

ORIGINAL ARTICLE

# Left Ventricular Assist Device and Drug Therapy for the Reversal of Heart Failure

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## ABSTRACT

### BACKGROUND

In patients with severe heart failure, prolonged unloading of the myocardium with the use of a left ventricular assist device has been reported to lead to myocardial recovery in small numbers of patients for varying periods of time. Increasing the frequency and durability of myocardial recovery could reduce or postpone the need for subsequent heart transplantation.

### METHODS

We enrolled 15 patients with severe heart failure due to nonischemic cardiomyopathy and with no histologic evidence of active myocarditis. All had markedly reduced cardiac output and were receiving inotropes. The patients underwent implantation of left ventricular assist devices and were treated with lisinopril, carvedilol, spironolactone, and losartan to enhance reverse remodeling. Once regression of left ventricular enlargement had been achieved, the  $\beta_2$ -adrenergic-receptor agonist clenbuterol was administered to prevent myocardial atrophy.

### RESULTS

Eleven of the 15 patients had sufficient myocardial recovery to undergo explantation of the left ventricular assist device a mean ( $\pm$ SD) of  $320\pm 186$  days after implantation of the device. One patient died of intractable arrhythmias 24 hours after explantation; another died of carcinoma of the lung 27 months after explantation. The cumulative rate of freedom from recurrent heart failure among the surviving patients was 100% and 88.9% 1 and 4 years after explantation, respectively. The quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire score at 3 years was nearly normal. Fifty-nine months after explantation, the mean left ventricular ejection fraction was  $64\pm 12\%$ , the mean left ventricular end-diastolic diameter was  $59.4\pm 12.1$  mm, the mean left ventricular end-systolic diameter was  $42.5\pm 13.2$  mm, and the mean maximal oxygen uptake with exercise was  $26.3\pm 6.0$  ml per kilogram of body weight per minute.

### CONCLUSIONS

In this single-center study, we found that sustained reversal of severe heart failure secondary to nonischemic cardiomyopathy could be achieved in selected patients with the use of a left ventricular assist device and a specific pharmacologic regimen.

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**H**EART FAILURE IS A MAJOR CAUSE OF death and disability in both developed and developing countries.<sup>1,2</sup> The molecular, cellular, biochemical, and structural changes occurring in the myocardium, often referred to as remodeling, have been studied extensively in patients with heart failure.<sup>3-8</sup> One intriguing feature of remodeling is that at least some of its manifestations can occasionally be reversed.<sup>5,9</sup> There is now compelling evidence that prolonged, near-complete unloading of the left ventricle with the use of a left ventricular assist device (a mechanical pump) is associated with structural reverse remodeling<sup>10</sup> that can be accompanied by functional improvement.<sup>11-13</sup> However, recovery that is sufficient to permit explantation of the device has been observed in only 5 to 24% of patients in various series,<sup>14-19</sup> with a relatively high incidence of early recurrence.<sup>17</sup>

To try to increase the incidence and durability of recovery, we have developed a form of combination therapy that consists of a HeartMate left ventricular assist device (Thoratec) and drugs known to enhance reverse remodeling, followed by the use of the  $\beta_2$ -adrenergic-receptor agonist clenbuterol (approved for clinical use in humans in the United Kingdom, Canada, and some European countries but not in the United States). The rationale for this form of therapy has been described previously.<sup>7</sup> We conducted a prospective study of this combination therapy.

## METHODS

### PATIENTS

The study population consisted of patients who received a HeartMate left ventricular assist device at Harefield Hospital, Harefield, United Kingdom, for nonischemic cardiomyopathy, in the absence of histologic evidence of acute myocarditis, and who became clinically stable 4 or more weeks after insertion of the device. The indication for insertion of the left ventricular assist device was the development of severe heart failure that was not responsive to intensive medical treatment, including inotropic support, with evidence of impending or actual multiorgan failure due to low cardiac output. The study was approved by the ethics committee of the Royal Brompton and Harefield National Health Service Trust. All patients provided written informed consent.

### PHARMACOLOGIC THERAPY

Pharmacologic management consisted of two stages. In the first stage (intended to enhance reverse remodeling), treatment with four drugs was initiated immediately after the patient had been weaned from inotropic therapy with adequate end-organ recovery. The four drugs and the maximum titrated doses were as follows: lisinopril, 40 mg daily; carvedilol, 50 mg twice daily; spironolactone, 25 mg daily; and losartan, 100 mg daily.

The second stage of pharmacologic therapy was instituted after maximal regression in the left ventricular end-diastolic diameter had been achieved while the left ventricular assist device was in place. When a constant left ventricular size had been maintained for at least 2 weeks, according to echocardiographic assessment, clenbuterol was administered at an initial dose of 40  $\mu$ g twice daily, then at a dose of 40  $\mu$ g three times daily, and finally at a dose of 700  $\mu$ g three times daily. The dose was adjusted to maintain the resting heart rate at a level below 100 beats per minute. Before clenbuterol was started, carvedilol was replaced by the selective  $\beta_1$ -blocker bisoprolol.

