

ORIGINAL ARTICLE

Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation

Leslie W. Miller, M.D., Francis D. Pagani, M.D., Ph.D., Stuart D. Russell, M.D.,
Ranjit John, M.D., Andrew J. Boyle, M.D., Keith D. Aaronson, M.D.,
John V. Conte, M.D., Yoshifumi Naka, M.D., Donna Mancini, M.D.,
Reynolds M. Delgado, M.D., Thomas E. MacGillivray, M.D.,
David J. Farrar, Ph.D., and O.H. Frazier, M.D.,
for the HeartMate II Clinical Investigators*

ABSTRACT

BACKGROUND

The use of left ventricular assist devices is an accepted therapy for patients with refractory heart failure, but current pulsatile volume-displacement devices have limitations (including large pump size and limited long-term mechanical durability) that have reduced widespread adoption of this technology. Continuous-flow pumps are newer types of left ventricular assist devices developed to overcome some of these limitations.

METHODS

In a prospective, multicenter study without a concurrent control group, 133 patients with end-stage heart failure who were on a waiting list for heart transplantation underwent implantation of a continuous-flow pump. The principal outcomes were the proportions of patients who, at 180 days, had undergone transplantation, had cardiac recovery, or had ongoing mechanical support while remaining eligible for transplantation. We also assessed functional status and quality of life.

RESULTS

The principal outcomes occurred in 100 patients (75%). The median duration of support was 126 days (range, 1 to 600). The survival rate during support was 75% at 6 months and 68% at 12 months. At 3 months, therapy was associated with significant improvement in functional status (according to the New York Heart Association class and results of a 6-minute walk test) and in quality of life (according to the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires). Major adverse events included postoperative bleeding, stroke, right heart failure, and percutaneous lead infection. Pump thrombosis occurred in two patients.

CONCLUSIONS

A continuous-flow left ventricular assist device can provide effective hemodynamic support for a period of at least 6 months in patients awaiting heart transplantation, with improved functional status and quality of life. (ClinicalTrials.gov number, NCT00121472.)

From the University of Minnesota, Minneapolis (L.W.M., R.J., A.J.B.); the University of Michigan, Ann Arbor (F.D.P., K.D.A.); Johns Hopkins Hospital, Baltimore (S.D.R., J.V.C.); Columbia University, New York (Y.N., D.M.); Texas Heart Institute, Houston (R.M.D., O.H.F.); Massachusetts General Hospital, Boston (T.E.M.); and Thoratec, Pleasanton, CA (D.J.F.). Address reprint requests to Dr. Miller at Washington Hospital Center, 110 Irving St. NW, Rm. 1F-1208, Washington, DC 20010-2975, or at leslie.w.miller@medstar.net.

Drs. Miller and Pagani contributed equally to this article.

*Other investigators for the HeartMate II study are listed in the Appendix.

N Engl J Med 2007;357:885-96.
Copyright © 2007 Massachusetts Medical Society.

THERAPY WITH A LEFT VENTRICULAR ASSIST device is an established form of treatment for patients with refractory heart failure.¹ In the United States, most patients undergoing implantation of such a device as a bridge to heart transplantation have received support from pulsatile volume-displacement devices that fill with and eject blood in a cyclic fashion that is analogous to the systole and diastole of the native heart.²⁻⁷ These devices provide excellent hemodynamic support and improve survival but have substantial constraints, including the need for extensive surgical dissection, the requirement that the recipient have a large body habitus, the presence of a large-diameter percutaneous lead, audible pump operation, and limitations in long-term mechanical durability that frequently require subsequent operations for device exchange.^{8,9}

More recently, several left ventricular assist devices have been developed with continuous-flow, rotary-pump technology (Fig. 1). One advantage of these newer pumps is a smaller device size, with the potential for extending therapy to underserved populations, including some women and adolescents.^{9,10} Another advantage is the potential for greater long-term mechanical reliability owing to a simplified design that requires only a single moving part, an internal rotor. Other benefits include less noise from the device and greater comfort for patients than with the typical pulsatile device.

Continuous-flow pumps — including the HeartMate II Left Ventricular Assist System (Thoratec),¹⁰ the MicroMed DeBakey Ventricular Assist Device (MicroMed),¹¹ the Jarvik 2000 Heart (Jarvik Heart),¹² and the VentrAssist Left Ventricular Assist System (Ventracor)¹³ — are the subject of ongoing clinical evaluation in the United States. We report on results from a large observational clinical study of a continuous-flow left ventricular assist device.

METHODS

STUDY DESIGN

The study was conducted at 26 centers in the United States between March 2005 and May 2006 and was supervised by the sponsor (Thoratec). Investigators in the clinical affairs and biostatistics departments at Thoratec designed the trial in ongoing consultation with the Food and Drug Administration (FDA) and the clinical investigators.

Coordinators at each site collected all study data, which were then forwarded to the data analysis center of the sponsor. The academic authors had independent access to the data; they vouch for the completeness and accuracy of the data and the analyses.

A data and safety monitoring board, consisting of five independent physicians who were not investigators in the study, met routinely to review study compliance, adverse events, quality of life, and outcomes of patients. These five physicians were compensated for their time, but none have any financial interest in Thoratec or stand to gain financially from the outcome of the trial. A clinical events committee of four independent physicians reviewed, classified, and adjudicated the causes of death and all adverse events.

The study was conducted in compliance with FDA regulations for Good Clinical Practices. The protocol was approved by the FDA and the institutional review board at each participating center.

