Heart Failure Reviews (2019) 24:55–67
https://doi.org/10.1007/s10741-018-9695-y

Exercise rehabilitation in ventricular assist device recipients: a meta-analysis of effects on physiological and clinical outcomes

Liza Grosman-Rimon[1] · Spencer D. Lalonde[2] · Nina Sieh[3] · Maureen Pakosh[1] · Vivek Rao[4,5] · Paul Oh[1] · Sherry L. Grace[1,3,4]

Published online: 6 April 2018

Abstract

Exercise rehabilitation in heart failure patients has been shown to improve quality of life (QoL) and survival. It is also recommended in clinical practice guidelines for ventricular assist device (VAD) recipients. However, there have only been two meta-analyses on the effects of exercise rehabilitation in VAD patients, on only two outcomes. The objective of the review was to quantitatively evaluate the effect of exercise rehabilitation in VAD recipients on functional capacity, exercise physiology parameters, chronotropic responses, inflammatory biomarkers and neurohormones, heart structure and function, and clinical outcomes. The following databases were systematically searched: CCTR, CDSR, CINAHL, EMBASE, PsycInfo, and Medline through to November 2015, for studies reporting on VAD recipients receiving ≥ 2 sessions of aerobic training. Citations were considered for inclusion, and data were extracted in included studies as well as quality assessed, each by two investigators independently. Random-effects meta-analyses were performed where possible. The meta-analysis showed that compared to usual care, exercise rehabilitation significantly improved peak VO_2 ($n = 74$, mean difference = 1.94 mL kg^{-1} min^{-1}, 95% CI 0.63–3.26, $p = 0.004$) and 6-min walk test distance ($n = 52$, mean difference = 42.46 m, 95% CI 8.45–76.46, $p = 0.01$). No significant differences were found for the ventilatory equivalent slope (VE/VCO_2) or ventilatory anaerobic threshold (VAT). In the six studies which reported QoL, exercise rehabilitation was beneficial in four, with no difference observed in two studies. Exercise rehabilitation is associated with improved outcomes in VAD recipients, and therefore should be more systematically delivered in this population.

Keywords Cardiac rehabilitation · Heart-assist devices · Exercise therapy · Oxygen consumption

Abbreviations

HF	Heart failure
VADs	Ventricular assist devices
LVAD	Left ventricular assist device
QoL	Quality of life
Peak VO_2	Maximal oxygen consumption (ml/kg/min)
VE/VCO_2	Ventilatory equivalent
VAT	Ventilatory anaerobic threshold

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10741-018-9695-y) contains supplementary material, which is available to authorized users.

✉ Sherry L. Grace
sgrace@yorku.ca

[1] Toronto Rehabilitation Institute, University Health Network, Toronto, ON, Canada

[2] Western University, London, ON, Canada

[3] School of Kinesiology and Health Science, Faculty of Health, York University, Bethune 368, 4700 Keele St, Toronto, ON M3J 1P3, Canada

[4] University of Toronto, Toronto, ON, Canada

[5] Cardiovascular Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada

Introduction

Heart failure (HF), the fastest growing cardiovascular disease [1], is chronic and progressive, such that it becomes refractory to optimal medical management [2, 3]. Where transplantation is not an option, mechanical circulatory support devices are a life-saving therapy for the treatment of end-stage HF. While ventricular assist devices (VADs) improve cardiac output and peripheral circulation, exercise intolerance persists in these patients [3–6]. Not only does the resulting exertional dyspnea and fatigue significantly impair quality of life (QoL) [7], but decreased exercise capacity (i.e., peak VO_2) is associated with decreased patient survival.

Previous studies have documented that aerobic exercise training in HF patients improves QoL and survival [8–10]. As VADs emerge as a destination therapy, we must assess whether exercise rehabilitation can improve outcomes in this population. Indeed, clinical practice guidelines recommend patient exercise and cardiac rehabilitation attendance, but the guidelines also concede that the effects in this population have not been well-studied [12]. There have been several narrative reviews on the effects of exercise rehabilitation in this population published recently [13, 14], but only two systematic reviews with meta-analyses to our knowledge (one was an abstract only, focused only on functional capacity [15]; and in the other, the only outcomes assessed quantitatively were peak VO_2 and QoL [16]). Therefore, the objectives of this study were to systematically review the evidence regarding the effects of exercise training/rehabilitation in VAD recipients on a broader range of key outcomes, namely functional capacity, exercise physiology parameters, chronotropic responses, inflammatory biomarkers and neurohormones, heart structure and function, and clinical outcomes (i.e., QoL and adverse events). The aim was to quantitatively pool findings where possible.

Methods

A systematic review was performed to identify and appraise relevant studies and quantify the effects of exercise rehabilitation on physiological and clinical outcomes in VAD recipients. The protocol was registered on PROSPERO (CDR42016035438). The methods were based on the Cochrane Collaboration handbook [17].

Inclusion and exclusion criteria

The systematic review included studies where the population was male or female adults (i.e., age > 18) with heart failure supported by a VAD (left, right, or BiVAD). The VADs could be old or new generation (i.e., pulsatile or continuous-flow devices [axial or centrifugal]), implanted as a bridge-to-transplant or destination therapy. Patients must have been prescribed cardiac rehabilitation or structured exercise training/rehabilitation, consisting of either supervised or unsupervised aerobic activity, of at least two sessions. Studies with a randomized controlled trial, cohort, case-control, prospective, quasi-experimental, or observational design were included. Studies that were not in the English language, animal studies, abstracts only, and case studies and those that did not present original research (i.e., meta-analyses, systematic reviews, comments, and editorials) were excluded. Finally, to be included in the meta-analysis, studies had to report outcomes in an intervention group (exercise training) and a control group (no exercise training), both pre- and post-exercise rehabilitation.

Outcomes of interest

Physiological and clinical outcomes were collected: (1) functional capacity (e.g., peak VO_2, 6-min walk test [distance]); (2) exercise physiology parameters (e.g., the ventilatory equivalent (VE/VCO_2) and ventilatory anaerobic threshold (VAT)); (3) chronotropic responses (e.g., heart rate at peak exercise, heart rate reserve); (4) inflammation or inflammatory biomarkers (e.g., cytokines, chemokines, C-reactive protein levels) and neurohormones (e.g., brain natriuretic peptide, norepinephrine, epinephrine, and angiotensin II levels); (5) heart function and structure (e.g., left and right ventricle diameters [mm], ejection fraction); and (6) clinical outcomes, including QoL (psychometrically validated scales), and adverse events related to exercise (e.g., death, re-hospitalization, morbidity, arrhythmias). For the latter, only adverse events that were specifically related to the exercise rehabilitation were considered.

Search strategy

The following databases were searched: CCTR (Cochrane Central Register of Controlled Trials—CENTRAL), CDSR (Cochrane Database of Systematic Reviews), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Embase (Excerpta Medica dataBASE), PsycINFO, and MEDLINE. Year of publication was not restricted, and the searches were from database inception through November 2015. The search strategy was designed to retrieve the maximum number of studies possible from the pool of studies available on the above databases. MeSH terms and free terms relating to exercise rehabilitation in VAD recipients were used (see supplemental Table 1 for search strategy used for Medline as an example). A scientist with intensive experience in exercise physiology and VAD research (LGR) worked with an information scientist (MP) to ascertain terms used for the search in the database.

