Transplant International

ORIGINAL ARTICLE

Exercise capacity, muscle strength and objectively measured physical activity in patients after heart transplantation

Miek Hornikx[1], Lucas Van Aelst[2], Guido Claessen[2], Walter Droogne[2], Gabor Vörös[2], Stefan Janssens[2] & Johan Van Cleemput[2]

1 Department of Rehabilitation Sciences, University Hospitals Leuven, KU Leuven-University of Leuven, Leuven, Belgium
2 Department of Cardiovascular Sciences, University Hospitals Leuven, KU Leuven-University of Leuven, Leuven, Belgium

Correspondence
Dr Miek Hornikx, Physical Medicine and Rehabilitation, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.
Tel.: +(32) (0)16344467;
e-mail: miek.hornikx@kuleuven.be

SUMMARY

Maximal exercise capacity of patients after heart transplantation (HTX) remains limited, affecting their quality of life. Evidence on the evolution of muscle strength and physical activity (PA) post-HTX is lacking, but a prerequisite to tailor cardiac rehabilitation programmes. Forty-five consecutive patients were evaluated every 3 months during the first year post-HTX. Functional exercise capacity (Six minutes walking distance test (6MWD)), peripheral (Quadriceps strength (QF)) and respiratory (Maximal inspiratory strength (MIP)) muscle strength were evaluated. PA (number of steps (PAsteps), active time (PAactive) and sedentary time (PAsed)) was objectively measured. 6MWD, QF, MIP, PAsteps and PAactive significantly improved over time ($P < 0.001$). No change in PAsed was noticed ($P = 0.129$). Despite improvements in 6MWD and QF, results remained substantially below those of age-and gender-matched healthy subjects. One year post-HTX, 30% of patients presented with peripheral muscle weakness. Baseline levels of 6MWD and QF were significantly higher in patients with pretransplant LVAD-implantation and this difference was maintained during follow-up. cardiac rehabilitation, combining aerobic exercise training and peripheral muscle strength training, is mandatory in patients post-HTX. Inspiratory muscle training should be implemented when respiratory muscle weakness is present. Programmes improving physical activity and reducing sedentary time post-HTX are essential.

Transplant International 2021; 34: 2589–2596

Key words
cardiac rehabilitation, exercise capacity, heart transplantation, muscle strength, physical activity

Received: 25 April 2021; Revision requested: 10 September 2021; Accepted: 11 October 2021; Published online: 3 November 2021

Introduction

In selected patients with end-stage chronic heart failure, heart transplantation (HTX) offers the prospect of improving both survival and quality of life [1–3].

Despite undisputable improvements in cardiac function post-HTX, maximal exercise capacity of patients 1 year after surgery is, on average, only half that of age- and gender-matched healthy subjects [2,3]. The evolution of maximal exercise capacity and the reasons for the persistent deconditioned state of patients post-HTX have been investigated extensively and has been associated with poor prognosis [3]. Both central and peripheral abnormalities might be responsible [2,4]. Cardiac dysfunction

doi:10.1111/tri.14139

is the most important central abnormality and is at least partially caused by cardiac denervation. Typical for cardiac denervation is that heart rate increase during exercise depends on circulating catecholamines rather than on autonomic regulation. This results in a delayed and blunted increase in heart rate during exercise. On top of cardiac denervation, allograft diastolic dysfunction aggravates cardiac dysfunction [2,4,5]. With regard to peripheral abnormalities, notable changes in the muscles of patients post-HTX include a decreased level of type I (oxidative) fibres and a reduction in capillary density and oxidative enzyme capacity [2,6]. These changes might be caused by the inactive state of patients pre-HTX and the use of corticosteroids and other immunosuppressive medication post-HTX [2]. Muscle abnormalities, in combination with endothelial dysfunction and abnormal sympathetic activation, result in a reduced oxygen delivery to and utilization by the working muscles [2]. This abnormal oxidative muscle metabolism post-HTX gives rise to metabolite accumulation in the muscles leading to overactivation of muscle metaboreceptors. Consequently, the so-called muscle metaboreflex response is initiated, resulting in peripheral vasoconstriction, symptoms of dyspnoea and early interruption of exercise [7].