STUDY SUBJECTS

Patients with end-stage heart failure who were on a waiting list for heart transplantation at each center were eligible for study enrollment. (Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.) Patients were required to have symptoms of New York Heart Association (NYHA) class IV heart failure and to be ill enough to have high priority for transplantation (United Network for Organ Sharing status 1A or 1B). Exclusion criteria included severe renal, pulmonary, or hepatic dysfunction; active uncontrolled infection; a mechanical aortic valve; aortic insufficiency; an aortic aneurysm; the presence of other mechanical circulatory support, except for an intraaortic balloon pump; and technical obstacles thought by the investigator to pose an increased surgical risk. All participating patients provided written informed consent.

BASELINE ASSESSMENT

We collected baseline data on all enrolled patients. Assessments included demographic characteristics, health history, NYHA functional class, surveys on quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires), blood chemical values, hematologic data, neurologic status, and concomitant medications.

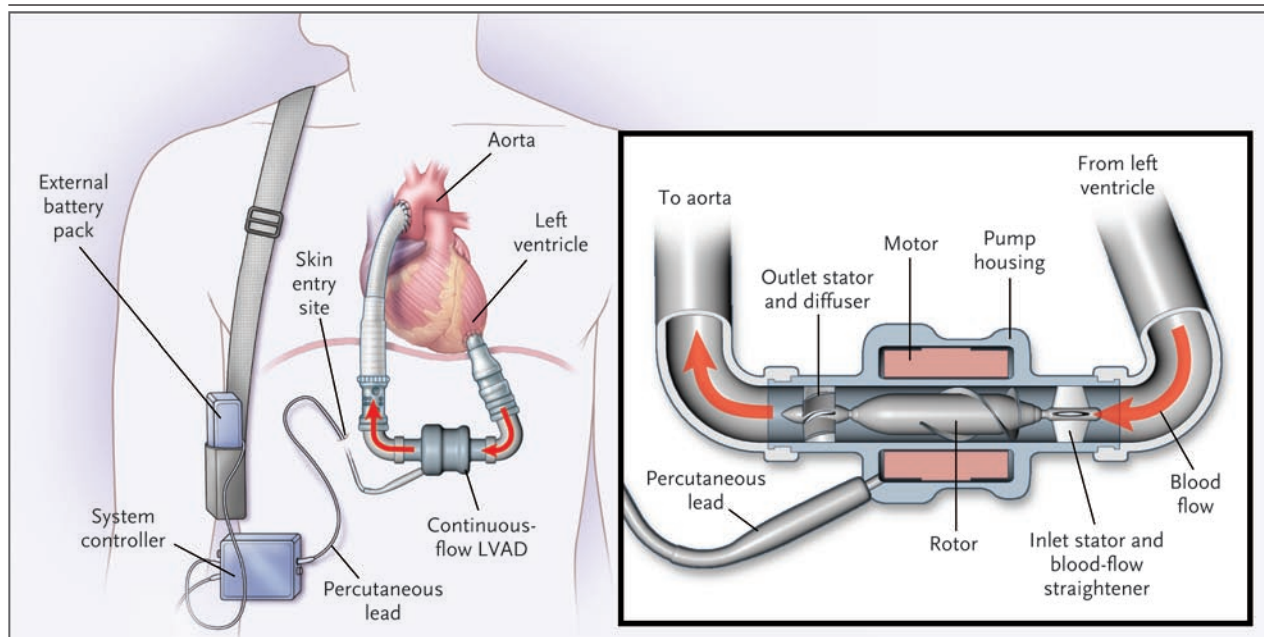


Figure 1. Components of the Continuous-Flow Left Ventricular Assist Device (LVAD).

The inflow cannula is inserted into the apex of the left ventricle, and the outflow cannula is anastomosed to the ascending aorta. Blood exits through the left ventricular apex and into the left ventricular assist device, which pumps throughout cardiac diastole and systole into the ascending aorta, with the rotor being the only moving part. The left ventricular assist device pump is placed within the abdominal wall or peritoneal cavity. A percutaneous lead carries the electrical cable to an electronic controller and battery packs, which are worn on a belt and shoulder holster, respectively.

CONTINUOUS-FLOW PUMP

The pump used in this study was the Heartmate II LVAD (Thoratec), which is a continuous-flow device consisting of an internal axial-flow blood pump with a percutaneous lead that connects the pump to an external system driver and power source (Fig. 1).¹⁰ The pump contains an internal rotor with helical blades that curve around a central shaft. When the rotor spins on its axis, kinetic energy is imparted to the blood, which is drawn continuously from the left ventricular apex through the pump and into the ascending aorta. The pump has an implant volume of 63 ml and generates up to 10 liters per minute of flow at a mean pressure of 100 mm Hg. Details of the device's function and the approach to surgical implantation have been described elsewhere.^{10,14}

FOLLOW-UP AFTER DEVICE IMPLANTATION

After implantation of the device, a standardized antithrombotic regimen was implemented with initiation of heparin followed by transition to warfarin as well as aspirin and dipyridamole (see the Supplementary Appendix). Postoperative medical

care (including inotropic, antiarrhythmic, and heart-failure therapy) was managed according to each investigator's preference and usual practice. Data on performance of the device and hemodynamics of patients were recorded every 8 hours for 3 days, daily through day 14, and weekly through day 30 while the patient was hospitalized. The results of a physical assessment and laboratory tests and a list of medications were recorded on days 1, 3, 5, 7, 11, 14, 21, and 28 after implantation of the device while the patient was hospitalized. After 30 days, device measurements, laboratory evaluations, and physical assessments were required on a monthly basis.

After patients were discharged home, they were assessed over the telephone at least every 2 weeks; they returned to the investigational study site for follow-up, equipment review, and general status assessment weekly for the first 4 weeks and then monthly until the final outcome. Assessment of quality of life and a 6-minute walk test were completed at baseline and 1 month, 3 months, and 6 months after implantation of the device. Re-admissions to the hospital and adverse events (in-

cluding suspected device malfunction) were recorded throughout the study as they occurred with the use of standardized definitions (see the Supplementary Appendix). All deaths of patients and causes of death were determined at autopsy when possible or by examination of medical records or by interviews with family members. Final adjudication was determined by the clinical events committee.