### MONITORING OF RECOVERY

Echocardiography was performed before implantation and then weekly after implantation for the first month, every 2 weeks for 6 months, and monthly thereafter. During the first month, measurements were obtained when the left ventricular assist device was on. After week 4, measurements were obtained both when the device was on and when it was off (after the administration of 10,000 IU of heparin and hand-pumping three times every 15 seconds to prevent blood stagnation inside the pump) at 5 and 15 minutes. We measured the left ventricular diameter during systole and diastole, the ejection fraction (according to the ellipse formula for single-plane volume determination), and the left atrial diameter. The inflow valve of the left ventricular assist device was also assessed for evidence of regurgitation.

If the left ventricular assist device could be stopped for 20 minutes with no ill effects, a 6-minute walking test was performed, with repeated echocardiographic measurements to determine inotropic reserve. Once the patients were able to walk 450 m in 6 minutes while the device was off, with no deterioration of the echocardiographic measurements, cardiopulmonary exercise tests

were performed monthly with the device on and with it off.

Cardiac catheterization was performed before implantation, before the start of clenbuterol therapy, and before explantation. Right-sided and left-sided pressures and cardiac output were measured (with the device on and then off for 15 minutes), and a left ventriculogram was obtained (with the device off).

#### EXPLANTATION AND FOLLOW-UP

Explantation was considered if the following criteria were met while the left ventricular assist device was off for 15 minutes: a left ventricular end-diastolic diameter of less than 60 mm, a left ventricular end-systolic diameter of less than 50 mm, and a left ventricular ejection fraction (LVEF) of more than 45%; a left ventricular end-diastolic pressure (or pulmonary-capillary wedge pressure) of less than 12 mm Hg; a resting cardiac index of more than 2.8 liters per minute per square meter of body-surface area; and maximal oxygen consumption ( $\text{VO}_2 \text{ max}$ ) with exercise of more than 16 ml per kilogram of body weight per minute and an increase in minute ventilation ( $V_E$ ) relative to the production of carbon dioxide ( $\text{VCO}_2$ ) ( $V_E/\text{VCO}_2$  slope) of less than 34.

The device was explanted by means of a minimally invasive technique<sup>20</sup> in all patients except one who had an abscess around the device that extended around the outflow graft. Lisinopril, spironolactone, and losartan were restarted after explantation, but clenbuterol was discontinued. Carvedilol was restarted in place of bisoprolol.

All patients were assessed at our center at monthly intervals with echocardiography, cardiopulmonary exercise tests, and a determination of brain natriuretic peptide concentrations. Catheterization of the right and left heart was performed 3 months and 1 year after explantation. Quality of life was assessed 3 years after explantation according to the score on the Minnesota Living with Heart Failure Questionnaire.<sup>21</sup>

#### STATISTICAL ANALYSIS

Values are expressed as means  $\pm$ SD. Values before implantation and before explantation of the left ventricular assist device were compared with the use of the Wilcoxon signed-rank test (SAS software, release 8.02). A nonparametric rank-sum test was used to assess the effects of age, left ventricular

dimensions, and duration of heart failure on recovery.

## RESULTS

#### CHARACTERISTICS OF THE STUDY POPULATION

Between December 1999 and July 2001, a total of 27 patients underwent insertion of ventricular assist devices at Harefield Hospital. All patients had severe heart failure with evidence of organ dysfunction due to low cardiac output. The bilirubin level was elevated (indicative of hepatic dysfunction) in all patients, and the urinary output was less than 0.5 ml per kilogram per hour despite adequate filling and the use of inotropes (indicative of renal dysfunction) in 20. Of these 27 patients, 3 were excluded from the study because they had ischemic cardiomyopathy.

Of the 24 patients with nonischemic cardiomyopathy, 4 underwent implantation of the device as salvage therapy on compassionate grounds and were excluded from the study. These four patients were in cardiogenic shock while receiving very large doses of at least four inotropes, with combined renal and hepatic failure; three of them had gross acidosis, three required an intraaortic balloon pump, and one required extracorporeal membrane oxygenation. An additional five patients were considered to be potential candidates for the study at the time of implantation of the device but did not complete the course of pharmacologic therapy. Four of these patients died in the perioperative period, and severe abdominal complications developed in one on the eighth perioperative day; he died of disseminated sepsis 138 days after implantation of the left ventricular device, having received low doses of the stage 1 drugs but no stage 2 therapy.