Unlike data on maximal exercise capacity, longitudinal data on muscle strength post-HTX are scarce. A sufficient level of muscle strength and exercise capacity, which can be obtained by following evidence-based cardiac rehabilitation, is necessary in order to return to work and to perform other kinds of daily physical activity (PA). In addition, being physically active is proven to provide health benefits in the general population [8,9]. Tackling physical inactivity in patients post-HTX might, therefore, require specific attention.

The aim of our study was to measure the evolution of peripheral and respiratory muscle strength and PA in the first year post-HTX in order to estimate the need for and the content of cardiac rehabilitation. That way, the functioning of patients post-HTX and their quality of life can be optimized. Our hypothesis was that both peripheral and respiratory muscle strength and PA would improve during the course of the study, but remain below levels of age-and gender-matched healthy subjects.

Materials and methods

Subjects

Sixty two patients (male/female; 18–67 years), who underwent a heart transplantation (HTX) between July 2017 and February 2021, were addressed for the study. Patients, not being able to perform tests for functional exercise capacity and muscle strength because of musculoskeletal, neurological or other medical problems, were excluded.

Fifty-five patients post-HTX (89%) were finally included and 45 patients (82%) were followed for a period of 1 year. One patient died 4 months post-HTX because of post-transplant lymphoproliferative disorder. All patients signed a written informed consent. The study was approved by the local ethical committee. The flow chart of the study is depicted in Fig. 1.

Design

The study was a prospective observational study.

Measurements

Patients were tested at 5 timepoints postoperatively. The first evaluation was performed at hospital discharge, thereafter patients were tested every 3 months until the end of the first year. Patients were advised to follow physiotherapy at home during the first 6 weeks after surgery. Subsequently, participation in a cardiac rehabilitation programme of 6 months was recommended.

Six minutes walking distance test

Functional exercise capacity was evaluated by a six minutes walking distance test (6MWD), in a 50-meter corridor. Patients were asked to cover as much distance as possible in 6 min. Heart rate and oxygen saturation were continuously monitored. The Borg Rating of Perceived Exertion scale was interrogated before and after the test. Standard encouragement was provided during the test. Results were compared with reference values developed by Troosters *et al.* [10] Functional intolerance was defined as 6MWD < 300 meter.

Muscle strength

Peripheral muscle strength. Isometric quadriceps strength (QF) was measured using the Biodex dynamometer (Biodex System 4 pro; Enraf Nonius; Delft; The Netherlands). Peak extension torque was evaluated at the right side at 60° knee flexion. The test was performed at least three times and the highest of two reproducible tests (<5% difference) was used for further analyses. Reference values for QF, developed by Decramer *et al.* [11], were used for comparison. Patients were labelled as having peripheral muscle weakness (PMW) when QF < 70% predicted.

Transplant International 2021; 34: 2589–2596

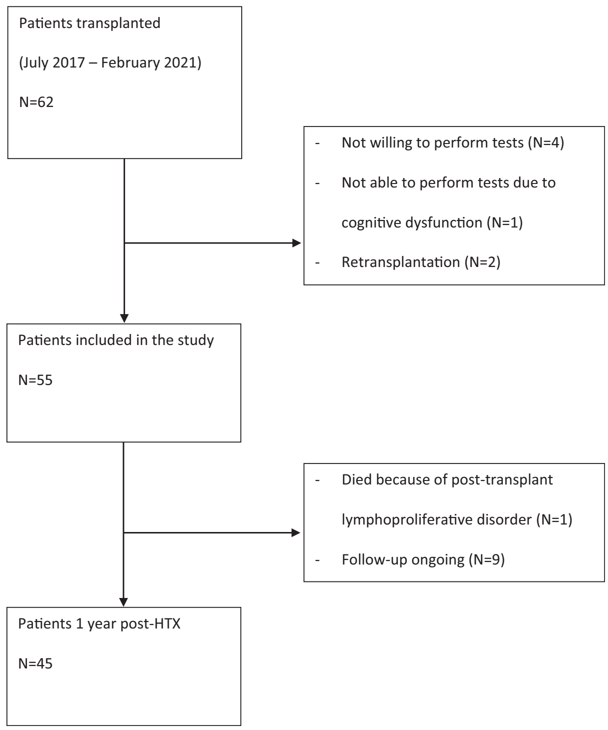

Figure 1 Flow chart of the study.