Reference lists from identified reviews were hand-searched for potentially relevant articles. Experts in the area were also consulted for other potential articles.

Selection of studies

Identified citations from each database were downloaded to EndNote, and duplicates were removed. The final list of citations was imported to *covidence.org* to facilitate study selection.

The first screening of the citations was conducted independently by two reviewers (SL and NS) based on titles and

abstract only. A third reviewer (SLG) resolved conflicting ratings and then arbitrated the final decision.

The full-text articles of potentially relevant citations were imported into *covidence.org*. The full texts were then evaluated for potential inclusion independently by two reviewers (SL and NS). Where a study was closely related to the subject matter, but some required information for inclusion was not reported, the corresponding author was contacted to request the information. A third reviewer resolved any conflicting ratings and then arbitrated the final decision (SLG).

Data extraction process and quality assessment

Two authors (LGR and NS) independently extracted study and patient characteristics, intervention and comparator details, and outcome data from included studies using a piloted database with dictionary, following calibration. A third author (SL) reconciled the extracted data points and arbitrated any discrepancies.

The Cochrane risk of bias tool could not be applied as non-randomized trials were included, given the newness of this area. Using the Downs and Black Quality Assessment tool [18], two reviewers independently assessed the quality of each study (NS and LGR). Discrepancies were resolved by a third reviewer (SL). The tool is comprised of 27 items. Scores were summed, with a maximum of 31 indicative of the highest quality.

Data synthesis and analysis

Data for each outcome were reviewed and summarized quantitatively through meta-analyses where > 2 studies reported the given outcome, and it was deemed there was sufficient consistency across these studies to warrant pooling. Effects of exercise rehabilitation on outcomes that did not meet these criteria were summarized qualitatively.

Meta-analyses were performed using RevMan version 5.3, to estimate the pooled effect for the outcomes and the 95% confidence interval (CI). Comprehensive Meta-Analysis Software (version 3) was used to conduct the meta-regression analysis.

Continuous outcomes were expressed as mean differences; dichotomous outcomes were expressed as relative risks (RRs). Standard errors were converted to standard deviation. Data from each study were pooled using inverse variance and random-effect meta-analysis methods. Heterogeneity among included studies was explored qualitatively and quantitatively, using the chi-square test of heterogeneity, and I^2 statistic. Meta-regression was performed to assess the effect of exercise program duration, sex, age, and study quality on the pooled effect where possible. A p value ≤ 0.05 was considered significant.

Results

Figure 1 summarizes the study selection process. Ultimately, 16 articles were included (Table 1).

Study, patient, and intervention characteristics

As shown in Table 1, with regard to the characteristics of included studies, the average overall quality rating was 12.56 and ranged from 1 to 24. Five (31.2%) studies were conducted in the USA, three (18.7%) in Austria, and two (12.5%) Greece. Studies were published between 1994 and 2015. Eleven (68.7%) studies reported recruitment initiation dates, which ranged from 1988 to 2011; 9 (56.3%) studies reported end dates, which ranged from 1992 to 2012. Regarding design, all (100.0%) included studies were single-center, and 4 (25.0%) were randomized controlled trials. The average overall study sample size was $N = 51.1$, ranging from 6 to 280 participants. The average sample size for the intervention group was $n = 19.2$ (range = 6–41) and for the control group was $n = 17.6$ (range = 7–36).

With regard to patients, in terms of sociodemographic characteristics, the average age in the intervention group was 48.0 ± 11.2 years (range = 31.0–63.4) and in the control group was 50.7 ± 8.9 years (range, 40.9–64.6). The mean percentage of female participants across studies was 13.9%, and the range was from 0.0 to 31.0%. From a clinical perspective, HF etiology was reported in 11 (68.7%) studies; the average percentage of patients with the etiology of ischemic cardiomyopathy was 33.0% and ranged from 22.7 to 50.0%. New York Heart Association class was reported in 6 (37.5%) studies; the average class was 3.8 and ranged from 2 to 4. Four (25.0%) studies reported Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) level, and the mean percentage of patients at INTERMACS level 1 was 26.75% (range = 15.0–50.0%). Left ventricular ejection fraction was reported in four (25.0%) studies, with the average percentage at 17.2% (range = 13.0–21.0%).

Regarding mechanical circulatory support in participants, VAD therapy was used as a bridge-to-transplantation in 14 (87.5%) studies. The mean duration of VAD support was 14.8 weeks, ranging from 3 to 27 weeks. In most studies (n = 12; 75%), the type of mechanical circulatory support used was an LVAD; 1 (6.2%) participant had an LVAD or BiVAD; and 2 (12.5%) participants had an LVAD, BiVAD, or EXCOR. With regard to VAD flow, in 10 (62.5%) studies, they were continuous; in 4 (25.0%), they were pulsatile; and 2 (12.5%) studies contained a mix of continuous and pulsatile VADs.

As shown in Table 1, with regard to the exercise intervention in the included studies, in 15 (93.8%) studies, it was delivered within the cardiac rehabilitation setting. Among these studies, in 8 (50.0%), the exercise program was supervised; in 2 (12.5%), it was unsupervised; and in 3 (18.7%)