The remaining 15 patients were enrolled in the study and received the combination therapy. The demographic characteristics, diagnoses, duration of heart failure, and care of these patients are shown in Table 1, as are echocardiographic and hemodynamic measurements. Histologic evaluation of tissue obtained during implantation of the device in the 15 patients showed interstitial and replacement fibrosis, with myocyte hypertrophy, nuclear enlargement, and occasional vacuolated myocytes, features that are compatible with dilated cardiomyopathy. Conventional light microscopy showed no lymphocytic myocarditis, but occasional

Table 1. Preimplantation Characteristics of the Patients.\*

Patient No.	Age yr	Sex	Diagnosis	NYHA Class	Heart Failure mo	Inotropic Therapy $\mu\text{g}/\text{kg}/\text{min}$	Intraaortic Balloon Pump	Ventilator Support
1	15	M	IDCM	4	15	Norepinephrine, 0.13; dobutamine, 7.2; and enoximone, 3.1; for 6 days	No	Yes
2	49	M	IDCM	4	156	Dopamine, 3.7; and dobutamine, 7.7; for 25 days	No	No
3	33	F	IDCM	4	24	Dobutamine, 6.2; and dopamine, 2.7; for 3 days	Yes (1 day)	No
4	46	M	IDCM	4	63	Epinephrine, 0.02; and dopamine, 2.6; for 10 days	No	No
5	17	M	IDCM	4	13	Epinephrine, 0.5; and dopamine, 1.85; for 1 day	No	No
6	41	M	Cardiomyopathy after chemotherapy	4	102	Epinephrine, 0.07; dobutamine, 8.7; and dopamine, 6.9; for 10 days	Yes (1 day)	No
7	35	M	IDCM	4	72	Norepinephrine, 0.1; and dopamine, 3; for 4 days	No	No
8	53	M	IDCM	4	129	Dopamine, 2.5; for 14 days	No	No
9	56	M	IDCM	4	120	Dobutamine, 7.7; dopamine, 2.4; and enoximone, 0.2; for 4 days	No	No
10	30	M	IDCM	4	1	Norepinephrine, 0.09; dobutamine, 4.6; dopamine, 3.7; and milrinone, 0.17; for 2 days	Yes (2 days)	Yes
11	25	F	IDCM	4	1	Epinephrine, 0.08; dobutamine, 5; and dopamine, 2.5; for 1 day	No	No
12	41	M	IDCM	4	6	Dopamine, 5; for 1 day	No	No
13	38	F	Postpartum cardiomyopathy	4	1	Dobutamine, 3.1; and dopamine, 1.7; for 1 day	No	No
14	30	M	IDCM	4	12	Dobutamine, 5; for 2 days	No	No
15	17	M	IDCM	4	96	Dopamine, 3; and milrinone, 0.4; for 1 day	No	No

foci of mixed chronic inflammation surrounding damaged myocytes were noted, suggesting inotrope-related myocardial damage.

During the second stage of pharmacologic therapy, when the administration of clenbuterol

was begun, a mild tremor developed in most of the study patients, muscle cramps in four, and diaphoresis in one. No new arrhythmias occurred, although there was a clinically significant increase in the heart rate, as would be expected with

Table 1. (Continued.)

Patient No.	Time from Echocardiography to Implantation <i>days</i>	Left Ventricular End-Systolic Diameter <i>mm</i>	Left Ventricular End-Diastolic Diameter	Ejection Fraction %	PCWP <i>mm Hg</i>	Cardiac Index <i>liters/min/m<sup>2</sup></i>	Device
1	0	60	70	19	14	2.3	HeartMate I
2	3	87	96	< 10	30	1.57	HeartMate I
3	1	56	63	10	24	1.8	HeartMate I
4	25	57	64	19	24	1.8	HeartMate I
5	11	74	81	10	29	—	HeartMate I
6	0	58	65	12	22	1.92	HeartMate I
7	3	71	79	<10	21	2.12	HeartMate I
8	2	76	89	14	12	1.63	HeartMate I
9	5	87	95	<10	32	1.25	HeartMate I
10	1	66	72	<10	38	1.59	HeartMate I
11	1	28	38	15	20	2.57	HeartMate I
12	5	64	71	10	26	1.75	HeartMate II
13	1	64	70	24	—	—	HeartMate I
14	1	69	74	18	30	0.88	HeartMate I
15	0	81	83	<10	27	1.91	HeartMate I
Mean		69.3±10.5	76.6±11	12±6	24.9±7	1.8±0.7	

\* The patients are listed in chronological order according to the date of implantation of the device. NYHA New York Heart Association, PCWP pulmonary-capillary wedge pressure, IDCM idiopathic dilated cardiomyopathy, and dashes not measured.

