Heart Failure

Reversal of Severe Heart Failure With a Continuous-Flow Left Ventricular Assist Device and Pharmacological Therapy
A Prospective Study

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Background—We have previously shown that a specific combination of drug therapy and left ventricular assist device unloading results in significant myocardial recovery, sufficient to allow pump removal, in two thirds of patients with dilated cardiomyopathy receiving a Heartmate I pulsatile device. However, this protocol has not been used with nonpulsatile devices.

Methods and Results—We report the results of a prospective study of 20 patients who received a combination of angiotensin-converting enzymes, β-blockers, angiotensin II inhibitors, and aldosterone antagonists followed by the β2-agonist clenbuterol and were regularly tested (echocardiograms, exercise tests, catheterizations) with the pump at low speed. Before left ventricular assist device insertion, patient age was 35.2±12.6 years (16 male patients), patients were on 2.0±0.9 inotropes, 7 (35%) had an intra-aortic balloon pump, 2 were hemofiltered, 2 were ventilated, 3 had a prior Levitronix device, and 1 had extracorporeal membrane oxygenation. Cardiac index was 1.39±0.43 L·min⁻¹·m⁻², pulmonary capillary wedge pressure was 31.5±5.7 mm Hg, and heart failure history was 3.4±3.5 years. One patient was lost to follow-up and died after 240 days of support. Of the remaining 19 patients, 12 (63.2%) were explanted after 286±97 days. Eight had symptomatic heart failure for ≤6 months and 4 for >6 months (48 to 132 months). Before explantation, at low flow for 15 minutes, ejection fraction was 70±7%, left ventricular end-diastolic diameter was 48.6±5.7 mm, left ventricular end-systolic diameter was 32.3±5.7 mm, mVO₂ was 21.6±4 mL·kg⁻¹·min⁻¹, pulmonary capillary wedge pressure was 5.9±4.6 mm Hg, and cardiac index was 3.6±0.6 L·min⁻¹·m⁻². Estimated survival without heart failure recurrence was 83.3% at 1 and 3 years. After a 430.7±337.1-day follow-up, surviving explants had an ejection fraction of 58.1±13.8%, left ventricular end-diastolic diameter of 59.0±9.3 mm, left ventricular end-systolic diameter of 42.0±10.7 mm, and mVO₂ of 22.6±5.3 mL·kg⁻¹·min⁻¹.

Conclusions—Reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved in a substantial proportion of patients with nonpulsatile flow through the use of a combination of mechanical and pharmacological therapy. (Circulation. 2011;123:381-390.)

Key Words: cardiac transplantation ■ cardiomyopathy ■ heart failure ■ heart-assist device

Left ventricular (LV) assist devices (LVADs) are increasingly used to treat patients with advanced deteriorating heart failure (HF). Their principal use to date has been as a bridge to transplantation, and now results have improved enough for their increasing use as destination therapy. Interest is also rapidly developing in the exciting area of using these devices as a bridge to recovery. Unloading of the myocardium with an LVAD has been reported to induce myocardial recovery in small numbers of patients with severe HF. However, it has rarely been thought to be sufficient to allow pump removal and result in sustained good myocardial function.7,8

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We have developed a strategy that combines prolonged mechanical unloading with LVAD support with specific pharmacological interventions first to maximize the incidence of recovery in patients with dilated cardiomyopathy (DCM) and second to improve durability of recovery after explanta-
The strategy is divided into 2 phases. The pharmacological interventions of the first phase are designed to reverse the pathological hypertrophy and remodeling and to normalize cellular metabolic function. This consists of very high doses of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II antagonists, aldosterone antagonists, and digoxin. When maximal reverse remodeling has been achieved, as judged by echocardiographic measurements of LV dimensions with the pump running at minimal speed, the β-blocker is switched to a β1-blocker, and the drug clenbuterol is given as the second phase. Clenbuterol has been shown to induce physiological hypertrophy in several experimental models, including those with pressure-overload hypertrophy.11–13

We have previously used this strategy with the pulsatile Heartmate I device. This resulted in recovery sufficient to allow pump removal in around two thirds of patients with advanced DCM. Furthermore, these patients remained well 5 years later with good quality of life,14 suggesting that this recovery was durable.

Although the pulsatile volume-displacement devices provide excellent hemodynamic support and improved survival, they have many constraints, including the need for extensive surgical dissection, the presence of a large-diameter lead (more prone to infection), an audible pump, the need for medium to large body habitus, and limited long-term durability. These limitations have resulted in a transition to the use of rotary devices. The continuous-flow pumps are smaller and quieter and usually have a less traumatic surgical implantation procedure. They have only 1 moving part, the rotor, and hence are more durable.

However, the hydrodynamic characteristics of pulsatile and continuous-flow VADs vary markedly, and it is not known whether the latter are as effective in promoting myocardial recovery. With continuous-flow devices, the characteristics of unloading are different, testing of underlying myocardial function is more complex, and optimizing medication is likely to be more difficult because of reduced pulse pressure. A strategy of combining pharmacological therapy to promote recovery with the continuous-flow devices has not been evaluated to date. Hence, we have performed a systematic study combining drug therapy with LVAD support in 20 prospective patients with dilated nonischemic cardiomyopathy eligible for bridge to heart transplantation receiving the Heartmate II (HMII) device.

