CARDIOPULMONARY SUPPORT AND PHYSIOLOGY

MIDTERM FOLLOW-UP OF PATIENTS WHO UNDERWENT REMOVAL OF A LEFT VENTRICULAR ASSIST DEVICE AFTER CARDIAC RECOVERY FROM END-STAGE DILATED CARDIOMYOPATHY

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Objective: Cardiac recovery in end-stage idiopathic dilated cardiomyopathy recently occurred after temporary support with a left ventricular assist device. We report the case histories of patients who underwent removal of the device more than 4 years ago.

Methods: Since June 1994, 23 patients with end-stage idiopathic dilated cardiomyopathy who were supported by a left ventricular assist device or biventricular assist device for 1 to 26 months (mean, 6 months) underwent removal of the device after complete or extensive cardiac recovery, as revealed by echocardiography.

Results: Seven patients (group A) had recurrent cardiac failure after 4 to 24 months. Transplantation was performed in 6 patients, and one died while on the waiting list. Three patients died of noncardiac causes within a period of 4 months and 3 days after removal of the assist device. Stable cardiac recovery occurred in 13 patients (group B) for 3 to 49 months (mean, 23 months). At the time of implantation, there were no significant differences between the groups with regard to age, hemodynamics, left ventricular ejection fraction, left ventricular internal diameter in diastole, and autoantibody levels. The increase of ejection fraction and the decrease of left ventricular internal diameter in diastole after 2 months were highly significant. The patients in group A had longer histories of heart failure and first cardiac symptoms and duration of assist when compared with group B. Group B demonstrated a quicker cardiac recovery on the assist device, and thus support was shorter. Also, the degree of recovery at assist device explantation was more complete in group B. The age at the time of device placement was the only influencing factor for duration on the assist device. The probability of recurrence of heart failure was influenced by the duration of heart failure.

Conclusions: In selected patients with idiopathic dilated cardiomyopathy, lasting recovery can be achieved after unloading with a left ventricular assist device. Lasting cardiac recovery seems to be related to functional normalization and a more rapid recovery during the unloading period. (J Thorac Cardiovasc Surg 2000;120:843-55)

In a subset of patients with end-stage idiopathic dilated cardiomyopathy (IDC) who required a mechanical cardiac assist device, we recently found that removal could be conducted without transplantation after the recovery of cardiac function.^{1,2}

In contrast to the past, when analysis of cardiac tissue was done when cardiac function had severely deteriorated, the use of cardiac assist devices has enabled us for the first time to examine myocardial tissue at the time of considerably deteriorated cardiac function and

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Table I. Patient demographic data and follow-up observations

Patient No.	Year of implantation	Duration on assist support (d)	Type of assist device	Follow-up observation	Group (A, B, or C)
1	1994	160	Novacor LVAD	Persistent recovery since 4 y, working	B
2	1994	243	Novacor LVAD	Persistent recovery since 45 mo, working	B
3	1994	347	Novacor LVAD	Persistent recovery, died after 2.5 y because of chronic infection of left ventricular apex	B
4	1995	200	TCI LVAD	Persistent recovery since 41 mo, working	B
5	1996	200	Novacor LVAD	Recurrent heart failure, died after 2 y during left heart catheter	A
6	1994	794	Novacor LVAD	Recurrent heart failure, LVAD (Berlin Heart) after 7 mo, heart transplantation	A
7	1996	66	Novacor LVAD	Died after 4 mo, pulmonary embolism	C
8	1996	201	Novacor LVAD	Recurrent heart failure, heart transplantation	A
9	1996	30	Novacor LVAD	Persistent recovery since 26 mo	B
10	1996	67	Novacor LVAD	Persistent recovery since 26 mo, working	B
11	1996	233	Berlin Heart BVAD	Recurrent heart failure, heart transplantation after 17 mo	A
12	1996	418	Novacor LVAD	Recurrent heart failure, heart transplantation after 6 mo	A
13	1996	105	Novacor LVAD	Died after 8 d, pulmonary bleeding	C
14	1996	181	TCI LVAD	Recurrent heart failure, heart transplantation after 4 mo	A
15	1997	62	Novacor LVAD	Persistent recovery since 21 mo, working	B
16	1997	51	Novacor LVAD	Persistent recovery since 21 mo	B
17	1997	83	Novacor LVAD	Recurrent heart failure, heart transplantation after 7 mo	A
18	1997	74	Novacor LVAD	Persistent recovery since 19 mo, working	B
19	1997	36	Novacor LVAD	Persistent recovery since 18 mo, working	B
20	1997	54	Novacor LVAD	Died after 3 d, septic shock	C
21	1997	48	Novacor LVAD	Persistent recovery since 14 mo, working	B
22	1998	62	Novacor LVAD	Persistent recovery since 12 mo, working	B
23	1998	224	TCI LVAD	3 mo without LVAD, stable	B
Mean		171			
Range		30-794			
SD		174.6			