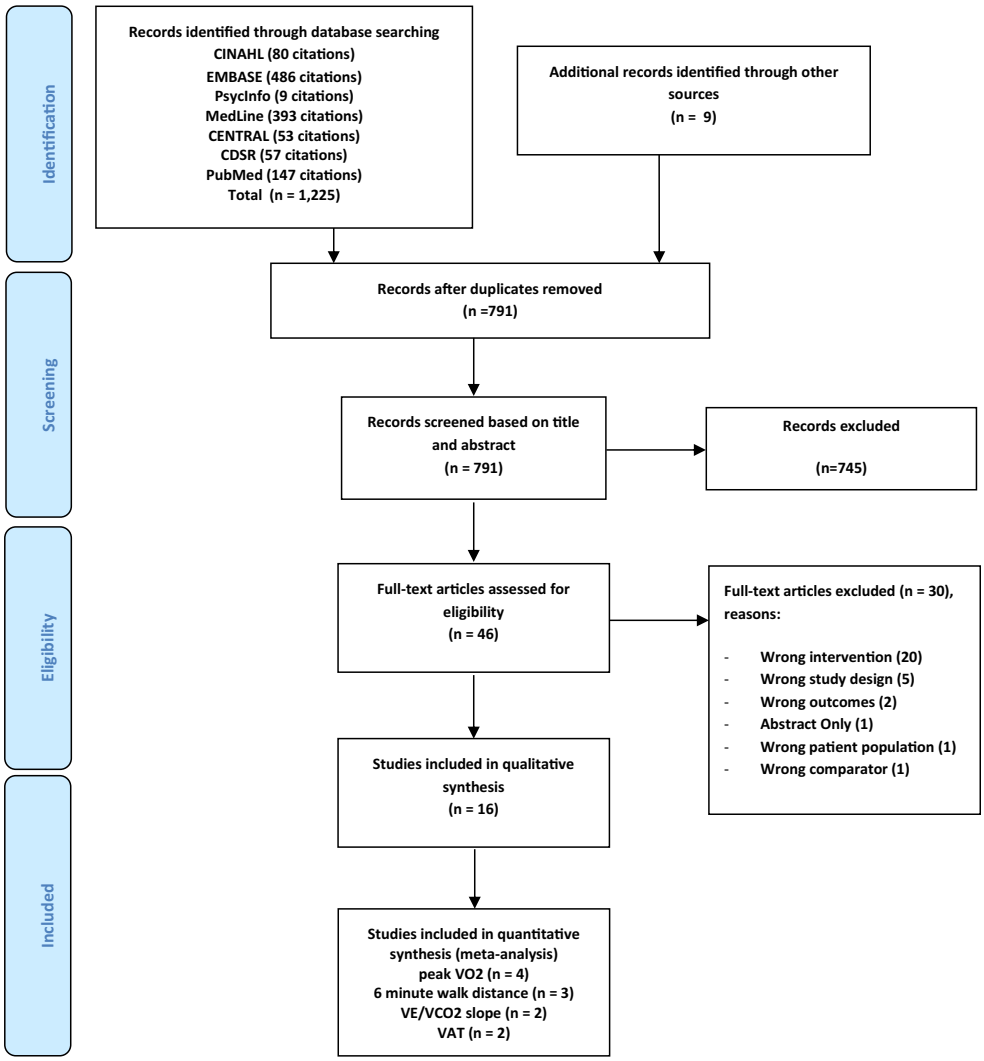

Fig. 1 Study selection process

studies, a combination of supervised or unsupervised sessions were delivered, and 3 did not report these data). A detailed description of the exercise interventions is presented in Table 1. Duration of the exercise program was reported in 10 (62.5%) studies, ranging from 2 weeks to 8 months. Exercise frequency was reported by 12 (75.0%) studies and ranged from 2 to 7 times per week. The lowest dose or number of sessions (where both were reported) was 12 [20]. In the 6 (37.5%) studies in which adherence to the exercise program was reported, it was high (88–100%).

Outcome results

As shown in Table 1, 13 (81.2%) studies reported functional capacity indicators ($n = 11$ for peak VO_2; $n = 3$ for 6-min walk distance). For both peak VO_2 and 6-min walk distance, a benefit was reported. Five (31.2%) reported exercise physiology parameters ($n = 5$ for VE/VCO_2 slope; $n = 4$ for VAT-VO_2; $n = 4$ for respiratory exchange ratio). With regard to the latter, exercise rehabilitation did not have an impact in any of the studies. It was determined that meta-analysis could be performed for two functional capacity indicators (peak VO_2 and 6-min walk distance) and two exercise physiology parameters (VE/VCO_2 slope and VAT-VO_2).

Three (18.7%) studies reported chronotropic responses ($n = 3$ for peak heart rate; $n = 1$ for resting heart rate). Two of these studies reported improvement of peak heart rate, and one study reported no change following exercise training. For resting heart rate, there was no significant difference by group or time in the one study where it was reported. No studies reported inflammatory biomarkers. One (6.2%) study reported neurohormones, specifically B-type natriuretic peptide. A reduction was observed, but it was unclear whether it was significant. Two (12.4%) studies reported indicators of heart structure and function ($n = 1$ for ejection fraction; $n = 1$ for left ventricular end-diastolic dimension). A benefit for ejection fraction with exercise rehabilitation was not clear.

With regard to clinical outcomes, six (3.7%) studies reported QoL ($n = 3$ for Short-Form General Health Survey [35]; $n = 1$ for Sickness Impact Profile physical activity subscales

Table 1 Study and patient characteristics for included papers examining the effects of exercise training/rehabilitation in VAD recipients on physiological and clinical outcomes

Study author, year, country	Study design, quality score[a] (/30)	Participants: VAD type; sample size, mean age, proportion female; duration after implant (weeks)	Exercise intervention: frequency, intensity, minutes/session, duration (weeks); type/mode; resistance training (yes/no)	Outcomes
Adamopoulos et al. 2013 [19], Greece	RCT, 12	CF-VAD 27% ($n = 6$) PF-VAD 73% ($n = 16$) LVAD 59% ($n = 13$) BiVAD 41% ($n = 9$) Berlin Heart (number in each group are NR) CF-LVAD and PF-LVAD models NR 22, 39.7, 9.1%, NR	4×/week, moderate intensity Borg 12–14, 45 min, 12 weeks, treadmill or bicycle, Y (inspiratory muscle training)	Functional capacity: peak VO2 (ml/kg/min)pre-intx 12.9 ± 1.2; post-intx 18.0 ± 0.8; pre-control 12.0 ± 0.8; post-control 13.7 ± 0.7. Significant differences between groups.
Compostella et al. 2014 [20], Italy	RCT,13	CF-LVAD 100% ($n = 26$) Jarvik-2000 ($n = 24$) Berlin Heart ($n = 2$) 26, 63.4, 11.5%, 5.5 weeks	6×/week, NR, NR, 2 weeks, NR, Y	Functional capacity: peak VO_2 (ml/kg/min) post-intx 12.5 ± 3.0; post-control 13.6 ± 2.9. No significant differences between groups. Chronotropic responses: peak HR (bpm) post-intx 112.4 ± 18.8; post-control 101.5 ± 16.1. Significant differences between groups Exercise physiology parameters: VE/VCO_2 post-intx 32.2 ± 3.6; post-control 33.9 ± 8.5. No significant difference between groups. Exercise physiology parameters: AT-VO_2 (ml/kg/min) post-intx 10.4 ± 2.5; post-control 10.9 ± 2.2. No significant difference between groups. Heart function and structure: ejection fraction (%) post-intx 20.3 ± 6.3; post-control 24.4 ± 4.0. Significant difference between groups
deJonge et al. 2001 [21], Netherland	Observational cohort, 13	PF-LVAD 100% ($n = 15$) Pneumatic TCI HeartMate ($n = 15$), 15, 37.0, 0.0%, 8 weeks; 12 weeks; 48 weeks	3-5×/week, Borg 2 to 4 (light to somewhat hard intensity) 20–40 min, NR, bicycle, treadmill, or rowing machine, Y	Functional capacity: peak VO_2 (ml/kg/min) ($n = 10$) 8 weeks post-LVAD implantation 21.3 ± 3.8; 12 weeks post-LVAD implantation 24.2 ± 4.8. Significant differences between groups. ($n = 15$) 12 weeks post-LVAD implantation 23.0 ± 4.4. No significant differences. ($n = 9$) 12 weeks post-LVAD implantation 22.8 ± 5.3; 12 weeks post-HTx 24.6 ± 3.3; 1 year post-HTx 26.2 ± 3.8. No significant differences between groups. Exercise Physiology parameters: VE/VCO_2 ($n = 10$) 8 weeks post-LVAD implantation 39.4 ± 10.1; 12 weeks post-LVAD implantation 36.3 ± 8.2. Significant differences between groups. ($n = 9$) 12 weeks post-LVAD implantation 37.2 ± 7.8; 12 weeks post-HTx 33.0 ± 4.4; 1 year post-HTx 33.7 ± 4.7. No significant differences between groups. Exercise physiology parameters: AT-VO_2 (ml/kg/min) ($n = 10$) 8 weeks post-LVAD implantation 14.8 ± 2.2; 12 weeks post-LVAD implantation 15.8 ± 4.0. No significant differences between groups. ($n = 15$) 12 weeks post-LVAD implantation 15.4 ± 3.7. No significant differences.

