Safety, adherence and efficacy of exercise training in solid-organ transplant candidates: a systematic review

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Safety, adherence and efficacy of exercise training in solid-organ transplant candidates: a systematic review

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ABSTRACT

Background: Patients awaiting solid-organ transplantation may be encouraged to undertake exercise training to improve pre- and post-transplant outcomes. However, the safety, adherence and efficacy of exercise training in this population remain unclear.

Methods: All randomized, non-randomized and non-controlled trials of exercise training interventions in solid-organ transplant candidates were included. The Cochrane risk of bias tool and a modified Newcastle-Ottawa scale were used to assess procedural quality. Safety was defined as the number of reported adverse events during exercise training. Adherence was evaluated from session attendance, and efficacy as changes in cardiorespiratory fitness (CRF), exercise capacity, muscular strength, health-related quality of life (HR-QoL) and lung function.

Results: Eleven studies involving 874 patients were included: four randomized controlled, one non-randomized controlled and six non-controlled trials. Six studies included heart transplant candidates and five involved patients awaiting lung transplantation. Three trials included aerobic-only training, one incorporated resistance-only exercise and seven combined modalities. Twelve adverse events were reported with four due to exercise, although methods to collect these data were often omitted. Exercise adherence ranged from 82.5-100%, but was poorly described. No significant between–group changes attributable to exercise training were demonstrated. However, significant within-group improvements in CRF, exercise capacity, muscular strength, lung function and HR-QoL were observed.

Conclusions: Patients awaiting heart or lung transplant appear to tolerate exercise training despite the larger number of adverse events compared to

other high-risk populations. Exercise training demonstrated within-group benefits for several outcomes, with no significant between-group differences. Randomized controlled trials with sufficient statistical power are required for all solid-organ transplant candidates.

Keywords: exercise training, solid-organ transplant candidate

INTRODUCTION

Exercise testing is increasingly utilized to measure cardiorespiratory fitness (CRF) and exercise capacity to assist in pre-transplant surgical risk stratification [1-3]. It is well established that CRF, usually determined from the measurement of maximal aerobic power ($\dot{V}O_{2max}$), is one of the strongest predictors of all-cause mortality [4-8]. Poor CRF is present in patients listed for transplant [9-11]. The prognostic importance of reduced CRF and exercise capacity is clinically relevant, as it is associated with increased peri- and post-transplant mortality, and a longer duration of stay in intensive care [12-17].

The implementation of physical activity through exercise training (ET) is an evidence-based, cost-effective strategy shown to prevent and treat a diversity of chronic conditions [18,19]. It is well-documented that ET can improve CRF and exercise capacity, in addition to several other physiological and psychological health outcomes such as muscle strength and mass, lung function, and health-related quality of life [20],[21]. Patients diagnosed with chronic diseases are advised to undertake ET to limit deconditioning and improve health outcomes [22-25]. Furthermore, ET may improve peri- and post-operative outcomes in patients awaiting organ transplantation, which could have significant implications for the management of patients prior to surgery [26,27]. However, it is not clear if ET is safe and achievable in these populations. Furthermore, it remains uncertain whether the well-established health benefits associated with ET are also observed in patients with end-

Abbreviations: 1-RM, one repetition maximum; 6MWD, six minute walk distance; CONSORT, Consolidated Standards of Reporting Trials; CPET, cardiopulmonary exercise testing; CRF, cardiorespiratory fitness; ET, exercise training; HIIT, high intensity interval training; HR-QoL, health-related quality of life; MET, metabolic equivalents; MHS, mental health summary score; MICT, moderate intensity continuous training; MVC, maximum voluntary contraction; PHS, physical health summary score; Pi_{max}, maximal inspiratory mouth pressure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; $V_E/\dot{V}CO_2$, ventilatory equivalents of carbon dioxide; $\dot{V}O_{2max}$, maximal oxygen uptake; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold; W_{peak}, peak work capacity

stage disease processes. Therefore, the aim of this study is to systematically review the safety, adherence and efficacy of ET in solid-organ transplant candidates.

METHODS

We conducted and reported this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement [28]. The following databases were systematically examined from the earliest time point to December 2014, with the search limited to the English language: PubMed, Medline, Sports Discus and Web of Science. The search phase developed and used is as follows: ("exercise training" OR "exercise" OR "exercise therapy" OR "physical therapy") AND ("transplant" OR "organ-transplant" OR "solid-organ transplant" OR "liver transplantation" OR "liver transplant" OR "heart transplantation" OR "heart transplant" OR "kidney transplantation" OR "kidney transplant" OR "lung transplantation" OR "lung transplant") AND ("candidate" OR "pre-transplant" OR "before transplantation" OR "before transplant" OR "awaiting transplant" OR "awaiting transplantation"). Reference lists of retrieved articles were examined to locate additional studies that potentially met the inclusion criteria.

For articles to be included in the review, the following criteria were satisfied: a) the study specified the mode/s of ET performed, b) the entire population were listed for solid-organ transplantation, c) the intervention lasted a minimum of three weeks and d) all patients were ≥ 18 years old. We excluded animal and case studies.

