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Exercise performance during the first two years after left ventricular assist device implantation

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Abstract

Exercise performance of patients with left ventricular assist devices (LVADs) improves after post-implant cardiac rehabilitation (CR). Few studies assess the effectiveness of a CR and its long-term effect of exercise performance. For this purpose, we retrospectively analyzed data from LVAD patients, who underwent a stationary CR twice after pump implantation. Data from exercise training and cardiopulmonary exercise tests (CPET) were analyzed. 15 patients (age 57 ± 10 y, male 87%) were admitted to the rehabilitation clinic twice 39 ± 18 and 547 ± 197 days after LVAD implantation. An improvement from the beginning to the end of the second CR was observed in bicycle ergometer training (14.0 ± 8.8 vs. 35.7 ± 14.7 W, $p < 0.001$), in muscular strength (e.g. leg press: 41 ± 10 vs. 53 ± 14 kg, $p < 0.001$) and in six minute walk distance (421 ± 126 m vs. 480 ± 133 m, $p = 0.040$). Between the first and the second CR improvement in all the training modules was observed as well as an increase in CPETs peak workload (56 ± 24 vs. 83 ± 26 W, $p < 0.001$) but not in peak oxygen consumption (12.3 ± 3.2 vs. 12.2 ± 4.0 ml/min/kg, $p = 0.906$). Thus, overlong implant periods, patient showed improvement of their exercise performance in the submaximal load range, but no change in the aerobic capacity was observed.

Keywords

Continuous-flow left ventricular assist devices; cardiac rehabilitation; exercise performance

Introduction

An increasing number of patients receive LVADs not only as a bridge to transplantation, but also for their lifetimes, as a destination therapy (1). Although their quality of life and their

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heart failure symptoms improve immediately after LVAD implantation (2), most patients still have a markedly impaired exercise capacity (3–6). Dunlay et al. (7) showed in their study only a slight improvement of the peak oxygen consumption (VO_2) (+0,9 ml/kg/min) when comparing pre-LVAD implantation with one year later. This improvement was not statistically significant, with most of the patients (72%) having a peak- $\text{VO}_2 < 14$ ml/min/kg independent on indication, etiology, or age at implant. A better Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level at implantation also did not correlate with improved peak- VO_2 (8). Leibner et al. (9) found in their population that after a slight increase of peak- VO_2 within the first 3 to 6 months post LVAD implantation, no further changes could be observed up to one year, and the percentage of the predicted value remained severely limited.

More recently, the number of patients on long-term LVAD support has been substantially growing, leading to cardiac rehabilitation (CR) programs aimed at improving the limited functional capacity and the health status and at the optimisation of life quality in this particular patient population. Studies are available concerning the effectiveness and safety of exercise training during a CR program just after LVAD implantation (10–15), however the available evidence is still not strong enough to draw conclusive guidelines for LVAD patients (16). To the authors knowledge, data are lacking in addition to these reports about the long-term exercise performance related to a second CR stay and whether this is effectively improves patients' physical performance. In this study we report a single center experience with a series of patients who underwent two CRs within the first two years after LVAD implantation.

Methods

A retrospective observational cohort study was approved by the Institutional Review Board of Lower Austria. Data from LVAD patients were collected and retrospectively analyzed among all patients who underwent a stationary rehabilitation program twice between September 2010 and March 2014. In our center patients are usually informed at the end of the first CR about the possibility of a second CR in about a year. After this year has passed, if patients are still on device and if there are no contraindications for a second CR stay (i.e. occurrence of severe adverse event), patients are contacted by phone and referred to the rehabilitation clinic. Among the patients who underwent both rehabilitation stays, those with a time between surgery and first rehabilitation beginning greater than 120 days were excluded from the analysis. Data related to the training sessions and the exercise tests during both CR stays were used both to evaluate the changes in physical performance within the first two years after pump implant and the margins for improvement available from a repeated, later CR.

Rehabilitation program, medical training therapy and diagnostic tests

For both rehabilitation periods the same rehabilitation program and diagnostic tests were performed as reported in a previous study (15).