Respiratory muscle strength. Maximal inspiratory strength (MIP) was measured according to the Black and Hyatt procedure [12]. Briefly, MIP measurements were performed form residual volume (RV). The test was repeated until 3 stable measurements (<5% difference) could be obtained. The highest value was used and compared with reference values from Rochester and Aurora [13]. Respiratory muscle weakness (RMW) was defined as MIP<70% predicted [14].

Physical activity

PA was assessed using a validated PA monitor, the Dynaport MoveMonitor (McRoberts BV; The Hague; The Netherlands). The device was inserted in an elastic belt and positioned on the lower back at the height of the second lumbar vertebra, nearby the body's centre of mass. Patients received the activity monitor at every study visit and were asked to wear the device for the following 7 consecutive days at home during daytime hours. Number of steps (PAsteps), active time (PAactive: walking and standing) and sedentary time (PAsed: lying and sitting) were registered. Days with a wearing time <8 hours were excluded from the analysis [15] and at least 3 weekdays of monitoring were considered necessary to obtain a reliable PA pattern [16].

Other data

Demographic data, pretransplant LVAD-implantation, days on waiting list, time on intensive care unit (ICU) and total hospital duration were retrieved from the medical file of the patients. Participation in physiotherapy at home and cardiac rehabilitation was interrogated during every visit.

Statistical analyses

SAS Enterprise guide 7.1 was used to perform the statistical analyses. To check normality of data, a Shapiro-Wilk test was performed. If data were normally distributed, mean ± std was used. Otherwise, data were expressed as median [Q1-Q3]. Categorical variables were analysed using a Fisher's Exact test. A repeated measures ANOVA (proc mixed procedure) was applied to determine the time, group and interaction effect of 6MWD, muscle strength and PA. The level of significance was set at $\alpha = 0.050$.

Results

Baseline characteristics and measurements at hospital discharge

Baseline characteristics of the participants are presented in Table 1. The mean age of the study group was 49 ± 14 years. The majority of patients were male (67%) and diagnosed with nonischaemic heart disease before HTX. An overview of the measurements at hospital discharge is provided in Table 2. As expected, 6MWD was severely impaired at hospital discharge and muscle strength was moderately affected. Patients were physically inactive, with high sedentary time.

Evolution of functional exercise capacity, muscle strength and physical activity

6MWD, QF and MIP significantly improved over time ($P < 0.001$). The most important improvements in QF and MIP were seen during the first 6 months of follow-up, while improvements in 6MWD were seen up to 9 months post-HTX. A significant time effect in PAsteps and PAactive ($P < 0.001$) could be noticed. Significance was only reached when compared with baseline levels. PAsed did not significantly change during the first postoperative year ($P = 0.129$). (Fig. 2) After 1 year, MIP reached normal values (95 ± 23% predicted), while 6MWD (78 ± 12% predicted) and QF

(79 ± 17% predicted) remained lower compared with age-and gender-matched healthy subjects.

Despite the improvements in QF and MIP, 30% of patients presented with PMW and 15% of patients with RMW at the end of the first year. All patients were capable of walking more than 300 meter during the 6MWD.

Difference between patients with and without pretransplant LVAD-implantation

Baseline characteristics and measurements at hospital discharge in patients with and without pretransplant LVAD-implantation are shown in Tables 3 and 4. A significant time and group effect in 6MWD (time effect: $P < 0.001$; group effect: $P = 0.005$) and QF (time effect: $P < 0.001$; group effect: $P = 0.004$) could be detected. MIP ($P < 0.001$), PAsteps ($P < 0.001$) and PAactive ($P = 0.002$) significantly improved in patients with and without pretransplant LVAD-implantation. The time effect in PAsed was not significant, however, a clear trend was visible ($P = 0.052$) and attributable to a significant decrease in patients without a pretransplant LVAD-implantation ($P = 0.002$) (Fig. 3).

Table 2. Measurements at hospital discharge.

Variable	
Functional exercise capacity	
6MWD (meter)	410 [321–466]
6MWD (% predicted)	53 ± 12
FI, *N* (%)	8 (19)
Peripheral muscle strength	
QF (Nm)	116 ± 53
QF (% predicted)	65 ± 21
PMW, *N* (%)	27 (61)
Respiratory muscle strength	
MIP (cmH_2O)	−67 ± 25
MIP (% predicted)	63 ± 21
RMW, *N* (%)	28 (67)
Physical activity	
PAsteps (number/day)	3416 ± 1240
PAactive (minutes/day)	195 ± 73
PAsed (minutes/day)	615 ± 106
Wearing time (minutes/day)	812 ± 79

Data are presented as mean ± std, median [Q1-Q3] or as *N* (%).