Group A, Recurrence of heart failure (n = 7); group B, lasting cardiac recovery (n = 13); group C, death after weaning (n = 3).

subsequently when cardiac function has been improved as a result of mechanical decompression of the heart. Therefore, discussion has focused on several questions, which have opened up a host of new and ongoing research activities. The interesting questions that arise today are as follows:

1. Which type of assist system and ventricular unloading modus would allow recovery?
2. What degree of recovery reached during the assist period is consistent with the prospect of durably restored cardiac function?
3. What kind of medication would support the maintenance of the once-reached cardiac recovery state?
4. What type of myocardial disease is amenable to cardiac recovery? In particular, could this be an IDC or rather chronic myocarditis?³⁻⁵
5. What are the molecular changes of the myocardium after the heart has recovered with the aid of mechanical unloading?⁵

Although questions 4 and 5 await a future that is dependent on larger patient numbers and increased

intensity of research in this field, at least the initial doubts as to whether cardiac recovery might last for a longer period can be answered positively on the basis of our present experience with 23 such patients whose clinical status after device removal is outlined in this report.

Patients and methods

Between June 1994 and January 1999, 84 patients with end-stage heart failure were supported with either a Novacor (n = 63; Baxter Healthcare Corp, Novacor Division, Oakland, Calif) or a TCI (n = 21; Thermo Cardiosystems, Inc, Woburn, Mass) left ventricular assist device (LVAD).

Of this cohort, 65 patients had IDC, and 19 had ischemic cardiomyopathy. Patients with ischemic heart disease were excluded from the study. Of the group with IDC, 23 underwent removal of the LVAD when cardiac function had undergone complete or near-complete restoration during a decompression period of between 30 and 794 days.

The 42 patients with IDC who did not attain cardiac functional improvement to near normal values were also excluded from the study. At the time of device placement, these 42

Table II. Patient hemodynamic characteristics and autoantibodies at the time of assist device placement

Patient No.	Sex	Age at implant (y)	First cardiac symptoms (y)	Manifest heart failure (y)	Preimplantation status			
					Inotropic drugs	CI ($L \cdot \min^{-1} \cdot m^{-2}$)	Mean PAP (mm Hg)	Autoantibodies (LU)
1	M	38	4	1	Dopamine, dobutamine	1.5	36	5.9
2	M	42	2	2	Dopamine, dobutamine	1.4	38	7
3	M	58	4	1	Dopamine, dobutamine	1.4	40	7
4	M	52	4	4	Epinephrine, dopamine, dobutamine, phosphodiesterase inhibitor	1.5	33	5.2
5	M	55	7	4	Dopamine, dobutamine	1.5	34	8.2
6	M	37	5	<1	Dopamine, dobutamine	1.9	28	5.4
7	M	36	4	4	Dopamine, dobutamine, epinephrine	1.8	41	6.1
8	M	47	>13	13	Epinephrine	1.7	37	5.5
9	M	32	3	3	Dopamine, dobutamine	1.8	31	4
10	M	42	1	1	Dopamine, dobutamine	2.0	33	4.2
11	M	53	12	7	Dopamine, epinephrine	1.9	35	7.1
12	M	61	30	8	Dopamine, epinephrine	1.8	31	3.4
13	F	58	9	2	Dopamine, dobutamine	1.7	34	5.4
14	M	64	5	3	Dopamine, dobutamine	1.4	45	2.9
15	M	43	6	4	Dopamine, dobutamine	1.6	18	4.4
16	M	41	4	1	Dopamine, dobutamine	1.5	24	5.5
17	M	35	24	17	Epinephrine, dopamine, phosphodiesterase inhibitor	1.4	47	8.3
18	M	42	1	1	Epinephrine	1.1	31	6.4
19	M	22	1	1	Dopamine, dobutamine, phosphodiesterase inhibitor	2.2	43	4.6
20	M	18	1	1	Dopamine	1.8	38	6.5
21	M	31	<1	<1	Dopamine, dobutamine	2.2	31	4.6
22	M	41	>1	1	Dopamine, dobutamine	1.9	37	5.3
23	M	56	10	2	Dopamine, dobutamine	1.7	32	5.2
Mean		43.7	6.6	3.7		1.7	34.7	5.6
Range		18-64	<1-30	<1-17		1.1-2.2	18-47	2.9-8.3
SD		12.1	7.4	4.2		0.27	6.52	1.4

CI, Cardiac index; PAP, pulmonary artery pressure.

patients showed a mean left ventricular ejection fraction (LVEF) and a left ventricular internal diameter in diastole (LVIDd) of $17\% \pm 5\%$ and 77 ± 10 mm, respectively.