### Methods

#### Patients

The study sample consisted of 20 consecutive patients receiving an HMII LVAD at the Harefield Hospital for nonischemic DCM without histological evidence of acute myocarditis between February 27, 2006, and January 2, 2009, as a bridge to transplantation recruited to this study (Figure 1). The indication for insertion of the LVAD was severe HF not responsive to intensive medical treatment, including inotropic support with or without intra-aortic balloon pump support, with evidence of (impending or actual) multorgan failure caused by low cardiac output. The study was approved by the ethics committee of the Royal Brompton and Harefield NHS Foundation Trust. All patients provided written informed consent. Patients were informed of the existence of the study before implantation, but full informed written consent was obtained in the early postoperative period (once extubated and weaning inotropes). The cohort were followed up until all were explanted, transplanted, or listed for transplantation, and all explanted patients were at least 8 weeks after explantation.

#### Pharmacological Therapy

The pharmacological management consisted of 2 stages. The first stage (intended to enhance reverse remodeling) included 4 drugs initiated immediately after weaning of inotropic support once there was adequate end-organ recovery and titrated (against symptoms, potassium, and renal function) to the following maximum doses: lisinopril 40 mg daily; carvedilol 25 mg 3 times daily; spironolactone 25 mg daily; digoxin 125 μg daily, and losartan 100 mg daily.
The second stage of pharmacological therapy was instituted if the LV end-diastolic diameter (LVEDD) measured with the pump at 6000 rpm for 15 minutes became ≥60 mm. If the LVEDD was still reducing, we waited until maximal regression had occurred. The carvedilol was then stopped and replaced by the selective β1-blocker bisoprolol (up titrated to a maximum of 10 mg daily), and clenbuterol was started at 40 μg twice daily and increased to 700 μg 3 times daily. The dose was titrated to maintain a resting heart rate <100 bpm.

Monitoring Recovery

Echocardiograms were performed before implantation and then monthly after implantation. Postimplantation measurements were obtained with the LVAD at full speed initially, followed by a reduction in pump speed to 6000 rpm in increments of 1000 rpm over 1 to 2 minutes, after changing the low-speed alarm to 8000 if the international normalized ratio was >2 (if below this, 10 000 U intravenous heparin was given first). The study was stopped if the patient became symptomatic. Echocardiographic measurements and images were repeated after 5 and 15 minutes (with the pump at 6000 rpm). Measurements included LV diameters in systole and diastole and ejection fraction (EF; by the single-plane ellipse formula). The LVAD inflow was also assessed for regurgitation. If reduction of LVAD support was tolerated for 15 minutes, a 6-minute walk test was performed with the device still at 6000 rpm, followed by repeated echocardiographic measurements to determine the LV response to exercise (inotropic reserve). Once the patient achieved a 6-minute walk distance of 450 m, a cardiopulmonary exercise test was performed monthly both with the device on and again at 6000 rpm (if the international normalized ratio >2; otherwise, 10 000 U intravenous heparin was given).

Right and left heart cardiac catheterization was performed before implantation and explantation for right atrial, pulmonary artery, and pulmonary capillary wedge (PCWP) pressures, LV end-diastolic pressure, and cardiac output (both thermodilution and Fick) with the device on and at 6000 rpm for at least 15 minutes. Coronary angiography was performed to confirm normal coronaries, together with a left ventriculogram with the LVAD at 6000 rpm for 15 minutes. Dye was injected through the outflow conduit to ensure that there was no significant forward or backward flow at 6000 rpm to verify the reliability of the functional data obtained.

Explantation and Follow-Up

Explantation was considered when the following criteria were achieved with the LVAD at 6000 rpm for 15 minutes: (1) LVEDD <60 mm, LV end-systolic diameter (LVEDS) <50 mm, and EF >45%; (2) LV end-diastolic pressure or PCWP <12 mm Hg; (3) resting cardiac index (CI) >2.8 L \cdot min^{-1} \cdot m^{-2}; and (4) maximal oxygen consumption with exercise (mVO2) >16 mL \cdot kg^{-1} \cdot min^{-1}.

These criteria were considered the minimum for explantation, and if the above parameters were still improving, the combination therapy was restarted rather than bisoprolol. They were titrated as far as possible up to lisinopril 40 mg daily, spironolactone 25 mg daily, digoxin 125 μg daily, carvedilol 25 mg 3 times daily, and losartan 100 mg daily. After explantation, all patients were assessed initially weekly and then at monthly intervals with echocardiograms and cardiopulmonary exercise tests.

Statistical Analysis

Values are expressed as mean±SD (minimum to maximum) unless stated otherwise. Matched pre-LVAD and preexplantation values were compared by use of the Wilcoxon signed-rank test (SPSS, version 16.0, Lead Technologies; SPSS Inc, Chicago, IL). A non-parametric Mann-Whitney U test was used to compare clinical parameters between patients with an HF history of <6 and >6 months and patients who did and did not recover. The Kaplan-Meier method was used to calculate freedom from death and recurrence of HF. A repeated measures ANOVA was performed to determine whether the differences in echocardiographic parameter (LVEDD, LVEDS, EF, fractional shortening [FS]) “responses” at 15 minutes of low speed between recovered and nonrecovered patients are due to data averaging or consistent trends over the support duration. The multilevel time modeling method is described in the online-only Data Supplement.