Table 1 (continued)

Study author, year, country	Study design, quality score[a] (/30)	Participants: VAD type; sample size, mean age, proportion female; duration after implant (weeks)	Exercise intervention: frequency, intensity, minutes/session, duration (weeks); type/mode; resistance training (yes/no)	Outcomes
				($n = 9$) 12 weeks post-LVAD implantation 14.4 ± 4.0; 12 weeks post-HTx 15.9 ± 3.3; 1 year post-HTx 18.7 ± 2.5. No significant differences between groups. Exercise Physiology parameters: RER ($n = 10$) 8 weeks post-LVAD implantation 1.2 ± 0.1; 12 weeks post-LVAD implantation 1.2 ± 0.1. No significant differences between groups. ($n = 15$) 12 weeks post-LVAD implantation 1.2 ± 0.1. No significant differences. ($n = 9$) post 12 weeks LVAD implantation 1.2 ± 0.1; post 12 weeks HTx 1.1 ± 0.1 post 1 year HTx 1.1 ± 0.0. No significant differences between groups.
Hayes et al. 2012 [22], Australia	RCT, 21	CF-LVAD 100% ($n = 14$) VentrAssist LVAD ($n = 14$) 14, 47.9, 14.3%; 4.5 weeks	3×/week, variable; 30 min, 8 weeks, combination; Y	Functional Capacity: peak VO_2 (ml/kg/min) pre-intx 10.5 ± 2.3; post-intx 14.8 ± 4.9; pre-control 12.4 ± 1.7; post-control 15.3 ± 4.4. No significant group differences. Significant improvement from pre to post in both groups. Functional capacity: 6MWT (m) No significant group differences. Significant improvement from pre to post in both groups. QoL (SF-36): pre-intx 30.4 ± 10.7; post-intx 59.6 ± 24.2; pre-control 36.7 ± 12.2; post-control 53.0 ± 6.2. No significant group difference. Significant improvement from pre to post in both groups
Karapolat et al. 2013 [23], Turkey	Observational Cohort, 12	PF-LVAD 27% ($n = 3$) Berlin EXCOR ($n = 3$) CF-LVAD 73% ($n = 8$) HeartWare ($n = 8$) 11, 45.6, 26%, 12.7 weeks	3×/week, 60–70% of VO_{2max} Borg 12–14, 30 min aerobic and 90 min total (resistance + relaxation), 8 weeks, NR, Y	Functional capacity: peak VO_2 (ml/kg/min) pre-intx 14.68 ± 3.63; post-intx 15.13 ± 3.42. No significant difference between groups pre to post. Significant differences within intx group pre to post. QoL: (SF-36) (PCS) pre-intx 38.57 ± 36.37; post-intx 56.57 ± 25.23 (MCS) pre-intx 66.86 ± 13.80; post-intx 82.67 ± 16.91. No significant differences between groups pre to post. Significant differences within intx group in both PCS and MCS pre to post.
Kerrigan et al. 2014 [24], USA	RCT, 22	CF-LVAD 100% ($n = 26$) HeartWare ($n = 6$) HeartMate II ($n = 20$) 26, 55.0, 26.9%, 11.7 weeks	3×/week, 60% of heart rate reserve progressed up to 80% of heart rate reserve, 30 min, 6 weeks, treadmill and bicycle or arm ergometer or recumbent stepper, N	Functional capacity: peak VO_2 (ml/lkg/min) pre-intx 13.6 ± 3.3; post-intx 15.3 ± 4.4; pre-control 11.2 ± 2.0; post-control 11.8 ± 2.0. No significant difference between groups pre to post. Significant difference within intx group pre to post

Table 1 (continued)

Study author, year, country	Study design, quality score[a] (/30)	Participants: VAD type; sample size, mean age, proportion female; duration after implant (weeks)	Exercise intervention: frequency, intensity, minutes/session, duration (weeks); type/mode; resistance training (yes/no)	Outcomes
				Functional capacity: 6MWT (m) pre-intx 350.1 ± 64.7; post-intx 402.4 ± 89.3; pre-control 336.6 ± 59.0; post-control 356.0 ± 51.6. No significant differences between groups pre to post. Significant differences within intx group pre to post. Chronotropic Responses: resting HR (bpm) pre-intx 88 ± 13; post-intx 85 ± 12; pre-control 88 ± 18; post-control 91 ± 11. No significant differences between groups and within groups Chronotropic Responses: peak HR (bpm) pre-intx 128 ± 24; post-intx 132 ± 28; pre-control 116 ± 18; post-control 124 ± 25. No significant differences between groups and within groups. Exercise Physiology parameters: $VEVCO_2$ pre-intx 36.8 ± 8.7; post-intx 37.8 ± 8.8; pre-control 38.8 ± 8.0; post- control 37.2 ± 8.4. No significant differences between groups and within groups. Exercise Physiology parameter: AT-VO_2(ml/kg/min) pre-intx 10.0 ± 2.1; post-intx 10.9 ± 2.1; pre-control 9.1 ± 0.7; post-control 9.3 ± 1.0. No significant difference between groups pre to post. Significant difference within intx group pre to post. Exercise Physiology parameters: RER pre-intx 1.17 ± 0.08; post-intx 1.18 ± 0.08; pre-control 1.24 ± 0.09; post-control 1.20 ± 0.09. No significant differences between groups and within groups. QoL: (KCCQ) Intx 14.4-point increase; control 0.5-point increase. Significant improvements within intx and between groups pre to post. Adverse Events: 1 instance of hospitalization due to a syncopal episode immediately after an exercise session.
Kohli et al. 2011 [25], USA	Observational Cohort, 11	CF-LVAD 100% ($n = 12$) HeartMate II ($n = 12$) The study also has 30 total artificial hearts (The CardioWest TAH) 12, 51.2, 17.0%, 2.7 weeks	3-5×/week, Borg ≤ 13, 5-10 min progressed towards 30 min continuous aerobic activity, 8 weeks, treadmill or upper/lower extremity recumbent stepper, N	Mean arterial pressure pre 87 ± 8; post 95 ± 13. Significant improvement from pre to post
Kormos et al. 1994 [26], USA	Observational cohort, 8	PF-LVAD 100% ($n = 12$) Novacor N-100 ($n = 12$) 12, 43.8, 8.3%, NR	NR, NR, NR, NR, bicycle and walking, NR	Functional Capacity: peak VO_2 (ml/kg/min) pre-intx 10; post-intx 15. Significant improvement from pre to post. Chronotropic responses: Peak HR (%predicted) pre-intx 75%; post-intx 90%. Significant improvements from pre to post QoL (sickness impact profile physical activity subscale)