OUTCOMES

The principal outcomes were the proportions of patients who, at 180 days, had undergone transplantation, had undergone explantation of the device because of recovery of ventricular function, or had ongoing mechanical support and remained eligible for transplantation (i.e., were not removed from the waiting list owing to irreversible complications or clinical deterioration). Secondary outcomes included overall survival, survival while receiving device support, survival after transplantation, frequency of adverse events, assessment of functional class by a 6-minute walk test, independent evaluation of NYHA functional class by a physician, and quality of life. Patients who had the original continuous-flow pump replaced with another identical device and survived to 180 days were included in the group meeting the principal outcomes, whereas the three patients who had the original pump replaced with a different type of device were not included.

STATISTICAL ANALYSIS

Differences between measures of hemodynamics and quality of life before and after implantation of the device were analyzed with the use of an independent-samples t-test. For a comparison between categorical variables, Fisher's exact test was used. The level of statistical significance was set at $P < 0.05$. All statistical comparisons are two-sided. Biochemical and hemodynamic variables are presented as means (\pm SD), and medians and ranges were used where appropriate. Discrete variables are presented as percentages. Adverse events are presented both as the percentage of patients who had the event and as event rates per patient-year. Survival analysis for patients continuing on mechanical support was performed with the use of the Kaplan–Meier method with censoring for heart transplantation or cardiac recovery.

RESULTS

STUDY PATIENTS

A total of 133 patients who met study-entry criteria were enrolled in the study and underwent implantation of the continuous-flow pump as a bridge to cardiac transplantation. Most subjects were men with an average age of 50 years, and the primary cause of heart failure for the majority of patients was nonischemic cardiomyopathy (Table 1). Optimal oral medical therapy had failed in all patients, and all patients were receiving intravenous inotropic therapy, with 25% requiring more than one inotrope. Eleven percent of patients could not tolerate inotropes owing to cardiac arrhythmias. Forty-one percent of patients were on concomitant support with an intraaortic balloon pump.

CLINICAL COURSE

Five patients (4%) received temporary support from right ventricular assist devices for 3 to 93 days. These devices included two paracorporeal pneumatic devices and three short-term centrifugal pumps, two of which were converted to pneumatic devices. The median duration of postoperative inotropic support was 7 days. Seventeen patients (13%) required inotropic support for more than 14 days for right ventricular dysfunction. At 24 hours after implantation of the device, the cardiac index (liters per minute per square meter of body-surface area) increased from a mean (\pm SD) of 2.0 ± 0.6 preoperatively to 2.8 ± 0.7 ($P < 0.001$); at the same time, pulmonary-capillary wedge pressure decreased from 26 ± 8 to 16 ± 5 mm Hg, and mean pulmonary-artery pressure decreased from 37 ± 10 to 26 ± 7 mm Hg ($P < 0.001$ for both comparisons). The average pump flow index was 2.6 ± 0.5 liters per minute per square meter on the first day at a mean pump speed of 9236 ± 496 rpm and increased to 2.8 ± 0.4 liters per minute per square meter at 1 month at a mean pump speed of 9502 ± 525 rpm, with systolic and diastolic arterial blood pressures averaging 96 ± 16 and 73 ± 14 mm Hg, respectively. The international normalized ratio (INR) averaged 2.2 ± 0.7 at 1 month. Values remained relatively stable throughout the support period.

From baseline to 3 months, renal and hepatic function improved during circulatory support, as evidenced in a paired analysis of 67 patients by reductions in levels of serum creatinine (from

Table 1. Baseline Characteristics of the 133 Patients.*

Characteristic	Value	Characteristic	Value
Age — yr	50.1±13.1	Hematologic values	
Male sex — no. (%)	105 (79)	Hematocrit — %	34.8±5.2
Race — no. (%)†		White-cell count — per mm ³	8900±3200
White	92 (69)	Platelets — per mm ³	228,000±86,000
Black	30 (23)	International normalized ratio	1.3±0.4
Body-mass index	26.8±5.9	Concomitant medications — no. (%)	
Body-surface area — m ²	2.0±0.3	Inotropic agents	
Ischemic cause of heart failure — no. (%)	49 (37)	Intravenous	118 (89)
Left ventricular ejection fraction — %	16.3±5.7	Intolerance to inotropic agents owing to arrhythmias	15 (11)
Arterial blood pressure — mm Hg		Two or more inotropic agents	33 (25)
Systolic	95.8±14.6	Diuretic	109 (82)
Diastolic	61.7±11.3	ACE inhibitor	40 (30)
Pulmonary-capillary wedge pressure — mm Hg	26.1±7.9	Angiotensin II–receptor antagonist	7 (5)
Cardiac index — liters/min/m ²	2.0±0.6	Beta-blocker	51 (38)
Heart rate — beats per minute	91.8±18.5	Digoxin	61 (46)
Pulmonary-artery pressure — mm Hg		Hydralazine	25 (19)
Systolic	53.0±14.1	Amiodarone	54 (41)
Diastolic	28.2±8.8	Heparin	84 (63)
Mean	36.5±9.7	Warfarin	2 (2)
Pulmonary vascular resistance — Wood units	3.0±1.5	Aspirin	40 (30)
Central venous pressure — mm Hg	13.5±7.8	Mechanical device — no. (%)	
Right ventricular stroke-work index	564±272	Biventricular pacemaker	64 (48)
NYHA class	IV	Implantable cardioverter–defibrillator	98 (74)
Laboratory values		Intraaortic balloon pump	55 (41)
Serum sodium — mmol/liter	132.9±5.1	Mechanical ventilation	8 (6)
Serum albumin — g/dl	3.7±3.3		
Serum prealbumin — mg/dl	18.8±8.0		
Serum cholesterol — mg/dl	126±41		
Serum creatinine — mg/dl	1.4±0.5		
Estimated creatinine clearance — ml/min	75.1±36.8		
Blood urea nitrogen — mg/dl	31.4±17.6		
Serum alanine aminotransferase — U/liter	104±287		
Serum aspartate aminotransferase — U/liter	67±168		
Serum total bilirubin — mg/dl	1.2±0.8		
Serum lactate dehydrogenase — mg/dl	376±371		

