Worldwide Experience With the MicroMed DeBakey Ventricular Assist Device® as a Bridge to Transplantation

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Background—Ventricular assist device (VAD) support with pulsatile first generation pumps is a well-established therapy for bridging to transplantation. Shortcomings of this technology include limited applicability to small patients, noise, and high incidence of infection and pump malfunction. A second generation of pumps, spearheaded by the axial flow MicroMed DeBakey VAD®, is in clinical trials and potentially will address these shortcomings.

Methods and Results—Between November 13, 1998 and May 7, 2002, 150 patients worldwide underwent placement of the Micromed DeBakey VAD® as a bridge to transplantation. Prospectively acquired data including demographics, adverse events and outcomes was collected. Follow up is 100% with 30.4 patient-years of cumulative support time. Mean age was 48 ± 4 years and 18% were female. Twenty-three percent had prior sternotomy. Preoperatively, 25% were on balloon pump support, 20% had renal insufficiency, and 40% were on at least two inotropes with a mean cardiac index of 1.8 L/min/m². Mean support time was 75 ± 81 days. Linearized rates (events/patient-year) were: reoperation for bleeding 2.03, hemolysis 0.61, device infection 0.16, thromboembolic event 0.61, pump thrombus 0.61, and pump failure 0.13. Eight-two patients (55%) were either bridged to transplantation, recovery or are ongoing and 68 (45%) have died. Several patients have been supported as outpatients.

Conclusions—This initial experience suggests that bridging to transplantation can be successfully approached with a small and quiet axial flow pump that provides low incidence of device infection and pump failure. The incidence of pump thrombus and thromboembolism is being addressed by incorporation of heparin coating to all device surfaces. (Circulation. 2003;108[suppl II]:II-272-II-277.)

Key Words: bridge to transplantation ■ mechanical support ■ axial flow pumps ■ pulsatile versus continuous flow

"The first step toward knowledge is to know we are ignorant” . . .

Richard Cecil

The first generation pulsatile ventricular assist devices (VAD) have laid the foundation for the field of mechanical support. Indeed, these devices are capable of resuscitating and rehabilitating moribund end-stage heart failure patients and bridging them to transplantation with success rates that approximate 75%. In addition, these pumps are now routinely used as outpatient support providing a reasonable quality of life for its recipients.¹

The recent landmark REMATCH trial² demonstrated a survival and quality of life advantage at 1 and 2 years for end-stage heart failure patients who were not candidates for transplantation and who received the HeartMate I device when compared with those patients randomized to optimal medical therapy. Moreover, the trial established adverse event benchmarks against which new technologies must now be critically compared. The salutary results of this trial led to the recent approval of the HeartMate I pump by the Food and Drug Administration (FDA) for use as destination therapy in patients not considered candidates for transplantation.

Importantly, the clinical experience with pulsatile devices that now exceeds a decade, has underscored several shortcomings of this technology. Notably, these pumps are: (1) too large limiting the population that can be supported and rendering the implant surgery cumbersome and morbidity-ridden; (2) noisy, impacting on the quality of life of the recipient and his/her spouse or companion; (3) predisposed to infection due to the large and inflexible driveline; (4) comprised of several moving parts, increasing the chance for malfunction; and (5) very expensive, in the range of $70,000 per unit.

A second generation of miniaturized pumps have been developed as a potential answer to these shortcomings. They differ from the previous generation devices in that they produce continuous rather than pulsatile blood flow. A major intellectual obstacle to the viability of this technology was the determination of whether “nonphysiological” continuous blood flow could support end-organ function. Interestingly, examination of human circulatory physiology reveals that pulsatile blood flow is only present at the level of the named arteries (eg, aorta, pulmonary artery, femoral artery, etc). However, the true function of blood flow—nutrient delivery
and gas exchange—occurs at the capillary level, a point where pulsatility does not exist. This theoretical grounding provided an impetus for the evaluation of continuous flow in animal models and successful experience in the preclinical setting provided the framework for the initial clinical studies.