Table 1 (continued)

Study author, year, country	Study design, quality score[a] (/30)	Participants: VAD type; sample size, mean age, proportion female; duration after implant (weeks)	Exercise intervention: frequency, intensity, minutes/session, duration (weeks); type/mode; resistance training (yes/no)	Outcomes
				Physical functional well-being scores of outpatient LVAD patients compared to home-bound and in hospital improved in limitation to activity.
Kugler et al. 2012 [27], Germany	Quasi-Experimental, 13	CF-LVAD 100% ($n = 70$) HeartMate II ($n = 38$) HeartWare ($n = 32$) 70, 52.0, 13.6%; 6 weeks	3.5×/week, NR, 78 week, bicycle, N	Functional Capacity: peak VO_2 (ml/kg/min) Significant group differences with intx patients having higher functional capacity. Significant improvements from pre to post in both groups. QoL: (SF-36) PCS improved from pre to post in intervention group only. No significant group differences.
Laoutaris et al. 2011 [28], Greece	RCT, 24	CF-VAD 13% ($n = 2$) INCOR ($n = 2$) PF-VAD 87% ($n = 13$) EXCOR ($n = 13$) (NR whether it is BiVAD or LVAD) BiVAD 47% ($n = 7$) LVAD 53% ($n = 8$) 15, 38.3, 6.7%, 27.4 weeks	3-5×/week, moderate Borg 12–14, 45 min, 10 weeks, bicycle or treadmill, Y (inspiratory muscle training)	Functional Capacity: peak VO_2 (ml/kg/min) pre-intx 16.8 ± 3.7; post-intx 19.3 ± 4.5; pre-control 14.9 ± 4; post-control 14.8 ± 4.2. No significant difference between groups pre to post. Significant difference within intx group pre to post. Functional capacity: 6MWT(m) pre-intx 462 ± 88; post-intx 527 ± 76; pre-control 430 ± 41; post-control 448 ± 55. No significant difference between groups pre to post. Significant difference within intx group pre to post. Exercise physiology parameters: VE/VCO_2 pre-intx 40 ± 6.5; post-intx 35.9 ± 5.6; pre-control 41.4 ± 8.1; post-control 40.2 ± 7.3. No significant difference between groups pre to post. Significant differences within intx group pre to post Exercise physiology parameter: AT-VO_2 (ml/kg/min) pre-intx 12.0 ± 5.6; post-intx 15.1 ± 4.2; pre-control 12.2 ± 4.4; post-control 12.9 ± 3. No significant difference between groups pre to post. Significant differences within intx group pre to post. Exercise physiology parameters: RER pre-intx 1.13 ± 0.1; post-intx 1.2 ± 0.1; pre-control 1.1 ± 0.07; post-control 1.2 ± 0.1. No significant differences between groups and within groups from pre to post. QoL: (MLwHFQ) pre-intx 48.9 ± 12.8; post-intx 38.2 ± 11.6; pre-control 49.8 ± 9.5; post-control 50.8 ± 10.3. No significant difference between groups pre to post. Significant difference within intx group pre to post
Marko et al. 2015 [29], Austria	Observational cohort, 18	CF-LVAD 100% ($n = 41$) HeartMate II ($n = 9$) Heartware ($n = 32$) 41, 54.8, 20.0%; 6.9 weeks	NR, Borg 13, 30–90 min; 4.5 weeks; combination, Y	Functional capacity: peak VO_2 (ml/kg/min) pre-intx 11.3 ± 4.1; post-intx 14.5 ± 5.2. Significant improvement from pre to post. Exercise physiology parameters: RER

Table 1 (continued)

Study author, year, country	Study design, quality score[a] (/30)	Participants: VAD type; sample size, mean age, proportion female; duration after implant (weeks)	Exercise intervention: frequency, intensity, minutes/session, duration (weeks); type/mode; resistance training (yes/no)	Outcomes
				Pre-intx 1.1 ± 0.1; post-intx 1.1 ± 0.1. No significant improvement from pre to post Exercise physiology parameters: VE/VCO_2 pre-intx 37.8 ± 7.9; post-intx 33.7 ± 5.8. Significant improvement from pre to post Neurohormone levels BNP—27% reduction. Unclear if significant. Adverse events: 1 non-sustained instance of ventricular tachycardia
Morrone et al. 1996 [30], United States	Observational cohort, 12	PF-LVAD 100% ($n = 34$), HeartMate 1205 VE HeartMate 1000 IP Numbers of each device NR 34, 52.0, 20.6%, 11–≤334 days	NR, Borg 11–13, NR, NR, treadmill or bicycle, Y	Adverse events: 4 instances of an acute decrease in pump flow due to venous pooling, decreased driveline air volume, and hypovolemia
Nakatani et al. 1998 [31], Japan	Observational cohort, 6	LVAD 83% ($n = 5$) BiVAD 17% ($n = 1$) (VAD type and whether it is CF-LVAD or PF-LVAD NR) 6, 31.0, 16.7%, NR	2×/week, NR, NR, NR, bicycle, N	Heart function and structure: LVEDd (mm): 77.3 ± 7.7
Sapirstein et al. 1995 [32], USA	Observational cohort, 6	PF-LVAD 100% ($n = 19$) Pierce-Donachy ($n = 19$) 19, 51.0, 21.1%, NR	Daily, NR, NR, NR treadmill or bicycle, NR	
Wieselthaler et al. 2001 [33], Austria	Observational cohort, 1	CF-LVAD 100% ($n = 10$) DeBakey VAD ($n = 10$) 10, 52.0, 0.0%, NR	Daily, NR, NR, 6 weeks, bicycle, N	
Wieselthaler 2001 [34], Austria	Observational cohort, 9	CF-LVAD 100% ($n = 6$) DeBakey VAD ($n = 6$) 6, 53.0, 0.0%, variable	NR, NR, NR, NR Bicycle, NR	Functional capacity: peak VO_2 (ml/kg/min) (In one patient) post-intx 20 Adverse events: 1 instance of bicycle ischemic cardiomyopathy and infarction of right coronary artery

Raw scores reported where available at follow-up assessment points

LVAD left ventricular assist device, *BiVAD* biventricular assist device, *VAD* ventricular assist device (when not clear if LVAD or BiVAD), CF continuous flow, *PF* pulsatile flow, *NR* not reported, *HR* heart rate peak, *VO_2* maximal oxygen consumption (ml/kg/min), *QoL* Quality of Life, *SF-36* Study Short-Form General Health Survey, *MLwHFQ* Minnesota living with heart failure questionnaire, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *LVEDd* left ventricular end-diastolic dimension, *HTx* heart transplant, *RCT* randomized controlled trial, *intx* intervention, *PCS* physical component score, *MCS* mental component score, *6MWT* 6-min walk test (m), *RER* respiratory exchange ratio, *VE/VCO_2 slope* minute ventilation-carbon dioxide production relationship, *(VAT)-VO_2* oxygen uptake at ventilatory anaerobic threshold (ml/kg/min), *BNP* B-type natriuretic peptide, *METs* metabolic equivalents of task

[a] Downs and Black [1]. Highest quality rating is 31

[36]; $n = 1$ for Kansas City Cardiomyopathy Questionnaire [37]; and $n = 1$ for Minnesota Living with Heart Failure Questionnaire [38]). Exercise rehabilitation was beneficial in four (66%) studies. No difference in QoL scores were observed in two (33%) studies between patients who received and those who did not receive exercise rehabilitation (Table 1). Finally, in the nine studies that reported adverse events, in many cases, it was not clear whether the events were related to the exercise rehabilitation or VAD implantation.