6MWD, six minutes walking distance test; FI, functional intolerance; QF, quadriceps strength; PMW, peripheral muscle weakness; MIP, maximal inspiratory strength; RMW, respiratory muscle weakness; PAsteps, number of steps; PAactive, active time; PAsed, sedentary time.

Discussion

This study investigated the evolution of 6MWD, QF, MIP and PA during the first year post-HTX in a carefully phenotyped cohort of patients. 6MWD, QF and MIP significantly improved over time. We also observed significant improvements in PAsteps and PAactive, but this did not result in a reduction in PAsed. Despite the improvements in QF, 30% of the patients still presented with peripheral muscle weakness (PMW) after 1 year of follow-up. Somewhat surprisingly, baseline levels of 6MWD and QF were significantly higher in patients with pretransplant LVAD-implantation and this difference in favour of the LVAD population was maintained during follow-up.

Table 1. Baseline characteristics.

Variable	
Age (years)	49 ± 14
BMI (kg/m²)	24 ± 4
Gender (male, *N* (%))	30 (67)
Pretransplant LVAD-implantation (*N* (%))	24 (53)
Days waiting list (*N*)	194 [71–477]
Time on ICU (*N*)	5 [4–7]
Total hospital duration (*N*)	21 [18–24]

Data are presented as mean ± std, median [Q1–Q3], *N* or as *N* (%).

BMI, body mass index; LVAD, left ventricular assist device; ICU, Intensive care unit.

Comparison of our findings with data in literature is only possible for QF. Schaufelberger *et al.* [6] evaluated QF over a period of 6–9 months post-HTX in a very small number of patients, participating in a post-HTX rehabilitation programme. The nonsignificant improvement of 5% in the latter study was lower than the significant 19% improvement in QF we detected in our study. Focusing on PA, the baseline level of PAsteps in our study was somewhat higher compared with another study objectively measuring PA levels in patients post-HTX (3416 ± 259 steps vs. 3036 ± 439 steps (mean ± SEM)) [17]. With age and gender being similar in both studies, this baseline difference might be related to the use of a different activity monitor using different algorithms determining the number of steps. In both the study of Jakovljevic *et al.* [17] and our study, the average number of steps more than doubled from baseline to 1 year of follow-up. Despite the improvement in PAsteps during the first year post-HTX, only a sobering