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters. Right ventricular stroke-work index is the blood pressure in millimeters of mercury times the stroke volume in milliliters divided by the body-surface area in square meters. To convert the value for cholesterol to millimoles per liter, multiply by 0.02586. To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the value for bilirubin to micromoles per liter, multiply by 17.1. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

† Race was reported by the patient.

1.4±0.5 to 1.1±0.5 mg per deciliter [124±44 to 97±44 μmol per liter], $P<0.001$), blood urea nitrogen (30.3±16.9 to 18.6±9.8 mg per deciliter [11±6 to 7±3 mmol per liter], $P<0.001$), and serum alanine aminotransferase (48±41 to 32±29 U per liter, $P=0.006$). Most patients who were evaluated at 3 months after device implantation had improvement in at least two NYHA functional classes and improvement in a 6-minute walk test by a distance of more than 200 m (Table 2). Measures of quality of life significantly improved after device implantation on the basis of both survey instruments used ($P<0.001$).

OUTCOMES

All 133 patients were followed for at least 180 days or until either transplantation or death. Of these patients, 100 (75%) reached the principal outcomes of heart transplantation, cardiac recovery, or survival at 180 days with ongoing mechanical support and eligibility for transplantation (Table 3). Of these 100 patients, 56 underwent heart transplantation, 43 continued to receive support and were eligible for transplantation, and 1 did not need transplantation after recovery of cardiac function and explantation of the device (Fig. 2A). Of the 43 patients remaining on device support at 180 days, 32 were on the active list for heart transplantation, and 11 remained eligible for transplantation, including 4 who removed themselves from the transplantation list owing to a preference to continue mechanical support.

Among the 33 patients with unsuccessful outcomes were 25 patients who died before 180 days of support, with a median time to death of 38 days (range, 6 to 144). In addition, five patients became ineligible for transplantation during mechanical support owing to irreversible medical complications, and three patients underwent replacement of the continuous-flow pump with a different type of ventricular assist device (because of surgical complications that occurred shortly after pump implantation) and were withdrawn from the study. Two patients who underwent replacement of the continuous-flow pump with a second identical pump remained in the study, were alive on mechanical support at 216 and 367 days after the replacement, and are included as survivors in the actuarial survival curve. The overall rate of survival to transplantation, recovery, or continued support

with no pump replacement was 75% at 180 days (Table 3).

Overall actuarial survival for patients continuing to receive pump support was 89% at 1 month, 75% at 6 months, and 68% at 12 months (Fig. 2B). The median duration of support was 126 days (range, 1 to 600), with a mean of 168±148 days during a cumulative follow-up of 61.7 patient-years. The median time to transplantation was 97 days (range, 15 to 498), and the median time to cardiac recovery for three patients was 347 days (range, 161 to 380).

Twelve patients (9%) underwent transplantation during their initial hospital stay, and 18 patients (14%) died before discharge while receiving mechanical support. One hundred patients (75%) were discharged from the hospital while receiving mechanical support, with a median hospital stay after surgery of 25 days (range, 10 to 114). The median number of days out of hospital before transplantation, readmission, or death was 60 (range, 0 to 418). Fifty-four discharged patients required rehospitalization for complications, with a median duration of rehospitalization of 4 days (range, 0 to 57).

ADVERSE EVENTS

The most common adverse event was bleeding, primarily in the early postoperative period (Table 4). Eight patients (6%) had an ischemic stroke, and three (2%) had a hemorrhagic stroke. Five of these 11 events occurred within the first 2 days after device implantation. Five additional patients had transient ischemic attacks that were completely reversed. Nine patients were reported to have psychological symptoms. Eight patients had other neurologic events, six of which were completely reversed. Localized infection not related to device implantation occurred in 28% of patients, whereas device-related infection was observed in 14% of patients, with all infections involving the percutaneous lead and none involving the pump pocket. Five devices were replaced: two for pump thrombosis at 24 and 56 days after implantation and three for complications related to surgical implantation at 1, 15, and 32 days (Table 4).

The causes of death in the first 180 days after device implantation included sepsis (five patients), ischemic stroke (five), multisystem organ failure (four), hemorrhagic stroke (three), anoxic brain

Table 2. Functional Status and Quality of Life.*

Variable	Baseline	3 Months	P Value
NYHA functional class			
No. of patients evaluated	133	78†	
Mean class	4.0±0.0	1.9±0.7	
Patients with paired measurements — no.	NA	78	
Class — no. (%)			
I	0	25 (32)	
II	0	40 (51)	
III	0	11 (14)	
IV	133 (100)	2 (3)	
Improvement in functional class in paired measurements	NA	2.1±0.7	<0.001
Distance walked in 6 minutes			
No. of patients performing test	25	56	
No. of patients not performing test			
Unable for medical reason‡	105	13	
For other reason§	3	13	
No. of values included in mean distance	130	69	
Mean distance — m	42±97	292±212	
Patients with paired data¶			
No. of patients	NA	66	
Mean paired change — m	NA	250±232	<0.001
Patients with improved distance >200 m — no. (%)	NA	38 (58)	
Quality of life			
Minnesota Living with Heart Failure questionnaire			
No. of patients completing questionnaire§	114	77	
Mean score	73±25	45±25	
Patients with paired data¶			
No. of patients	NA	61	
Mean paired change in score	NA	-27±26	<0.001
Kansas City Cardiomyopathy questionnaire**			
No. of patients completing questionnaire¶	113	77	
Overall summary score	33±19	57±20	
Clinical summary score	39±22	65±22	
Patients with paired data¶			
No. of patients	NA	60	
Mean paired change in overall score	NA	22±19	<0.001
Mean paired change in clinical score	NA	25±22	<0.001

* Plus-minus values are means ±SD. NA denotes not applicable.