Results

Characteristics of the Study Population

The study population consisted of 23 consecutive patients who received an HMII LVAD at the Harefield Hospital for nonischemic DCM between February 27, 2006, and January 2, 2009. Three of the patients died early postoperatively (1 at 11 days of a perioperative pulmonary embolus, 1 [a patient with a prior bone marrow transplantation] at 24 days of sepsis, and 1 at 25 days of a cerebrovascular accident). These patients never woke up postoperatively and thus did not provide consent and were not enrolled. The remaining 20 patients were consented for the study. Five patients also received an HMII for ischemic heart disease, and 5 had “other” diagnoses that were excluded from the study (Figure 1): hypertrophic cardiomyopathy (n=1), multiple congenital ventricular septal defect (n=1), Becker muscular dystrophy (n=1), and severe mitral regurgitation (n=2; both had a prolapsing anterior cusp before LVAD implantation with significant mitral regurgitation, and although both patients showed significant improvement in LV function, it was decided before implantation that assessment of LV function would be too unreliable, so they were not included). In addition, during the same period, 1 patient received a Jarvik 2000, 1 received a Thoratec percutaneous ventricular assist device, 3 received a Heartware LVAD, and 2 received a Heartmate I LVAD. Although some of these patients recovered, they were not included or considered for this prospective study, which studied the HMII continuous-flow device.

The Study Sample

Of the 20 patients with DCM receiving an HMII as a bridge to transplantation who were enrolled in the study, 16 were men. The demographics for individual patients are shown in Table 1. Mean age was 35.2±12.6 years (16 to 58 years); all were in New York Heart Association class IV with decompensating HF. They were on a mean of 2.0±0.9 inotropes; 7 (35%) had intra-aortic balloon pump support; 2 were ventilated; and 2 were hemofiltered. Four patients required prior bridging support (because they were considered too sick for initial implantation with a long-term device): 3 with a Levitronix for 52.3±24.3 days and 1 with extracorporeal membrane oxygenation for 6 days. Preoperatively, CI was 1.39±0.43 L \cdot min^{-1} \cdot m^{-2}; PCWP, 31.5±5.7 mm Hg; pulmonary artery saturation, 43.7±12.6%; creatinine, 1.8±1.0 mg/dL (155.5±87.2 μmol/L); and bilirubin, 2.8±1.5 mg/dL (47.1±26.1 μmol/L). Echocardiography showed that preoperative LVEDD was 71.7±8.9 mm (57 to 91 mm), LVEDS was 65.7±7.7 mm (51 to 82 mm), and EF was 14.6±6.6% (7% to 34%). Mean HF history was 3.2±3.5 years (range, 1.5 to 132 months; median, 21 months). Three patients required...
Centrimag) support for a period of 24.3 additional right ventricular assist device (Levitronix dobutamine; Mi, milrinone; BIVAD, biventricular assist device; Hem, haemofiltered; NM, not measured; and ECMO, extracorporeal membrane oxygenation.

Table 1. Preimplantation Characteristics in Chronological Order (by Implantation Date)

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<th>IABP</th>
<th>Ventilated</th>
<th>Preoperative Temporary Support</th>
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<th>LVESD, mm</th>
<th>EF, %</th>
<th>Creatinine, g/dL</th>
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IABP indicates intra-aortic balloon pump; IDCM, idiopathic DCM; FIDCM, familial cardiomyopathy; NAd, noradrenaline; Ad, adrenaline; Dop, dopamine; Dob, dobutamine; Mi, milrinone; BIVAD, biventricular assist device; Hem, haemofiltered; NM, not measured; and ECMO, extracorporeal membrane oxygenation.

*Before bridging device insertion.

addition to right ventricular assist device (Levitronix Centrimag) support for a period of 24.3 ± 9.1 days.

Histological evaluation of tissue obtained at LVAD implantation in all these patients showed interstitial and replacement fibrosis with myocyte hypertrophy, nuclear enlargement, and occasional vacuolated myocytes, compatible with DCM. Microscopy showed no lymphocytic myocarditis.

At the end of phase I therapy, the mean ± SD (minimum to maximum; median) daily doses of the drugs achieved were 31.25 ± 13.7 mg (5 to 40 mg; 40 mg) lisinopril in 18 patients, 37.2 ± 16.3 mg (9.375 to 75 mg; 37.5 mg) carvedilol, 25 mg (25 ± 0 mg; 25 mg) spironolactone, 121.7 ± 14.3 μg (62.5 to 125 μg; 125 μg) digoxin in 19 patients, and 77.8 ± 26.4 mg (50 to 100 mg; 75 mg) losartan in 9 patients. One patient did not receive spironolactone (hyperkalemia), 1 did not receive digoxin (bradycardia), 1 did not receive carvedilol (dizziness but tolerated bisoprolol), 2 did not tolerate lisinopril (severe cough but tolerated losartan), and 11 did not tolerate losartan (already maximally tolerant of other medications). Sixteen patients reached the criteria to receive clenbuterol (once LVEDD was ≤ 60 mm with the pump at 6000 rpm for 15 minutes). Of these, 4 (25%) developed muscle cramps, which resolved, and 2 developed a mild tremor (1 resolved). Once recovered, 2 patients developed ventricular tachycardia on the LVAD, considered to be the result of suction of the pump rather than clenbuterol. The mean clenbuterol dose reached was 1886.3 ± 459.5 μg daily together with 9.4 ± 3.1 mg bisoprolol daily.

Frequency and Characteristics of Recovery

Twelve of the 20 patients (60%) enrolled showed sufficient recovery to meet the explantation criteria described above. One patient (patient 16) who received an LVAD after an 8-year HF history after decompensating on 2 inotropes and an intra-aortic balloon pump recovered well postoperatively but became lost to follow-up. Hence, she did not receive a significant drug or testing protocol. She was then transferred to our center after an out-of-hospital arrest extremely acidic and hypothermic and confirmed brain-stem dead. If she is excluded, then 12 of 19 patients (63.2%) who received the protocol recovered sufficiently to allow pump removal.