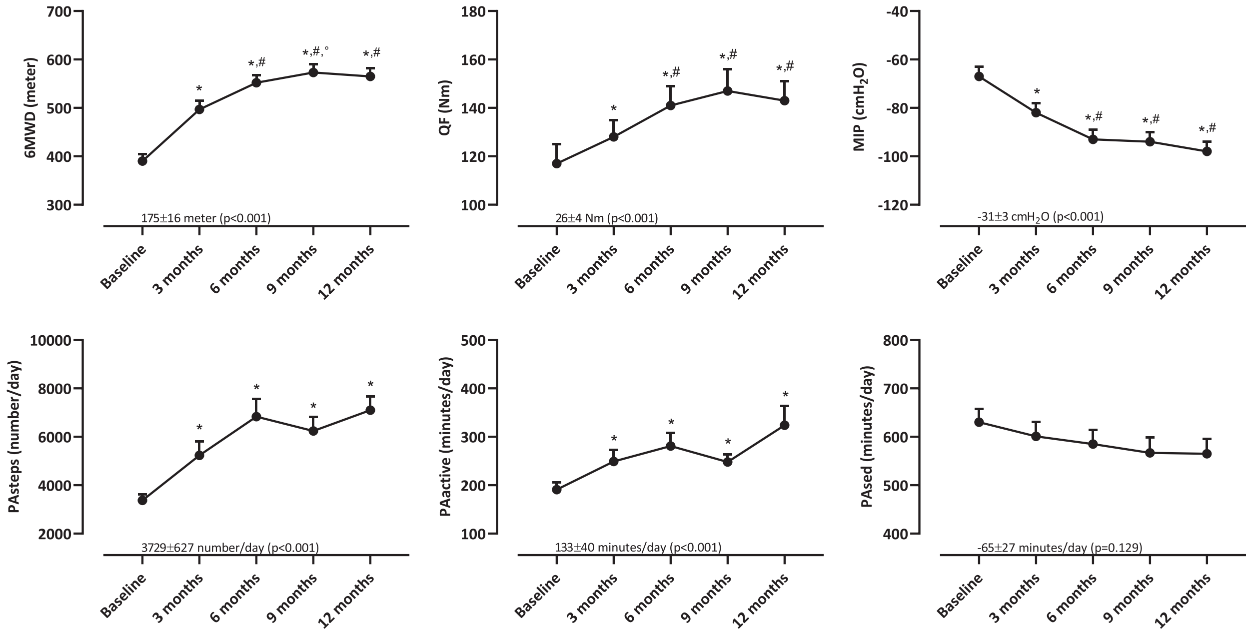

Figure 2 Evolution of functional exercise capacity, muscle strength and physical activity during 1 year of follow-up. 6MWD: Six minutes walking distance test; QF: Quadriceps strength; MIP: Maximal inspiratory strength, PAsteps: Number of steps, PAactive: Active time; PAsed: Sedentary time. The mean evolution from baseline to 1 year of follow-up is depicted in the figure. *: significant result from baseline; #: significant result from 3 months; ° significant result from 6 months. $P < 0.050$.

Table 3. Baseline characteristics of patients with and without pretransplant LVAD-implantation.

Variable	LVAD (n = 24)	No-LVAD (N = 21)	P-value
Age (years)	46 ± 15	52 ± 12	0.132
BMI (kg/m²)	23 ± 4	25 ± 4	0.116
Gender (male *N* (%))	19 (79)	11 (52)	0.057
Days LVAD (*N*)	439 ± 311		
Days waiting list (*N*)	384 ± 306	199 ± 203	0.023
Most recent waiting place pre-HTX			
Home, *N* (%)	22 (92)	20 (95)	1.000
ICU, *N* (%)	1 (4)	1 (5)	
Ward, *N* (%)	1 (4)	0 (0)	
Time on ICU (*N*)	6 ± 7	8 ± 8	0.381
Total hospital duration (*N*)	22 ± 9	24 ± 10	0.468

Data are presented as mean ± std, median [Q1–Q3], *N* or as *N* (%).

BMI, body mass index; LVAD, left ventricular assist device; ICU, intensive care unit.

$P < 0.050$.

13% of patients in our study succeeded in reaching the recommended daily level of 10 000 steps [18], associated with improved health outcomes in the general population [8,9]. Programmes improving PA, reducing sedentary time and evaluating their health benefits in patients post-HTX might be valuable. Future research on this topic is warranted and studies should include longer follow-up periods, since a behavioural change is necessary to alter PA levels [19]. Subanalyses revealed that both 6MWD and QF at hospital discharge were significantly higher in patients with pretransplant LVAD-implantation and increased in a similar way over time in comparison to patients without pretransplant LVAD-implantation. The fact that patients with pretransplant LVAD-implantation had higher levels at hospital discharge might be explained by the presumed beneficial effects of the improved haemodynamics on the peripheral limitations before and up to HTX [20]. Another

Table 4. Measurements at hospital discharge in patients with and without pretransplant LVAD-implantation.

Variable	LVAD (*N* = 24)	No-LVAD (*N* = 21)	*P*-value
Functional exercise capacity			
6MWD (meter)	431 ± 99	355 ± 89	0.013
6MWD (% predicted)	55 ± 13	50 ± 11	0.198
FI (<300 meter) (*N* (%))	1 (4)	7 (35)	0.017
Peripheral muscle strength			
QF (Nm)	134 ± 54	96 ± 46	0.015
QF (% predicted)	69 ± 19	60 ± 22	0.118
PMW (*N* (%))	13 (57)	14 (67)	0.548
Respiratory muscle strength			
MIP (cmH_2O)	−70 ± 22	−64 ± 29	0.444
MIP (% predicted)	64 ± 20	63 ± 22	0.869
RMW (N (%))	14 (64)	14 (70)	0.750
Physical activity			
PAsteps (number/day)	3009 ± 1184	3946 ± 1157	0.071
PAactive (minutes/day)	168 ± 75	230 ± 58	0.042
PAsed (minutes/day)	618 ± 128	611 ± 74	0.866
Wearing time (minutes/day)	794 ± 79	836 ± 77	0.222

Data are presented as mean ± std or as *N* (%).