Quantitative results

Four studies could be included in the meta-analysis for peak VO_2, all of which were randomized trials. The heterogeneity was considered moderate ($I^2 = 47.0\%$). As shown in Fig. 2, there was significant improvement in peak VO_2 with exercise rehabilitation compared to usual care ($p = 0.004$). Meta-regression analysis results indicated that the effect was not related to age ($p = 0.10$), sex ($p = 0.44$), exercise program duration ($p = 0.10$), or study quality ($p = 0.51$).

Three studies could be included in the meta-analysis for the 6-min walk test outcome, again all of which were randomized trials. The heterogeneity was considered low ($I^2 = 0.0\%$). As shown in Fig. 3, results showed significant improvement in 6-min walk distance with exercise rehabilitation compared to usual care ($p = 0.01$).

Two randomized trials were included in the meta-analysis for VE/VCO_2 slope. The heterogeneity was considered moderate ($I^2 = 55.0\%$). There was no significant improvement in VE/VCO_2 slope with exercise rehabilitation (supplementary Fig. 1).

Finally, 2 randomized trials were included in the meta-analysis for VAT outcome. The heterogeneity was considered moderate ($I^2 = 51.0\%$). The meta-analysis did not demonstrate significant improvement in VAT with exercise rehabilitation.

Discussion

Exercise rehabilitation is generally beneficial for VAD recipients. In particular, exercise rehabilitation is established as effective in increasing functional capacity across multiple indicators, and QoL, but potentially not some exercise physiology parameters. Overall, these findings support conclusions from the previous narrative reviews [14], initial meta-analyses [15, 16], and clinical practice guideline recommendations [11], that VAD recipients should receive exercise rehabilitation.

Consistent with previous meta-analyses in this area [15, 16], exercise rehabilitation was associated with significantly greater improvement in functional capacity compared to controls, as reflected by peak VO_2 and 6-min walk test distance. Clinical endpoints such as mortality were not assessable due to inconsistency in the reporting; however, it may be reasonable to postulate that the degree of increased functional capacity observed may translate into reduced mortality [39–42].

There have been no previous meta-analyses reporting on exercise physiology parameters to our knowledge. This initial one suggests no significant improvements with exercise rehabilitation, but further study is warranted prior to drawing firm conclusions. Qualitatively, results suggested improvements in chronotropic responses with exercise rehabilitation.

Also consistent with the meta-analysis in this area [15, 16], overall, an impact of exercise rehabilitation on QoL was found. Improvements in QoL are especially important endpoints in the context of patients on long-term VAD destination therapy not listed for transplantation.

Some initial guidance is now available to assist clinicians in the cardiac rehabilitation setting working with VAD recipients [13, 43–45]. In the studies reviewed herein, VAD patients generally were trained 2 weeks to 8 months, 2–7 times per week. Most were trained in a supervised setting, with many transitioning to unsupervised exercise. It may be reasonable to introduce a program of low-impact activity such as on an exercise bike under careful supervision in a cardiac rehabilitation center and gradually advance the prescription intensity and broaden exercise modalities. Given the clinical complexity, each patient will have different endurance capabilities as a starting point. From our experience as a large cardiac center, many of our patients live remotely from the hospital and cardiac rehabilitation center. Therefore, transitioning to unsupervised exercise once patient safety and confidence are established may be preferable. Future larger multi-center studies should be conducted to determine whether home-based exercise in patients who live at a distance from cardiac rehabilitation could be safe.

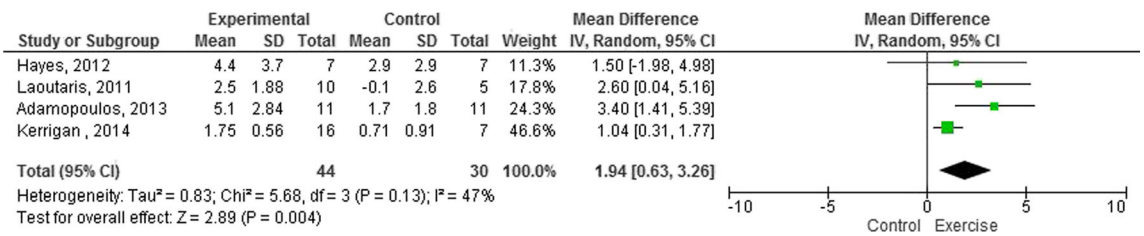

Fig. 2 Significant improvement in peak VO2 with exercise rehabilitation compared to usual care

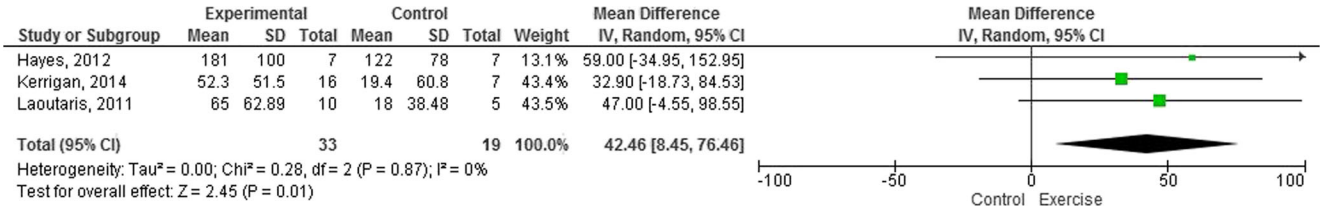

Fig. 3 Significant improvement in 6-min walk distance with exercise rehabilitation compared to usual care

Limitations

Caution is warranted in interpreting these results, particularly given the small pool of available studies and that some studies included in the qualitative summary were of low quality. First, the lack of benefit observed for some outcomes (e.g., VE/VCO_2 and VAT) may be due to low power. The meta-analyses for VE/VCO_2 slope and VAT in particular are very limited, with only two studies. Future exercise training studies in patients supported by circulatory support should report these exercise testing parameters.

Second, the small number of studies precluded planned sensitivity analyses, including study quality, sex, age, and device parameters. With regard to the latter in particular, in most studies, devices were newer-generation continuous flow; however, in over one-quarter of the studies, patients with pulsatile-flow devices were included; these were from an early era of mechanical support when outcomes were generally poorer, and most patients were bridge-to-transplant versus destination therapy in contemporary practice. Indeed, pulsatile-flow devices are no longer in use, and therefore are not relevant to current clinical practice. Although previous studies have shown that implantation of pulsatile or continuous-flow VADs provided equivalent degrees of exercise capacity [4], different VAD devices may differentially affect exercise training outcomes. For example, the physiology of the new continuous devices is different than that of the old pulsatile flow pumps, as it provides non-physiological low-pulsatile blood flow. However, the meta-analysis included only studies from 2011 onwards, which are relatively newer studies.