One patient (patient 13) who required 58 days of preoperative support with a biventricular assist device (Levitronix) because of end-organ failure before his HMII developed a dense left hemiparesis after his HMII upgrade and biventricular assist device removal. A computed tomography scan showed a large right middle cerebral artery embolism. He recovered well from this event, eventually managed the 6-minute walk and exercise testing, and recovered enough for device explantation after 439 days of LVAD support.

Immediately before explantation in the 12 patients, the mean LVEF (with the pump at 6000 rpm for 15 minutes) was 70 ± 7% (P < 0.005 versus before implantation), FS was 31.9 ± 6.1% (P < 0.005), LVEDD was 48.6 ± 5.7 mm (P < 0.005 versus before implantation), and LVESD was 32.3 ± 5.7 mm (P < 0.005 versus before implantation). With
the pump at 6000 rpm, the mean 6-minute walk distance was
657±75 m and m\(\dot{V}O_2\) was 21.6±4 mL·kg\(^{-1}\)·min\(^{-1}\).

At the end of the phase I therapy and before clenbuterol
was started, the EF was 64.3±6.8\% (pump at 6000 rpm for 15
minutes, \(P=0.3\) versus before explantation), the FS was
29.3±4.7\% (\(P=0.3\) versus before explantation), LVEDD was
50.3±6.1 mm (\(P=0.3\) versus before explantation), LVESD
was 35.2±4 mm (\(P=0.4\) versus before explantation), and
m\(\dot{V}O_2\) at 6000 rpm was 21.0±3.5 mL·kg\(^{-1}\)·min\(^{-1}\) (\(P=0.7\)
versus before explantation). The time course of the LVEDD,
LVESD, FS, EF, and m\(\dot{V}O_2\) measured at 6000 rpm (for 15
minutes) in the 12 patients who recovered is shown in Figures
2 and 3. Time modeling of the serial 15-minute echocardiograms
at 6000 rpm showed that over a period of 1 year,
recovered patients had a reduction in LVEDD and LVESD
(negative slope), whereas in nonrecovered patients, the di-

Dimensions increased (LVEDD, 12.2±2.9 versus 4.3±3.0;
LVESD, 6.8±1.2 versus 2.0±1.5). Similarly, both EF and

Figure 2. Time course of LVEDD, LVESD, FS, and EF at 6000 rpm (for 15 minutes) in recovered patients.

Figure 3. Time course of m\(\dot{V}O_2\), at 6000
rpm in the recovered patients. CVA indicates cerebrovascular accident.
FS at 6000 rpm for 15 minutes increased in the recovered and decreased in the nonrecovered patients over the 1-year period (FS slope, 14.5±3.3 versus −3.4±3.6; EF slope, 22.3±5.9 versus −7.6±6.4; Figure 4). For the 12 patients undergoing device explantation, the number of days of LVAD support was 286±97 (median, 248 days; interquartile range, 334.5–213.75–120.75 days).

Cardiac catheterization before device explantation (at 6000 rpm for 15 minutes) in the 12 patients showed a mean PCWP of 5.9±4.6 mm Hg (P<0.01 versus 28.8±4.8 mm Hg [on inotropic support] before implantation), cardiac output of 6.2±1.4 L/min (P<0.01 versus 2.5±0.8 L/min before implantation), CI of 3.6±0.6 L·min⁻¹·m⁻² (P=0.01 versus before implantation), and pulmonary artery saturation of 68.3±9.7% (P=0.08 versus before implantation). The device was explanted with a minimally invasive technique (previously described) in 7 patients, with a limited median sternotomy and left thoracotomy in 1 patient, and by median sternotomy in 4 patients.

Nonrecovered Patients
The patients who did not recover are shown in Table 2. The first had good echocardiographic data on pump and after 15 minutes at 6000 rpm but developed chest pain during the 6-minute walk and the mVO₂ at 6000 rpm. Furthermore, during cardiac catheterization, her PCWP rose and CI dropped on reduction to 6000 rpm. Patient 16 is described in detail above. The other 6 patients tolerated the testing at 6000 rpm but did not reach explantation criteria as shown in Table 2 (data at the time of listing shown). Three patients were transplanted. All 3 required postoperative Levitronix support for the transplanted heart. The first of these had the posttransplant Levitronix removed after 6 days and remains alive and well. The second patient had the VAD implanted on day 7; it was removed on day 47, but extracorporeal membrane oxygenation was required on day 81, and he died on day 82 after transplantation. The third required mechanical support from the day of transplantation and died 38 days after transplantation. The remaining 4 patients are now listed for transplantation (Table 2); 1 initially showed good recovery, but his myocardial function started to worsen with recurrent driveline infections and deteriorated enough for him to require transplantation listing (patient 14).

A direct comparison of the preoperative parameters in those who did and did not recover is shown in Table 3. A direct comparison of patients with a preoperative history of HF >6 and ≤6 months is shown in Table 4. All 8 patients with symptoms >6 months (1 familial) recovered (2 of which required preoperative ventilation, and 2 required bridging support), and 4 with symptoms >6 months (1 familial) recovered.