The rehabilitation program consisted of aerobic and strength training as well as walking and gymnastics. For the determination of the intensity of the training sessions we used the

perceived level of exertion according to the Borg scale (17). An exertion of somewhat harder intensity (grade 13 in the Borg scale) was attempted. Aerobic training consisted of bicycle ergometry with an interval training schema. Strength training consisted of two series of 12 repetitions of five muscle groups of the lower extremities. Walking and gymnastic training was organized into groups with the aim of shifting the patient into a better performing group. There were five different walking groups each walking along paths covering different distances, elevation and duration (W1 was the group with the lowest distance and duration, W5 with the highest). The gymnastic groups were also divided in five grades performing different exercises (coordination, strength and balance training) with different intensities and in different body positions.

A CPET was routinely performed at the end of each rehabilitation period and its protocol was adapted to the estimated workload of the patient with an aimed duration of 8-12 minutes. A six minute walk test (6MWT) (18) was introduced in the clinical routine only in February 2013 and data were therefore available only for the second CR.

Blood serum concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP), evaluated using an immunological test, the glomerular filtration rate (GFR), calculated using the modification of diet in renal disease (MDRD) formula, the alanine amino transferase (ALT) and the hemoglobin concentration were also measured.

The pharmacological heart failure therapy and its changes between the two rehabilitations periods were also analyzed. The most used angiotensin converting enzyme (ACE)-inhibitors (such as Ramipril, Lisinopril), β -blocker (Bisoprolol) and diuretics (Furosemide, Spironolactone, Xipamid) were considered.

Acquired data and statistical analysis

The number of training sessions, the training intensity and duration for the bicycle ergometry training and the lifted weight for strength training were recorded. Walking and gymnastic groups in which the patient trained were recorded as well. Adverse events and complications associated with training or leading to a withdrawal from the training were also carefully documented.

The bicycle training was performed in an interval mode using standardized modules with increasing intensity of the peak work load and the recovery phases. The high-intensity phase lasted 20-30 seconds and the recovery phase 60 seconds. To get a more precise quantification of the interval training, mean workload (p_{mean}) was calculated by weighting the workloads for both the high-intensity and the recovery phase by the respective durations using the equation: $p_{\text{mean}} = (p_{\text{peak}} * t_{\text{peak}} + p_{\text{rec}} * t_{\text{rec}}) / (t_{\text{peak}} + t_{\text{rec}})$. Here p_{peak} represents the peak workload at the phase of high training intensity, t_{peak} the duration of the high-intensity phase, p_{rec} the workload of the recovery phase and t_{rec} the duration of the recovery phase (19). Values were calculated over the whole active training time, excluding the 3 minutes warm-up at the beginning and the 3 minutes cool-down phase with no or very low load.

The following parameters from the CPET were analyzed: duration of the test, peak workload, percentage of expected workload, relative peak oxygen consumption (VO_2), absolute peak- VO_2 normalized by body weight, percentage of peak- VO_2 according to Wassermann formula, metabolic equivalents (METs), workload at the first ventilatory threshold (VT1), VO_2 at VT1, percentage of predicted peak VO_2 at VT1, respiratory exchange ratio (RER) at peak- VO_2 , ventilatory equivalent ratio for carbondioxide (VE/VCO_2) at VT1.

Four time points were considered in the analysis: the beginning and the end of the 1st rehabilitation period (in the following text denoted by B1 and E1), as well as the beginning and the end of the 2nd rehabilitation period (in the following text denoted by B2 and E2). Where not otherwise specified, variables are considered averaged during the whole rehabilitation stay.

To statistically assess the observed changes, Student's t-test and the Wilcoxon signed-rank test for paired differences were used. The latter test was used when the variables were not normally distributed. Normality was tested using the Shapiro–Wilk test. A level of significance $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 22.0 (IBM, ArmonkNY, USA).