Moreover, while most studies were comprised of patients with an LVAD, some studies included patients with other device types as well, such as BiVADs. These patients are likely to have poorer outcomes, and therefore inclusion of these devices may have led to under-estimation of exercise rehabilitation effects. Moreover, BiVADs are no longer clinically available, and therefore the corresponding findings are again not applicable to current clinical practice. Clearly, there is need for a current, multi-center, larger trial.

Directions for future research

The included studies applied different exercise protocols (some including resistance training), which would augment heterogeneity. Further investigation is required to understand the effect of the duration, intensity, mode, and frequency of aerobic exercise on outcomes, to support guideline recommendations for exercise prescription. Empirical guidance as to when it is safe to start an exercise rehabilitation program after such a complex surgical intervention as VAD implantation is also required. Moreover, the impact of VAD settings such as pump speed and power deserve more consideration [46, 47].

More studies of the impact of exercise rehabilitation on chronotropic responses, inflammatory biomarkers, neurohormones, and heart structure and function are also needed. There was insufficient data to pool quantitatively for these outcomes. With accumulating studies in the VAD population, it is hoped that the effects of exercise rehabilitation specifically on adverse events can also be characterized (e.g., respiratory distress, bleeding, suction events, rhythm disturbances). Finally, longer-term outcome data is needed to establish the impact of exercise rehabilitation on mortality and morbidity.

In conclusion, in this systematic review and meta-analysis on the benefits of exercise rehabilitation for VAD recipients, findings demonstrated it is effective in improving physiological and clinical outcomes. Specifically, VAD recipients exhibited significant increases in peak VO_2 and 6-min walk distance with exercise compared to controls. Improvements in QoL and chronotropic responses were also observed. These results provide support for clinical practice recommendations that VAD recipients receive exercise training. Cardiac rehabilitation societies should develop educational programs for professionals to increase capacity to treat this population.

Acknowledgements We wish to thank Dr. Dennis J. Kerrigan and Dr. Kate Hayes who kindly provided additional data for the meta-analysis. We also gratefully acknowledge Dr. Susan Marzolini for advice on analyses.

Compliance with ethical standards

Conflict of interest Dr. Vivek Rao is a consultant to CorMatrix, and Heart-Ware. The other authors have no conflicts of interest to disclose.

References

1. Mancini D, Goldsmith R, Levin H, Beniaminovitz A, Rose E, Catanese K, Flannery M, Oz M (1998) Comparison of exercise

performance in patients with chronic severe heart failure versus left ventricular assist devices. Circulation 98:1178–1183
2. Jakovljevic DG, George RS, Nunan D, Donovan G, Bougard RS, Yacoub MH, Birks EJ, Brodie DA (2010) The impact of acute reduction of continuous-flow left ventricular assist device support on cardiac and exercise performance. Heart 96:1390–1395
3. Simon MA, Kormos RL, Gorcsan J 3rd et al (2005) Differential exercise performance on ventricular assist device support. J Heart Lung Transplant 24:1506–1512
4. Haft J, Armstrong W, Dyke DB et al (2007) Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. Circulation 116:18–15
5. Leibner ES, Cysyk J, Eleuteri K, el-Banayosy A, Boehmer JP, Pae WE (2013) Changes in the functional status measures of heart failure patients with mechanical assist devices. Am Soc Artif Intern Organs 59:117–122
6. Grosman-Rimon L, McDonald MA, Pollock Bar-Ziv S et al (2013) Chronotropic incompetence, impaired exercise capacity, and inflammation in recipients of continuous-flow left ventricular assist devices. J Heart Lung Transplant 32:930–932
7. Pruijsten RV, de Jonge N, Kirkels JH, Klöpping C, Doevendans PAFM, Oosterom A, Kemperman H, Lahpor JR (2008) Left ventricular assist device: a functional comparison with heart transplantation. Neth Heart J 16:41–46
8. Jaski BE, Lingle RJ, Kim J, Branch KR, Goldsmith R, Johnson MR, Lahpor JR, Icenogle TB, Piña I, Adamson R, Favrot LK, Dembitsky WP (1999) Comparison of functional capacity in patients with end-stage heart failure following implantation of a left ventricular assist device versus heart transplantation: results of the experience with left ventricular assist device with exercise trial. J Heart Lung Transplant 18:1031–1040
9. Gullestad L, Myers J, Edvardsen T, Kjekshus J, Geiran O, Simonsen S (2004) Predictors of exercise capacity and the impact of angiographic coronary artery disease in heart transplant recipients. Am Heart J 147:49–54
10. Belardinelli R, Georgiou D, Cianci G, Purcaro A (1999) Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 99:1173–1182
11. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, Morgan JA, Arabia F, Bauman ME, Buchholz HW, Deng M, Dickstein ML, el-Banayosy A, Elliot T, Goldstein DJ, Grady KL, Jones K, Hryniewicz K, John R, Kaan A, Kusne S, Loebe M, Massicotte MP, Moazami N, Mohacsi P, Mooney M, Nelson T, Pagani F, Perry W, Potapov EV, Eduardo Rame J, Russell SD, Sorensen EN, Sun B, Strueber M, Mangi AA, Petty MG, Rogers J, International Society for Heart and Lung Transplantation (2013) The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 32:157–187
12. Bristow MR, Hershberger RE, Port JD, Gilbert EM, Sandoval A, Rasmussen R, Cates AE, Feldman AM (1990) Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation 82:I12–I25
13. Alsara O, Perez-Terzic C, Squires RW, Dandamudi S, Miranda WR, Park SJ, Thomas RJ (2014) Is exercise training safe and beneficial in patients receiving left ventricular assist device therapy? J Cardiopulm Rehabil Prev 34:233–240
14. Jung MH, Gustafsson F (2015) Exercise in heart failure patients supported with a left ventricular assist device. J Heart Lung Transplant 34:489–496
15. Toufik MH, Alok S, Muhammad A, et al. (2016) Effect of cardiac rehabilitation on functional capacity in left ventricular assist device patients: a systematic review and meta-analysis. American Association of Cardiovascular and Pulmonary Rehabilitation 31st Annual Meeting Scientific Abstracts 295–6
16. Ganga HV, Leung A, Jantz J, Choudhary G, Stabile L, Levine DJ, Sharma SC, Wu WC (2017) Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: a systematic review. PLoS One 12:e0174323
17. Higgins J, Green S, Becker L, et al. (2011) Overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. http://handbook.cochrane.org/chapter_22/22_overviews_of_reviews.htm (accessed 27 Feb 2015)
18. Downs SH, Black N (1998) The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52:377–384
19. Adamopoulos S, Gouziouta A, Mantzouratou P, Laoutaris ID, Dritsas A, Cokkinos DV, Mourouzis I, Sfyrakis P, Iervasi G, Pantos C (2013) Thyroid hormone signalling is altered in response to physical training in patients with end-stage heart failure and mechanical assist devices: potential physiological consequences? Interact Cardiovasc Thorac Surg 17:664–668
20. Compostella L, Russo N, Setzu T, Compostella C, Bellotto F (2014) Exercise performance of chronic heart failure patients in the early period of support by an axial-flow left ventricular assist device as destination therapy. Artif Organs 38:366–373
21. de Jonge N, Kirkels H, Lahpor JR, Klöpping C, Hulzebos EJ, Brutel de la Rivière A, Robles de Medina EO (2001) Exercise performance in patients with end-stage heart failure after implantation of a left ventricular assist device and after heart transplantation: an outlook for permanent assisting? J Am Coll Cardiol 37:1794–1799
22. Hayes K, Leet AS, Bradley SJ, Holland AE (2012) Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. J Heart Lung Transplant 31:729–734
23. Karapolat H, Engin C, Eroglu M, Yagdi T, Zoghi M, Nalbantgil S, Durmaz B, Kirazlı Y, Özbaran M (2013) Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. Transplant Proc 45:3381–3385
24. Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, Swaffer M, Brawner CA, Lanfear DE, Selektor Y, Velez M, Tita C, Keteyian SJ (2014) Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the rehab-VAD randomized controlled trial. JACC Heart failure 2:653–659
25. Kohli HS, Canada J, Arena R, Tang DG, Peberdy MA, Harton S, Flattery M, Doolin K, Katlaps GJ, Hess ML, Kasirajan V, Shah KB (2011) Exercise blood pressure response during assisted circulatory support: comparison of the total artificial [corrected] heart with a left ventricular assist device during rehabilitation. J Heart Lung Transplant 30:1207–1213
26. Kormos RL, Murali S, Dew MA, Armitage JM, Hardesty RL, Borovetz HS, Griffith BP (1994) Chronic mechanical circulatory support: rehabilitation, low morbidity, and superior survival. Ann Thorac Surg 57:51–57 discussion 7-8
27. Kugler C, Malehsa D, Schrader E, Tegtbur U, Guetzlaff E, Haverich A, Strueber M (2012) A multi-modal intervention in management of left ventricular assist device outpatients: dietary counselling, controlled exercise and psychosocial support. Eur J Cardiothorac Surg 42:1026–1032
28. Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Kallistratos MS, Koulopoulou M, Voudris V, Cokkinos DV, Sfirakis P (2011) Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. Eur J Cardiovasc Prev Rehabil 18:33–40