† Of the 82 patients who were alive at 3 months, 4 did not undergo NYHA evaluation because of issues related to staff availability, scheduling, or oversight.

‡ Patients in this category were assigned 0 m in distance walked.

§ Some patients did not perform the indicated tests or complete the questionnaire because of issues related to staff availability, scheduling, or oversight; other patients underwent heart transplantation or died during the interval.

¶ Performance was compared with that at baseline measurement.

|| Scores on the Minnesota Living with Heart Failure questionnaire range from 0 to 105, with higher scores indicating a worse quality of life.

** Scores on the Kansas City Cardiomyopathy questionnaire range from 0 to 100, with higher scores indicating a better quality of life.

DISCUSSION

Table 3. Outcomes of the 133 Patients.*

Outcome	Value
Principal outcomes at 180 days — no. of patients (%)	100 (75)
Heart transplantation†	56 (42)
Cardiac recovery with device explanted‡	1 (1)
Ongoing device support >180 days	43 (32)
On waiting list for transplantation§	32 (24)
Eligible for transplantation¶	11 (8)
Other outcomes — no. of patients (%)	33 (25)
Death at <180 days	25 (19)
Ongoing device support at >180 days but ineligible for transplantation owing to medical issues	5 (4)
Device replaced with another LVAD; patient withdrawn from study	3 (2)
Transplantation, recovery of cardiac function, or ongoing support at 180 days — no. of patients (%)**	105 (79)
With no pump replacement — no. (%)††	100 (75)
Alive with LVAD support — no. ‡‡	
At 1 mo	89±3
At 6 mo	75±4
At 1 yr	68±6
Alive after transplantation — no. (%)§§	
At 30 days	64/68 (94)
At 1 yr	12/15 (80)

* LVAD denotes left ventricular assist device.

† An additional 12 patients underwent transplantation after 180 days.

‡ An additional two patients had recovery with the device removed at 347 and 380 days.

§ One patient subsequently died at 326 days.

¶ Of 11 patients who were eligible for transplantation, 4 removed themselves from the waiting list owing to a preference to continue mechanical support (1 of whom underwent transplantation at 21 months); 3 were not on the list because of inadequate social support and smoking, alcohol abuse, or a failed drug test; 3 had reversible illness (1 of whom subsequently underwent transplantation at 16 months and 1 of whom was on the waiting list at 7 months); and 1 was being evaluated for potential cardiac recovery but was placed on the waiting list at 13 months.

|| Two patients subsequently died at 184 and 191 days.

** This category includes the 100 patients who met the principal outcomes plus 5 patients who remained on device support but were not eligible for transplantation owing to medical issues.

†† This category includes the 105 patients listed above minus 5 patients who received pump replacements (3 who withdrew from the study and 2 who remained in the study on continuous-flow LVAD support).

‡‡ Plus-minus values are means ±SE for actuarial survival.

§§ For patients who reached the stated interval (actual survival).

injury (two, one after a protamine reaction and one after a hemothorax with cardiac arrest), right heart failure (two), and miscellaneous other causes (four). There was one device-related death caused by an inflow graft that was accidentally twisted during implantation.

In this study, we evaluated the use of a continuous-flow left ventricular assist device as a bridge to heart transplantation. We found that this device provided effective mechanical circulatory support in patients with refractory heart failure. Circulatory support with the continuous-flow pump significantly improved the hemodynamic status of patients and was associated with significant improvements in functional status, as assessed with a 6-minute walk test, and in NYHA functional class and quality of life, as measured by both the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires.

The use of a continuous-flow pump was not without the risk of complications. Significant adverse events included postoperative bleeding, stroke, right heart failure, and percutaneous-lead infection. At 6 months, 19% of patients had died while on device support, 4% had medical complications that precluded transplantation, and 2% had had their devices replaced by another type of left ventricular assist device. Although some of these events may be attributable to the severity of the patient's illness rather than to the device itself, they are indicative of the risks faced in this setting.

It has previously been shown that therapy with a left ventricular assist device substantially improves survival in patients with refractory heart failure. In a randomized comparison of patients ineligible for heart transplantation, the survival of patients assigned to ventricular assist support was 52% at 1 year, as compared with 25% for those assigned to medical therapy alone.¹⁵ Although randomized comparisons have not been performed in patients who are mechanically bridged to transplantation, the magnitude of benefit of device support appears to be similar in this population.² We did not perform a direct comparison between patients receiving the continuous-flow pump either with those not receiving any device support or with those receiving a pulsatile-flow device. However, in previous reports involving patients who received pulsatile-flow pumps, approximately 70% of patients survived to transplantation or cardiac recovery.^{2,4,7} In our study, the overall survival of patients who underwent transplantation, recovered cardiac function, or continued to receive mechanical support while remaining a candidate for transplantation was estimated to be 70% at 1 year.