6MWD, six minutes walking distance test; FI, functional intolerance; QF, quadriceps strength; PMW, peripheral muscle weakness; MIP, maximal inspiratory strength; RMW, respiratory muscle weakness; PAsteps, number of steps; PAactive, active time; PAsed, sedentary time.

P < 0.050.

explanation might be that most patients are included in a rehabilitation trajectory after LVAD-implantation, improving their physical capacity before the HTX. The impaired recovery in muscle strength and functional exercise capacity of patients without LVAD-implantation was somewhat surprising since both patients with an without LVAD-implementation were advised to follow physiotherapy and cardiac rehabilitation (completion of 6 months cardiac rehabilitation: LVAD: 64% vs. no-LVAD: 60% (*P* = 1.000)). From a physiological perspective, larger improvements following cardiac rehabilitation are expected in patients with lower baseline levels of muscle strength and functional exercise capacity. Evidence on the potential for further improvement beyond 1 year post-HTX is absent, but not likely since the largest improvements during a cardiac rehabilitation trajectory are expected during the first 3 months. Our data clearly show that PA is complex and not only determined by the level of muscle strength and functional exercise capacity. Behavioural, social and environmental variables are related to PA and this might explain why patients without LVAD-implantation reached higher levels of PA despite lower results in muscle strength and functional exercise capacity compared with patients with LVAD-implementation. Implementing techniques to improve PA and reduce sedentary time in combination with cardiac rehabilitation might be valuable. Future studies, comparing patients with and without LVAD-implementation in terms of muscle strength and functional exercise capacity are essential to confirm our findings.

Although our study showed an improvement in most parameters over time, with a near normalization of MIP (95 ± 23% predicted), results of 6MWD (78 ± 12% predicted) and QF (79 ± 17% predicted) remain reduced compared with age-and gender-matched healthy subjects. Evidence on MIP immediately after cardiac surgery is scarce and outdated. Johnson *et al.* [21] showed a reduction of 30% in MIP after cardiac surgery and suggested that this reduction might be the result of postoperative decline in peripheral muscle strength and concomitant pain. Stein *et al.* [22] confirmed this reduction within the first 7 days postsurgery and demonstrated an increase of 5% during the first month postoperatively. Another finding of the latter study was that in-hospital rehabilitation resulted in a better recovery of MIP after cardiac surgery. Data on the long-term recovery in MIP is absent. The near normalization of MIP detected in our study, might be explained by the fact that the inspiratory muscles are in constant use while breathing, facilitating recovery in inspiratory muscle strength. Failure for normalization of