Study selection process and data extraction

The titles and abstracts of all articles were initially screened by one reviewer (MW). Two reviewers (MW and TP) then screened the remaining titles and abstracts. Following this, two reviewers (MW, TP) independently screened full papers of potentially eligible abstracts. Disagreements were resolved by consensus.

All data was extracted by a single reviewer (MW) and checked by another (TP). Following the study selection phase, it became apparent there was only evidence for heart and lung transplant candidates and as such, this will form the focus of the review.

Quality assessment

Quality of the included articles was assessed using the Cochrane risk of bias tool for studies with a control group [29], and a modified Newcastle-Ottawa scale for cohort trials [30] (Supplementary material 1).

RESULTS

Study design and research quality

The electronic search resulted in 1,341 articles, of which 1,292 were excluded after title and abstract review (Figure 1). The remaining 49 articles were examined in full text form, with 11 articles including four randomized controlled trials [31-34], one non-randomized controlled trial [35], and six non-controlled trials [36-41] deemed eligible. Summary of outcome measures are included in Tables 1 and 2.

Procedural quality is summarised in Table 3 for controlled trials and Table 4 for cohort studies. Only two (40%) randomised-controlled trials were deemed

to be at a low risk of bias. The majority of cohort studies (83%) scored 7 points, indicating good study quality.

Randomized-controlled trials

Four randomized control trials were included [31-34]. Two studies randomized participants to ET or a control group [32,33]. One randomized participants to either health education and exercise or health education only [34]. The final trial randomized participants to either high intensity interval-training (HIIT) or moderate intensity continuous training (MICT) [31].

Non-randomized controlled trials

One trial utilized non-compliant patients as a control group [35]. Because this trial was originally designed as a prospective cohort study, groups were not randomized.

Non-controlled trials

Six non-controlled studies were included. Four trials performed a prospective investigation of a single exercise group with pre- and post-intervention testing [36-39,41]. The remaining two investigations retrospectively analysed data collected from a rehabilitation program [41]

Participants

A total of 874 participants were enrolled in the eleven studies, with 660 (52.5% male) participating in ET. The sample sizes ranged from nine [34] to 345 patients [40]. Ten studies provided demographic details regarding age

and gender [31-34,36-41]. Participant age ranged from 38.3±15.9 years [33] to 52.0±8.5 years [38,41].

Disease etiology

Six studies included heart transplant candidates [32,33,35,36,38,41] and the remaining five involved patients awaiting lung transplantation [31,34,37,39,40]. The etiology of end-stage heart failure was reported in three studies; ischemic (n=5) and idiopathic cardiomyopathy (n=22), coronary artery disease (n=18), myocarditis (n=2), idiopathic hypertrophic sub-aortic stenosis (n=1) and dilated cardiomyopathy (n=15) [32,33,41]. Two studies classified disease etiology as unspecified advanced heart failure (n=21) [35,36]. The remaining study reported etiology as a percentage of the cohort, which included ischemic (48%), idiopathic (43%) and congenital (9%) cardiomyopathy [38]. Three studies included patients who had all received a left ventricular assist device as a bridge to heart transplantation [32,33,41].

All studies involving lung transplant candidates reported disease etiology. These included chronic obstructive pulmonary disease (n=173), pulmonary fibrosis (n=121), cystic fibrosis (n=72), idiopathic interstitial pneumonia (n=39), sarcoidosis (n=15), pulmonary emphysema (n=14), bronchiectasis (n=13) and other causes (n=21) [31,34,37,39,40].

Time relative to surgery

Ten trials reported a total of 121 (13%) participants receiving a transplant during the time enrolled in the study [31-41]. Only one study provided the average wait-time (185±217 days) [40] for a transplant, with no investigations

reporting the average wait-time to receive a transplant following the intervention.

Exercise interventions involving heart-transplant candidates

Frequency, length and duration

Frequency of ET was reported in five studies, ranging from two to seven days per week [32,33,35,36,38]. All trials that described frequency also detailed the intervention length which varied from four to 26 weeks [35,36]. Exercise duration ranged from 15 minutes to 1 hour [32,35]. Only one study failed to report either the length or frequency of the exercise intervention [41]. Additionally, one intervention did not specify the duration of each exercise session [36].

Modality

Two studies prescribed a combination of aerobic and resistance-training [32,41], and one trial incorporated both aerobic and inspiratory muscle exercise [33]. Aerobic training only was performed in two trials [35,38]; the remaining intervention included resistance-based training only [36]. Types of aerobic training included cycling and/or treadmill walking [32,33,35,38,41]. Resistance training included full body, dynamic muscular contractions, incorporating free weight, machine and body weight exercises [32,36,41]. The study by Dean and colleagues (2011) was the exception with participants performing single limb resistance training, targeting the biceps and triceps muscle groups, combined with isometric forearm contractions [36].

Location

All studies specified the exercise intervention was located at a hospital facility [32,33,35,36,38,41]. Five intervention were delivered as part of an inpatient or outpatient program [33,35,36,38,41]. One study recruited and trained participants as part of inpatient care and continued ET on discharge from hospital [32].