Clinical Course and Survival After Explantation
Survival after explantation was 83.3% at 30 days and 1, 2 and 3 years. One patient (patient 8) died 14 days after explantation. He was 21 years of age with familial DCM with signs of good recovery (before explantation after 15 minutes at 6000 rpm: EF, 61%; LVEDD, 41 mm; LVESD, 30 mm; mVO₂, 27.4 mL·kg⁻¹·min⁻¹; cardiac output, 6.4 L/min; CI, 4 L·min⁻¹·m⁻², and PCWP, 6 mmHg) and was explanted after 260 days of support. At explantation, the transesophageal echocardiogram showed new thrombus in the ascending aorta around the coronary sinuses; hence, the aortic root was explored while the pump was run at maximal speed in an attempt to stop the valve opening. However, by the time the root was explored, there was no thrombus remaining. Subsequently, it took several attempts to wean him from cardiopulmonary bypass, and a Levitronix short-term LVAD had to be
inserted. By postoperative day 6, he was weaning from inotropes and extubated. However, he then became septic, which started resolving when he had an intracerebral hemorrhage, and he died on postoperative day 14.

A second patient (patient 7) died 26 days after explantation. He had had reasonable recovery (before explantation at 6000 rpm: mV˙O2, 21.5 mL·kg⁻¹·min⁻¹; cardiac output, 7.06 L/min; CI, 3.4 L·min⁻¹·m⁻²; PCWP, 2.0 mm Hg; pulmonary artery saturation, 70%; EF, 59%; LVEDD, 58 mm; and LVESD, 43 mm) but had recurrent driveline infection (Enterobacter cloacae, Acinetobacter baumanii). He was explanted after 474 days of support once the driveline infections were considered under control. After explantation, he was extubated in the operating room and initially did extremely well. However, on day 3, he was out of bed defecating when he became very sweaty and tachycardic and had a ventricular fibrillation arrest. He required cardiopulmonary resuscitation, reintubation, and extracorporeal membrane oxygenation insertion (postarrest EF, 5%). Unfortunately, he made a poor neurological recovery, and computed tomography suggested ischemic change. Hence, extracorporeal membrane oxygenation was withdrawn, and he died (day 26 after explantation).

Another patient (patient 4) required 7 days of short-term right ventricular assist device support after explantation owing to intraoperative air passing down the right coronary artery. However, she recovered well and is now extremely well and active 690 days after explantation with an LVEDD of 48 mm, an LVESD of 35 mm, and an EF of 61%.

There were no HF recurrences in the remaining 10 patients; hence, the cumulative freedom from death and recurrence of HF in the explanted group was 83.3% at 30 days and 1 and 3 years (Figure 5). Figure 5 also shows the freedom from death, transplantation, or HF recurrence after explantation for all 23 patients with nonischemic cardiomyopathy initially receiving an HMII at our institution who were potentially eligible for the study (including 3 not enrolled).

Follow-Up After Explantation
Follow-up was at least 8 weeks after all patients were explanted, transplanted, or listed for transplantation. After a mean follow-up of 430.7±337.1 days (56 to 1112 days), all 10 surviving patients have remained in New York Heart Association class I with a mean EF of 58.1±13.8%, LVEDD of 59.0±9.3 mm, LVESD of 4.2±10.7 mm, and mV˙O2 of 22.6±5.3 mL·kg⁻¹·min⁻¹. Mean creatinine is 1.3±0.5 g/dL (113±47 μmol/L) and bilirubin is 1.1±0.4 mg/dL (18.7±μmol/L).

Patients were restarted on lisinopril, carvedilol, spironolactone, losartan, and digoxin. Average doses achieved were lisinopril 34 mg (in all patients), carvedilol 28.8 mg (in all patients), digoxin 119 μg (in all patients), spironolactone 25 mg (in 7 of 10 patients), and losartan 75 mg (in 2 of 10 patients).

Discussion
This prospective study has shown that reversal of severe HF secondary to nonischemic cardiomyopathy can be achieved in a high proportion of patients with continuous-flow pumps combined with aggressive pharmacological therapy. To the best of our knowledge, this is the first study to show this result.

Improvement in myocardial function in patients on LVAD support was first shown by Frazier et al, who began successfully explanting these devices. The Berlin group has also successfully explanted patients on LVADs, and some patients now have a long follow-up. However, the incidence of recovery has always been thought to be low. Mancini et al
published a recovery rate of only 5%; other series have shown that 11% to 24% of nonischemic patients recover sufficiently to allow device removal, often including patients with acute myocarditis. Furthermore, the rate of relapse back into HF was relatively high in most series. The rate and durability of recovery in our series using a strategy combining LVADs with drug therapy are significantly higher than previously reported after LVAD support. Patients with a long history of HF were able to recover, although the rate of recovery was higher in those with a short history; this was also seen in the Berlin series but not in our previous Heartmate I recovery series.

The second-generation continuous-flow pumps are being increasingly used. They have only 1 moving part, the rotor, unlike the first-generation devices, and hence are more durable. Prolonged durability allows more time to promote recovery, but it is not yet known whether continuous-flow devices are as effective at unloading and inducing clinical recovery. The data presented here provides evidence that this is the case.

The Texas Heart Institute has recovered several patients with chronic DCM from the HMII device (O.H. Frazier, MD, personal communication). The Berlin group has explanted 5 patients on the Incor device—in some by removing the inlet cannula, in others by plugging it off. In theory, continuous-flow pumps might unload the ventricle less effectively than pulsatile devices, particularly if the pump speed is suboptimal; on the other hand, they unload continuously, whereas the pulsatile pumps are asynchronous with the cardiac cycle and might intermittently load the ventricle. Hence, data from several centers now suggest that continuous-flow pumps can unload enough to recover patients with chronic HF sufficiently to have the device explanted.