Results

Demographics

Of the 91 patients who attended a CR just after LVAD implantation, between September 2010 and July 2013, 32 were eligible for a second rehabilitation. Patients were excluded if they were not on device (transplanted $n=20$, dead $n=17$, weaned $n=2$), or if they had at least one adverse event ($n=20$), which was either severe or did not result in a full recovery. From the 32 eligible patients, 15 refused a second CR for personal reasons and 1 patient completed the 2nd CR in another center. Among the 16 patients who attended the second rehabilitation, one was excluded from the study because of a prolonged time (>120 days) between surgery and commencement of the CR. For a schematic tabulation of the study patients please refer to Figure 1. The remaining 15 patients came directly from the hospital to the rehabilitation center the first time 39 ± 18 days after LVAD implantation and stayed for 35 ± 6 days and for the second time 542 ± 197 days after implantation, staying 27 ± 7 days. The demographics, clinical characteristics and comorbidities of the study subjects are summarized in Table 1. Among these parameters, a remarkable increase of the body weight at the second CR compared to the first CR should be noted (from 82.5 ± 10.9 kg to 92.6 ± 10.2 kg, $p < 0.001$). One patient received an implantable cardioverter defibrillator (ICD) and one patient a cardiac resynchronisation therapy (CRT) before attending the second rehabilitation stay. Nicotine abuse decreased significantly in the second stay; no patient was a smoker at this time, compared to 4 in the first CR ($p = 0.032$). Six of the study patients had an adverse event between the two CRs, however these were not judged as a contraindication for a second CR.

Medical training therapy

During the 2nd CR (B2 vs. E2) an improvement of the duration of the training and of the average workload for the bicycle ergometry training (Table 2) was observed. Also the average lifted weight of five muscle groups increased (Table 3).

All patients performed bicycle training during the first CR. One of the patients could not perform bicycle training at the second CR because of orthopedic problems. Compared the end of the first CR to the end of the second CR (E1 vs. E2) the number and duration of the training sessions and the achieved mean workload in the bicycle ergometer training improved (Table 2)

All patients performed strength training during both CR. The average weight used for the five muscle groups improved as shown in Table 3.

Patients showed also improvement in their gymnastic group (2 ± 1 to 3 ± 1 , $p=0.014$) and walking group (2 ± 1 to 3 ± 1 , $p=0.001$). There were no training-related complications recorded during both CR periods.

Diagnostic tests

The results from the analysis of the CPET are shown in Table 4. Two patients were not able to perform the CPET because of mask phobia and orthopedic problems, the remaining 13 performed all the CPET at the end of the first period. At the end of the second CR the patient with mask phobia could perform only a cardiac stress test, therefore data about ventilation are available only for 13 of the 14 patients. Peak workload and the percentage of the expected workload increased significantly. However, relative peak- VO_2 did not increase, and even slightly decreased although not significantly, absolute peak VO_2 increased, but also not significantly. A considerable gain of body weight (82.5 ± 10.9 vs. 92.6 ± 10.2 kg, $p<0.001$) was observed in the same period (Table 1). The percentage of the predicted peak- VO_2 at the VT1 slightly increased, although not significantly. The ventilatory equivalent for CO_2 at the VT1 slightly decreased. All patients performed the CPET until exhaustion, reaching a RER of 1.09 ± 0.08 , very close to the value of 1.1 that is accepted as an excellent exercise effort (20). The number of patients who reached a $\text{RER}>1.1$ was 5 during the first CR and 6 during the second CR.

Because of a later introduction of the 6MWT, only 10 patients performed the 6MWT during the second CR. These could significantly improve their walked distance during the training at the 2nd CR stay from 421 ± 126 m to 480 ± 133 m ($p=0.040$).

A clear reduction of the NT-proBNP from 3325 ± 3234 pg/ml to 1390 ± 1212 pg/ml ($p=0.003$) was observed between the two CR periods. Renal function decreased as indicated from the increase of serum creatinine from 1.3 ± 0.6 mg/dl to 1.66 ± 0.6 ($p=0.002$). GFR decreased from 70.8 ± 40.8 to 53.0 ± 23.8 ml/min ($p=0.003$). A slight increase in hemoglobin from 11.3 ± 1.5 vs. 12.3 ± 2.1 g/dl ($p=0.108$) was observed between the two periods, but still staying beneath the normal range. The ALT stayed at the normal range during this period (Table 1).