**Table 2.** Postimplantation Events in the Study Patients.\*

Patient No.	Inotropic Therapy	Duration of Ventricular-Assist-Device Support	Duration of Stage 1 Pharmacologic Therapy† <i>days</i>	Duration of Stage 2 Pharmacologic Therapy‡	Explantation or Transplantation
1	Dopamine, enoximone (3 days)	294	252	38	Explantation
2	Noradrenaline, adrenaline, dopamine, enoximone (2 days)	384	336	45	Explantation
3	Noradrenaline, enoximone, adrenaline, dopamine (7 days)	503	334	161	Explantation
4	Noradrenaline, adrenaline, dopamine, enoximone, isoproterenol (4 days)	413	235	168	Transplantation
5	Adrenaline, dopamine (4 days)	234	169	60	Explantation
6	Adrenaline, dopamine (5 days)	828	199	222	Transplantation
7	Noradrenaline, dopamine, enoximone (5 days)	388	203	179	Explantation
8	Noradrenaline, adrenaline, dopamine, enoximone (5 days)	577	129	442	Explantation
9	Noradrenaline, adrenaline, dopamine, enoximone (2 days)	223	73	147	Explantation
10	Noradrenaline, dopamine, milrinone (4 days)	519	181	221	Transplantation
11	Noradrenaline, adrenaline, dopamine, enoximone (5 days)	101	41	54	Explantation
12	Dopamine, milrinone (2 days)	156	135	18	Explantation
13	Noradrenaline, adrenaline, dopamine, enoximone (2 days)	603	121	428	Explantation
14	Noradrenaline, adrenaline, dopamine (5 days)	63	40	17	Explantation
15	Noradrenaline, dopamine, milrinone (4 days)	601	113	236	Transplantation

a  $\beta$ -adrenergic agonist. Serial measurements of cardiac enzymes were not performed, but serum creatine kinase levels were not elevated in the patients in whom muscle cramps developed. No other side effects were noted.

#### FREQUENCY AND CHARACTERISTICS OF RECOVERY

Of the 15 patients who received a complete course of the combination therapy, 11 (73%) had sufficient recovery to meet the explantation criteria (Table 2). This number represents 46% of all 24 patients

who received a left ventricular assist device for nonischemic cardiomyopathy (including those who did not survive the perioperative period and those who received a device on compassionate grounds). For patients undergoing explantation, the mean duration of support with a left ventricular assist device was  $320 \pm 186$  days (range, 63 to 603). In one patient, explantation was required because of device failure. In three patients, severe infection was present at the time of explantation.

The mean LVEF (with the pump off for 15 min-

Table 2. (Continued.)

Patient No.	Reason for Explantation or Continued Use of Device	Postoperative Follow-up days	Outcome Events	Current NYHA Class <sup>§</sup>
1	Met criteria for explantation, had abscess around device	2058	None	I
2	Met some criteria for explantation, device failed	828	Died of carcinoma 27 mo after explantation	
3	Met criteria for explantation	1790	None	I
4	Had not met criteria for explantation at 403 days	1837	None	I
5	Met criteria for explantation	1963	Underwent transplantation 33 mo after explantation	I
6	Had not met criteria for explantation at 421 days	1	Died from primary graft failure	
7	Met criteria for explantation	1785	None	I
8	Met criteria for explantation	1519	None	I
9	Met criteria for explantation	1767	None	I
10	Had not met criteria for explantation at 402 days, device failed	1454	None	I
11	Met criteria for explantation, device led to infection	1832	None	I
12	Met criteria for explantation	1706	None	I
13	Met criteria for explantation	1	Died 24 hr after explantation	
14	Met criteria for explantation, device led to infection	1760	None	I
15	Had not met criteria for explantation at 349 days	1168	None	I

\* The patients are listed in chronological order according to the date of implantation of the device. Therefore, the sequence of patients is the same as that in Table 1.

† Stage 1 included four drugs that were initiated immediately after the patient had been weaned from inotropic therapy and were gradually increased to the following maximum doses: 40 mg of lisinopril daily, 50 mg of carvedilol twice daily, 25 mg of spironolactone daily, and 100 mg of losartan daily.