During follow-up, they improved to mean optimal left ventricular values of LVEF ($35\% \pm 8\%$) and LVIDd (59 ± 6 mm), which seemed to us to be insufficient for removal of the assist device.

There were 22 men and 1 woman with ages at the time of LVAD implantation that ranged from 18 to 64 years. All had some, mostly insignificant, symptoms of cardiac disease that dated back to between 1 and 30 years previously. The history of manifest heart failure was quite variable and ranged from 6 months to 17 years (Table I).

At the time of LVAD implantation, the patients had invariably reached a state of conventionally untreatable heart failure, and they were receiving intravenous inotropic medication, predominantly dopamine and dobutamine, which in some instances was combined with phosphodiesterase inhibitors, or epinephrine. No lasting improvement was observed despite such medication. Hemodynamic data

revealed elevated pulmonary artery pressures and a depressed cardiac index LVIDd that ranged from 62 to 92 mm and severely impaired ventricular function with LVEF data of between 10% and 20% (Table II). Implantation of an LVAD was decided on as an emergency procedure in all patients, with the primary goal of keeping the patient alive until a later cardiac transplantation could be performed.

Nineteen patients received a Novacor 100 system (Baxter), one patient received an air-driven TCI HeartMate 1000 IP system (Thermo Cardiosystems, Inc), two patients received an electrically driven TCI HeartMate 1000 vented electric system, and one, who needed biventricular support, received the pneumatically driven Berlin Heart system (Mediport Kardiatechnik, Berlin, Germany) with a trans-left atrial-transmitral cannula, which directly drained the left ventricle.

After assist device implantation, repeated transesophageal echocardiography was performed by the same operator, and the cardiac dimensions and the ventricular functions were measured. When improvement of LVIDd

Table III. Patient echocardiographic data

Patient No.	Echocardiography					
	LVEF (%)					
	Before assist device	After 2 mo	Before explantation	After explantation	Latest died or listed for transplant	Present permanent recovery
1	15	65	55	50		49
2	15	40	45	45		51
3	10	35	48	45	45	
4	12	35	45	48		50
5	15	33	41	43	33	
6	15	30	35	38	28	
7	14	50	47	47	40	
8	16	40	40	36	31	
9	15	*	50	50		33
10	17	49	44	50		37
11	18	35	38	37	20	
12	20	24	40	35	32	
13	18	30	40	45	45	
14	20	40	40	35	17	
15	15	49	49	49		45
16	15	49	49	50		43
17	15	47	47	41	25	
18	15	44	44	45		35
19	20	*	45	50		50
20	15	60	60	53	53	
21	15	50	50	50		49
22	19	48	48	58		49
23	10	39	50	50		50
Mean	15.6	42.5	45.7	45.7	33.5	45.1
Range	10-20	24-65	35-60	35-58	17-53	33-51
SD	27	10.1	5.7	6.2	11.2	6.5

*The assist system of patients 9 and 19 were explanted after 30 and 36 days, respectively.

and LVEF was noted, the investigations were repeated during short periods of pump halt of up to 20 minutes, with one single pump stroke every 20 seconds. Once the decision for LVAD explantation had been made, all the patients with the Novacor and TCI devices had their pumps reprogrammed to a fixed-rate pumping mode on the assumption that this would exert some load on the left ventricles and train them before explantation.

The prospect of elective pump explantation was taken into consideration when, on repeated investigation, the LVIDd had dropped below 60 mm and the LVEF had risen to more than 40%. This was the case in patients 1 to 5, 8 to 10, 12, 13, 15 to 17, and 20 to 23. Elective explantation was performed in all after between 1 and 14 months (mean, 5 ± 4 months) of assist duration.

In patients 6, 7, 11, 14, 18, and 19, complications derived from the assist systems prompted us to remove the assist device, although the degree of recovery was not considered optimum in every instance (patients 6, 11, and 14). Thus, explantations were performed after 36 to 181 days (mean, 89 ± 34 days) of assist support.

The procedure of assist device removal was based on the principle of leaving the heart as unmolested as possible. Thus, for the patients with Novacor and TCI devices, the pump housing pocket in the left upper abdominal wall quadrant was entered, the inflow and outflow cannulas were transected in their Dacron graft portion, the pump was removed, and the remainder of the cannulas leading to the left ventricular apex and to the ascending aorta were left in place and securely oversewn. In the patients with a TCI device, an additional left-sided thoracotomy was performed to reach the Dacron part of the otherwise titanium-covered inflow cannulas. In the patient with a biventricular assist device (BVAD) and a transmitral cannula, re sternotomy was performed, and the cannulas were removed without extracorporeal circulation.