Intensity

Aerobic training

Exercise intensity was reported in all trials that included aerobic training [32,33,35,38,41]. The reporting intensity varied, including percentages of aerobic power reserve, six-minute walk distance (6MWD) speed, maximum work intensity, heart rate at ventilatory threshold and rating of perceived exertion. All aerobic training was prescribed at a light to moderate intensity [42].

Resistance training

The quality of reporting resistance-based strength training intensity was variable. Dean and colleagues [36] prescribed isometric resistance based on maximum voluntary contraction (MVC). Intensity was initially set at 60% of MVC and was increased and maintained at 70-80% MVC after two days of training for the remainder of the intervention. Two studies reported sets, repetitions and intensity of exercises [32,36]. Dean and colleagues [36] prescribed resistance exercise at a high set (5-7 sets), moderate-to-high repetition range (12-20 repetitions), with participants instructed to exercise at

a rating of perceived exertion of ≤13 out of 20. Hayes et al. (2012) prescribed a low set (2 sets), moderate repetition (10 repetitions) program [32].

Supervision

Four studies reported that all exercise sessions were supervised by qualified health professionals (e.g. exercise physiologists, physiotherapists or rehabilitation nurses) [32,35,36,41]. One study performed exercise with partial supervision; aerobic training was performed unsupervised for 30-45 minutes per day, with participants required to attend supervised inspiratory muscle training sessions two to three times per week [33]. The remaining aerobic-based intervention was unsupervised [38].

Safety

The definition, assessment and reporting of adverse events was poorly described. No trials provided a statement regarding the method to rate adverse event severity. Only one study reported adverse events (four) due to ET [41]. The number/percentage withdrawals due to adverse or non-adverse events were often omitted from the results. Four studies concluded that ET was safe, but did not report any data on adverse events to support this [32,33,36,38]. Ben-Gal et al. (2000) reported no significant cardiovascular events occurred during the exercise sessions [35]. However, two patients withdrew from this intervention due to an inability to tolerate the training.

Adherence

Adherence was defined by attendance at the prescribed ET sessions. Three studies assessed adherence to an exercise program by recording training

attendance [32,35,36]. One intervention reported adherence as a percentage of attendance at exercise sessions [35]. Hayes and colleagues [32] reported that patients attended an average of 21.3±1.5 of the 24 exercise sessions. The final study did not report an objective measure of adherence, but stated that “that no patients stopped or had difficulty maintaining the program” [36].

Efficacy

$\dot{V}O_{2peak}$, VT and Ventilatory Equivalents for Carbon Dioxide ($V_E/\dot{V}CO_2$)

Significant within-group increases in $\dot{V}O_{2peak}$ following ET were observed in the trials [32,33,35,38] that reported $\dot{V}O_{2peak}$, ranging from 13% (16.8±3.7 to 19.3±4.5 mL/kg/min; p=0.008) [33] to 29% (10.5±2.3 to 14.8±4.9 mL/kg/min; p<0.05) [32]. The trial that reported the largest relative increase in $\dot{V}O_{2peak}$ prescribed a combination of training modalities. Three trials implemented a control group design [32,33,35]. There were no significant differences in $\dot{V}O_{2peak}$ between intervention and control arms.

Three of the four studies that reported data on $\dot{V}O_{2peak}$ analyzed the change in VT [33,35,38]. Consistent with $\dot{V}O_{2peak}$, there were significant increases in all groups that undertook exercise, ranging from 20% (12.0±5.6 to 15.1±4.2 mL/kg/min; p=0.01) [33] to 36% (7.2 to 11.3 mL/kg/min; p<0.001) [38]. There were no significant between-group changes in VT.

One study reported the change in the $V_E/\dot{V}CO_2$ slope following an exercise intervention [33]. An elevated $V_E/\dot{V}CO_2$ slope reflects ventilation-perfusion mismatching which is prevalent in heart failure [43]. Following 10-weeks of combined aerobic and inspiratory muscle training, Laoutaris et al. [33]

demonstrated a significant within-group decrease in the $V_E/\dot{V}CO_2$ slope in the exercise group (40.0±6.5 to 35.9±5.6; p=0.009), indicating improvements in pulmonary blood flow distribution and ventilation/perfusion matching. No significant between-group change in the $V_E/\dot{V}CO_2$ slope was observed.

Exercise Capacity

Two studies reported the change in peak work capacity (W_{peak}) [32,35] with both trials observing significant within-group improvements. Hayes and colleagues [32] noted a 43% improvement following an eight-week exercise intervention (42±15.4 to 74.5±31.3 W, p<0.05). Likewise, Ben-Gal et al. [35] observed a 25% improvement over a 26-weeks (51.5±1.3 to 69.5±10 W, p=0.005). There were no significant between-group changes in W_{peak} [32,35].

Three studies incorporated 6MWD within their protocol [32,33,35]. All trials demonstrated significant within-group improvements following exercise compared to baseline, ranging from 12.3% (462±88 to 527±76 m, p=0.005) [33] to 33.9% (351±77 to 531±131 m, p<0.05) [32]. No significant between-group differences in 6MWD were observed.