Pump speed setting did not change between the two CRs leading to the same mean pump flow rate during the first and second CR: 5.7 ± 0.5 vs. 5.3 ± 1.0 l/min ($p=0.278$), respectively.

The only significant in pharmacological therapy was the dosage of bisoprolol, which increased from an average of 2.7 ± 1.6 to 4.6 ± 4.1 mg/day ($p=0.027$). In 5 Patients the administration of Spironolactone was discontinued (Table 1).

Discussion

Fifteen patients finished two CR stays within the first two years following LVAD implantation with observable improvement of muscular strength and coordination, as well as of submaximal aerobic activity. The workload during the bicycle interval training was seen to be greater at the second CR (Table 2). A significant increase of strength in four of the five muscle groups targeted by the training program was also observed (Table 3). Further, patients were able to nearly double the walking distance during training, and to perform more challenging gymnastic exercises.

Despite this general improvement, the relative cardiopulmonary performance remained nearly the same, (Table 4). A considerable weight gain was observed in the same period (Table 1), with all but one patient gaining about 10 kg since their first CR. This might reflect the reversal of several deleterious factors in advanced heart failure that is for example systemic inflammatory and neurohumoral activation. The increase in weight might have influenced the slightly decreased peak- VO_2 .

Considering the absolute peak- VO_2 (not normalized by body weight), an increase, not statistically significant, could be observed. The peak workload, on the other hand, significantly increased probably because of an improvement in neuromuscular coordination and more practice during bicycling. Despite a higher workload, the percent of its expected value remains rather low ($42 \pm 12\%$). The low peak- VO_2 values are comparable to data from other studies with patients on support more than one year. Leibner et al. (9) describes in his population a peak- VO_2 of 11.2 ± 1.7 ml/kg/min. In 70% of the patients from the study of Dunlay et al. (7) the peak- VO_2 was lower than 14 ml/kg/min. The severely reduced left ventricular function, despite mechanical circulatory support, and depressed right ventricular function are among the potential factors contributing to the limited exercise capacity. Unfortunately, because of sparse echocardiographic data, the relative importance of these factors could not be addressed in the current study. In addition, respiratory abnormalities, peripheral factors including deconditioned skeletal muscle, and a pump set at a constant speed also appear as limiting factors (21). The reverse-remodeling of myocardial cellular hypertrophy, eventually leading to atrophy without functional improvement of cardiac function may also contribute to reduced exercise capacity (22). However, this aspect could not be assessed because histological evaluation of cellular remodelling was unavailable.

The scientific community has started questioning the validity of peak- VO_2 as a parameter that describes the condition of LVAD patients, favoring parameters from submaximal tests (e.g. 6MWT) to reflect the condition of these patients (23). For heart failure patients, the 6MWT distance and the peak- VO_2 are linearly correlated (21, 23). The 6MWT distance

apparently also reaches a plateau. In a previous large multicenter destination therapy trial, the mean distance covered in the 6MWT after one year remained nearly the same as that measured 3 months post LVAD implantation (319 ± 191 vs. 318 ± 164 m) (24). In another retrospective study the mean distance was 393 ± 290 m one year after implantation (25). In this study the distance covered at the end of the 2nd CR rose to 480 ± 133 m, remarkably better than the cited values approaching the 10th percentile of a 50-59 years old healthy man (26). Since the 6MWT was introduced later, we could not determine the improvement relative to the first CR. However the longer distance, together with other training variables, may indicate a benefit of a second CR, especially in the submaximal load range. A reason for the dissociation between maximal and submaximal performance may be that LVADs are able to provide sufficient support at rest and during submaximal work, but insufficient support during maximal performance, because of the constant pump speed. It has indeed already been shown, that exercise capacity with increasing pump speed can be improved compared with that at constant pump speed, especially for patients with more preserved right ventricular function (27).

The value of the percentage of the predicted maximal VO_2 at the VT1, a parameter derived from submaximal workload and therefore independent of patient motivation was $30\pm7\%$, below the threshold of 40% (28), expressing again deconditioning of the skeletal muscle after two CR's. This deconditioning also shows that although at the first CR all patients were instructed on how to continue the training at home, they were probably not following these recommendations. Notwithstanding potential remains to improve aerobic muscle metabolism with regular supervised exercise during an ambulatory cardiac rehabilitation program.

