoints (such as exercise performance and cellular recovery) have been shown to be similar for the two types of devices [24–26]. However, concerns have remained about the ability of partial unloading of the left ventricle to favorably influence altered pulmonary hemodynamics in end-stage heart failure patients. As a result of this lack of definitive evidence (at least until recently) [27], concerns have lingered about the efficacy of circulatory support provided by continuous-flow (versus pulsatile) devices. In particular, despite the well-documented efficacy of pulsatile LVADs in ameliorating pulmonary hypertension, it remains uncertain whether or not continuous-flow devices similarly improve the altered pulmonary hemodynamics of end-stage heart failure patients [28]. However, recent reports using continuous-flow devices other than the HeartMate II have demonstrated their efficacy in ameliorating pulmonary hypertension [29].

The increased incidence of GI bleeding in HeartMate II patients is of concern. An increased incidence of GI bleeding with continuous flow devices was first reported by Letsou and colleagues [30]. They observed a similarly high incidence of GI bleeding of 14% in a series of heart failure patients supported by the Jarvik 2000 axial-flow LVAD [30]. The cause of bleeding in all 3 of their patients was due to arteriovenous (AV) malformations. Whether GI bleeding is related to the need for anticoagulation or whether it is linked to continuous flow effects or to relatively lower pulsatility is unclear. A similar physiologic state that occurs with continuous-flow devices is also seen in patients with aortic stenosis; such patients, like those implanted with continuous flow devices, experience narrow pulse pressure. It is interesting that aortic stenosis is also associated with GI bleeding [31, 32]. A phenomenon of "acquired von Willebrand" disease may be responsible for the occurrence of GI bleeding in patients with aortic stenosis [33]. Whether this phenomenon of acquired von Willebrand disease also occurs in patients with continuous-flow devices remains to be seen. Our strategy with HeartMate II patients with GI bleeding has been to temporarily discontinue anticoagulation therapy as well as to reduce the pump flow speeds. The rational of reducing pump flow speeds is to increase the pulse pressure in these patients, thereby reducing a potential risk factor for the occurrence of GI bleeding. Using this strategy, we have not had any recurrence of GI bleeding, and the discontinuation of anticoagulation has not resulted in the occurrence of thromboembolism. Clearly, further investigation is essential to definitively characterize GI bleeding in all continuous flow device patients, including HeartMate II patients.

Our single-center study was limited by its relatively small number of patients. In addition, we did not have a comparison group of patients treated with pulsatile devices. However, all of our HeartMate II patients underwent LVAD placement over a relatively short period (approximately 2 years), so the surgical techniques and perioperative treatment protocols were consistent for this group of HeartMate II patients (except for the changes that we described earlier in the anticoagulation protocol).

In conclusion, the extremely low postoperative mortality rate and the low incidence of adverse events makes the HeartMate II LVAD an ideal device to be used as BTT therapy. In addition, the HeartMate II LVAD has benefited from duplicating several features of the original HeartMate XVE, especially in that both confer a low thromboembolic risk. The favorably low thrombogenecity and low thromboembolic risk associated with the HeartMate II makes it ideal as destination therapy as well. With an increasing focus on destination therapy as a real alternative for heart failure patients, the features and outcomes associated with the HeartMate II LVAD deserve attention [34]. Clearly, the increased incidence of GI bleeding is of concern; strategies to optimize anticoagulation as well as understanding the exact relationship between GI bleeding and continuous-flow devices will allow for improved outcomes in this population of end-stage heart failure patients.

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DISCUSSION

DR MICHAEL A. ACKER (Philadelphia, PA): I want to thank and congratulate Dr John and his colleagues from the University of Minnesota for this very important paper. I think it is very important for not only this audience but also the audience of heart failure cardiologists out there to realize how phenomenal these results are and how it probably represents a real step forward over our first-generation pulsatile devices. Importantly, these results that Dr John showed at the University of Minnesota have largely been reproduced, though not quite as good, in the recently completed prospective multicenter trial of HeartMate II for bridge to transplantation. The FDA panel has approved this device, and it is expected this approval is forthcoming for bridge to transplantation. I might note that of all new LVADs in trial right now, they are all continuous flow. There are approximately five or six in human trial, and what is exciting is that the early results for each of these devices mirror the excellent results that we are seeing with HeartMate II.

This is a comparison of the HeartMate II pivotal trial as a bridge to transplantation, to the HeartMate XVE, which is the only approved device that has saved many patients. The dramatic decrease in adverse events is very striking: Bleeding requiring reoperative surgery is down by a half; most importantly, percutaneous lead infections is about a tenth, and I might add that in Dr John's series, there was no pocket infection; stroke was decreased by half; and RV failure was also decreased. Importantly, though, there was a device malfunction in this group the rate of device malfunction is dramatically less than seen with HeartMate I.

