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Prognostic Relevance of Poor Physical Performance After a Short Period of Intensive Cardiac Rehabilitation in the Early Phase of Axial-flow LVAD Support: A Preliminary Report

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ABSTRACT

Background: Left Ventricular Assist Devices (LVAD) improve clinical compensation and survival rate of chronic heart failure patients. Scant data are available on the level of physical performance attainable by LVAD patients in the early phases after device implant, and its possible prognostic implications.
Aims of the study: To evaluate exercise tolerance of LVAD patients in the first 2 months of support, and to verify if early performance could provide prognostic information.
Methods and Results: We evaluated 38 patients assisted by axial-flow LVAD within 2 months of implantation, by means of six-minute walking tests (6MWT) and Cardiopulmonary exercise test (CPET). After 15.9±4.1 days of intensive in-hospital rehabilitation, 19 patients demonstrated good physical performance, reaching a 6MWT distance of 402±41 m ("better performers"); 19 patients walked less than the median of 360 m (279±67 m; "poor performers"). At final CPET, a workload <32 W and a peak oxygen uptake <11.7 ml/kg/min allowed similar stratification of the patients. During a median follow-up of 611 days (range 72-2432 days), 15 deaths occurred (no significant difference between poor and better performers). Anyway, when a distance of 300 m at final 6MWT was used as discriminating cut-off, patients that walked shorter distances presented worse long-term outcomes (Kaplan-Meier curves: log rank χ^2 11.798, p=0.001). Good discrimination to predict long-term survival was given also by inability to perform the final CPET or by poor performance (values of W-max or peak-VO_2 below the median, respectively of 32 W and 11.7 ml/kg/min; Kaplan-Meier survival curves: respectively χ^2 9.890, p=0.002 and χ^2 4.151, p=0.042).
Atrial fibrillation, impaired renal function, abnormal chronotropic response to exercise and wider fluctuations of International Normalized Ratio (INR) values during hospitalization were also associated with poor prognosis and deserve further investigation.
Conclusions: Within the first 2 months of circulatory assistance, axial-flow LVAD patients still present reduced workload capacity that can improve with a short period of intensive exercise-based rehabilitation. Patients who reach a satisfactory performance (at least 300 m at 6MWT; 32 W or 11.7 ml/kg/min peak-VO_2 at CPET) present better long-term prognosis. Pre-discharge physical evaluation is feasible and provides useful predictive indication about long-term survival in these patients.

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KEYWORDS: Left ventricle assist device; Chronic heart failure; Cardiac rehabilitation; Long-term prognosis; Six-minute walk test; Cardiopulmonary exercise test; Oxygen uptake; Renal failure; Atrial fibrillation.

ABBREVIATIONS: 6 MWT six-minute walk test; ACE: Angiotensin Converting Enzyme; AF: Atrial Fibrillation; AVO: Aortic Valves Opening; BSA: Body Surface Area; CHF: Chronic Heart Failure; ChRes: Chronotropic Reserve; CPET: Cardiopulmonary Exercise Test; CR: Cardiac Rehabilitation; $eCrCl_{BSA}$: Estimated Creatinine Clearance Normalized to a body surface area of 1.73 m^2; EF: Ejection Fraction of left ventricle; Hb: Haemoglobin; HR: Heart Rate; HRR: Heart Rate Recovery; ICD: Implantable Cardioverter-Defibrillator; INR: International Normalized Ratio; LDH: Lactate Dehydrogenase; LVAD: Left Ventricle Assist Device; LVEDD: Left Ventricle End-Diastolic Diameter; LVEDV: Left Ventricle End-Diastolic Volume; NT-pro-BNP: N-Terminal Prohormone of Brain Natriuretic Peptide; NYHA: New York Heart Association; PAPs: Pulmonary Artery Pressure systolic; peak-VO_2: Peak Oxygen Uptake at CPET, in ml/kg/min; SD: Standard Deviation; TAPSE: Tricuspid Annular Plane Systolic Excursion.

INTRODUCTION

Long-term support of Chronic Heart Failure (CHF) patients by a Left Ventricular Assist Device (LVAD) leads to an increase of the circulatory output and an overall improvement of clinical compensation and survival rate.[1] In the last few years, axial-flow rotatory pumps have been increasingly utilized[1,2]; these pumps have proven effective in providing a valid hemodynamic support and have shown a favourable risk-to-benefit ratio.[3]

Although it is currently known that the positive changes on circulatory function occur early after beginning of LVAD support,[4] there is a definite lack of studies assessing the exercise capacity of LVAD patients in the initial phases of circulatory support. Little is still known also about the relationship between physical fitness in the early phases and long-term overall mortality.

To the best of our knowledge, during the first 3 months since device implantation a rather limited number of patients supported by axial-flow LVADs has been observed so far in a few studies.[5-10] These studies demonstrated that the exercise capacity and the hemodynamic-respiratory findings persisted poor despite the mechanical support, with values of peak oxygen uptake reported to be around 50% of the expected values. Only the study by Hasin et al[10] described the relationship between persistent exercise intolerance in the early period after beginning of axial-flow LVAD support and worse long-term prognosis; in that study, anyway, patients observed within the first 2 months since device implantation have been excluded from analysis.