The clear reduction of the NT-proBNP to 1390 ± 1212 pg/ml hints at an improvement of the heart failure condition and hemodynamics, but it is still in a high range. At the second CR the only observed changes in medication were the discontinuation of diuretics in 5 patients, probably because of an observed deterioration of renal function and an increase in β -blocker dosage, as recommended for LVAD patients (29). Because of this increase the resting heart rate recorded before the CPET was lower at the second CR in comparison to the first CR (70 ± 9 vs. 83 ± 15 bpm $p=0.012$). However the peak heart rate during the CPET was unchanged (111 ± 29 vs. 107 ± 24 bpm, $p=0.545$). Thus it seems unlikely that chronotropic incompetence would lead to a lack of improvement in the peak- VO_2 .

Certain limitations on these results are because of the small sample size and to the retrospective character of this study. From the 91 patients that performed the first CR, only 32 were eligible for the second CR, with 16 performing it in our center and 1 in another center Figure 1. Nevertheless the patients in this study yield data similar to one of our previous studies which included 41 consecutive patients (10), suggesting the representativeness of this sample. Still there is a risk of a biased selected population, because of the low numbers. Nonetheless, the observations presented here should be valuable for future comparison. As already mentioned, systematic evaluation of any specific echocardiographic data about the right ventricle, and the aortic and mitral valve was not possible because of sparse data. Nevertheless it would be very interesting to correlate these data with the parameters of the CPET especially the VO_2 max. Unfortunately, the ventilatory

equivalent for CO₂ at VT1 and not the minute ventilation carbon dioxide production slope (VE/VCO₂ slope) was documented; the latter would have been a much better prognostic parameter in the CPET.

Conclusion

This study shows that a clear long-term improvement in submaximal physical activity can be achieved, but in the absence of changes in peak oxygen uptake. A second CR about 1.5 years after LVAD implantation improves physical performance, indicating that training of the peripheral musculature is apparently improved and that a longer continuation of medically guided exercise training in an ambulatory setting appears warranted.

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Figure 1.

Table 1

Baseline demographics, laboratory tests and most used medication at the end of both CRs (E1-E2)

Demographics		1 st CR		2 nd CR		p
		Mean ± SD	n (%)	Mean ± SD	n (%)	
Sex	Male		13 (87)		13 (87)	
	Female		2 (13)		2 (13)	
Age (years)		57±9		58±9		
Weight (kg)		82.5±10.9		92.6±10.2		<0.001
BMI (kg/m ²)		27.2±3.7		30.4±3.1		<0.001
Pump type	HeartWare		8 (53)		8 (53)	
	HeartMate II		7 (47)		7 (47)	
Pre-op INTERMACS 1-3			12 (80)		12 (80)	
Etiology	Ischemic		9 (60)		9 (60)	
	Idiopathic		6 (40)		6 (40)	
Comorbidities	Diabetes		6 (40)		6 (40)	
	COPD		3 (20)		3 (20)	
	CKD		7 (47)		7 (47)	
	Nicotine abuse		4 (27)		0 (0)	0.032
POD at rehab admission		39±18		542±197		<0.001
Hb (g/dl)		11.3±1.5		12.33±2.1		0.108
GFR MDRD (ml/min)		70.8±40.8		52.7±23.8		0.003
NT-proBNP (pg/ml)		3325±3234		1390±1212		0.003
ALT (U/l)		23.5±12.3		26.7±15.6		0.460
Pharmacological therapy	Bisoprolol (mg)	2.7±1.6	13 (87)	4.6±4.1	13 (87)	0.027
	Lisinopril (mg)	7±3.3	5 (33)	8.5±3.1	5 (33)	0.077
	Ramipril (mg)	4.2±2.8	6 (40)	5±2.3	6 (40)	0.219
	Furosemid (mg)	49.1±33.2	15 (100)	46±26.9	15 (100)	0.891
	Spironolactone(mg)	52.8±30.7	11 (66)	59.9±28.9	6 (40)	0.311
	Xipamid (mg)	38.7±6.2	8 (53)	37±7.2	5 (33)	0.782