The current FDA-approved devices that have a pulsatile, volume-displacement design have significant limitations related to the size of the device, limited mechanical durability, and adverse events, such as infection. The effort to develop alternative approaches to ventricular assist device support has been in part motivated by these perceived shortcomings of the pulsatile pumps. In our study, adverse events per patient-year with the continuous-flow pump showed an acceptable risk profile, as compared with that reported for a pulsatile-flow pump,² with respect to bleeding requiring surgery (0.78 vs. 1.47 events per patient-year), drive-line infection (0.37 vs. 3.49), stroke (0.19 vs. 0.44), other nonstroke neurologic events (0.26 vs. 0.67), and right heart failure requiring a right ventricular assist device (0.08 vs. 0.30). The higher incidence rate of infection with the pulsatile-flow pump in the previous study may have been related in part to the large diameter of the percutaneous lead (which is 50% larger than that of the continuous-flow pump used in our study) and the absence of a restraining device or belt to limit the movement of the percutaneous lead.

Although continuous-flow pumps may have some advantages over pulsatile pumps, as suggested by these comparisons, the devices also pose new or continuing challenges related to the treatment of patients. These issues include the risk of pump thrombosis and thromboembolism, with the requirement for higher levels of antithrombotic therapy than are required for some pulsatile devices and a consequent risk of bleeding. Infection remains a potential concern, as with all circulatory devices that have a percutaneous component. Mechanical failure may not be totally obviated by continuous-flow pump technology, although it appears to be less frequent than with some pulsatile pumps. Other issues include the need to determine the optimal pump-speed settings to provide sufficient blood flow without ventricular arrhythmias and difficulty in detecting vital signs in a systemic circulation with minimal pulsatility. A previous concern that diminished pulsatile pressure and flow might have unfavorable effects on major organ function has been dispelled,¹⁶ although few patients have received support for very extended periods.¹⁷

Several limitations of our study should be noted. As mentioned above, we did not perform a direct, randomized comparison of the continuous-flow pump with any other device or with medical

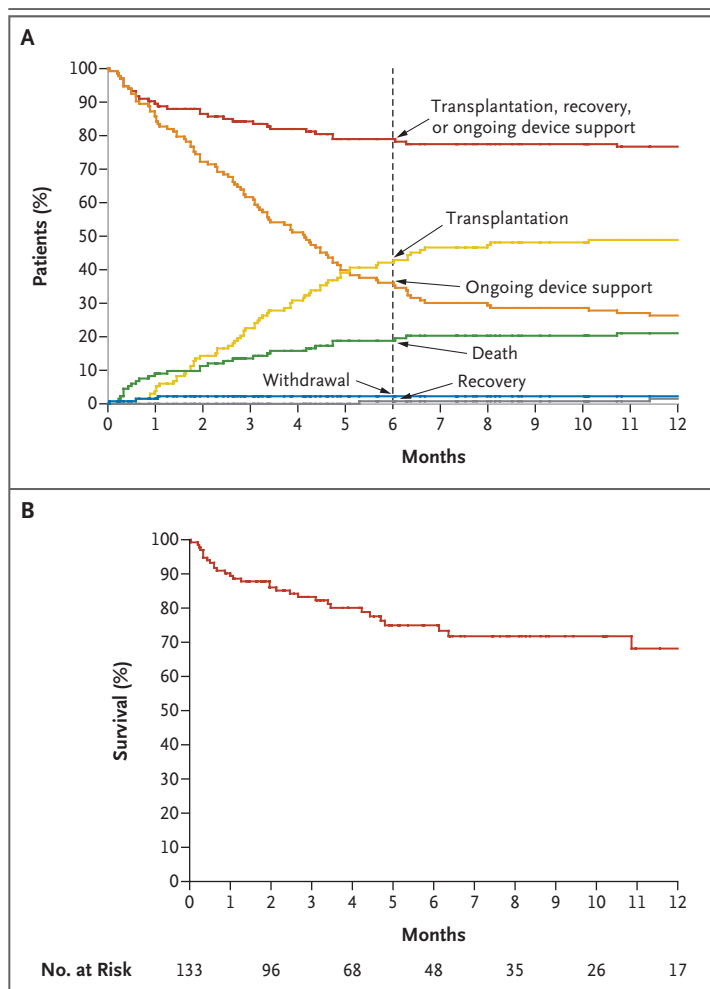


Figure 2. Outcomes for 133 Patients after Implantation of the Continuous-Flow Left Ventricular Assist Device.

Panel A shows all outcomes over time. After 6 months of mechanical support, the outcomes were as follows: 56 patients had undergone heart transplantation (42%); 48 continued to receive mechanical support (36%), 5 of whom were ineligible for transplantation; 25 had died while receiving mechanical support (19%); 3 had withdrawn from the study (2%); and 1 had had recovery of ventricular function after explantation of the device (1%). A total of 105 patients (79%) had undergone transplantation, had undergone explantation of the device with recovery of ventricular function, or continued to receive mechanical support. Panel B shows the Kaplan-Meier analysis of survival for patients who continued to receive mechanical support, with data censored for heart transplantation and recovery of ventricular function. Withdrawal from the study was counted as a death.

management alone, and thus we cannot describe the comparative benefits of this form of therapy. We were not able to assess the functional status and quality of life of all patients in our study, which raises the concern that the estimates of typical benefit with respect to these end points may be subject to ascertainment bias. Finally, a