After assist device explantation, the patients began taking anticoagulants (Coumadin) for 6 months because the cannulas had been left in situ, and it was assumed that the apex cannula might become an origin of thromboembolism. In addition, β -blocker angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists were administered permanently.

<i>Echocardiography</i>					
<i>LVIDd (mm)</i>					
<i>Before assist device</i>	<i>After 2 mo</i>	<i>Before explantation</i>	<i>After explantation</i>	<i>Latest died or listed for transplant</i>	<i>Present permanent recovery</i>
72	42	48	58		58
70	50	46	48		51
70	64	54	56	61	
69	47	49	52		54
78	42	43	56	58	
74	60	64	55	68	
77	52	42	43	55	
72	59	64	67	68	
73	*	40	41		66
77	60	55	60		72
84	65	52	62	80	
84	54	66	68	72	
68	57	51	50	50	
77	53	66	67	75	
83	55	59	60		65
64	55	55	54		59
82	56	56	59	77	
93	54	54	58		67
81	*	48	51		56
62	40	40	54	54	
78	50	50	53		55
67	55	55	54		56
81	59	50	50		56
75.5	53.8	52.5	55.5	65.3	59.6
62-93	40-65	40-66	41-68	50-80	51-72
7.4	6.8	7.8	6.9	10.2	6.4

Before, during, and after the assist period, a spectrum of studies were conducted into the morphology of the myocardium, the immunohistology, and the autoantibodies against cardiac structures and the mediators of IDC. Because none of the data of these studies have reached a state where they could provide convincing predictors of the potential for myocardial recovery, they will be presented at a later time on the basis of larger data numbers.

Three groups were formed because of the clinical need of further interventions as a result of recurrence of heart failure (group A), stable clinical status (group B), and death of the patients (group C, Table I).

Statistical analysis. Our statistical model contained 2 dependent variables (LVEF and LVIDd) and 3 independent variables (group allocation, age at the time of device placement, and repeated measures).

Analysis of variance (ANOVA) was performed to calculate the significance of the independent variables. We used the Duncan multiple-range test as a mean separation test. Because the requirements for ANOVA were not completely satisfied in all variables, the results of the ANOVA were confirmed by

means of a nonparametric test (Kruskal-Wallis). The results of repeated measures were confirmed by use of the Wilcoxon test.

A Cox model was developed to test for variables that influence the time with an assist device and the recurrence of heart failure.

Results

Of the 23 patients, 13 have since had stable cardiac function without any signs of deterioration of echocardiographic data both in left ventricular dimensions and in LVEF in the majority. In 3 patients of this group (patients 9, 10, and 18), some decline of cardiac function parameters has been observed, although without clinical relevance to date (Table III).

Cardiac stability has now been observed for between 3 months and 4 years (mean, 23 ± 14 months) as of April 1999. This has been seen in 3 patients for more than 3 years, in 11 for longer than 1 year, and in 1 for a shorter time. In some instances (patients 2 and 4) fur-

Fig 1. Mean LVEF and LVIDd at the time of implantation (*pre-assist*), 2 months after device placement (*after 2 months*), before explantation (*pre-explant*), and 1 week after device removal (*post-explant*).

Fig 2. Differences in mean LVEF and LVIDd before and after device placement with regard to the 4 age groups.

ther improvement of cardiac function was noted, even after removal of the assist device (Table III).

Seven patients had recurrent heart failure 4 to 24 months (mean, 11 ± 7 months) after pump explantation. In 1 patient (patient 6) another assist system (Berlin Heart LVAD from the left ventricular apex to the descending aorta) had to be implanted by means of a left thoracotomy in an emergency situation. This patient and patients 8, 11, 12, 14, and 17 underwent heart transplantation between 4 and 17 months after removal of the assist device.

Four patients died of causes unrelated to heart failure, 1 patient (patient 20) on day 3 after pump removal because of septic shock, 1 (patient 13) on day 8 from massive pulmonary bleeding, 1 (patient 7) after 4 months as a result of a pulmonary embolism, and 1

(patient 3) after 2.5 years because of a severe infection of the myocardium at the site of the apical cannula. The 3 patients who died within 4 months of device removal were excluded from the comparison and statistical analysis.