Three axial flow devices are currently undergoing clinical trials worldwide including the Jarvik 2000 Flowmaker, the HearMate II, and the MicroMed DeBakey VAD®. The latter, has been the most widely used device and constitutes the subject of this report.

Methods
All patients in the US (n=24, 3 centers) and in Europe (n=126, 11 centers) underwent implantation of the MicroMed VAD® with the intention of bridging to transplantation as part of a clinical trial. Exclusion criteria included postcardiotomy cardiac failure, cardiogenic shock due to acute myocardial infarction of less than 48 hours duration, as well as any criteria that contraindicated future cardiac transplantation. The trial was approved by each center’s institutional review board and the subjects gave written informed consent. In the US, the trial was conducted as a safety and feasibility trial with investigational device exemption approval from the FDA to implant 30 devices. Demographic, adverse event and outcome data were collected for each trial participant in prespecified case report forms that were then retrieved by the company and assembled into a database. The database was then queried to obtain the data presented in the manuscript. Linearization and hazard function analysis were performed to calculate the incidence of adverse events. T-tests were used for comparison of means and a two-tailed probability value <0.05 was considered significant.

Device and Surgical Procedure
Device Description
Briefly, the device is a miniaturized, electromagnetically actuated, fully implantable titanium axial flow pump weighing 93 g. The internal pump system consists of a titanium inflow cannula and apical ring, the housing unit containing the impeller (only moving part) and motor, and a Vasutech gel weave vascular graft that exits the pump as an outflow conduit and connects to the aorta. An integral flow probe encircles the outflow graft providing real-time cardiac output. The pump is designed to achieve 5 L/min against 100 mm Hg pressure with a speed of 10,000 rpm. The flow curves, speed, current and power are displayed in a bedside monitor unit (CDAS or clinical data acquisition system) that is accessed to make adjustments to the pump speed. A pump motor cable along with the flow probe’s wire exit transcutaneously and connect to the external controller. The latter, consisting of the controller module, battery packs and battery charger, is designed to operate the pump. To facilitate mobility and eventual hospital discharge, the pump can be actuated by two 12-volt DC batteries for 4 to 6 hours.

Surgical Procedure
In general, the heart is exposed via standard median sternotomy and full cardiopulmonary bypass support is established with atrio-aortic cannulation. In most instances, implantation proceeds without cardioplegic arrest. Transesophageal echocardiography (TEE) is routinely used to rule out the presence of aortic insufficiency, intracardiac thrombus and/or atrial septal defect (or patent foramen ovale) that may require further intervention. In addition, TEE guides intracardiac deairing, and provides superior imaging of inflow cannula placement, right ventricular function, and left ventricular decompression.

Without the need to extend the median sternotomy incision, a small pericardial pocket is created to house the pump under the left costal margin. The left ventricular apex is cored out and an apical ring is sewn to the apex. The inflow cannula is inserted into the left ventricular cavity and secured to the apical ring. A small incision is made in the left lower quadrant and the thin driveline is routed transcutaneously and connected to the controller. Next, the outflow graft is tailored to reach the ascending aorta. A partial occluding clamp is placed along the greater curvature of the ascending aorta and the graft is anastomosed in end-to-side fashion using standard suture technique. In difficult reoperative cases, the device can be implanted to the descending aorta via a left thoracotomy. The graft is deaired and the patient is weaned from cardiopulmonary bypass as the device is actuated. Usually, inotropic support for the right heart is used. In some instances, intra-aortic balloon pump support and inhaled nitric oxide are employed.