In order to evaluate the feasibility of a multicentre observational study on physical performance in the early period of support by a continuous-flow left ventricle assistance device and its relation with long-term prognosis, we decided to conduct a preliminary study a small group of patients assisted by a LVAD. Specific aims were: 1- to verify how patients could afford sub maximal or symptom limited exercise tests after a short period of intensive cardiac rehabilitation (CR) within 2 months since device implantation; 2- to analyze the significance of clinical parameters and exercise tolerance as predictors of long-term prognosis.

MATERIAL AND METHODS

Patients

We observed 38 consecutive patients (5 females; mean age: 62.0±8.5 years, range 44-73), transferred from the Cardiac Surgeries of the Universities of Bologna, Siena and Udine, Italy, to our CR Unit for a period of intensive exercise-based rehabilitation, within 2 months since implantation of an axial-flow LVAD (Jarvik-2000 Flowmaker; mean time from implant 32.7±13.8 days; range 14-61 days). LVAD had been applied as destination therapy in 28 patients or as bridge to transplantation in 10 patients for end-stage heart failure. In the same period of time, other 4 patients had been admitted to our CR, but were not considered for this study as they entered >2 months after implant of the LVAD.

Before LVAD implantation, all the patients were in NYHA class IV and were dependent from high dose inotrope infusion. The pathogenesis of CHF was coronary artery disease in 19 cases (50%) and dilated cardiomyopathy in 19 patients (50%); the mean time from first diagnosis of the underlying disease to LVAD implant was 9.5±8.0 years.

The greatest majority of the patients (37 subjects, 97%) had an ICD implanted; 30 patients (79%) were in sinus rhythm and 8 in atrial fibrillation.

All patients were under oral anticoagulation, with a target INR 1.8-2.2; the dose of warfarin taken by each patient was recorded, as well as the fluctuations of his/her INR during the in-hospital observation (expressed as standard deviation of the mean of the values of INR); 92% of the patients were also taking antiplatelet drugs (35 patients: aspirin 100 mg/day, 1 patient: clopidogrel 75 mg/day, 2 patients: aspririn and clopidogrel).

Eight (21%) patients were receiving digoxin, 18 (47%) were on beta-blockers, 16 (42%) were on ACE-inhibitors or angiotensin receptor blockers, and 22 (58%) were treated with diuretics; the average dose of furosemide was 37 mg/day and the average dose of carvedilol was 14 mg/day. Thus the primary treatment of the heart failure in LVAD patients was the device, as medical therapy was still suboptimal at the time of the physical evaluation.

Laboratory data were collected for all the patients at

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least at admission and at discharge from CR, and included evaluation of hemolysis, renal function (estimated creatinine clearance obtained by the Cockcroft-Gault formula and normalized to a body surface area of 1.73 m^2, $eCrCl_{BSA}$),[11,12] troponin-T, NT-pro-BNP, thyroid hormones, glycemic metabolism and glycated hemoglobin.

The rehabilitative protocol consisted of short-term (2 weeks, or more if needed) residential rehabilitation, during which patients participated in 3 daily sessions of exercise-based training, six days per week, including respiratory exercises, aerobic training and calisthenics. During the whole in-hospital rehabilitative period, the device rotation speed was maintained unmodified, as initially set by the cardiac surgery team to allow maximum support while avoiding suction events (range from 10000 to 11000 rpm, corresponding to an average nominal device output at rest of 4 to 5 L/min).

A transthoracic echocardiogram was performed at rest in all patients within few days from the pre-discharge evaluation of physical performance. Left ventricular end-diastolic diameter (LVEDD)[13] and volume (LVEDV), ejection fraction (EF), estimated pulmonary artery systolic pressure (PAPs), tricuspid annular plane systolic excursion (TAPSE)[14,15] and degree of opening of the aortic valves (AVO) were recorded. AVO was arbitrary graded as 0 if no valve opening occurred during prolonged observation, 1 if some opening was present only during the 8 seconds of periodic slow-down of rotation of the device, 2 if valve opening was visible during most cardiac cycles.

Evaluation of Physical Performance

The distance covered during a six-minute walk test was measured at admission (6MWT-in) and at the end of the rehabilitation period just before discharge (6MWT-out); the tests were performed in an indoor unobstructed 30 m long corridor, according to the recommendations of the American Thoracic Society.[16] For the purposes of this study, we divided the patients into two groups, according to the results of the pre-discharge 6-minute walking test: values above the median of 6MWT-out classified them as "better performers", while values below the median or incapacity to perform the test classified them as "poor performers".

With the aim to give indications as precise as possible about the physical activities affordable at home, on the day before discharge the patients' physical performance was evaluated also by means of a symptom-limited cardiopulmonary exercise test (CPET). A resting haemoglobin concentration (Hb), determined within 2 days of the exercise test, was available for each patient.

CPET Methodology and Parameters

The tests were performed in the late mornings, at least 3 hours after a light meal, on a computer driven bicycle ergometer (Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, CH; Ergoselect 100 ergometer, Ergoline GmbH, Bitz, D). A progressive ramp protocol was used, with a load of 4 to 10 W/min, adapted to age, sex and weight of the patient in order to produce a stress test of about 10 min duration; the test started at 0 W (after a 1 min warm-up period at 0 W, 60 rpm), until subjective exhaustion, or incapacity to maintain a pedal cadence >40 rpm, or appearance of arterial hypotension or vasoconstriction or other criteria of interruption.