Despite these excellent results, questions linger on continuous flow devices and the long-term effects of decreased pulsatility, such as why is GI bleeding increased? Is LV unloading sufficient, especially when one compares it with pulsatile devices? And do we still need an automatic flow algorithm for automatic control?

I have several questions. The first question is this: continuous flow devices are believed by many not to unload the left ventricle as well as pulsatile devices and as such they will choose HeartMate I for patients with severe pulmonary hypertension maybe who are not transplant candidates to promote resolution of pulmonary hypertension in later transplant. Do you believe this is true, and if so, is there a group of patients where HeartMate I is still indicated?

Second question: HeartMate I is associated in some centers with a high incidence of sensitization and high PRA, which can delay or preclude safe transplantation. Have you seen this or

other study centers seen this in HeartMate II, and if not, why not?

Third question: do you feel there is a need for an algorithm that will allow automatic adjustment of flows both to maximize flows and avoid "suckdown" for any given situation?

Fourth question: can you conjecture on the long-term effects of decreased pulsatile pressure such as the GI bleeding incidence you saw?

And finally, and most importantly, have these excellent results been reproduced in your older destination patients, and if so, can you conjecture on whether HeartMate II should be moved into less sick patients and whether you will be able to convince heart failure cardiologists to refer these patients so as to improve their quality of life?

I want to thank the Association for the privilege of discussing this important paper.

DR JOHN: Thank you, Dr Acker, for those kind comments. In response to the first question as to whether the HeartMate I is still indicated, I would like to make this remark. In this current era of increasing use of continuous flow devices, there have been three groups of patients who are believed to still benefit from the HeartMate I. One is the very large patient, the second group is the patient who cannot tolerate anticoagulation, and the third was what Dr Acker alluded to, patients with severe pulmonary hypertension. With increasing experience, we and others have shown that the HeartMate II can be safely used in all these groups. We have shown that patients with the HeartMate II can tolerate long periods without anticoagulation, without experiencing an increased incidence of thromboembolic events. We have also seen that in the very large patient as well as the patient with severe pulmonary hypertension that the HeartMate II satisfactorily reverses the adverse pulmonary hemodynamics, making them eligible for transplantation. The one group in which the HeartMate XVE may be superior is in the very sick cohort of patients and pulsatile flow may be better for this extremely sick group of patients with multisystem organ failure.

The lower rates of allosensitization that are being seen with the HeartMate II may reflect the current era in which we have learned to significantly reduce the incidence of bleeding, both by improved surgical techniques as well as better preoperative optimization. The smaller size of the current HeartMate II device reduces the need for extensive dissection as the pump pocket size is significantly smaller. As a result, these patients receive significantly less blood and blood products, which has contributed to the lower levels of sensitization in this era.

The third question was regarding the "suckdown" effect. If you do increase the speeds in the HeartMate II to very high levels, especially in the face of inadequate preload, these patients will experience a suckdown effect on the ventricle. This can precipitate ventricular arrhythmias and even death. It may be favorable to incorporate an algorithm in continuous flow pumps to prevent the suckdown effect that may be seen with continuous flow pumps. In the absence of that, it should be stressed that it is important to balance speed at which the pump is run to achieve flows that are adequate for the patient's body size and to maintain adequate end-organ perfusion (in addition to optimizing preload).

I think the effects of long-term reduced pulsatile pressure have not translated into adverse end-organ function. We have shown reversal of end-organ dysfunction, both renal and hepatic function, in patients supported with these pumps. There have been several other reports in the literature that have shown resolution and maintenance of end organ perfusion with continuous flow devices. Clearly, the increased incidence of GI bleeding with continuous flow devices is of concern. Is it the reduced pulse pressure or the need for anticoagulation that is contributing to the bleeding in these patients remains to be seen? An increased incidence of GI bleeding is also seen patients with aortic stenosis, a condition that shares the low pulse pressure state with patients with continuous flow devices. We are studying this phenomenon in greater detail to identify risk factors for GI bleeding in patients with continuous flow devices.

I certainly agree with Dr Acker that these results and those duplicated by many other centers have set the stage for the use of these devices in less sick patients. Data from the DT trial are still ongoing, although anecdotally what we are seeing are better results in patients using the HeartMate II as compared with the HeartMate XVE. These improved results not only primarily reflect the fact that we have a better pump in the HeartMate II, but secondarily, also reflect on lessons that we have learned from years of experience with the HeartMate XVE as well as other devices while caring for patients with end-stage heart failure requiring circulatory support. Thank you.