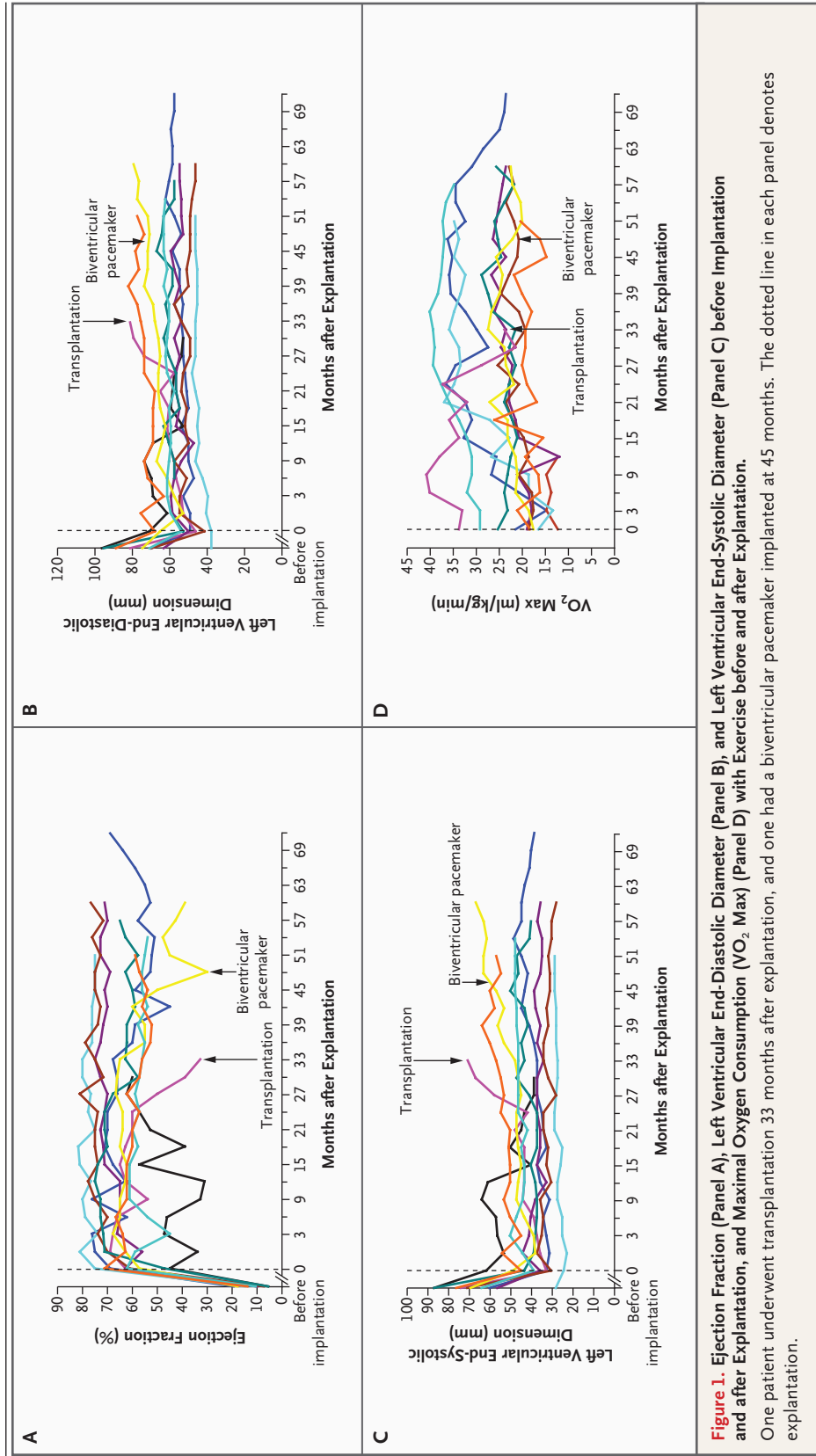
‡ Stage 2 was instituted after maximal regression in the left ventricular end-diastolic diameter had been shown while the left ventricular assist device was in place. Clenbuterol was administered at an initial dose of 40  $\mu$ g twice daily, then at a dose of 40  $\mu$ g three times daily, and finally at a dose of 700  $\mu$ g three times daily.

§ NYHA denotes New York Heart Association.

utes) was  $64 \pm 8\%$  before explantation as compared with  $12 \pm 6\%$  before implantation ( $P=0.001$ ), the mean left ventricular end-diastolic diameter was  $55.9 \pm 8.3$  mm as compared with  $75.1 \pm 16.3$  mm ( $P=0.002$ ), and the mean left ventricular end-systolic diameter was  $39.6 \pm 6.5$  mm as compared with  $66.9 \pm 16.3$  mm ( $P=0.002$ ). Before explantation, the mean walking distance in 6 minutes (with the pump off) was  $632 \pm 231$  m, and the mean  $\text{VO}_2$  max (with the pump off) was  $20.7 \pm 6.1$  ml per kilogram per minute, with a mean  $\text{VE}/\text{VCO}_2$  slope of  $32.5 \pm 7.9$ . Cardiac catheterization before explantation (with the pump off) showed a mean right atrial pressure of  $5.6 \pm 3.4$  mm Hg, a pulmonary-capillary wedge pressure of  $9.0 \pm 4.1$  mm Hg (as

compared with  $23.8 \pm 9.7$  mm Hg during inotropic therapy before implantation,  $P=0.004$ ), a cardiac output of  $5.4 \pm 1.2$  liters per minute, a cardiac index of  $2.8 \pm 0.7$  liters per minute per square meter, and a pulmonary-artery oxygen saturation of  $66.9 \pm 4.8\%$ .