Expired gas was collected by means of a tightly fitting face mask and continuously analyzed during the exercise test (Schiller Grantor CS-200 Power Cube) to measure oxygen uptake (VO_2), carbon dioxide production and minute ventilation. The oxygen uptake at the peak of the exercise (peak-VO_2) was calculated as the average over a 20 seconds period and was expressed as relative to body weight (ml/Kg/min); the peak exercise capacity was expressed in Watt as maximum sustained workload (W-max).[17-19]

A 12-lead electrocardiogram was monitored during the whole test. Peak heart rate (peak HR) as well as the heart rate recovery immediately after exercise (difference between peak HR and the heart rate recorded at 1st and 2nd minute of recovery, HRR-1 and HRR-2) have been recorded. We evaluated also the chronotropic response to exercise, defined as percentage of the increase in heart rate (HR) from rest to peak exercise divided by the difference between maximal HR and resting HR (ChRes = [peak HR-resting HR / (220-age, in males) or (200-age, in females)-resting HR] × 100).

Long-Term Follow-Up

After discharge from CR, all the patients were followed-up at regular intervals at the dedicated out-patient clinics of the three University Hospitals. A periodic home visit was also paid to all patients by a nurse and by an electronic engineer; they checked the regular function of the device and reported all possible complaints to the medical staff. Occurrence and time of heart transplantation and all-cause mortality (and causes of death) were documented.

Statistical Analysis

SPSS 15 Statistics Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) was used for the analysis. The descriptive statistics are expressed as mean±standard deviation for continuous variables; categorical variables are presented as absolute values with percentages.

Differences between groups have been evaluated by means of the Student *t*-test for unpaired samples.

Due to the low number of cases observed, only univariate analyses were performed to evaluate determinants of exercise tolerance and long-term survival. In the assumption that the

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study population was not normally distributed, correlations between parameters have been tested by Spearman non-parametric two-tail test. Association between exercise performance and survival was evaluated using Kaplan-Meier survival analysis. Pearson's chi-squared test was used to study the distribution of outcomes in relation to categorical variables. A p value <0.05 was considered statistically significant.

Statement

All the participants have been informed about the procedures they were undergoing; a written consent was obtained from all the patients before performance of CPET. The usual diagnostic and follow-up routine for the CR have been applied and no special test or treatment was performed; anyway, approval of the Provincial Ethics Committee was obtained for the study.

RESULTS

The main clinical characteristics of the patients and the results of the physical tolerance tests are summarized in Table 1, with a comparison between the better and poor performers at the final 6MWT.

Patients

All the patients in the cohort were critically ill before device implantation; at the time of observation, their mean EF continued highly depressed (EF 20±8%; range 5-34). The estimated systolic pulmonary artery pressure was within normal limits in the majority of the cases, while it was elevated in 2 patients (range 25-60 mmHg); the average TAPSE values were around the lower limits of normal, with wide variations among the patients (range 7-21 mm). In two-thirds of the cases, the aortic valve opened only during the 8 seconds per minute of slowing-down of the device rotation speed; in 1 patient no opening was observed, while in 11 cases the valve opened almost at every heart cycle.

All patients had laboratory signs of haemolysis, with average values of LDH (range 693-1390 U/l) that were two times the upper normal limits (450 U/l) and serum haptoglobin levels below the detection limits (<5.8 mg/dl) of our laboratory in all the cases.

At admission to CR, the plasma concentrations of NT-pro-BNP (range 345-7325 pg/ml) were moderately elevated in 9 patients (3 among the poor performers and 6 among the better performers).

While in our CR centre the mean hospital stay for chronic heart failure patients is 14.8±2.3 days, LVAD assisted patients needed only a slightly longer duration of residential rehabilitation (15.9±4.1 days; Student t-test: p=0.049).

Evaluation of Physical Performance

Seven patients (18%) were not able to perform the initial 6MWT, due to profound debilitation; after the short period of intensive rehabilitation, 6 (16%) patients were still not able to perform the final test: 4 patients were still not able to walk without support, 2 patient suffered complications and were transferred back to the original Hospital.

The median of the results of the final 6MWT was 360 meters; this value was used to separate the patients into two groups: 19 patients that walked a distance equal or greater than the median were classified as "better performers"; the 19 patients that did not perform the 6MWT-out or walked <360 m were classified as "poor performers".

Those patients who performed both tests gained an average of 106 meters (+40%; for the whole group p<0.001; for poor performers p=0.009; for better performers p<0.001). A correlation was evident between results of 6MWT-in and results of 6MWT-out for the whole group (Spearman ρ: correlation coefficient 0.504; p=0.005).

Eight patients were not able to perform the final CPET: 4 patients had still a profound muscular deconditioning, 1 case suffered of airways infection by Cytrobacter Coseri, and 3 patients had to be transferred back to intensive care due to major complications.

Patients who performed the final cardiopulmonary exercise test were able to sustain a rather poor workload (W-max) and reached also a quite depressed peak-VO_2, both in absolute terms and as percentage of the expected. At the time of the CPET, the patients presented a moderate degree of anaemia; anyway, no correlation was found between Hb levels and W-max (ρ 0.005, p=0.979) or peak-VO_2 (ρ 0.088, p=0.649). The Hb level did not correlate with peak HR (ρ 0.154, p=0.555), HR recovery at 1 min (ρ 0.083, p=0.708), HR recovery at 2 min (ρ 0.129, p=0.558), or chronotropic reserve (ρ -0.020, p=0.923).