Muscular Strength

Only one study reported outcome measures of muscular strength [36]. Dean and colleagues (2011) showed no change in isometric handgrip strength of either the trained (29±5 to 33±4 kg) or untrained (36±7 to 37±5 kg) arms over a 4-week strength program [36].

Health-related Quality of Life

Two studies assessed the impact of ET on health-related quality of life (HR-QoL) [32,33]. Hayes and colleagues [32] demonstrated significant within-group improvements in the Short Form 36 (SF-36) questionnaire domains of physical functioning, social functioning, physical health and total score for both exercise and control groups ($p<0.05$). The exercise intervention group also demonstrated significant within-group improvements in bodily pain, vitality and mental health ($p<0.05$). Laoutaris and colleagues [33] found 10-weeks of ET resulted in a significant within-group improvement in the Minnesota Living with Heart Failure Questionnaire for the intervention (48.9±12.8 to 38.2±11.6, $p<0.005$) but not the control group (49.8±9.5 to 50.8±10.3, $p<0.30$). No significant between-group differences in HR-QoL were observed in any study.

Lung Function

One intervention reported lung function prior to and following ET [33]. Laoutaris and colleagues [33] demonstrated significant within-group improvements in maximal inspiratory mouth pressure (Pi_{max}) (95.5±28.0 to 131.8±33.0 cmH_2O, $p<0.005$), sustained-Pi_{max} (340±193 to 484±195 $cmH_2O/s10^3$, $p<0.005$) and inspiratory capacity (1.7±0.7 to 2.4±0.9 L, $p<0.008$) in the exercise group. There were also non-significant within-group improvements in predicted forced vital capacity, forced expiratory volume in one-second, and their ratio. No significant between-group difference in any lung function outcome was observed.

Exercise interventions involving lung-transplant candidates

Frequency, length and duration

Five studies reported the frequency of ET [31,34,37,39,40], ranging from two [34] to six [31] days per week. Three studies also provided details on the length of the intervention, ranging from three [31] to 12 [37,39] weeks. The exception was Li and colleagues [40] who retrospectively analysed data from a pulmonary rehabilitation program where patients completed 15 to 16 weeks of ET before transplantation. Four trials reported the duration of each exercise session, varying from 30 to 120 minutes [31,34,40]. One trial did not specify session duration [39], but explained that exercise prescription was in accordance with pulmonary rehabilitation guidelines [44].

Modality

Four studies implemented a combination of aerobic and resistance-based strength training [31,34,37,40]. Aerobic-training modes included cycling ergometery and/or treadmill walking [31,34,37,40]. Resistance-based strength training included full body, dynamic muscular contractions, incorporating a combination of free-weight, machine and body weight exercises [31,34,37,40]. The remaining study implemented Nordic pole walking [39].

Location

The majority of trials conducted in lung transplant candidates were delivered as an outpatient ET program [34,37,39,40]. ET locations were predominantly hospital/institution-based. Only one study incorporated a combination of hospital and home-based ET [39].

Intensity

Aerobic Training

All trials included aerobic exercise and reported intensity [31,34,37,39,40]. Several methods of reporting exercise intensity were used including percentage of peak work rate (%W_{peak}) [31,34], percentage of estimated maximum heart rate [39,40], percentage of 6MWD speed [37] and rating of perceived exertion [40]. Exercise prescription was set at a light to moderate intensity. Gloeckl and colleagues [31] were the exception, comparing the effectiveness of HIIT versus MICT. Participants in the HIIT group cycled at 100% W_{peak} for 30-seconds interspersed by 30-seconds of rest (0% W_{peak}). MICT training involved participants cycling at 60%W_{peak}. The total exercise duration per session increased from 12 to 36 minutes for HIIT and 10 to 30 minutes for MICT over a three-week period which was divided into two shorter duration sessions (12-15 minutes) on training days in the second and third weeks, respectively.

Resistance training

The reporting of resistance training intensity for lung transplant candidates was incomplete with methodological details varying between studies (e.g. weight, set and repetition range). Four trials prescribed resistance training with two describing a method of determining and monitoring intensity [31,34,37,40]. Florian and colleagues [37] implemented a one repetition maximum (1-RM) test to prescribe an intensity equivalent to 30% of 1-RM for resistance training, progressively increasing by 0.5 kg every seven sessions. Gloeckl and colleagues [31] prescribed a weight that patients could perform a

maximum of 20 repetitions per set. Both trials opted for a low number of sets with a moderate-to-high number of repetitions [31,37].

Supervision

Four studies reported that all exercise sessions were supervised [31,34,37,40]; only one study employed partial supervision [39].