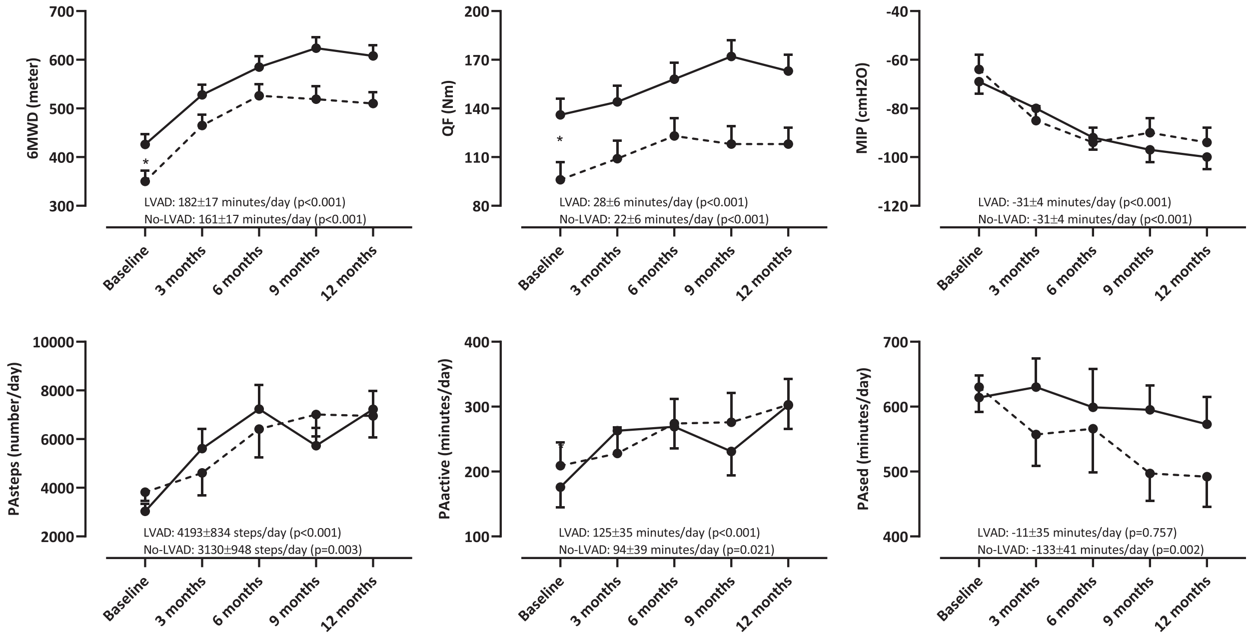

Figure 3 Evolution of functional exercise capacity, muscle strength and physical activity during 1 year of follow-up in patients with (solid line) and without (dashed line) pretransplant LVAD-implantation. The mean evolution from baseline to 1 year of follow-up in each group is depicted in the figure. 6MWD: Six minutes walking distance test; QF: Quadriceps strength; MIP: Maximal inspiratory strength. PAsteps: Number of steps, PAactive: Active time; PAsed: Sedentary time. *: significant difference between both groups at baseline. $P < 0.050$.

6MWD, might be attributable to cardiac denervation which is only partially restored in the first year post-HTX [23,24]. Another explanation for the reduction in 6MWD might relate to the residual PMW. PMW post-HTX is typically associated with the use of corticosteroids and other immunosuppressive medication. Our data showed that PMW was still present in 30% of patients 1 year post-HTX [2]. After correction for completion of the advised and evidence-based cardiac rehabilitation trajectory of 6 months (61% of patients) [25], 38% of our patients suffered from PMW 1 year post-HTX. Future studies are necessary to confirm these findings and to investigate barriers and facilitators for participation and completion of cardiac rehabilitation. Based on our results, cardiac rehabilitation programmes should consist of a combination of aerobic exercise training and peripheral muscle strength training [25]. The majority of studies available apply moderate intense continuous training (MICT), but recent literature points to the positive effects of high intensity interval training (HIIT) in patients post-HTX [3,23,25]. Since evidence on HIIT is scarce in patients post-HTX, future studies are definitely necessary and should include a control group receiving another type of exercise strategy and should investigate the best-applied number and length of HITT intervals. Inspiratory muscle training (IMT) should be added to aerobic exercise training and peripheral muscle strength training, when MIP results remain below 70% predicted. Evidence on the effects of IMT in patients post-HTX is absent, but this intervention is proven to be effective in combination with aerobic exercise training in improving MIP, dyspnoea and exercise capacity in patients with CHF [26,27]. Based on our study, 15% of patients were diagnosed with RMW after 1 year of follow-up.

We recognize the limitations of our study. The relatively small number of patients prohibits examination of subgroups. More specifically, comparing patients who finalized their cardiac rehabilitation programme with those who did not, was not feasible. Correction for confounding factors such as age, pre-HTX status, prolonged ICU stay, medication, hospitalization, comorbidities and fulfilling cardiac rehabilitation was not feasible because of the small sample size. The fact that this study was a single centre study makes it difficult to generalize our results. Future studies, including a larger patient group are necessary to confirm our findings.

In conclusion, functional exercise capacity, muscle strength and PA improve during the first year post-HTX. Cardiac rehabilitation programmes should consist of a combination of aerobic exercise training and peripheral muscle strength training. Programmes should be supplemented with IMT in patients with RMW. Maintaining focus on promoting PA remains key.

Authorship

MH: designed study, performed study, collected data, analysed data and wrote paper. JVC: designed study and wrote paper. LVA, Guido Claessen, Walter Droogne, Gabor Vörös and Stefan Janssens: wrote paper.

Funding

The authors have declared no funding.