Patients who were able to walk a longer distance at the final 6MWT reached also a significantly higher oxygen uptake at the pre-discharge CPET (ρ 0.651, p<0.001) and supported higher work load (ρ 0.448, p=0.013); Figure 1.

No correlation was found between the distance walked during the 6MWTs and the ejection fraction (6MWT-in: ρ -0.111, p=0.583; 6MWT-out: ρ 0.341, p=0.070), or between 6MWT-out and the end-diastolic diameter or end-diastolic volume of the left ventricle (respectively: ρ 0.021, p=0.933; and ρ 0.155, p=0.514). Similarly, left ventricle diastolic dimensions or EF did not demonstrate any correlation with parameters of performance at CPET (LVEDD *vs.* peak-VO_2: ρ -0.330, p=0.182; LVEDD *vs.* W-max: ρ -0.361, p=0.141; EF vs peak-VO_2: ρ 0.062, p=0.754; EF *vs.* W-max: ρ 0.180, p=0.359).

Poor performance patients were older than better performers. An inverse correlation was found between age and distance walked at the final 6MWT (6MWT-in: ρ -0.059, p=0.752; 6MWT-out: ρ -0.393, p=0.026), while no correlation was evi-

		All LVADs (n=38)	Poor performers * (n=19)	Better performers* (n=19)	*p value
Mean Age (years)		62.0±8.5	64.8±7.9	58.0±8.3	<0.05 (0.013)
Gender: M/F		33/5	15/4	18/1	ns (0.150)
Disease duration (years)		9.5±8.0	7.9±6.6	9.8±8.8	ns (0.510)
Dilated cardiomyopathy, n (%)		19 (50)	8 (42)	11 (58)	ns (0.330)
Time from LVAD implant (days)		32.7±13.8	32.6±11.5	29.5±14.7	ns (0.465)
Atrial fibrillation, n (%)		8 (21)	5 (26)	3 (16)	ns (0.125)
Intracardiac defibrillator, n (%)		37 (97)	19 (100)	18 (95)	ns (0.381)
Duration of intensive CR (days)		15.9±4.1	16.5±6.9	15.4±4.1	ns (0.580)
Follow-up (days)	average	877±626	673±457	885±728	ns (0.288)
	Median (95% CI)	611 (425-881)	625 (419-848)	588 (233-1404)	ns (0.288)
BSA, m^2		1.80±0.16	1.80±0.16	1.80±0.16	ns (0.981)
$eCrCl_{BSA}$, ml/min/1.73 m^2		74.2±24.1	64.1±22.2	84.3±22.3	<0.05 (0.024)
Known diabetes, n (%)		9 (24)	3 (16)	6 (32)	ns (0.184)
HbA_{1c} (% of Hb) in patients with diabetes		5.4±0.9	5.3±0.7	5.5±1.0	ns (0.826)
Hypothyroidism, n (%)		5 (13)	3 (16)	2 (10)	ns (0.686)
Hb levels (g/dl)		10.9±1.1	10.7±1.1	11.2±1.2	ns (0.306)
LDH, U/l		904.6±285.3	826.0±163.0	924.2±325.5	ns (0.495)
NT-pro-BNP, pg/ml		1450.8±2232.0	921.3±510.9	1715.5±1126.5	ns (0.647)
Average INR during hospitalization		2.23±0.36	2.34±0.40	2.18±0.29	ns (0.212)
Average of SD of INR		0.53±0.44	0.65±0.55	0.40±0.25	ns (0.108)
LVEDD, mm		59.7±10.8	60.0±12.0	59.5±10.8	ns (0.921)
LVEDV, ml/m^2		102.0±40.6	98.0±43.7	105.7±39.3	ns (0.674)
Ejection Fraction (%)		19.6±7.8	19.6±7.8	22.6±5.7	ns (0.234)
PAPs, mmHg		40.1±9.0	36.7±2.3	42.2±11.1	ns (0.440)
TAPSE, mm		15.8±4.3	17.6±3.5	14.2±4.5	ns (0.104)
Aortic valve opening	Score 0, n (%)	1 (3)	1 (5)	0	ns (0.296)
	Score 1, n (%)	26 (67)	11 (58)	15 (79)	
	Score 2, n (%)	11 (29)	7 (37)	4 (21)	
Average carvedilol dosage, mg/day		13.7±8.1	12.5±0.0	13.7±8.1	ns (0.771)
Average furosemide dosage, mg/day		37.5±49.2	31.2±32.2	26.8±31.0	ns (0.722)
Patients on oral anticoagulation + antiaggregation, n (%)		22 (61)	10 (52)	12 (63)	ns (0.631)
6MWT					
6MWT-in, m		262.5±61.7 (n = 31)	227.8±59.2 (n = 13)	287.5±51.5 (n = 18)	<0.01 (0.006)
6MWT-out, m		352.0±80.6 (n = 32)	278.8±66.9 (n = 13)	402.0±41.3 (n = 19)	<0.001
Δ-6MWT, m		106.5±98.5	75.1±85.5	129.6±103.1	ns (0.117)
CPET parameters		**(n = 30)**	**(n = 11)**	**(n = 19)**	
W-max, W		35.1±10.5	28.3±5.9	39.1±10.7	<0.01 (0.005)
Peak-VO_2, ml/Kg/min		12.0±3.1	10.5±2.5	13.0±3.0	<0.05 (0.028)
Peak-VO_2 percentage of expected (%)		47.1±12.8	46.0±12.1	47.7±13.4	ns (0.734)
Peak HR, bpm		116.1±19.6	111.2±17.0	118.8±21.1	ns (0.459)
HRR-1, bpm		12.8±11.4	15.7±15.7	11.3±8.7	ns (0.379)
HRR-2, bpm		19.7±14.7	21.2±19.7	19.0±12.2	ns (0.732)
Chronotropic reserve, %		35.8±24.0	31.6±25.2	34.1±25.1	ns (0.810)