The pharmacological interventions of the very high doses of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II antagonists, aldosterone antagonists, and digoxin reverse the pathological hypertrophy and remodeling. Whereas these patients would not tolerate such doses while in decompensating HF because of hypotension and renal failure, once on the device with good cardiac output and restored renal function, they can tolerate them at very high doses. This proved to be the case for patients on continuous-flow pumps despite the reduced pulsatile flow. Once maximal reverse remodeling (as judged by LV dimensions at 6000 rpm) has been achieved, clenbuterol is given to induce “physiological hypertrophy.” Because this combination was given to all recovered patients, the contribution of the clenbuterol is difficult to ascertain, but we believe it enhances the durability of recovery. It is possible that intermittently lowering the pump speed to open the aortic valve and increase myocardial work might be an alternative way to retrain the left ventricle and cause physiological hypertrophy in the future.

We believe that regular testing of myocardial function is crucial to the identification of patients with significant recovery. This necessitates an accurate and safe way of testing function while on mechanical support. We have previously shown that testing patients with the pulsatile Heartmate I device switched off after heparinization is safe and effective at assessing myocardial function, but testing myocardial function in patients with continuous-flow pumps is much more difficult because switching off the device results in backflow of blood through the device back into the LV, much like acute aortic regurgitation. This can be prevented by reducing the continuous-flow LVAD speed to a rate at which there is no forward flow or backflow, thus allowing an

### Table 3. Direct Comparison of the Preoperative Parameters in Those Who Did and Did Not Recover

<table>
<thead>
<tr>
<th>Preoperative Demographic</th>
<th>Recovered and Explanted (n=12)</th>
<th>Did Not Recover (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.5±13</td>
<td>37.8±12</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>10/2</td>
<td>6/2</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Familial DCM</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Inotropes, n</td>
<td>2.3±0.9</td>
<td>1.8±1.2</td>
</tr>
<tr>
<td>Intra-aortic balloon pump, n</td>
<td>3/12</td>
<td>4/8</td>
</tr>
<tr>
<td>Ventilated, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HF history, median</td>
<td>3.5 (1.5–84)</td>
<td>67 (12–132)</td>
</tr>
<tr>
<td>(minimum–maximum), mo*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HMII support, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levitronix</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ECMO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF, %</td>
<td>14.8±6</td>
<td>14.3±6</td>
</tr>
<tr>
<td>EDD, mm</td>
<td>69.2±6.8</td>
<td>74.8±10.6</td>
</tr>
<tr>
<td>ESD, mm</td>
<td>64±6</td>
<td>67±10</td>
</tr>
<tr>
<td>CI, L m−1 m−2</td>
<td>1.4±0.5</td>
<td>1.3±0.5</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>28.8±4.8</td>
<td>35±5</td>
</tr>
<tr>
<td>Creatinine, g/dL</td>
<td>1.5±0.8</td>
<td>1.7±1</td>
</tr>
<tr>
<td>Bilirubin, g/dL</td>
<td>3.0±1.8</td>
<td>2.7±1.5</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>767±785</td>
<td>71±73</td>
</tr>
<tr>
<td>Required RVAD</td>
<td>2/12</td>
<td>1/8</td>
</tr>
</tbody>
</table>

ECMO indicates extracorporeal membrane oxygenation; AST, aspartate aminotransferase; and RVAD, right ventricular assist device.

### Table 4. Outcome and Preoperative Parameters of Patients Presenting With a History of HF ≤6 and >6 Months

<table>
<thead>
<tr>
<th>History of HF, mo</th>
<th>Patients, n</th>
<th>Recovered, n</th>
<th>Age, y</th>
<th>Sex, M/F</th>
<th>Diagnosis</th>
<th>No Inotropes</th>
<th>IABP</th>
<th>Ventilated</th>
<th>Preoperative Support</th>
<th>LVEDD, mm</th>
<th>LVESD, mm</th>
<th>EF, %</th>
<th>Creatinine, g/dL</th>
<th>Bilirubin, g/dL</th>
<th>PCWP, mm Hg</th>
<th>CI, L m−1 m−2</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6</td>
<td>8</td>
<td>8</td>
<td>36.6±11.4</td>
<td>9/3</td>
<td>IABD/FDM</td>
<td>1.8±1.0</td>
<td>5/12</td>
<td>None</td>
<td>IABD/FDM</td>
<td>74.3±9.5</td>
<td>67±8.8</td>
<td>14.8±5.1</td>
<td>2.0±1.0</td>
<td>2.6±1.6</td>
<td>33.2±5.1</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>&gt;6</td>
<td>12</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76.0±5.3</td>
<td>62.3±4.3</td>
<td>14.1±8.8</td>
<td>1.5±0.9</td>
<td>3.2±1.4</td>
<td>27.8±5.8</td>
<td>1.45±0.6</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

IABP indicates intra-aortic balloon pump; FDCM, family history of cardiomyopathy; N/A, not applicable.
accurate assessment. On the basis of a detailed HMII echocardiographic investigation, which has been the subject of a separate study,18 we have found that this occurs when the HMII speed is reduced to 6000 rpm. Therefore, testing was performed at 6000 rpm in this study.

In most centers, LVADs are implanted either as a bridge to transplantation or as destination therapy and the underlying myocardial function is not tested. Thus, they are unlikely to demonstrate or have a very high rate of recovery. Wider testing is likely to reveal more recovery and increased rates of explantation.

Unfortunately, the number of usable donor hearts has been declining over recent years, necessitating an alternative approach for these patients. Furthermore, patients explanted as a result of myocardial recovery avoid the need for immunosuppression and its associated complications and spare the donor heart for another individual. Even if patients should decompensate and require transplantation at a later stage, this approach is likely to extend their overall lifespan considerably.