Conflict of interest

The author(s) declare(s) that there is no conflict of interest.

Acknowledgements

We would like to acknowledge Ipek Guler Caamano Fajardo for her help with the statistical analysis.

REFERENCES

1. Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Failure* 2016; **18**: 891.
2. Tucker WJ, Beaudry RI, Samuel TJ, *et al.* performance limitations in heart transplant recipients. *Exerc Sport Sci Rev* 2018; **46**: 144.
3. Yardley M, Gullestad L, Nytrøen K. Importance of physical capacity and the effects of exercise in heart transplant recipients. *World J Transplant* 2018; **8**: 1.
4. Marconi C, Marzorati M. Exercise after heart transplantation. *Eur J Appl Physiol* 2003; **90**: 250.
5. Nytrøen K, Myers J, Chan KN, Geiran OR, Gullestad L. Chronotropic responses to exercise in heart transplant recipients: 1-yr follow-up. *Am J Phys Med Rehabil* 2011; **90**: 579.
6. Schaufelberger M, Eriksson BO, Lonn L, Rundqvist B, Sunnerhagen KS, Swedberg K. Skeletal muscle characteristics, muscle strength and thigh muscle area in patients before and after cardiac transplantation. *Eur J Heart Fail* 2001; **3**: 59.
7. Crisafulli A, Tocco F, Milia R, *et al.* Progressive improvement in hemodynamic response to muscle metaboreflex in heart transplant recipients. *J Appl Physiol* 2013; **114**: 421.
8. Kohl HW, Craig CL, Lamber EV, Alkandari SI, Leetongin G, Kahlmeier S. The pandemic of physical inactivity: global action for public health. *Lancet* 2012; **380**: 294.
9. World Health Organisation: Global recommendations on physical activity for health. 2010.
10. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999; **14**: 270.
11. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 1994; **150**: 11.
12. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969; **99**: 696.
13. Rochester DF, Arora NS. Respiratory muscle failure. *Med Clin North Am* 1983; **67**: 573.
14. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol* 2006; **47**: 757.
15. Demeyer H, Burtin C, Van Remoortel H, *et al.* Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program. *Chest* 2014; **146**: 318.
16. Scheers T, Philippaerts R, Lefevre J. Variability in physical activity patterns as measured by the SenseWear Armband: how many days are needed? *Eur J Appl Physiol* 2012; **112**: 1653.
17. Jakovljevic DG, McDiarmid A, Hallsworth K, *et al.* Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. *Am J Cardiol* 2014; **114**: 88.
18. Tudor-Locke C, Craig CL, Brown WJ, *et al.* How many steps/day are enough? For adults. *Int J Behav Nutr Phys Act* 2011; **8**: 79.
19. Knittle K, Nurmi J, Crutzen R, Hankonen N, Beattie M, Dombrowski SU. How can interventions increase motivation for physical activity? A systematic review and meta-analysis. *Health Psychol Rev* 2018; **12**: 211.
20. Rogers JG, Aaronson KD, Boyle AJ, *et al.* Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol* 2010; **55**: 1826.
21. Johnson D, Kelm C, To T, *et al.* Postoperative physical therapy after coronary artery bypass surgery. *Am J Crit Care Med* 1995; **152**: 953.
22. Stein R, Maia CP, Silveira AD, Chiappa GR, Myers J, Ribeiro JP. Inspiratory muscle strength as a determinant of functional capacity early after coronary artery bypass graft surgery. *Arch Phys Med Rehabil* 2009; **90**: 1685.
23. Nytrøen K, Gullestad L. Exercise after heart transplantation: An overview. *World J Transplant* 2013; **3**: 78.
24. Grupper A, Gewirtz H, Kushwaha S. Reinnervation post-heart transplantation. *Eur Heart J* 2018; **39**: 1799.
25. Anderson L, Nguyen TT, Dall CH, Burgess L, Bridges C, Taylor RS. Exercise-based cardiac rehabilitation in heart transplant recipients. *Cochrane Database Syst Rev* 2017; **4**: Cd012264.
26. Wu J, Kuang L, Fu L. Effects of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Congenit Heart Dis* 2018; **13**: 194.
27. Laoutaris ID. The 'aerobic/resistance/inspiratory muscle training hypothesis in heart failure'. *Eur J Prev Cardiol* 2018; **25**: 1257.