LVAD: patients with left ventricular assist device; p: level of statistical significance, between the groups of poor *vs.* better poor performers; BSA: body surface area; $eCrCl_{BSA}$: estimated creatinine clearance normalized to a body surface area of 1.73 m^2; CR: cardiac rehabilitation; Hb: haemoglobin; LDH: lactate dehydrogenase; INR: international normalized ratio; SD: standard deviation; LVEDD: left ventricle end-diastolic diameter; LVEDV: left ventricle end-diastolic volume; PAPs: estimated pulmonary artery systolic pressure (mmHg); TAPSE: tricuspid annular plane systolic excursion (mm); 6MWT: distance (meters) walked during a six-minute walking test; 6MWT-in: 6MWT at admission; 6MWT-out: 6MWT ad discharge; Δ-6MWT: difference between 6MWT-in and 6MWT-out; CPET: cardiopulmonary exercise test; W-max: maximum sustained workload; peak-VO2: peak oxygen uptake; HRR-1 and HRR-2: heart rate recovery 1 and 2 min after end of exercise.

Table 1: Main clinical characteristics of the patients and results of the exercise tolerance tests.

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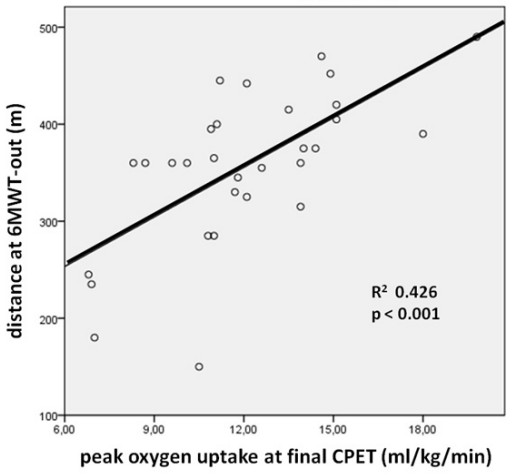

Figure 1: Correlation between peak oxygen uptake at pre-discharge CPET and distance walked during the final 6MWT.

dent with results of CPET (age *vs* peak-VO_2 χ^2 -0.138, p=0.468; age *vs*. W-max χ^2 -0.114, p=0.549).

No correlation was evident between sex and level of performance (χ^2 2.073, p=0.150), or between duration of the disease and distance walked (ρ -0.098, p=0.594). Patients with diabetes were equally distributed among the poor and better performance groups (χ^2 1.768, p=0.184); the mean value of glycated haemoglobin was similar in the patients of both groups.

Kidney function was worse in older patients, as demonstrated by the inverse correlation between $eCrCl_{BSA}$ and patients' age (ρ -0.738, p<0.001). The cases with worse performance at 6MWT-out had mean $eCrCl_{BSA}$ values significantly lower than those of better performers, but no direct correlation existed between individual $eCrCl_{BSA}$ and results of 6MWT-out (ρ 0.336, p=0.108), or peak-VO_2 at final CPET (ρ 0.252, p=0.313) or W-max (ρ -0.002, p=0.994).

Long-Term Follow-Up

Patients had been followed for a median of 611 days after device implantation (range 72-2432); for the poor performers the median follow-up was 625 days, while for better performers it was 588 days.

Seven patients have been transplanted during the follow-up period (4 in the better and 3 in the poor performance group); they were all alive at the time of follow-up. A total of 15 patients died during the observation period: in 1 instance the cause of death was due to pump thrombosis (after 432 days of support), while it was linked to intestinal ischemia in 1 case (72 days of support), hemorrhagic stroke in 1 case (1598 days), in 1 case severe right ventricular failure, in 3 cases (after 438, 906 and 1151 days), sepsis and multi-organ failure in 4 cases (after 230, 419, 597 and 625 days), non-cardiac causes in 3 cases (hepatic cancer 1 case; head trauma 2 cases), unknown causes in 2 cases.

At the time of final follow-up evaluation, 9 deaths had occurred in the group of poor performers and 6 in the group of better performers (not significant difference: χ^2 0.991, p=0.319); even at intermediate follow-up evaluation, no significant difference was observed between the two groups (1 year follow-up: χ^2 0.230, p=0.631; 2 years follow-up: χ^2 1.576, p=0.209).