Results
There were 150 patients who underwent device implantation in 3 American and 11 European centers between November 13, 1998 and July 7, 2002. Mean age of recipients was 48 ± 14 years (range, 12 to 73) and 18% (n=27) were female. The most common etiology of heart failure was ischemic, followed by dilated cardiomyopathy. Smallest body surface area was 1.4 m² (range, 1.4 to 2.34 m²). Mean cardiac index at the time of implantation was 1.8 L/min/m² and mean capillary wedge pressure was 29 mm Hg. Cumulative support time is 30.4 patient-years. Longest support time was 441 days. Twelve patients (8%) have been supported for at least 6 months.

The preoperative clinical profile underscoring the critical condition of these patients at the time of implantation included renal insufficiency in 20%, intra-aortic balloon pump dependency in 25% and need for mechanical ventilation in 19%. Forty percent of patients were on at least 2 inotropes.

The incidence of major adverse events and linearized rates are depicted in Table 1. Hazard analysis to account for the differing incidence of adverse events over time is graphically depicted in Figure 1. Reoperation for bleeding was the most common complication following VAD placement. The incidence of device related infection and pump failure were particularly low. Infections were all related to the driveline site as no real preperitoneal pocket exists. The causes of mechanical failure included a recessed connector pin (n=2), a broken wire (n=1) and a controller failure (n=1), all occurring early in the trial.

Of 17 cases of pump thrombus, 11 (64%) had a successful resolution with transplantation, pump exchange or thrombolysis. Interestingly, there were no strokes associated with pump thrombus. Hemolysis occurred unpredictably and
resolved spontaneously in most instances. Only two patients
hemolysis in association with pump thrombus. In both in-
stances, it occurred within two weeks of the diagnosis of
pump thrombus. Elevations in lactic dehydrogenase were not
uncommon but did not correlate with peaks in plasma-free
hemoglobin and were of uncertain clinical relevance.

Table 2 documents the outcomes for all patients. In the
European series, bridging to transplantation was successful in
nearly 50% of patients. In the smaller US cohort, the success
rate has been 66%.

In an effort to elucidate the ability of the MicroMed VAD®
to support large patients, 103 patients for whom complete
data were available were divided into two groups according
to BSA (median BSA was 1.9 m²). Mean pump speed, pump
flow and indices of renal (blood urea nitrogen and creatinine)
and hepatic (total bilirubin) function for the duration of
support were extracted from each patient’s datasheet and
comparisons were made between small (BSA < 1.9 m²) and
large (BSA ≥ 1.9 m²) patients. (The definition of small and
large was arbitrarily made around the median BSA of 1.9 m².)

While no statistically significant difference was present
with regard to pump speed, larger patients had statistically
significant higher pump flows (Table 3). Renal function did
not differ significantly between smaller and larger patients
but larger patients had lower total bilirubin levels.

Regardless of patient size, the pump was generally run
within a narrow range of speeds (between 9200 and 9600
RPM). Patients with larger BSAs had higher pump output.
This is likely the result of larger blood return to the left
ventricle resulting in higher left ventricular end-diastolic
pressure (LVEDP). Because pump flow is directly propor-
tional to the pressure difference across the pump (LVEDP—
aortic diastolic pressure), the higher LVEDP translates into
higher pump flows. The interrelationship between BSA, pump speed and pump flow is best depicted in Figure 2. For
any pump speed (x-ordinate), pump flow (z-ordinate) in-
creases with increasing BSA (y-ordinate).

To evaluate the safety and feasibility of a physiologically
responsive controller, an algorithm based on heart rate
variability was developed and tested in 5 patients at the
University of Vienna. Figure 3 depicts a representative
effect of exercise on pump flow under control
conditions (no physiological algorithm). As the patient’s
heart rate increased, a modest increase in pump flow oc-
curred, as expected. When the heart rate algorithm was
activated, the patient’s rise in heart rate was detected by the
controller that triggered a rise in pump speed. The latter,
in turn, resulted in a dramatic increase in pump flow (Figure 4).
As exercise ceased and heart rate returned to baseline, pump
speed and pump flow were appropriately reduced. The system
remained stable even at heart rates as high as 220 bpm. No
switchover to manual mode was necessary. Ventricular suc-
tion occurred very rarely and was documented by the real-