29. Marko C, Danzinger G, Kaferback M et al (2015) Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. Eur J Prev Cardiol 22:1378–1384
30. Morrone TM, Buck LA, Catanese KA, Goldsmith RL, Cahalin LP, Oz MC, Levin HR (1996) Early progressive mobilization of patients with left ventricular assist devices is safe and optimizes recovery before heart transplantation. J Heart Lung Transplant 15: 423–429
31. Nakatani T, Sasako Y, Kobayashi J, Komamura K, Kosakai Y, Nakano K, Yamamoto F, Kumon K, Miyatake K, Kitamura S, Takano H (1998) Recovery of cardiac function by long-term left ventricular support in patients with end-stage cardiomyopathy. ASAIO J 44:M516–M520
32. Sapirstein JS, Pae WE Jr, Aufiero TX, Boehmer JP, Pierce WS (1995) Long-term left ventricular assist device use before transplantation. ASAIO J 41:M530–M534
33. Wieselthaler GM, Schima H, Dworschak M, Quittan M, Nuhr M, Czerny M, Seebacher G, Huber L, Grimm M, Wolner E (2001) First experiences with outpatient care of patients with implanted axial flow pumps. Artif Organs 25:331–335
34. Wieselthaler GM, Schima H, Lassnigg AM, Dworschak M, Pacher R, Grimm M, Wolner E (2001) Lessons learned from the first clinical implants of the DeBakey ventricular assist device axial pump: a single center report. Ann Thorac Surg 71:S139–S143 discussion S44-6
35. Failde I, Ramos I (2000) Validity and reliability of the SF-36 health survey questionnaire in patients with coronary artery disease. J Clin Epidemiol 53:359–365
36. Bergner M, Bobbitt RA, Carter WB, Gilson BS (1981) The sickness impact profile: development and final revision of a health status measure. Med Care 19:787–805
37. Green CP, Porter CB, Bresnahan DR, Spertus JA (2000) Development and evaluation of the Kansas City cardiomyopathy questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 35:1245–1255
38. Rector TS, Cohn JN (1992) Assessment of patient outcome with the Minnesota living with heart failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan multicenter research group. Am Heart J 124:1017–1025
39. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, Schneider S, Schwarz A, Senges J (2002) Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 106:3079–3084
40. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R (1993) Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA cooperative studies group. Circulation 87:VI5–V16
41. Corra U, Mezzani A, Bosimini E et al (2004) Cardiopulmonary exercise testing and prognosis in chronic heart failure: a prognosticating algorithm for the individual patient. Chest 126:942–950
42. Lund LH, Aaronson KD, Mancini DM (2005) Validation of peak exercise oxygen consumption and the heart failure survival score for serial risk stratification in advanced heart failure. Am J Cardiol 95:734–741
43. Piepoli MF, Corra U, Adamopoulos S et al (2014) Secondary prevention in the clinical management of patients with cardiovascular diseases. Core components, standards and outcome measures for referral and delivery: a policy statement from the cardiac rehabilitation section of the European Association for Cardiovascular Prevention & Rehabilitation. Endorsed by the Committee for Practice Guidelines of the European Society of Cardiology. Eur J Prev Cardiol 21:664–681
44. Corra U, Pistono M, Mezzani A et al (2011) Cardiovascular prevention and rehabilitation for patients with ventricular assist device from exercise therapy to long-term therapy. Part I: exercise therapy. Monaldi Arch Chest Dis = Archivio Monaldi per le malattie del torace 76:27–32
45. Haufe S, Bara C, Eigendorf J, et al. (2017) Physical activity guided by pulse pressure in patients with continuous flow left ventricular assist devices: a pilot study. Circulation 135:1567–1569
46. Fresiello L, Buys R, Timmermans P, Vandersmissen K, Jacobs S, Droogne W, Ferrari G, Rega F, Meyns B (2016) Exercise capacity in ventricular assist device patients: clinical relevance of pump speed and power. Eur J Cardiothorac Surg 50:752–757
47. Hayward CS, Fresiello L, Meyns B (2016) Exercise physiology in chronic mechanical circulatory support patients: vascular function and beyond. Curr Opin Cardiol 31:292–298

What is already known about this subject?

Ventricular assist device (VAD) recipients have persistently reduced functional capacity and hence low quality of life. Early data suggest that exercise rehabilitation may improve both functional capacity and quality of life.

What does this study add?

Through meta-analysis, exercise rehabilitation was shown to result in significantly improved functional capacity (peak VO_2 and 6-min walk test distance) when compared to usual care. Benefits were also observed in quality of life and chronotropic responses, but not exercise physiology parameters.

How might this impact on clinical practice?

These results provide support for clinical practice recommendations that VAD recipients receive exercise training. Cardiac rehabilitation societies should develop education programs for professionals to increase capacity to treat this population.