Figure 2A presents the Kaplan-Meier survival plot for the whole period of follow, with patients stratified according to results of pre-discharge 6MWT; an analysis was also made for intermediate follow-up, at 1 and 2 years since LVAD implantation. Although there was a tendency towards higher survival rates for the group of better performers at the final long-term follow-up, the differences were not statistically significant (Mantel-Cox log rank: long-term follow-up: χ^2 3.091, p=0.079; intermediate 1 year follow-up: χ^2 0.115, p=0.734; intermediate 2 years follow-up: χ^2 0.959, p=0.328). A further evaluation was made also using the value of 300 meters at 6MWT-out as discriminating cut-off, as used in previous studies:[10] patients that walked less than 300 m presented worse long-term outcomes in comparison to patients that walked longer distances. The Kaplan-Meier curves are presented in Figure 2B (Mantel-Cox log rank: χ^2 11.798, p=0.001).

Good discrimination to predict long-term survival rate was given by inability to perform the final CPET or by a poor performance, defined as values of W-max or peak-VO_2 below the median respectively of 32 W and 11.7 ml/kg/min. The Kaplan-Meier survival curves for the two groups with W-max or peak-VO_2 above or below the median are presented in Figures 3A and Figure 3B (Mantel-Cox log rank respectively: χ^2 9.890, p=0.002; χ^2 4.151, p=0.042).

Patients with reduced chronotropic reserve (below the median of 22.37%) at the pre-discharge CPET did not present different long-term mortality in comparison to the patients with more preserved ChRes (4 deaths among 13 patients with ChRes below the median, *vs.* 7 among 13 patients with higher ChRes;

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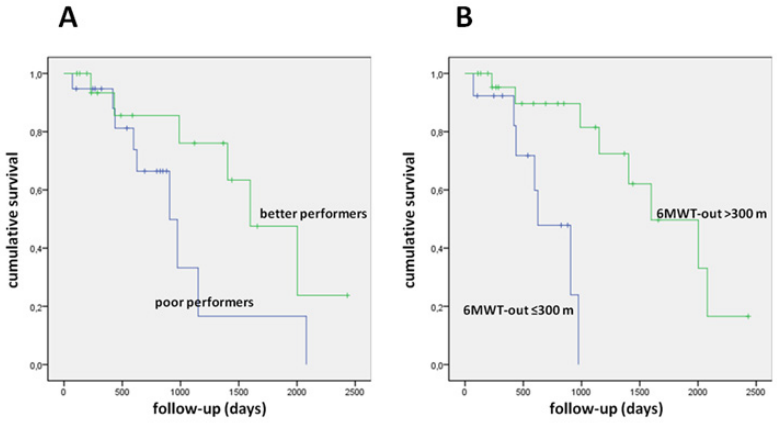

Figure 2: Patients survival according to the median value (360 m) of the distance walked at the final 6MWT (A) and according to a distance of 300 m (B), performed after a short period of intensive, exercise-based cardiac rehabilitation (Kaplan-Meier survival plot).

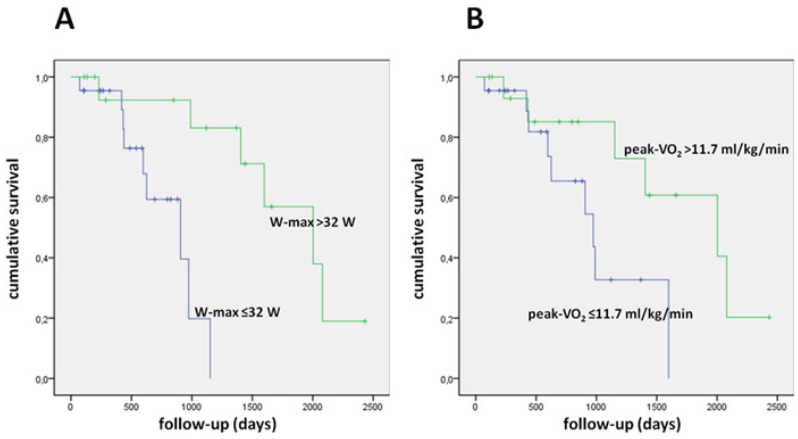

Figure 3: Kaplan-Meier survival curves for the groups of patients with peak workload (W-max, in A) or peak oxygen uptake (peak-VO_2, in B) above or below the median at pre-discharge CPET.

χ^2 1.418; p=0.234).

Age over the median of 62 years did not predict long-term mortality (Mantel-Cox log rank for the Kaplan-Meier survival curves of patients ≥62 years *vs.* <62 years old: χ^2 0.760, p=0.383).

Seven out of 21 patients with body surface area (BSA) lower than 1.867 m^2 died during the follow-up period, but the correlation between low BSA and long-term mortality did not reach statistical significance (χ^2 1.944; p=0.163).

During the CR period, two thirds of the patients that subsequently died had an $eCrCl_{BSA}$ ≤60 ml/min (mean 48.8±7.8 ml/min); the correlation between reduced $eCrCl_{BSA}$ and mortality was statistically significant (χ^2 7.248; p=0.007).

Ten out of 17 patients with Atrial Fibrillation (AF) died during the follow-up, *vs.* 5 patients out of 10 in sinus rhythm who survived (χ^2 4.821; p=0.028).