In patients 2 to 4, in whom chronic infections of the pump pocket had been observed, chronic suppuration and fistulas recurred, which required secondary removal of the ascending graft in patients 2 and 4 after 21 and 20 months, respectively, and removal of the apical cannula in patients 3 and 4 after 21 and 20 months, respectively. Whereas in patients 2 and 4 the further course has since been uneventful for 45 and 41 months, respectively, chronic apex infection in patient 3 led to recurrent sanguination that necessitated two successive emergency operations. The patient died of the sequelae

Fig 3. Differences in mean LVEF and LVIDd before and after device placement with regard to group A (recurrence of heart failure), group B (lasting recovery), and group C (death after weaning unrelated to cardiac function).

Fig 4. Differences in mean LVEF and LVIDd before device removal and 1 week thereafter with regard to the 4 age groups.

after a catastrophic hemorrhage, even though he still had well-preserved cardiac function up to the very end.

An ANOVA for the time before and after device placement (repeated measures) with LVEF and LVIDd as dependent variables showed statistical significance for both parameters ($P = .0001$). After 2 months, there was a significant increase of LVEF and a significant decrease of LVIDd (Fig 1).

For LVEF, the factor age classes (18-35, 36-45, 46-55, and 56-64 years of age) showed no significance before implantation. Two months after implantation, factor age classes showed an overall significance ($P = .0002$, Fig 2). Those patients who were younger than 46 years of age had significantly higher values for LVEF than the older patients. For LVIDd, factor age classes showed no significance.

Furthermore, preimplantation LVEF and LVIDd showed no significance for factor group (A, B, and C). For LVEF 2 months after implantation, the factor group (A, B, and C) had highly significant results ($P = .003$), although not for LVIDd. After 2 months, group A showed significantly lower values for LVEF (Fig 3).

An analysis of the data before and after device explantation (repeated measures) showed statistical significance for LVIDd ($P = .01$) but not for LVEF. After explantation, there was a significant increase of LVIDd (Fig 1).

A significant difference was also found between the age classes. The patients who were younger than 36 years had significantly higher values for LVEF when compared with the older ones (before explantation, $P = .002$; after removal, $P = .0001$; Fig 4). The factor group showed significance before explantation ($P = .0002$) and after

Fig 5. Differences in mean LVEF and LVIDd before device removal and 1 week thereafter with regard to group A (recurrence of heart failure), group B (lasting recovery), and group C (death after weaning unrelated to cardiac function).

Fig 6. Results of a Cox regression model (survival analysis). The cumulative probability of nonexplantation over the time on assist support.

explantation ($P = .0001$, Fig 5). Before and after explantation, group A showed significantly lower LVEF values.

The significance pattern for LVIDd is different. A difference between the groups could be observed before ($P = .003$) and after explantation ($P = .0006$). The patients in group A had significantly higher values for LVIDd before and after device removal when compared with both other groups.

Additionally, the following significant differences were visible with regard to the groups. Significant differences could be detected for the variable duration on assist support ($P = .04$), first cardiac symptoms ($P = .004$), and manifest heart failure ($P = .004$).

The duration on assist support in group A was significantly longer than that in group C. The time of first cardiac symptoms and manifest heart failure in group A was significantly greater than in groups B and C.

A stepwise regression model, according to Cox, revealed that the probability of nonexplantation decreased with time on assist support (Fig 6). Furthermore, the age at the time of device implantation was the only influencing factor for the duration on assist device ($P = .02$, Fig 6).

The functional relationship between the age at the time of device placement and duration on assist support could be best fitted by a hyperbolic function with an r^2

Fig 7. Results of a Cox regression model (survival analysis), showing the cumulative probability of heart failure nonrecurrence.

value of 0.48. A further Cox model revealed that the probability of recurrence of heart failure decreases with increasing follow-up time (Fig 7). The variable duration of heart failure does significantly influence the probability of recurrence of heart failure and therefore the need for cardiac transplantation ($P = .02$).

Discussion

The data of the patients presented in this report demonstrate that lasting recovery of cardiac function for at least several years can be achieved by prolonged LVAD support for end-stage heart failure caused by IDC in some patients. The potential of erstwhile severely dilated and impaired hearts toward such a functional restoration has been observed by several investigators; however, it has remained doubtful whether such a recovery might be transient and whether a relapse of heart failure might occur as a rule.⁶⁻¹¹ In fact, 7 of our 23 patients who underwent assist device explantation when we believed their hearts were sufficiently recovered did have a recurrence of heart failure and had to undergo cardiac transplantation.

Statistical analysis of the available data shows a significant improvement of LVEF and LVIDd before and after 2 months of assist device placement. However, for the time before and after device removal, LVIDd revealed significant re-enlargement, whereas LVEF remained unchanged. Enlargement of the left ventricle expresses higher volume load caused by the missing pump and has to be accepted as a normal adaptation process after device removal. The constant LVEF

demonstrates, however, that because of the reverse remodeling of the myocardium by application of the assist device, there is an increased and obviously stable contractility.