Safety

The definition and reporting of adverse events was poorly described. No intervention provided a definition of what constituted an adverse event. Furthermore, the severity of an adverse events and details on whether ET instigated and/or exacerbated adverse events were omitted. Two studies reported that no adverse events occurred as a result of ET [31,39]. However, a Consolidated Standards of Reporting Trials (CONSORT) diagram included in the article by Gloeckl and colleagues [31] indicated that seven patients discontinued the intervention due to ‘acute exacerbations. No comment was made regarding the etiology of any exacerbation or whether they were a result of ET. However, the authors specified that that no serious adverse events were observed. Manzetti and colleagues (1994) reported that patients could safety participate in a pulmonary rehabilitation program [34]. Similarly, Li and colleagues [40] did not provide any information regarding adverse events, but stated that despite the severity of lung disease, patients were able to participate in the program.

Adherence

Four studies monitored adherence to ET by recording attendance [31,37,39,40]. Two trials reported the percentage of sessions attended, ranging from 85-100% [37,39]. Although Florian and colleagues [37] reported 100% adherence to the exercise intervention, patients were excluded from the analysis if they did not attend all 36 sessions. Gloeckl et al. [31] reported the average number of sessions for HIIT (14.9±1.9 sessions) and MICT (14.7±1.5 sessions) groups from a possible 18 sessions for the intervention. Li and colleagues [40] reported that patients attended 47±59 sessions of pulmonary rehabilitation, however did not include the maximum number of sessions each patient could attend.

Efficacy

Exercise capacity

CPET was not used in any study involving lung transplant candidates. Li and colleagues [40] estimated $\dot{V}O_{2max}$ and exercise capacity (METs) based on the distance travelled on the treadmill during the test [42]. Results demonstrated significant within-group increases in estimated $\dot{V}O_{2max}$ (0.69±1.4 mL/kg/min; $p<0.001$) and exercise capacity (0.20±0.39 METs; $p<0.001$) following ET.

Change in W_{peak} was reported in two studies [31,34]. Only Gloeckl and colleagues [31] observed significant within-group increases in W_{peak} (HIIT 12.0±8.5 W, $p<0.05$; MCT 9.3±10.1 W, $p<0.05$) following training. No significant between-group change was observed.

Three interventions reported results for 6MWD [31,34,37]. Manzetti and colleagues [34] demonstrated significant within-group differences in 6MWD for

the intervention (232±87 to 299±161 m, p<0.03) and control (277±190 to 350±132 m, p<0.03) groups. Gloeckl et al. reported significant within-group improvements in 6MWD and percentage of predicted 6MWD in the HIIT (35.4±28.9 m, p<0.05; 14.1±12.7%, p<0.05) and MICT (35.7±42.2 m, p<0.05; 15.5±25.1%, p<0.05) groups [31]. Similarly, Florian and colleagues [37] reported significant improvements in 6MWD (367±136 to 439±114 m; p=0.001) and percentage of predicted 6MWD (56.6±22.6 to 75.5±16.6 m; p=0.001). There were no significant between-group changes in trials that included a control group [31,34].

Muscular Strength

Only one of the four studies that included resistance training reported muscular strength as an outcome measure [40]. Li and colleagues [40] reported a significant increase in training volume calculated by the product of total repetitions and training weight of the elbow flexor (55±45 to 76±81, p<0.001) and knee extensor (37±28 to 53±44, p<0.001) muscle groups.

Health-related Quality of Life

All studies in lung transplant candidates assessed HR-QoL [31,34,37,39,40]. Four studies used the SF-36 questionnaire [31,37,39,40], with three reporting the Physical Health Summary (PHS) and Mental Health Summary (MHS) component scores [31,39,40]. Gloeckl and colleagues [31] reported significant within-group improvements in the MHS of the HIIT group (9.7±13.0; p<0.05) and PHS of the MICT group (4.3±6.9; p<0.05). Jastrzebski et al. [39] reported a significant improvement in PHS at six (27.2±8.2 to 29.9±9.1; p<0.05) and 12 weeks (27.2±8.2 to 30.8±7.3; p<0.05) compared to baseline. In contrast, Li

and colleagues [40] reported a significant decline in the MHS (47±11 to 45±12; p<0.05), but demonstrated significant improvements across all domains of the St. George Respiratory Questionnaire (p<0.05). Manzetti and colleagues [34] used a combination of Quality of Wellbeing, Quality of Life Index and Symptom Frequency/Symptom Distress scales, with only the Quality of Wellbeing demonstrating significant within-group improvements in both the intervention (0.55±0.02 to 0.61±0.05; p<0.005) and control (0.58±0.07 to 0.71±0.08; p<0.005) arms.

Pulmonary Function

Lung function was reported in two studies [31,39]. Gloeckl and colleagues [31] compared the rating of perceived dyspnea during exercise between HIIT and MICT. Patients performing HIIT had a significantly lower rating of perceived exercise dyspnea compared to the MICT group (6.2±1.6 to 7.2±1.4; p=0.012). Improvements in lung function outcomes were observed in both studies including forced expiratory volume in one second, percentage of predicted forced expiratory volume in one second, predicted alveolar diffusion, partial pressure of oxygen tension and partial pressure of carbon monoxide tension.