Four patients underwent heart transplantation after completing the full course of combination therapy (Table 2). Transplantation was performed because of lack of myocardial recovery in three patients and the development of appreciable mitral, tricuspid, and aortic regurgitation in one. Although the numbers were too small for meaningful analysis, we found no evidence that age, left ventricular dimensions, or the duration of heart



**Figure 1.** Ejection Fraction (Panel A), Left Ventricular End-Diastolic Diameter (Panel B), and Left Ventricular End-Systolic Diameter (Panel C) before Implantation and after Explanation, and Maximal Oxygen Consumption (VO<sub>2</sub> Max) (Panel D) with Exercise before and after Explanation.

One patient underwent transplantation 33 months after explanation, and one had a biventricular pacemaker implanted at 45 months. The dotted line in each panel denotes explanation.

failure was a determinant of recovery. Of five patients with a left ventricular end-diastolic diameter of more than 80 mm, four recovered.

#### CLINICAL COURSE AND SURVIVAL

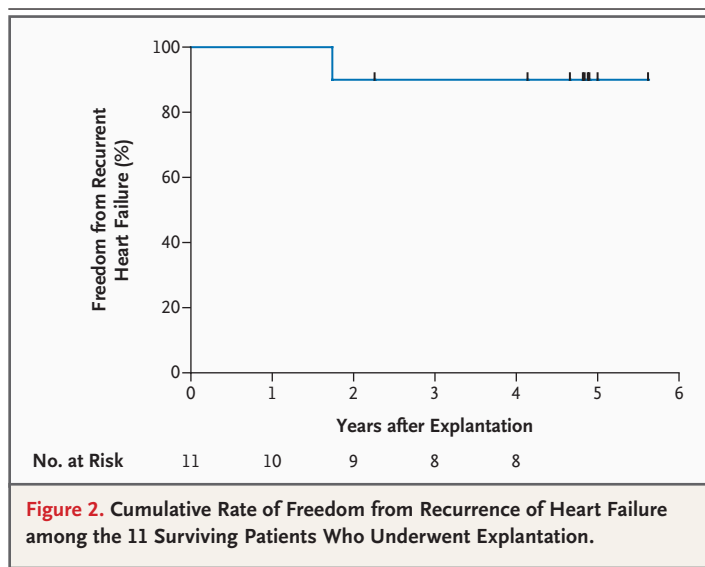
No patient died during the course of combination therapy. The actuarial survival rate 1 and 4 years after explantation was 90.9% and 81.8%, respectively. One patient died of intractable arrhythmia 24 hours after explantation, without evidence of deteriorating ventricular function, and another died of carcinoma of the lung 27 months after explantation. Of the four patients who underwent transplantation because they did not qualify for explantation, one died of primary graft failure in the perioperative period.

The minimum period of follow-up after explantation was approximately 4 years (range, 1519 to 2058 days; mean, 1799±153 days [59±5 months]). All surviving patients continued to be in New York Heart Association class I except one, in whom severe heart failure recurred, with progressive left ventricular dilatation and reduction of the ejection fraction (Fig. 1), after an episode of heavy alcohol consumption 21 months after explantation. He underwent successful transplantation 33 months after explantation. Among the surviving patients, the cumulative rate of freedom from recurrence of heart failure 1 and 4 years after explantation was 100% and 88.9%, respectively (Fig. 2).

The mean score on the Minnesota Living with Heart Failure Questionnaire (scores can range from 0 to 105, with higher scores indicating a worse quality of life) was 12.1±11.7 3 years after explantation. Of the eight patients surviving without a heart transplant, four are working, two are retired and lead very active lives, one is a mother looking after two children, and one does not work despite a normal exercise capacity.

#### ECHOCARDIOGRAPHIC AND LABORATORY DATA

Figure 1 shows the LVEF, end-diastolic diameter, and end-systolic diameter over time after the left ventricular device had been explanted. At a mean follow-up of 59±5 months, the mean LVEF was 64±12%, the mean left ventricular end-diastolic diameter was 59.4±12.1 mm, the mean left ventricular end-systolic diameter was 42.5±13.2 mm, and the mean  $\text{VO}_2$  max was 26.3±6.0 ml per kilogram per minute. An asymptomatic decline in the ejection fraction to 30% occurred in one patient 45 months after explantation (Fig. 1). He underwent implantation of a biventricular pacemaker,



**Figure 2.** Cumulative Rate of Freedom from Recurrence of Heart Failure among the 11 Surviving Patients Who Underwent Explantation.

with a subsequent increase in his ejection fraction to 45%.