### Table 2. Outcomes of 150 Patients Receiving the MicroMed DeBakey VAD as a Bridge to Transplantation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Europe</th>
<th>US</th>
<th>Carmeda*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridged to transplant</td>
<td>41</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Died</td>
<td>45</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Ongoing</td>
<td>1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Bridged to recovery</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>24</td>
<td>38</td>
</tr>
</tbody>
</table>

* Pumps with covalently coated heparin, recently available.
† Off label use, all in Europe.

### Table 3. Comparison of Pump Speed, Flow, and End-Organ Function between Smaller (BSA < 1.9) and Larger (BSA ≥ 1.9) Patients

<table>
<thead>
<tr>
<th>Body Surface Area</th>
<th>&lt;1.9 m²</th>
<th>≥1.9 m²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean body surface area (m²)</td>
<td>1.7±0.1</td>
<td>2.0±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Range body surface area (m²)</td>
<td>1.4–1.89</td>
<td>1.9–2.34</td>
<td></td>
</tr>
<tr>
<td>Mean pump speed (RPM)</td>
<td>9500±600</td>
<td>9700±400</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean pump flow (L/min)</td>
<td>4.2±0.9</td>
<td>4.8±0.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean blood urea nitrogen</td>
<td>26±12</td>
<td>38±12</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean serum creatinine (mg/dL)</td>
<td>1.0±0.5</td>
<td>1.4±0.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean total bilirubin (mg/dL)</td>
<td>2.8±1.3</td>
<td>2.4±2.0</td>
<td>0.009</td>
</tr>
</tbody>
</table>

All figures are average values for the duration of MicroMed VAD support.
time data acquisition during the clinical session of algorithm testing. The real-time flow signal was captured along with each instance that the algorithm indicated that a suction event had occurred. Suction events did not occur during the normal course of the algorithm control but could be provoked by coughing or a Valsalva maneuver. In these instances, the algorithm acted appropriately by reducing the speed of the pump until the suction event stopped. These events were not associated with discomfort to the patient.

Conclusions

Pulsatile ventricular assist device support remains the mainstay therapy in the bridging of decompensating end-stage heart failure patients to transplantation. Moreover, recent regulatory approval has opened the doors for these devices as permanent alternative therapies for patients with advanced heart failure who are not candidates for transplantation. Despite this success, there has been growing interest in examining continuous flow pumps for long-term patient support. This impetus is the result of the many potential advantages that these pumps can offer. Their design is smaller in size with less blood-contacting surfaces, no valves, air vents or compliance chambers. This miniaturization expands the potential pool of patients that can be supported but also renders the implanting operation much simpler. The pumps have fewer moving parts, make minimal noise and could possibly be more durable and less costly.

The initial skepticism regarding the ability to maintain adequate circulatory support and end-organ function with long-term continuous flow has been placated by the favorable clinical experiences with the MicroMed DeBakey VAD®. Moreover, the present experience described herein suggests that successful bridging to transplantation can be achieved with this device in 50% to 66% of cases. The incidence of major adverse events parallels that observed with the early experience with pulsatile devices.

The low incidence of pump infection and pump failure should be underscored. These properties coupled with the lesser cost renders these pumps an attractive alternative. Clearly, the experience with axial flow mechanical support is in its infancy and many challenges remain. In particular, the prevention and management of pump thrombus, the determination of the ability of small pumps to support large patients, and the development of a physiologically responsive controller.

Pump thrombus has been a problem in all three axial flow systems in clinical use. The exact mechanism that leads to the development of this problem remains uncertain. Does axial flow induce a prothrombotic milieu? Does pump thrombus develop in the cardiac chambers and then migrates into the pump or does it form in the pump de novo? Can risk factors be identified that are predictive of pump thrombus? While answers to these questions are actively being sought, it is also critical that simultaneous management algorithms be developed to effectively deal with the problem once its encountered.