DISCUSSION

Based on the evidence presented, there is a paucity of research investigating the safety, adherence and efficacy of ET in patients awaiting solid-organ transplantation. Adherence to ET by patients awaiting heart and lung transplant is high. However, given the poor quality of reporting adverse

events, small sample sizes and limited number of randomized-controlled trials, it is difficult to conclude whether ET is safe and/or provides physiological or psychological benefits compared to control.

Safety of training

A total of 660 participants completed approximately 1760 hours of ET, ranging from 25 to 120 minutes per session. A total of four adverse events were deemed to be exercise-induced. However, no serious adverse events were described. Therefore, when the number of adverse events were related to participant-training hours, the rate of an exercise-related event occurring is one in 434 hours. In comparison to patients receiving phase three cardiovascular rehabilitation [45], heart and lung transplant candidates are approximately twice as likely to have a non-life threatening exercise-related adverse event, based on this relatively small sample. However the reporting of safety was poorly described in the reviewed studies. Only one study in heart transplant candidates reported specific information on adverse events due to ET [41]. Furthermore, in line with the current CONSORT statement, only two studies produced a diagram providing information on study design and any event-related dropouts [31,32]. However, it was not clear whether dropouts were associated with the exercise intervention in these trials. The remaining studies that reported safety outcomes described ET to be ‘safe’ without objectively quantifying adverse event number and/or associated participant drop-outs [33-40]. No studies provided an adverse event definition or any information regarding adverse event severity. Given the concerns regarding ET in this severely deconditioned patient cohort, future studies should follow appropriate methodology in regards to adverse event reporting.

The intensity of ET is often debated among health professionals. The majority of trials prescribed aerobic ET at a light to moderate intensity. Historically, this intensity of ET has been implemented for 'high risk' populations that may be at greater risk of an adverse cardiovascular event [46]. Despite this, Gloeckl and colleagues [31] employed HIIT, an ET method shown to elicit superior improvements in CRF compared to MICT in other high risk populations [47,48]. It was also found that perceived exertional dyspnea was significantly lower in the HIIT group compared to the MICT group. This suggests that HIIT may elicit comparable physiological improvements to MICT without contributing to dyspnea exacerbation. Given exertional dyspnea is common in heart failure and chronic obstructive pulmonary disease; HIIT may be better tolerated compared to MICT.

Adherence to training

Adherence to ET is critical to optimize potential benefits, but may be challenging for patients with end-stage disease. Despite the well-recognized benefits associated with exercise, individuals often fail to maintain adherence to exercise prescriptions [49]. In the studies reviewed here, adherence with ET was high (82.5–100%), which was similar or better when compared to other interventions for older adults (78%) [50]. However, patients who volunteer for exercise-interventional research may represent an inherently motivated group that is not necessarily representative of the population in question. Based on the studies presented within this review, it is still unclear whether the influence of disease severity may have impacted upon exercise adherence. It has been suggested that the severity of organ-related disease is

a significant predictor of exercise training adherence in patients with heart failure [51] and those undergoing pulmonary rehabilitation [52]. This is an important consideration given that those patients who completed the intervention may have been less decompensated, in comparison to patients who were ineligible or discontinued the program due to functional difficulties related to the severity of their heart or lung disease.

Efficacy of training

Patients diagnosed with end-stage organ failure typically have significantly reduced CRF, often attributed to disease-related deconditioning. Manici and colleagues [12] were the first to identify the significance of pre-operative CRF for heart transplant candidates. Subsequent research has linked low pre-transplant CRF to unfavorable post-operative outcomes [53]. Specifically for heart transplant patients, a pre-operative $\dot{V}O_{2peak}$ <12 mL/kg/min is currently an indication for candidacy [54] while those with a $\dot{V}O_{2peak}$ >14 mL/kg/min have significantly improved wait-list survival [12]. There are currently no data on the relationship between CRF and outcomes in lung transplant candidates.

Heart transplant candidates showed ET induced improvements in $\dot{V}O_{2peak}$, from 2.5 [33] to 4.3 mL/kg/min [32]. An increase in $\dot{V}O_{2peak}$ of 3.5 mL/kg/min is associated with a 10-25% improvement in survival for the general population [53] However, in studies with a control group, this within-group improvement was not significantly different to controls. This is likely due to the small number of participants in combination with the significant increase in CRF in the control groups. Participants allocated to the usual care arm of the

controlled studies were advised to walk 5-7 days per week for 30-60 minutes most likely contributing to their increases in CRF.

Heart and lung transplant candidates had within-group improvements in exercise capacity (W_{peak} and 6MWD), ranging from 16.8% [31] to 43.6% [32], and 10.2% [31] to 33.8% [32], respectively. W_{peak} has been demonstrated to correlate well with $\dot{V}O_{2peak}$ [55,56]. Similarly, 6MWD evaluates global and systemic physiological response to submaximal exercise and may provide a better reflection of functional ability to perform activities of daily living [57]. Hayes and colleagues [32] demonstrated the greatest improvement in W_{peak} and 6MWD, most likely due to the prescription and progression of both cycle ergometry and treadmill walking. As with $\dot{V}O_{2peak}$, 6MWD has demonstrated prognostic importance in relation to morbidity and mortality in end-stage and transplant populations [58-61]. Given the prevalence of sarcopenia in end-stage diseases, with reductions in muscular strength and power, exercise-induced improvements in W_{peak} may indirectly reflect improvements in lean muscle mass and/or cellular respiration through both glycolytic and oxidative pathways [62]. There were however no statistically significant between-group differences. The sample size calculation performed by Gloeckl and colleagues was derived based on the assumption that HIIT would be as effective as MICT to detect the margin of minimal clinically important 6MWD difference (26 meters) [63] but not the change in W_{peak} [31]. Additionally, the change in $\dot{V}O_{2peak}$ was the primary outcome for one trial [32], which may not have provided sufficient statistical power to detect a between-group significant difference in exercise capacity outcomes.