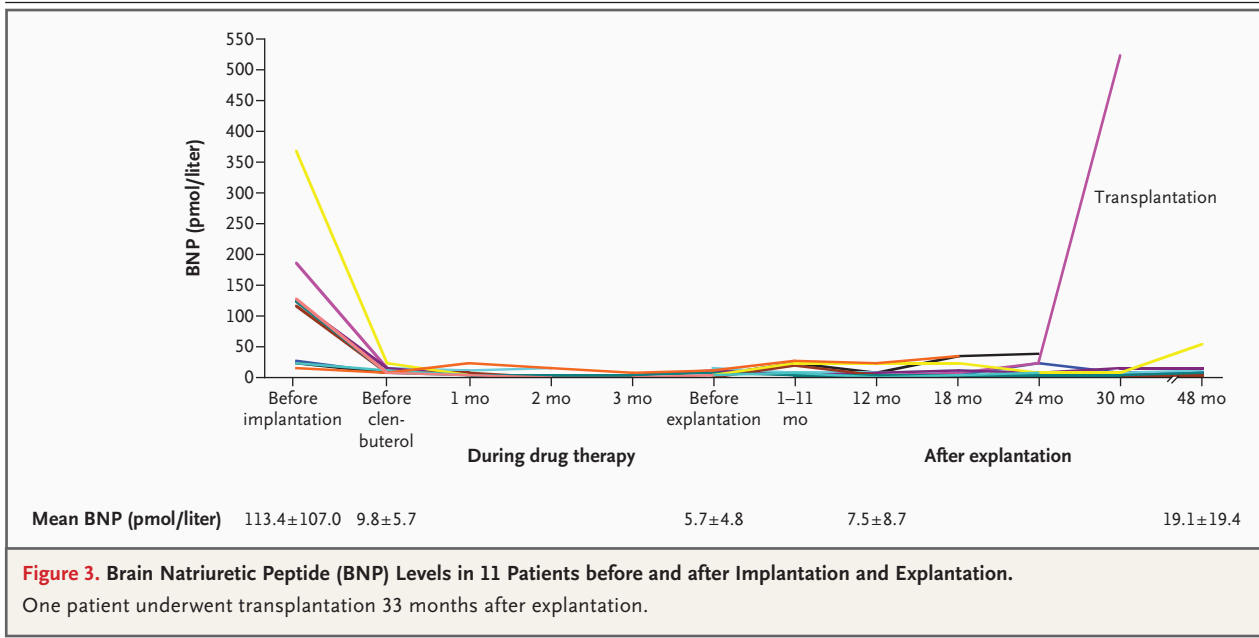
The changes in brain natriuretic peptide levels in the patients who underwent explantation are shown in Figure 3. The mean plasma level fell from 113.4±107.0 pmol per liter before implantation to 5.7±4.8 pmol per liter before explantation, 7.5±8.7 pmol per liter at 12 months, and 19.1±19.4 pmol per liter at 48 months.

#### HEMODYNAMIC VALUES

Among the patients whose devices were successfully explanted, mean hemodynamic values 3 months after explantation were as follows: right atrial pressure, 6.2±2.1 mm Hg; pulmonary-capillary wedge pressure, 12.8±6.9 mm Hg; left ventricular end-diastolic pressure, 12.9±5.9 mm Hg; cardiac output, 4.9±2.1 liters per minute; cardiac index, 2.4±1.0 liters per minute per square meter; and pulmonary-artery oxygen saturation, 69.8±29.9% (10 patients). One year after explantation, mean values were as follows: right atrial pressure, 5.1±3.3 mm Hg; pulmonary-capillary wedge pressure, 9.5±6.2 mm Hg; left ventricular end-diastolic pressure, 9.3±5.5 mm Hg; cardiac output, 4.9±2.1 liters per minute; cardiac index, 2.4±1.2 liters per minute per square meter; and pulmonary-artery oxygen saturation, 73.5±32% (eight patients).

#### DISCUSSION

We found that severe heart failure secondary to nonischemic cardiomyopathy can be reversed in selected patients without acute myocarditis with



**Figure 3. Brain Natriuretic Peptide (BNP) Levels in 11 Patients before and after Implantation and Explantation.**  
 One patient underwent transplantation 33 months after explantation.

the use of a specific sequence of mechanical and pharmacologic therapy.<sup>7</sup> Significant clinical improvement in these patients was associated with improvement in hemodynamics, exercise capacity, and quality of life, along with marked functional changes in the myocardium. Improvement was maintained for more than 4 years in most patients. Quality of life among the patients who underwent successful explantation compared favorably with that among patients with long-term implantation of ventricular assist devices.<sup>21</sup>

In our study, approximately 75% of the patients who received a full course of the combination therapy recovered. The overall rate of recovery among all patients with nonischemic cardiomyopathy who underwent implantation of a left ventricular assist device during this period was 46% at our institution, which may represent an underestimate of the benefit of the combination therapy, since this percentage includes patients who were excluded from the study group, who were not treated with a full course of the study regimen, or both. The rate and duration of recovery in our series were significantly higher than previously reported after implantation of left ventricular assist devices.<sup>14,17-19</sup> The rates in previously published studies were 5%,<sup>14</sup> 24%,<sup>17</sup> and 11% in a larger series<sup>18</sup> that included patients with acute myocarditis. The cumulative rate of freedom from recurrence of heart failure in our series was 88.9% at 4 years. The single patient in our series whose

condition worsened may have had an additional myocardial insult due to alcohol abuse.