As three deaths were due to ischemic causes, the possible correlation with INR oscillations during the in-hospital observation was examined: fluctuations of INR ≥0.39 (median of the standard deviation of the oscillations registered in all the patients) during the hospitalization period were correlated with future mortality (χ^2 4.800, p=0.028). No data are available about the coagulation parameters during the follow-up.

No correlation was found between concomitant use of antiplatelet drugs and long-term mortality (9 cases were taking antiplatelet therapy and 5 cases were not; χ^2 0.020, p=0.886).

Eight of the patients who died had a prolonged delay from surgery to beginning of rehabilitation, greater than the median of 28.5 days, but the correlation between time from surgery and long-term mortality was not statistically significant (χ^2 0.110; p=0.740). No correlation was found between duration of the period of rehabilitation (greater than the median of 15 days) and long-term mortality (chi-square 0.308; p=0.579).

The echocardiography parameters observed in the relatively early phases of LVAD support (LVEDD, LVEDV, EF, PAPs, TAPSE, opening of the aortic valve) did not help classify-

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ing the patients in relation to their long-term prognosis.

DISCUSSION

The implant of a left ventricular assist device in patients with advanced CHF leads to an improvement of hemodynamic parameters,[1-9,20-22] whose clinical effects are visible rather early after beginning of support.[4] However, physical performance could take some time to enhance from the initiation of circulatory assistance, and few data are available to indicate if an axial-flow LVAD could give enough support and permit LVAD recipients afford some physical activities already in the early phases after implantation.

A short period of intensive, exercise-based rehabilitation allowed our LVAD patients, recently submitted to implant of an axial-flow device as destination therapy, gain a significant improvement in walking distance at the pre-discharge 6MWT, already in a rather early period (on average <2 months) since beginning of circulatory assistance.

The absolute distance walked by our LVAD patients is slightly higher than that reported by Slaughter et al[23] in patients observed later (at 3 months) after implant of a continuous-flow device (319±191 m) and is substantially identical to that reported by Rogers et al[7] in continuous-flow LVAD patients observed 6 to 24 months after beginning of hemodynamic support as destination therapy (at 6 months: 350±198 m; at 24 months: 360±210 m). An absolute mean distance of 352 meters during the 6MWT-out and a mean improvement of 106 meters, obtained by our patients after short-term CR, can be considered as markers of good response to rehabilitation; the improvement of such simple functional independence measures is believed to reflect the acquisition of sufficient capacity of performing daily life activities.[24,25] In CHF patients, a walking distance ≥340 m and an increase of >50 m between 6 MWT-in and 6 MWT-out is known to be associated with a 23% increased likelihood of survival.[26] In axial-flow LVAD recipients, recently Hasin et al[10] reported for the first time somehow similar results: patients with better performance in a 6 MWT conducted >2 months after device implantation presented a significantly lower risk for late all-cause mortality in comparison to patients that walked less than 300 m.

It is interesting to notice that in this latter study one of the exclusion criteria was a 6 MWT performed <2 months since device implantation; our study, by the contrary, has been conducted exactly in the group of LVAD recipients observed and rehabilitated in a rather early phase. Also among our cases as in the study by Haskin, those patients that, in spite of the early beginning and the intensiveness of CR, were not able to reach a distance of ≥300 m at the final 6 MWT had a worse prognosis in comparison to those who walked longer distance.

Besides the 6 MWT-out, 30 of our patients (79%) were also able to sustain a stress test at the end of the short period of rehabilitation. Their average working capacity, expressed in terms of afforded workload and peak oxygen uptake, was anyway poor. Both W-max and peak-VO_2 were particularly low in the group of poor 6MWT performers; a good correlation was confirmed between 6MWT-out and peak-VO_2 also in LVAD-supported patients (figure 1).[27,28] Similarly to the 6MWT-out, patients with below the median values of W-max (32 W) and peak-VO_2 (11.7 ml/kg/min) presented worse long-term outcomes. Thus, evaluation of physical performance by a symptom-limited CPET or even by a simpler test like the 6MWT seems to be able to provide useful prognostic information in patients studied in the early phase after implant of an axial-flow LVAD.

Speculatively, patients reaching a higher level of performance after a short period of CR could have gained enough fitness to continue some kind of regular physical activities also after hospital discharge. A regular physical activity is known to have multiple positive effects in CHF patients,[29] that could be relevant also in LVAD-assisted cases. Even modest intensity isotonic exercise influences the integrity of the vascular endothelium and improves vascular repair, besides causing favourable adaptations in blood coagulation and inflammation markers,[30-32] that possibly lead to reduction of hemorrhagic or thrombotic complications. Physical activity reduces peripheral resistances and increases end organ perfusion.[33] The abnormalities of autonomic nervous system present in CHF are progressively reduced by physical exercise, conditioning a reduction of long-term arrhythmic risk and allowing favourable outcomes.[34,35] Right ventricle hypertrophy can be induced by isotonic exercises,[36] that could allow persistence of a normal right ventricular function even under an increased venous return in CHF patients supported by mechanical assistance of the left ventricle. A combination of these factors could eventually lead to improved survival of LVAD patients.