Table 2

Bicycle ergometry training results at the four investigated time-points: beginning and end of the first and the second cardiac rehabilitation stay (B1, E1, B2, E2, respectively)

Bicycle ergometry training	1 st CR (n=15)		2 nd CR (n=14)		p-value [*]	p-value [§]	p-value [#]
	Beginning (B1)	End (E1)	Beginning (B2)	End (E2)			
		Mean ± SD		Mean ± SD			
Number of sessions	-	9.7 ± 6.1	-	13.4 ± 12.5	0.029		
Duration (min)	14.1 ± 2	19.1 ± 4.5	16.3 ± 2.2	23.1 ± 4	0.039	0.004	<0.001
Average workload	3.7 ± 3	20.4 ± 16.5	14 ± 8.8	35.7 ± 14.7	<0.001	0.001	<0.001

^{*} p-values calculated between E1 and E2

[§] p-values calculated between B1 and E1

[#] p-values calculated between B2 and E2

Table 3

Strength training results at the four investigated time-points: beginning and end of the first and the second cardiac rehabilitation stay (B1, E1, B2, E2, respectively)

Strength Training	1 st CR (n=15)		2 nd CR (n=15)		p-value [*]	p-value [§]	p-value [#]
	Beginning (B1)	End (E1)	Beginning (B2)	End (E2)			
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD			
Number of sessions		7 ± 3		7 ± 2	0.678		
Leg press	27 ± 10	38 ± 14	41 ± 10	53 ± 14	0.002	0.002	<0.001
Leg extensor	7 ± 3	10 ± 6	13 ± 5	13 ± 5	0.062	0.014	0.093
Leg flexor	7 ± 3	10 ± 6	13 ± 6	15 ± 5	0.002	0.005	0.005
Leg abductor	14 ± 8	18 ± 8	25 ± 7	27 ± 7	0.000	0.004	0.015
Leg adductor	14 ± 8	20 ± 9	24 ± 7	27 ± 8	0.006	0.003	0.010

^{*} p-values calculated between E1 and E2

[§] p-values calculated between B1 and E1

[#] p-values calculated between B2 and E2

Table 4

Cardiopulmonary exercise test. Comparison between the first and the second cardiac rehabilitation.(E1-E2)

	End of 1 st CR (E1) (n = 13)	End of 2 nd CR (E2) (n= 14)	p-value
	Mean $\pm$ SD	Mean ($\pm$ SD)	
Duration (min)	7.6 $\pm$ 2.1	10.1 $\pm$ 2.4	0.003
Peak Workload (W)	55.7 $\pm$ 24.5	82.9 $\pm$ 26.2	<0.001
% of expected Workload	32 $\pm$ 13	42.4 $\pm$ 12.3	0.002
Relative Peak oxygen consumption (ml/min/kg)	12.3 $\pm$ 3.2	12.2 $\pm$ 4	0.906
Absolute Peak oxygen consumption (ml/min)	1017.8 $\pm$ 304.7	1141.8 $\pm$ 308.9	0.209
% VO ₂ peak Wassermann	34.7 $\pm$ 11.7	41.2 $\pm$ 11.6	0.092
Metabolic equivalent of task (METs)	3.8 $\pm$ 0.8	4.2 $\pm$ 1.4	0.834
Workload at ventilatory threshold 1 (W)	30.8 $\pm$ 10.2	49.7 $\pm$ 17.8	0.003
VO ₂ at VT1 (ml/min/kg)	8.4 $\pm$ 2.8	8.8 $\pm$ 2.3	0.787
% predicted VO ₂ at VT1 Wassermann	23.6 $\pm$ 9.9	29.9 $\pm$ 6.8	0.141
Respiratory Exchange Ratio at VO ₂ peak (RER)	1.09 $\pm$ 0.1	1.09 $\pm$ 0.08	0.879
Ventilatory equivalent for CO ₂ at VT1	37.7 $\pm$ 7.7	35.3 $\pm$ 3.9	0.259