LVADs are associated with improving survival and reducing complication rates. An increasing number of patients in the future are likely to have these devices implanted as an alternative to transplantation,2 and of these, all patients with nonischemic DCM are candidates for recovery. Furthermore, if LVADs start to be implanted at an earlier stage of HF, it is likely that more patients could recover.

Study Limitations
Although this study was prospective, it has a relatively small number of patients and no control group, making the specific role of clenbuterol difficult to ascertain. In addition, the combination therapy protocol used did not allow evaluation of the specific role of each phase I drug used because these drugs were titrated in parallel.

Conclusion
Our study has shown that a high rate of myocardial recovery from advanced HF can be achieved in patients with the use of a continuous-flow pump combined with drug therapy. We believe that results such as ours should encourage centers to promote and test for recovery.

Source of Funding
This work was supported by an educational grant from Thoratec Corp to Harefield Hospital.

Disclosures
None.

References


CLINICAL PERSPECTIVE

Myocardial recovery sufficient to allow pump removal is thought to be rare after left ventricular assist device support. We have previously shown that a specific combination of drug therapy and left ventricular assist device unloading results in recovery in two thirds of patients with dilated cardiomyopathy receiving a pulsatile device. However, there has been a transition to rotary devices, and this protocol has not been previously used with nonpulsatile devices. We report the results of a prospective study of 20 Heartmate II bridge to transplantation patients receiving a specific drug regimen consisting of a combination of angiotensin-converting enzymes, β-blockers, angiotensin II inhibitors, and aldosterone antagonists to maximize reverse remodeling, followed by the β2-agonist clenbuterol to promote “physiological hypertrophy” to maximize the incidence and durability of recovery. Patients were regularly tested (echocardiograms, exercise tests, catheterizations) with the pump at low speed. One patient was lost to follow-up and died. Of the remaining 19, 12 (63.2%) were explanted. Before explantation at low flow, echocardiographic, exercise test, and hemodynamic data were excellent. Actuarial survival without recurrence of heart failure was 83.3% at 1 and 3 years. Hence, a high rate of reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved with nonpulsatile flow with mechanical and pharmacological therapy. An increasing number of patients in the future are likely to have these devices implanted as an alternative to transplantation, and of these, all with nonischemic dilated cardiomyopathy are candidates for recovery. Our data suggest that using ventricular assist devices as a platform could result in myocardial recovery in a significant number of these patients.
Reversal of Severe Heart Failure With a Continuous-Flow Left Ventricular Assist Device and Pharmacological Therapy: A Prospective Study
Emma J. Birks, Robert S. George, Mike Hedger, Toufan Bahrami, Penny Wilton, Christopher T. Bowles, Carole Webb, Robert Bougard, Mohammed Amrani, Magdi H. Yacoub, Gilles Dreyfus and Asghar Khaghani

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Supplemental Data

Time-modelling analysis method
A multi-level time model analysis was performed using MLwiN version 2.4 for Windows (Centre for Multilevel Modelling, university of Bristol, United Kingdom, http://www.cmm.bristol.ac.uk/). The purpose of modelling is to determine the trends in the 15 minutes “low speed” echocardiographic parameters over a 1-year period. Responses measured included ventricular dimensions and function. The model assumes that for each patient there is a linear relationship between each response and time since operation. The intercept and the slope of this linear relationship are assumed to vary randomly. The intercept indicates the value of the response on day 0 after implant (extrapolated from the linear equation as patients are not tested until ≥1 month post device implantation). The model tested whether the slope is 0, or not with a positive value representing an increase in the response and a negative slope a reduction in the response. The response is the value of each ventricular dimension and function measured echocardiographically whilst the speed of the device is reduced to 6000 rpm for 15 minutes. The model assumes that for each patient there is a linear relationship between the mean of each measured parameter after each test and a 1-year period of support. The equation used for each group was: $y_{ij} = \beta_{0j} + \beta_{1j}t_{ij} + e_{ij}$; where: $y_{ij}$ is the response for patient $j$ after test $i$ (15 minutes low speed), $t_{ij}$ is the time point of the test $i$ (15 minutes low speed), for patient $j$, $e_{ij} = N(0,\sigma^2_e)$, $\beta_{0j} = N(\beta_0,\sigma_{u0}^2)$, $\beta_{1j} = N(\beta_1,\sigma_{u1}^2)$, $\text{cov}(\beta_{0j},\beta_{1j}) = \sigma_{u01}$. $y$ was measured on a monthly to 6 weekly interval so depending on the duration of support the number of $y$ measured for each patient varied. So, $\beta_0$ is the overall mean intercept (i.e. mean response at time 0) and $\beta_1$ is the overall mean slope (i.e. mean change in response per year). As stated in the main text each patient had serial echocardiographic examinations. $\sigma^2_e$ refer to within-patient variability while $\sigma_{u0}^2$, $\sigma_{u1}^2$, and $\sigma_{u01}$ relate to between-patient variability, with the main variance being the exact time-point, to the
nearest day, at which each examination was performed. It is the mean increase in the measured parameters after the 15 minutes “off-pump” test per year which is the main quantity of interest. The mean slope of the relationship refers to the change in the measured parameter over a period of time such that a positive slope indicates an increase in the value and a negative slope indicates a reduction in the value.
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중증 심부전 환자의 새로운 치료 전략:
좌심실 보조장치, 그 희망의 메세지는?