Scant data are present in literature reporting the effort tolerance of patients evaluated by CPET early after beginning of assistance by axial-flow LVADs. Demopoulos et al[8] studied a smaller number of LVAD patients (7 cases) comparing them to 14 CHF patients after 1 and 3 months since the index event; their LVAD patients reached a maximum workload significantly higher than our cases (W-max: LVAD 59±12 W after 1 month and 73 ±18 W after 3 months; CHF 83±26 W after 3 months; in comparison to our patients: $p<0.001$). In a paper by Maybaum et al,[5] an heterogeneous group of patients supported by different models of devices (only 1 patient with axial-flow pump) succeeded to work for 8.7±3.2 minutes during an exercise test performed one month after LVAD implantation. This result is not easily comparable with our data, as in Maybaum's work the protocol of exercise test is not detailed, while in our cases the effort intensity was adapted to age, sex and body weight of the patient in order to allow an optimal stress test duration of about 10 min.

Even though the afforded workload was low, the peak-VO_2 reached by our patients was similar to that reported in the cited study by Dimopoulos et al[8] (LVAD at 1 month 12.4±2.1

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ml/Kg/min, p=0.749; LVAD at 3 months 13.8±2.8 ml/Kg/min, p=0.169). Another report from the same group[6] and the cited paper by Maybaum et al[5] gave again similar results for LVAD patients studied 1 month after device implantation.

Besides adding information on the effort capacity of patients in the early period of LVAD support, our study demonstrates that inability to develop substantial workload and reach acceptable oxygen uptake at pre-discharge CPET are also predictors of poor long-term survival.

An impaired chronotropic response (ChRes) to exercise is generally considered as an indicator of cardiac autonomic abnormalities, related to the disease severity, and is regarded as a valid prognostic marker in chronic heart failure patients.[37] In LVAD implanted patients, ChRes abnormalities are reported to remain unchanged during the first 3 months after LVAD implantation, at least in a small study[8] in which the presented values were not dissimilar from those found in our group of patients (42±18% at 1 month and 57±31% at 3 months since implant, *vs.* 36±24% in our cases). These findings confirm the presence of profound cardiac autonomic nervous system abnormalities also in our cases, not (yet) influenced by the hemodynamic effects of the LVAD. The long-term prognostic effects of cardiac dysautonomia in axial-flow LVAD patients need to be assessed with further studies.

In a recent study by Komodo et al on axial-flow devices, a body surface area below a cut-off point of 1.867 m^2 was associated with increased mortality due to stroke or systemic bleeding.[38] Even though 7 deaths occurred in our cases among the patients with lower BSA, the correlation with mortality was not significant in our study, perhaps due to the relatively small cohort of patients.

Renal dysfunction is a well-known prognostic element for CHF patients; it is strongly and independently associated with an increased mortality and morbidity risk across a broad range of heart failure populations.[12,39,40] Also in our LVAD population, impaired renal function was a predictor of poor long-term prognosis. It is known that the increased flow generated by the circulatory assisting device modifies kidney perfusion and may improve renal function.[41,42] The persistence of impaired kidney function after two months of circulatory support in some of our patients may be an indicator of the presence of a more advanced renal disease, that could influence long-term outcomes.

In CHF patients, the presence of atrial fibrillation is associated with worse left ventricular filling and cardiac output, and is correlated with increased short- and long-term morbidity and mortality.[43] It is not yet clearly known what could be the relevance of AF on the overall (cardiac plus device) output in LVAD-supported individuals; no conclusive data are also available on the long-term impact of AF over morbidity and mortality of such patients.[44,45] As regards the cases we studied, more deaths occurred among the patients in atrial fibrillation than among patients in sinus rhythm. A presumably irregular level of anticoagulation could have contributed to ischemic deaths, as suggested by greater oscillations of the INR values during hospitalization among patients that died during follow-up. To the best of our knowledge, no data are yet available on the most appropriate anticoagulation level for LVAD patients in AF, as these cases are in the same time at higher thromboembolic (AF plus device) and higher hemorrhagic risk (concurrent use of antiplatelet drugs in some cases, plus effects of the device on von Willebrand coagulation factor).[46-48] Further studies are needed on this topic.

LIMITATIONS OF THE STUDY

This is a single-centre, retrospective study; it reports the results of cases observed in a cardiac rehabilitation unit, where patients were admitted within 2 months after device implantation. Consecutively admitted patients were included in the study, according to the inclusion/exclusion criteria. So, it is an observational, non-randomized study.

Strength of our study is that the patients are homogeneous for kind of implanted device (Jarvik-2000 Flowmaker), similar preoperative management procedures, and short time of first observation since begin of circulatory assistance; these selection criteria imply a limitation due to the reduced number of observed cases, that does not allow refined statistical analysis and conditions a modest statistical power. Nevertheless, our findings on the prognostic relevance of physical performance and renal function are in concordance with other studies on LVAD and CHF cases.

CONCLUSION

When observed within the first two months since beginning of circulatory support, CHF patients assisted by an axial-flow LVAD still present reduced workload capacity; those patients that after a short-term intensive exercise-based rehabilitation reach better physical performance, being able to walk at least 300 meters or to develop at least 32 W during a bicycle stress test, present better long-term prognosis. Performing a functional evaluation of LVAD-assisted patients before discharge from a cycle of early intensive cardiac rehabilitation seems to be useful to provide some prediction on their long-term survival.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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STATEMENT OF AUTHORSHIP

All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The authors have no relationship with biomedical device companies or other corporations whose products or services are related to the subject matter of the article.

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