A reduction in HR-QoL is common in transplant candidates due to the burden associated with the diagnosis and prognosis of end-stage disease; fatigue, loss of self-esteem, anxiety and depression can be attributed to this decline [64]. In particular, the pre-operative phase for transplant candidates is a time of significant psychological stress, contributing to anxiety disorders and depression [65]. Transplant patients often have reduced functional status, a major determinant of impaired HR-QoL, through negative impacts on daily activities and social interaction related to dyspnea, fatigue and pain [66]. Regular participation in exercise has been found to improve survival, and benefit overall well-being and functional status in chronic disease [66,67]. Within-group improvements in HR-QoL were generally observed following ET, particularly for lung transplant candidates. Interestingly, these improvements in HR-QoL were observed in as little as three weeks following initiation of ET, however were not significant in studies with a comparative control-group.

There remains a paucity of ET research for other solid-organ transplant candidates. The combined total of kidney and liver transplant candidates represents a significantly larger patient cohort compared to patients awaiting a heart or lung transplant. Regular aerobic and resistance ET elicits physiological and psychological benefits in hemodialysis recipients [68], and is suggested for patients diagnosed with end-stage liver disease [69]. Given the high prevalence of kidney disease-related cardiovascular and sarcopenic complications [70,71], in conjunction with the prognostic significance of impaired pre-transplant CRF [13-15,72], it seems logical that ET interventions in these populations warrants investigation.

CONCLUSION

The body of research evaluating the safety, adherence and efficacy of ET in patients awaiting heart or lung transplant surgery is relatively small. Trials are predominantly interventions with no control group and small sample sizes. Although adherence to the interventions was high indicating that ET is feasible, there were no physiological or psychological improvements compared to controls. This could be due to small sample sizes or control group participants increasing their exercise. In summary, ET is feasible in patients awaiting heart and lung transplant, however longer-term, adequately powered, randomized control trials are required to determine the safety and efficacy.

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Table 1: Randomised and non-randomised controlled trials of exercise training in solid-organ transplant candidates

Author	Study type	Organ	Disease Severity	n	Exercise Mode	Time/Frequency/ Intensity	Adverse Events	Outcome (Intervention)	Outcome (Control)	Adherence
Ben-Gal et al. (2000)[35]	Non-randomised	Heart	Severe end-stage congestive heart failure NYHA class IIIb or IV	12	Aerobic-only	25 min 2x/week 50% W_{peak}, RPE 14	No AE's reported	↑ $\dot{V}O_{2peak}$[a] ↑ VT[a] ↑ W_{peak}[c] ↑ 6MWD[c]	↓ $\dot{V}O_{2peak}$[a] ↓ VT[b] ↓ W_{peak}[c] ↔ 6MWD	92%
Laoutaris et al. (2011)[33]	Randomised	Heart	End stage heart failure requiring VAD support as a bridge to transplantation INTERMACS: Level I-III at implantation	15	Combo: Aerobic + IMT	30 min 3-5x/week RPE 12-14 60% SPi_{max}	NR	↑ $\dot{V}O_{2peak}$[a] ↑ VT[a] ↓ $V_E/\dot{V}CO_2$[a] ↑ 6MWD[c] ↑ QoL[c] ↑ Pi_{max}[c] ↑ SPi_{max}[c] ↑ IC[a]	↔ $\dot{V}O_{2peak}$ ↔ VT ↔$V_E/\dot{V}CO_2$ ↔ 6MWD ↔ QoL ↔ Pi_{max} ↔ SPi_{max} ↔ IC	NR
Hayes et al. (2012)[32]	Randomised	Heart	End stage heart failure requiring LVAD support as a bridge to transplantation INTERMACS: Level I-II at implantation	14	Combo: Aerobic + RT	60 min 3x/week 60% 6MWD speed 2 sets, 20 reps	No AE's reported	↑ $\dot{V}O_{2peak}$[b] ↑ W_{peak}[b] ↑ 6MWD[b] ↑ PFS[b] ↑ Bodily Pain[b] ↑ Vitality[b] ↑ Social Function[b] ↑ MHS[b] ↑ PHS[b] ↑ Total Score[b]	↑ $\dot{V}O_{2peak}$[b] ↑ W_{peak}[b] ↑ 6MWD[b] ↑ PFS[b] ↔ Bodily Pain ↔ Vitality ↑ Social Function[b] ↔ MHS ↑ PHS[b] ↑ Total Score[b]	21.3 ± 1.5 of 24 sessions
Manzetti et al. (1994)[34]	Randomised	Lung	NYHA class III or IV	9	Combo: Aerobic + RT	30 min 2x/week W_{peak} at VT	Patients can safely participate in pulmonary rehabilitation	↑ 6MWD[b] ↑ QWB[c]	↑ 6MWD[b] ↑ QWB[c]	NR
Gloeckl et al. (2011)[31]	Randomised	Lung	GOLD assessment stage IV FEV_1 (% predicted): 24±8 (HIIT), 27±7 (MICT)	60	Combo: Aerobic + RT	HIIT (12-36 min) MICT (10-30 min) 5-6x/week HIIT (100% W_{peak}) MICT (60% W_{peak})	No AE's reported	↑ W_{peak}[b] ↑ 6MWD[b] ↑ 6MWD (predicted)[b] ↔ Physical Health ↑ Mental Health[b]	↑ W_{peak}[b] ↑ 6MWD[b] ↑ 6MWD (predicted)[b] ↑ Physical Health[b] ↔ Mental Health	All patients adhered to the program