An analysis of whether the age of the patients may have an influence on changes in LVEF and LVIDd revealed that age had no influence before device placement but that it had a significant overall influence on both parameters 2 months after implantation. The heart function of younger patients improved significantly more than that in older patients. Even so, with regard to LVEF before and after device removal, younger patients showed considerably better function. Obviously, younger patients have a higher potential for recovery. Of course, there are those with a shorter time of first cardiac symptoms and manifest heart failure. Unfortunately, there were no data available to examine why younger patients have a higher potential for recovery (eg, whether they might have less replacement fibrosis or differences in the extracellular matrix). An analysis of the differences between groups A, B, and C revealed significant overall differences. Although no group differences were seen before device placement or 2 months after device implantation, significant differences were observed 2 months later with regard to LVEF and LVIDd. In group A, LVEF had improved less after 2 months. Even so, before and after explantation, LVEF and LVIDd were significantly lower or higher, respectively, when compared with that found in groups B and C. Although LVEF might not be an ideal parameter to assess cardiac function because of its dependence on different hemo-

dynamic conditions, it is easy to measure and seems to have considerable value for clinicians to predict the outcome after weaning from the assist device. Together with the Cox model that was calculated, it can be estimated that patients with a shorter duration of heart failure with a consequently higher LVEF had a lower probability for the development of recurrence of heart failure with the need for transplantation.

Lasting recovery seems to be related to patients with a shorter history of heart failure and also to a more rapid restoration of normal heart function initially after assist device implantation. This would support the assumption that recovery is more likely in a type of cardiac disease with an ongoing inflammatory component, which may be termed *chronic myocarditis*. Our experience with acute myocarditis in children who displayed fast recovery from complete heart failure and cardiac arrest during BVAD support of 1 and 2 weeks' duration would underline the importance of inflammation.^{12,13}

A significant difference could be discerned in the completeness of the cardiac recovery at the time of assist device explantation. The patients with lasting recovery (group B) had attained entirely normal function values, whereas the patients who had a relapse (group A) had a somewhat less than complete recovery.

In an earlier study, we also found that during the assist period, some patients reached a maximum of recovery with a subsequent decline followed by a later relapse. These patients had more frequently been in group A with such a missed optimum status. Interpretation was that ventricular unloading had occurred for too long, which may finally have resulted in cardiac atrophy.¹⁴

The type of LVAD seems to be important because complete drainage of the left ventricle appears to be mandatory to enable the heart to recover. This has been the case with the Novacor and the TCI systems, which both have large-bore inlet cannulas at the apex of the left ventricle and provide the most complete ventricular drainage. Atrial drainage appears to be unsuitable. At our institution, in more than 300 applications of the pneumatically driven Berlin Heart system and atrial drainage,¹⁵ cardiac recovery was observed not once. In the 1 patient with a BVAD in the patient group presented here, a transmitral atrial cannula was used, which allowed ventricular drainage, and cardiac recovery was observed. This patient, however, had recurrent heart failure and underwent transplantation. At explantation of the heart, fibrosis of the anterior mitral leaflets was observed, a fact which casts severe doubts on the longer use of such a cannulation system. However, short-term applications of such a system may be suc-

cessful without cardiac structure damage, as documented in children with acute myocarditis.¹³

On explantation of the Novacor and the TCI systems, the outflow and inflow cannulas were left in place. Explantation was commenced in patients with the Novacor device by opening the pocket that contains the device and ligating both the inflow and outflow conduits from below the diaphragm and in patients with TCI devices through an additional left thoracotomy to the inflow cannula. There has been concern about the complications that arise from these remnants. However, we have never observed any thromboembolism, whereas there have been 3 instances of graft infection that required removal of the infected cannulas. This was successful in 2 patients and proved incurable and eventually lethal in the third case. These graft infections were all observed in the first 4 patients weaned. Since that time, we have removed the cannulas and the surrounding cage as extensively as possible, and we have not seen any infection in the patients subsequently.

Permanent medical treatment with ACE inhibitors and β -blockers has been considered important to ensure lasting cardiac recovery after assist device explantation. This follows the experience that inhibition of the neurohumoral activation by ACE inhibitors and β -blockade has a positive effect on cardiac function and additionally is essential to influence the underlying disease process in IDC, where autoimmune aggression against β -receptors seems to play some role, as documented by our experience with immunoadsorption of such antibodies.^{16,17}

Thus, a somewhat clearer view has been achieved as to the prospect of myocardial recovery in IDC once the patient has been placed on an LVAD. However, no reliable predictors have been found with regard to the most important question of which patients with IDC might be candidates for an unloading and weaning protocol before assist device implantation. The only factor detected that influences the probability of heart failure is the duration of heart failure. Nevertheless, according to our overall experience with the weaning procedure, approximately 20% of the patients with an LVAD system who survive on the device can be weaned and expect durable, midterm, stable cardiac function.