The diagnosis of pump thrombus is suspected when pump power and current requirements increase and pump flow is reduced. Its onset tends to be gradual and not hemodynamically destabilizing, although can occasionally be precipitous. Finally, pump thrombus does not uniformly portend a fatal outcome. Indeed, 64% of patients were successfully rescued with transplantation, pump exchange, or thrombolysis.

A major effort to address the problem has been the incorporation of covalently bonded heparin (carmeda) to all surfaces of the pump. Precedent success with this approach exists with cardiopulmonary bypass circuits, vascular grafts, coronary stents, and other mechanical support devices. This process is thought to impart thromboresistance and minimize contact activation and inflammatory responses. The carmeda coated pumps have received CE Mark approval and have been also approved by the FDA for the US pivotal trial to start in 2003. Because of the limited

Figure 3. Representation of physiological parameters with exercise. As patient begins to exercise, heart rate increases and pump flow rises modestly. As exercise ends, heart rate drops and pump flow returns to baseline. Pump speed and power remain unchanged because physiological trigger is not activated. Courtesy of Dr. Heinrich Schima, Department of Cardiothoracic Surgery, University of Vienna.

Figure 4. Representation of physiological parameters with exercise. The heart rate-driven trigger control is activated. As patient begins to exercise, heart rate increases. This change is sensed by the controller which now triggers an increase in pump speed. This is accompanied by higher power requirements. The result is a dramatic rise in pump flow. As exercise ends, heart rate slows, and pump speed and power are reduced, resulting in a reduction of pump flow. Courtesy of Dr. Heinrich Schima, Department of Cardiothoracic Surgery, University of Vienna.
In summary then, this initial experience with the MicroMed DeBakey VAD® is promising and supports the continued evaluation of axial flow pumps for long-term support. The low incidence of pump failure and infection are very encouraging and the pumps are applicable to a wide range of patient sizes and rather easy to implant. The patients appreciate the easy mobility and quiet operation and outpatient support is possible. Many challenges including the elucidation of the pathogenesis of pump thrombus, its prevention and treatment, as well as better patient selection and the development of a physiologically responsive controller remain. While new technologies should be scrutinized and compared with the benchmarks established by the RE-MATCH trial, it is important to underscore that this technology is in its infancy and the steep learning curve is only now beginning to flatten.

Appendix

MicroMed DeBakey VAD® US and European Investigators and Study Centers

Europe:
- Roland Hetzer MD, Deutsches Herzzentrum Berlin, Germany; Ernst Wolner MD, University of Vienna, Austria; Jean-Noël Fabiani, MD, Hôpital Européen Georges Pompidou, France; Marko Turina MD, University Hospital of Zurich, Switzerland; Mario Vigano MD, Ospedale Policlinico San Matteo, Italy; Reiner Körfer MD, Herzzentrum Nordrhein-Westfalen, Germany; Friedrich-Wilhelm Mohr MD, University Leipzig, Germany; Hans Scheld, MD, Universitätssklinik Münster, Germany; Ettore Vitali, MD, Ospedalet Niguarda Cà Granda, Italy; Bruno Reichart, MD, Klinik der Herzchirurgische, Germany
- United States: Michael DeBakey, MD, and George Noon, MD, The Methodist Hospital, Texas; Patrick McCarthy, MD, Clinical Cleveland Foundation, Cleveland; Daniel J. Goldstein, MD, Newark Beth Israel Medical Center, Newark.

Addendum

As of April 23, 2003, 184 patients have received the MicroMed DeBakey VAD® as a bridge to transplantation, including 30 patients in the US. Cumulative support time is now 44.2 patient-years and 24 (13%) patients have been supported in excess of 6 months. Longest support time has been 492 days (Deborah Morley, MicroMed Inc, personal communication).

References


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