강석 민 교수 세브란스병원 심장내과

Summary

배경
저자들은 확장성 심근증 환자의 약 2/3 정도에서 약물 치료를 병용한 좌심실 보조장치(left ventricular assist device, Heartmate II)의 사용이 좌심실 기능을 유의하게 회복시킨다는 사실을 보고하였다. 그러나 이러한 치료 효과가 비박동식(nonpulsatile) 좌심실 보조장치에서 증명된 바 없다.

병원 및 결과
본 연구는 20명의 비혈액성 심근증 환자를 대상으로 한 임상적 연구로서 안지오텐신 전환효소 억제제, 베타 차단제, 안지오텐신 II 수용체 차단제, 알도스테론 길항제 등의 약물치료와 병용한 비박동식 좌심실 보조장치인 Heartmate II 사용의 효과를 여러 검사(심초음파 검사, 운동허혈검사, 심도자 검사)를 통해 평가하였다. 환자

Figure 1. Time modeling of the 6,000–rpm 15–minute echocardiogram over 1 year.
의 평균 연령은 35.2±12.6세(남자 16명)이었고, 2.0±0.9개의 장치 사용, 대동맥내 흉관 실험 7명(35%), 혈액 투석 사용 2명, 인공호흡기 사용 2명, 이전의 좌심실 보조장치(Levitronix device) 사용 3명, 재외막 산소 치료 1명 등의 과거력이 있었다. 좌심실 박출지수는 1.39 ±0.43L/min/m², 폐동맥 폐쇄압은 31.5±5.7mmHg, 심부전 유병 기간은 34.3±3.5년이었다. 주요이 불가능한 환자가 2명이었고, 남은 19명 중에서 12명(63.2%)이 평균 28±97일 후에 좌심실 보조장치를 제거하였다. 8명에서 6개월 이전에 심부전이 재발하였고, 4명은 6개월 이후에 심부전이 악화되었다. 좌심실 보조장치 제거 직전의 좌심실 구리률은 70±7%, 좌심실 이완기말 직경은 48.6 ±5.7mm, 좌심실 수축기말 직경 32.3±5.7mm, VO₂ max 21.6±4.4ml/kg/min, 폐동맥 폐쇄압은 5.9±4.6mmHg. 좌심실 박출지수는 3.6±0.6L/min/m²이었다. 1년 및 3년 후 재발 없는 심부전의 예상 생존율은 각각 83.3%이었다. 추적기간 동안(430.7±371.1일), 좌심실 보조장치를 제거한 생존자의 평균 좌심실 구리률은 58.1±13.8%, 좌심실 이완기말 직경은 59.0±9.3mm, 좌심실 수축기말 직경 42.0±10.7mm, VO₂ max 22.6±5.3ml/kg/min이었다.

Figure 2. Freedom from death, transplantation (TX), or heart failure recurrence/death after explantation in all 23 patients with nonischemic cardiomyopathy initially receiving an HMII who were potentially eligible for the study, includes the 3 early postoperative deaths in patients subsequently not recruited.
 Commentary

본 연구는 비허혈성 심근경색환자들을 대상으로 절차적인 약물치료와 더불어 시행한 비복통성 좌심실 보조장치의 사용이 대상환자의 약 63%에서 심실 기능을 유의하게 회복시키는 좌심실 보조장치를 제거할 정도로 매우 효과적임을 증명한 최초의 연구이다. 최근 의학의 발전으로 심혈관질환으로 인한 전세계 사망률은 감소하고 있는 추세이며, 국가적 자본과 사람들 사망률은 증가하고 있다. 최근에는 심부전 환자의 혈액학적 상태가 나빠지는 경우 약물만에 의존하는 시대에서 기계적으로 순환을 보조하는 시스템에 의존의 관심이 나아지고 있으며, 실제로 외래에서 암만에서 알기 심부전 환자치료에 적극적으로 사용되고 있다. 이 중에서 좌심실 보조장치는 1978년 Norman 등이 처음으로 사용하여 1983년 5일 후에 심장이식에 성공하며 좌심실 보조장치가 알기 심부전 환자에게 있어 심장이식으로의 교환 약물을 알 수 있다는 희망을 열어 주었다. 그러나 그 이후의 여러 연구 결과를 보면 비복통성 좌심실 보조장치 삽입 후 좌심실 기능 회복률은 매우 낮은 편이었으나 심부전이 악화되는 경우도 매우 높았다. 그러나 근래에 소량의 뉴턴관형명성 비복통성 좌심실 보조장치(Heartmate II, Jarvik, 2000, MicroMed-DeBakey 등)는 뚜렷한 좌심실 보조장치로 병의 크기를 작게 삽입하기가 쉽고, 소유비 저고, 내구성이 좋으며 장기적으로 사용이 가능함으로써 최근에 많이 사용되고 있다. 물론, 혈액학적상의 장점 및 좌심실 회복에 대한 효과에 대해서는 아직 논란의 여지가 있다.

본 연구 대상의 환자의 연령(66-88세)이 실제 임상에서 접하는 심부전 환자의 연령을 고려해 보면 비교적 젊은 연령이었다는 사실이 재확인되며 적절한 또는, 대상 환자의 심장 기능 상태는 대다수 나쁜 상태였으며, 좌심실 보조장치 삽입 후 좌심실 기능 회복률은 70-91%로 본 연구에서 좌심실 보조장치와 더불어 사용한 약물치료 방법이 매우 훌륭한 편이다. 즉, 안지오텔린, 완화효소 억제제, 베타 차단제, 안지오텔린 수용체 차단제, 알로스테라