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Discussion

Eric A. Rose (New York, NY). I congratulate Dr Hetzer and his colleagues for their pioneering efforts in describing what is now called by many the *bridge to recovery* scenario.

This series is the largest single-center patient experience I am aware of in which spontaneous recovery of myocardial function was observed in candidates for transplantation in whom LVADs are initially intended as a bridge to transplantation. Our own smaller experience at Columbia with 7 patients parallels that described by the Berlin group.

This intriguing observation now gives rise to more questions than answers. First and foremost are questions related to identification of the small subset of patients bridged to transplantation whose myocardium improves in this setting. Dr Hetzer's data suggest that patients with shorter durations of heart failure before implantation and those with early evidence of myocardial recovery after device implantation have the most favorable outcomes. This series includes only patients with IDC, yet we and others have also observed recovery in a small number of patients with ischemic left ventricular dysfunction.

My first question for Dr Hetzer focuses on the denominator of total patients bridged to transplantation. In our experience only approximately 5% of these patients spontaneously improved enough to allow explantation. What percentage of all patients receiving devices in Berlin have had explantation?

Second, I invite Dr Hetzer to speculate on whether he believes that active strategies to enhance spontaneous recovery (eg, cellular transplantation or gene therapies designed to improve myocardial function) might increase the frequency of recovery in the future.

Numerous technical details may also play a role in this phenomenon. Dr Hetzer suggests that complete left ventricular unloading is important. Have the Berlin investigators looked at any partial unloading regimens designed perhaps to wean patients from these devices?

Dr Hetzer also describes reducing device pump rates to 1 beat per minute for periods of as long as 20 minutes to assess full functional recovery. Has there been any thromboembolic morbidity associated with restitution of full pump rates?

Durability of restored function is unfortunately still suboptimal, with a substantial percentage of patients ultimately dying or requiring transplantation after device explantation. I would lastly like to ask you to speculate on how the durability of myocardial recovery might be improved.

Dr Hetzer. Thank you very much, Dr Rose, for your expert comments and questions. You were the first, to our knowledge, to have observed this type of recovery, and we were strongly stimulated by your experience and your report.

As to the questions that you have posed, the proportion of patients that might be candidates for a recovery and that might be candidates for explantation of a pump has probably been looked at in a more optimistic way in the past. We have been talking about something like 30% of patients with cardiomyopathy who might be candidates. I am not so sure whether we can maintain this high percentage.

Of approximately 230 patients we have treated by assist device implantation during this time span, 136 had IDC. About 10% of them had a successful long-term recovery after explantation. When we consider only those who had an apical drainage pump like a Novacor or a TCI device, which I personally believe is an essential prerequisite for recovery, then this proportion might go up to 20% because during the same time we had 67 patients with cardiomyopathy having had such assist devices.

We have not had any patient with an ischemic cardiomyopathy whose improvement has been sufficient to allow us to explant the pump. However, we have seen 3 children with very fulminant myocarditis who came to the operating room receiving closed chest massage and who, with a biventricular and transmitral cannula assist device, made a very fast recovery, within something like 1 or 2 weeks. Therefore, I think somewhere in between these long-term gradual recoverers, who may have a good long-term outcome, and these very rapid recoverers from viral myocarditis are probably the ranges where we are finding our patients. Unfortunately, as you already mentioned, we have no significant or reliable data or investigations on hand to tell us where the patients are in this broad range.

As to your second question concerning adjuvant therapy, we have not had any experience with, for example, cell transplantation, although I believe that this is a very exciting field and may very well be applicable to these patients. We have systematically started our patients on a regimen of β -blockers and afterload reduction, and I strongly believe that this is very important to have success.

As to the completeness of drainage, we have had many patients with atrial drainage, pneumatic extracorporeal systems, and the Berlin Heart System in this study, and not one patient with cardiomyopathy has shown significant recovery. From this, we deduced that complete drainage of the left ventricle, preferably through the apex, is an important prerequisite. This led to recovery also in a patient with a transmitral cannula directly draining the left ventricle, and this patient belongs to the group that had recurrent failure after explantation of the system. Therefore, at present, we are convinced that complete recovery for some time is important.

The question, of course, is how long. In an earlier study, which is going to be published soon in *The Annals of Thoracic Surgery*, we speculated whether there might be an ideal time point during the unloading period at which explantation of the pump should be undertaken. It may be that if we miss this ideal optimal time point, something like cardiac atrophy may occur, and later explantation might be less successful. However, this is all very speculative because it refers only to very small numbers and very discrete changes.