Event	Overall			0–30 Days			>30 Days		
	Patients with Event (%)	No. of Events	Event Rate per PY	Patients with Event	No. of Events	Event Rate per PY	Patients with Event	No. of Events	Event Rate per PY
Bleeding									
Requiring surgery	41 (31)	48	0.78	40	45	4.41	1	3	0.06
Requiring ≥2 units of packed red cells only	70 (53)	129	2.09	60	85	8.33	10	44	0.85
Ventricular arrhythmias†	32 (24)	49	0.79	24	26	2.55	8	23	0.45
Infection									
Local, not related to device	37 (28)	70	1.13	28	37	3.63	9	33	0.64
Sepsis	27 (20)	38	0.62	18	18	1.77	9	20	0.39
Percutaneous lead	18 (14)	23	0.37	0	0	0.00	18	23	0.45
Pump pocket	0	0	0.00	0	0	0.00	0	0	0.00
Respiratory failure	34 (26)	43	0.70	29	32	3.14	5	11	0.21
Renal failure	18 (14)	19	0.31	15	15	1.47	3	4	0.08
Right heart failure									
Need for right ventricular assist device	5 (4)	5	0.08	4	4	0.39	1	1	0.02
Need for extended inotropic support‡	17 (13)	17	0.28	12	12	1.18	5	5	0.10
Stroke									
Ischemic	8 (6)	8	0.13	5§	5	0.49	3	3	0.06
Hemorrhagic	3 (2)	3	0.05	2	2	0.20	1	1	0.02
Spinal cord infarct	1 (1)	1	0.02	0	0	0.00	1	1	0.02
Transient ischemic attack	5 (4)	6	0.10	2	2	0.20	3	4	0.08
Psychological	9 (7)	11	0.18	6	6	0.59	3	5	0.10
Other neurologic	8 (6)	10	0.16	3	3	0.29	5	7	0.14
Peripheral nonneurologic thromboembolic event	9 (7)	9	0.15	8	8	0.78	1	1	0.02
Device replacement¶	5 (4)	5	0.08	3	3	0.29	2	2	0.04
Device thromboses	2 (2)	2	0.03	1	1	0.10	1	1	0.02
Complications of surgical implantation**	3 (2)	3	0.05	2	2	0.20	1	1	0.02
Hemolysis	4 (3)	4	0.06	3	3	0.29	1	1	0.02
Hepatic dysfunction	3 (2)	3	0.05	2	2	0.20	1	1	0.02

* The cumulative duration of device support was 61.7 patient-years overall, 10.2 patient-years for 0 to 30 days, and 51.5 patient-years for more than 30 days. PY denotes patient-year.

† This event required cardioversion or defibrillation.

‡ The duration of support was for a period longer than 14 days or starting after day 14.

§ All events took place within the first 2 days after implantation.

¶ Devices were replaced with another HeartMate II in two patients and with another left ventricular assist device in three patients.

|| These events occurred on day 24 and day 56.

** Complications included a surgical pledget that was trapped in the pump (day 1), a temporary right ventricular assist device that caused a kink in the outflow graft (day 15), and malpositioning of the inflow cannula (day 32).

comparison of our findings with those of other groups is difficult, in part because the appropriate criteria for selection of patients for ventricular assist remain somewhat subjective.¹⁶⁻¹⁸ The persisting rate of death of 20 to 25% before transplantation seen in our study is similar to previous reports with other pumps and suggests that the selection of patients and the presence of adverse risk factors at the time of device implantation contribute more to adverse outcome than the device used.¹⁶

In conclusion, we evaluated the efficacy of a continuous-flow pump in providing mechanical circulatory support as a bridge to heart transplan-

tation. The results of this study show that effective hemodynamic support for periods of at least 6 months can be achieved with a continuous-flow left ventricular assist device, with improved functional status and quality of life.

Supported by Thoratec. Dr. Miller reports receiving consulting fees from Astellas and lecture fees and grant support from Thoratec; Dr. Russell, consulting fees from Thoratec; Dr. John, grant support from Bayer; Dr. Boyle, consulting and lecture fees from Thoratec; Dr. Conte, grant support from Paracor; Dr. Naka, consulting fees from Terumo Heart, Ventracor, Cardiomechs, and Gerson Lehrman Group Councils (for investment advice related to ventricular assist devices) and lecture fees from Thoratec; Dr. Frazier, consulting and lecture fees from Thoratec, Terumo Heart, and Jarvik Heart; and Dr. Farrar, being an employee of Thoratec and having equity ownership in the company. No other potential conflict of interest relevant to this article was reported.