The objective of the initial phase of mechanical and pharmacologic therapy is to reverse ventricular remodeling. Mechanical support with a left ventricular assist device has been shown to lead to a reduction in neuroendocrine activation<sup>22</sup> and myocyte hypertrophy.<sup>10</sup> Extensive data from clinical trials show that beta-blockers, angiotensin converting-enzyme inhibitors, angiotensin II-receptor blockers, and aldosterone antagonists can all reduce left ventricular remodeling.<sup>23-26</sup>

The benefit of the second stage of pharmacologic therapy is less firmly established. However, several lines of evidence suggest that selective stimulation of  $\beta_2$ -adrenergic receptors may be beneficial in the setting of heart failure. The highly selective  $\beta_2$ -antagonist ICI 118,551 inhibits contraction of isolated myocytes from patients with severe heart failure by 45% as compared with 5% for myocytes from persons without heart failure,<sup>27</sup> and adenovirus-mediated overexpression of  $\beta_2$ -adrenergic receptors results in improved ventricular function<sup>28</sup> and functional recovery of unloaded heart failure in a rabbit model.<sup>29</sup> Recently,  $\beta_2$ -agonists have been shown to have a beneficial effect on left ventricular remodeling after myocardial infarction in a rat model.<sup>30</sup> Furthermore, stimulation of cardiac myocytes with  $\beta_2$ -agonists seems to provide protection against apoptosis.<sup>31</sup>

The selective  $\beta_2$ -agonist clenbuterol, currently

approved in the United Kingdom for the treatment of asthma, has beneficial effects on excitation–contraction coupling and myocardial metabolism in experimental models.<sup>32,33</sup> In addition, clenbuterol has been found to cause mild myocardial hypertrophy.<sup>34</sup> Such hypertrophy may actually confer a physiological benefit, because studies of myocardial tissue during long-term use of left ventricular assist devices suggest that myocyte atrophy may occur in response to long-term mechanical unloading<sup>10,35,36</sup>; this effect may be prevented or reversed by clenbuterol. The use of  $\beta_2$  adrenergic receptor–agonists has also been shown to increase skeletal muscle strength in normal volunteers<sup>37</sup> and in a small number of patients with muscle weakness due to some forms of myopathy or neurogenic causes.<sup>38</sup>

The potential benefits of clenbuterol in cases of heart failure should be interpreted with caution, because adverse effects of this agent on the myocardium and the skeletal muscle have also been reported in animal models. Apoptosis and necrosis of myocytes have been reported,<sup>39,40</sup> particularly when the drug is given without  $\beta_1$ -blockade.<sup>41</sup> In our study the only adverse effects were mild tremor and muscle cramps. No serious side effects were observed.

Limitations of this study include the relatively small number of patients and the lack of a control group. In addition, the combination therapy used in this protocol did not allow for evaluation of the specific role of each drug used. These issues, as well as the question of which clinical characteristics are predictive of recovery, will need to be evaluated in future studies.

In this study we included two patients with factors that might have influenced their chance of recovery. One patient had received anthracycline,

which may render recovery less likely, and one had a peripartum cardiomyopathy, which is associated with a greater chance of spontaneous recovery than is expected in patients with idiopathic cardiomyopathy (although when these patients have persistently abnormal ventricular function, they face the same relatively poor prognosis as patients with dilated cardiomyopathy from any cause<sup>42</sup>). Cardiac dilatation was present in all patients except one, who had a normal-sized heart in the presence of severe systolic and diastolic dysfunction. This patient had no histologic evidence of myocarditis, with negative results of polymerase-chain-reaction testing for enterovirus (coxsackievirus), adenovirus, parvovirus, and Epstein–Barr virus, although myocarditis can be patchy.

In conclusion, we found that sustained reversal of severe heart failure secondary to nonischemic cardiomyopathy could be achieved in selected patients. Our regimen of mechanical and pharmacologic therapy may enhance the frequency and durability of myocardial recovery as compared with other therapeutic approaches, although a direct comparison of treatment protocols was not performed. The reproducibility and durability of these findings, as well as the mechanisms contributing to the findings, require further study in different groups of patients.

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