As to the fourth question, we have not seen any emboli during the pump subtrials. Of course, we were concerned about this, and the patients have always received extra heparin before undergoing those pump-off trials. Durability is a very open question, and I think nobody has an answer yet as to how to improve durability. The most important thing is to use

reliable morphologic data. We can ascertain which patients may have a durable recovery.

Dr O. Howard Frazier (*Houston, Tex*). In 1991, we discharged the first patient from the hospital with an implantable vented electric device. That patient was on the device for 504 days and then died of a stroke, but his heart at autopsy showed marked improvement. When we removed the device, it was working so well that we had to use him as a donor for his liver and kidney because I did not know how long he would have lasted.

The subsequent work that we reported invariably showed improvement in the idiopathic myopathies of varying degrees, but it invariably showed histologic, physiologic, and anatomic improvement. We have since removed the device from 3 patients. The longest period since explantation is now approaching 3 years, with a 5-year history of idiopathic myopathy. For the last 2 patients from whom we removed the device, we used a dobutamine stress test with the device off, and the patient was heparinized to give us some guidance. I think this is one way that you may be able to measure physiologic recovery.

I would like to remind you that every study in these idiopathic myopathies with prolonged unloading and with the patient's own heart acting as a control has shown improvement in the tumor necrosis factor α level; that work was done at Baylor. The Temple group has shown a disappearance of apoptosis. We have shown a normalization of the calcium endoplasmic reticulum function, which may be the earliest sign of heart failure. Therefore, I think that a large number of these patients with idiopathic myopathies will recover.

I would like to ask you about this problem, which in essence is a problem of the nature of the dose. How much, and how long? Are we undertreating, or are we overtreating? I am not sure myself, of course. I think we in the large centers are obliged to work together to try to answer those questions and perhaps save some of these patients from a needless transplant. Have you tried something like a physiologic test with dobutamine stress with the pump off?

Also, I am removing the pump entirely and doing a modification of a ventricular reduction procedure on these patients at the time of explantation. I do not know whether you have tried that or whether you are leaving the heart as is.

Dr Hetzer. Thank you very much, Dr Frazier. We have had so many common discussions about this interesting field. As to undertreatment or overtreatment, I would like to state again what I said before. There may be an ideal time to explant the pump, and this might be missed if we unload the heart for too long; this may be disadvantageous for later recovery. This is what we have done: Once we have seen significant improvement of the cardiac function, we have turned those pumps to a fixed rate mode to give a certain amount of extra load to those ventricles, with the idea that they should be trained somewhat for later removal of the device. We have no reliable proof as to whether this is important.

We have not attempted a concomitant ventricular reduction procedure. Once we have acquired enough experience with

this one, which we do not yet have, ventricular reduction may be a valid adjunct for those patients who have not reached a complete recovery, presumably in both dimensions and ejection fraction.

Dr Hikaru Matsuda (*Osaka, Japan*). As was already mentioned, it is difficult to find out what kind of patients can have this benefit from an LVAD, leading to the recovery. We have been looking for morphologic changes of the left ventricle, particularly for cell diameter and degree of apoptosis, evaluating the progress or regression of the disease during the support. We have not encountered a recovery case so far, but in 10 patients we looked for serial changes of the morphologic aspects. The ages were a little bit higher, with the mean age about 50 years, and we believe that the disease itself was in its very last phase. The cell diameter, fibrosis, and apoptosis gradually increased from the time of diagnosis to the time of the implantation of the devices, and at the time of the autopsy or at transplantation, it was worse. Therefore, in our patients the evidence showed that the disease itself was progressing and deteriorating, even under the unloading situation. Dr Frazier said that there was some evidence that the

unloading prevents apoptosis, but we need to think about this to treat more aggressively during the support so as to prevent apoptosis or the increase of fibrosis.

Did you check the serial changes of the histologic aspects of the left ventricle, and have you made a comparison between the patients who recovered and those who did not recover?

Dr Hetzer. Thank you, Dr Matsuda, for your question and comments. In the panel of studies that are ongoing, up to now we have not seen any reliable differences as to apoptosis and other morphologic parameters regarding the predictability of recovery and also the predictability of later durability of recovery. However, we do not have serial studies. We have not subjected those patients up to now to left ventricular biopsies during the assist period and afterward, which we probably should have done to obtain reliable data.

At present, we have only a core of the apex or some biopsy tissue at the time of implantation, but this is not conclusive enough. I realize that if we want more precise data, we have to be more invasive in those studies, but unfortunately, I cannot present such information to you right now.

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