APPENDIX

In addition to the authors, the following surgeons, cardiologists, and study coordinators participated in this study: *University of Michigan, Ann Arbor* — J. Haft, T. Koelling, B. Dyke, E. Devaney, S. Wright; *Johns Hopkins Hospital, Baltimore* — D. Yuh, S. Ullrich; *University of Minnesota, Minneapolis* — L. Joyce, M. Colvin-Adams, E. Missov, C. Toninato; *Columbia University, Presbyterian Hospital, New York* — K. Idrissi, A. Stewart, E. Rose; *Texas Heart Institute, Houston* — B. Kar, B. Radovancevic, I. Gregoric, F. Smart, A. Civitello, E. Massin, C. Gemmato; *Massachusetts General Hospital, Boston* — A. Agnihotri, J. Madsen, G. Vlahakes, M. Semigran, S. Ennis; *Barnes-Jewish Hospital, Washington University, St. Louis* — N. Moazami, G. Ewald, K. Shelton; *Shands Hospital, University of Florida, Gainesville* — C. Klodell, J. Aranda, N. Staples; *Sacred Heart Hospital, Spokane, WA* — T. Icenogle, J. Everett, M. Pullman; *Duke University Medical Center, Durham, NC* — C. Milano, J. Rogers, A. Lodge, L. Blue; *Ohio State University, Columbus* — B. Sun, D. Feldman, J. Sirak, S. Sudhaker, T. Yanssens; *Medical City Hospital, Dallas* — T. Dewey, M. Magee, M. Mack, A. Anderson, T. Worley; *University of Washington, Seattle* — E. Verrier, D. Fishbein, C. Salerno, G. Aldea, S. Andrus; *University of Pittsburgh Medical Center, Pittsburgh* — R. Kormos, D. McNamara, S. Weaver, K. Zehr; *University of Rochester, Strong Memorial Hospital, Rochester, NY* — T. Massey, L. Chen, W. Hallinan, V. Chiodo; *Hospital of the University of Pennsylvania, Philadelphia* — M. Acker, M. Jessup, R. Morris, S. Desai, M. O'Hara; *Jewish Hospital, Louisville, KY* — L. Gray, R. Dowling, S. Pagni, G. Bhat, P. Adkisson; *Cleveland Clinic Foundation, Cleveland* — N. Smedira, R. Starling, J. Navia, M. Banbury, R. Palumbo, T. Farillo; *St. Luke's Medical Center, Milwaukee* — A. Tector, J. Mendez, B. Pisani, J. Crouch, F. Downey, D. Kress, M. McDonald, D. O'Hair, M. Savitt, M. Miller; *University of Alabama, Birmingham* — J. Kirklín, R. Bourge, D. McGiffin, R. Benza, S. Pamboukian, B. Rayburn, J. Tallaj, S. Kinder; *LDS Hospital, Salt Lake City* — J. Long, S. Horton, D. Renland, J. Revenaugh, M. Eidson; *Sharp Memorial Hospital, San Diego, CA* — W. Dembitsky, B. Jaski, R. Adamson, S. Baradaran, S. Chillcott; *Methodist Hospital-Clarian, Indianapolis* — T. Wozniak, W. Ghumann, M. Turrentine, S. Becka; *Henry Ford Hospital, Detroit* — R. Brewer, B. Czarska, C. Williams, K. Leszczynski; *Sentara Norfolk General Hospital, Norfolk, VA* — J. Rich, J. Herre, L. Pine; and *Baptist Memorial Hospital, Memphis* — E. Garrett, T. Edwards, R. Carter, C. Porter.

Steering/Publication Committee — L. Miller, F. Pagani, O. Frazier, S. Russell, D. Farrar, Y. Naka, M. Slaughter; *Data Safety and Monitoring Board* — C. Yancy, S. Hunt, W. Holman, W. Richenbacher, D. Heijman; *Clinical Events Committee* — S. Moore, V. Jeevanandam, C. Thomas, S. Gordon; *Thoratec, Pleasanton, CA* — L. Damme (study management), J. Heatley (biostatistics), S. Reichenbach (program management).

REFERENCES

- Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112(12):e154-e235.
- Frazier OH, Rose EA, Oz MC, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg* 2001;122:1186-95.
- Deng MC, Edwards LB, Hertz MI, et al. Mechanical circulatory support device database of the International Society for Heart and Lung Transplantation: third annual report — 2005. *J Heart Lung Transplant* 2005;24:1182-7.
- Frazier OH, Rose EA, McCarthy P, et al. Improved mortality and rehabilitation of transplant candidates treated with a long-term implantable left ventricular assist system. *Ann Surg* 1995;222:327-36.
- Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to heart transplantation. *J Thorac Cardiovasc Surg* 1997;113:202-9.
- Portner PM, Jansen PG, Oyer PE, Wheelon DR, Ramasamy N. Improved outcomes with an implantable left ventricular assist system: a multicenter study. *Ann Thorac Surg* 2001;71:205-9.
- Slaughter MS, Tsui SS, El-Banayou A, et al. Results of a multicenter clinical trial with the Thoratec implantable ventricular assist device. *J Thorac Cardiovasc Surg* 2007;133:1573-80.
- Baldwin JT, Robbins RC. Executive summary for the National Heart, Lung, and Blood Institute Working Group on next generation ventricular assist devices for destination therapy. *Semin Thorac Cardiovasc Surg* 2005;17:369-71.
- Frazier OH, Kirklín JK, eds. Mechanical circulatory support. ISHLT monograph series. Vol. 1. Oxford, England: Elsevier, 2006.
- Griffith BP, Kormos RL, Borovetz HS, et al. HeartMate II left ventricular assist system: from concept to first clinical

- use. *Ann Thorac Surg* 2001;71:Suppl 3: S116-S120.
11. Goldstein DJ. Worldwide experience with the MicroMed DeBakey ventricular assist device as a bridge to transplantation. *Circulation* 2003;108:Suppl 1:II-272-II-277.
 12. Frazier OH, Myers TJ, Westaby S, Gregoric ID. Clinical experience with an implantable, intracardiac, continuous flow circulatory support device: physiologic implications and their relationship to patient selection. *Ann Thorac Surg* 2004;77:133-42.
 13. Esmore DS, Kaye D, Salamonsen R, et al. First clinical implant of the VentrAssist left ventricular assist system as destination therapy for end-stage heart failure. *J Heart Lung Transplant* 2005;24:1150-4.
 14. Goldstein D, Zucker M, Pagani FD, Frazier OH. Rotary ventricular assist devices. In: Frazier OH, Kirklin JK, eds. *Mechanical circulatory support*. ISHLT monograph series. Vol. 1. Oxford, England: Elsevier, 2006:77-104.
 15. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
 16. Thalmann M, Schima H, Wiesenthaler G, Wolner E. Physiology of continuous blood flow in recipients of rotary cardiac assist devices. *J Heart Lung Transplant* 2005;24:237-45.
 17. Westaby S, Frazier OH, Banning A, et al. Six years of continuous mechanical circulatory support. *N Engl J Med* 2006;355:325-7.
 18. Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116:497-505.

Copyright © 2007 Massachusetts Medical Society.

COLLECTIONS OF ARTICLES ON THE JOURNAL'S WEB SITE

The *Journal's* Web site (www.nejm.org) sorts published articles into more than 50 distinct clinical collections, which can be used as convenient entry points to clinical content. In each collection, articles are cited in reverse chronological order, with the most recent first.