AE's = adverse events; HIIT = high intensity interval training; MICT = moderate intensity continuous training; Combo = combination of aerobic and strength training or inspiratory muscle training; IMT = inspiratory muscle training; RT = resistance training; Pi_{max} = maximal inspiratory pressure; SPi_{max} = sustained inspiratory muscle strength; VT = ventilatory threshold; $V_E/\dot{V}CO_2$ = ventilatory equivalents for carbon dioxide; W_{peak} = peak work rate; RPE = rating of perceived exertion; $\dot{V}O2peak$ = peak oxygen uptake; 6MWD = six-minute walk distance; NR = not reported; MHS = mental health score; PHS = physical health score; QWB = quality of well-being; NYHA = New York Heart Association; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; VAD = ventricular assist device; LVAD = left ventricular assist device; FEV_1 = forced expiratory volume in one second; GOLD = Global Initiative for chronic obstructive lung disease

[a] = ≤0.01
[b] = ≤0.05
[c] = ≤0.005

Table 2: Non-controlled trials of exercise training in solid-organ transplant candidates

Author	Study design	Organ	Disease Severity	n	Exercise Mode	Time/Frequency/ Intensity	Adverse Events	Outcome	Adherence
Fonarow et al. (1997)[38]	Prospective	Heart	NYHA III or IV	121	Aerobic-only	30-45 mins 4x/week Self-perceived intensity <VT	NR	↑ $\dot{V}O_{2peak}$[c] ↑ VT[c]	NR
Dean et al. (2011)[36]	Prospective	Heart	Advanced heart failure	9	RT	NR 3x/week 60-80% MVC	No	↑ FMD[b] ↔ Grip strength	Authors stated that patients had no difficulty maintaining the program
Li et al. (2013)[40]	Retrospective	Lung	End-stage lung disease requiring transplantation	345	Combo: Aerobic + RT	90-120 mins 3x/week Symptom-limited intensity	NR	↑ $\dot{V}O_2$[c] ↑ METs[b] ↑ Treadmill duration[b] ↑ Caloric expenditure[b] ↑ Training volume (quadriceps and biceps)[b] ↑ SGRQ (symptom, activity, impact, total)	47 ± 59 sessions attended
Jastzebski et al. (2013)[39]	Prospective	Lung	End-stage lung disease requiring transplantation FEV_1 34% predicted	22	Aerobic-only	NR NR 75% HR_{max} from 6MWD	No AE's reported	↑ 6MWD (0-6 weeks)[b] ↑ 6MWD (6-12 weeks)[b] ↑ FVC[b] ↑ Social functioning[b] ↑ PHS[b]	85%
Florian et al. (2013)[37]	Prospective	Lung	End-stage lung disease requiring transplantation FEV_1 32.9 ±15.9% predicted	58	Combo: Aerobic + RT	90 mins 3x/week 60% 6MWD speed	NR	↑ 6MWD[c] ↑ 6MWD (predicted)[c] ↑ Post exercise dyspnea[c] ↑ Physical functioning[c] ↑ Vitality[c] ↑ Social functioning[c] ↑ MHS[c]	All patients adhered to the program
Morrone et al. (1996)[41]	Retrospective	Heart	End stage heart failure requiring LVAD support as a bridge to transplantation	34	Combo: Aerobic + RT	NR NR RPE 11-13	Yes	↑ Time on treadmill ↑ Intensity on treadmill	NR

AE's = adverse events; Combo = combination of aerobic and strength training or inspiratory muscle training; RT = resistance training; HR_{max} = maximum heart rate; VT = ventilatory threshold; W_{peak} = peak work rate; Rating of perceived exertion; MVC = maximum voluntary contraction; FMD = flow-mediated dilation; METs = metabolic equivalents; $\dot{V}O_2$ = oxygen consumption; $\dot{V}O_{2peak}$ = peak oxygen uptake; 6MWD = six-minute walk distance; NR = not reported; MHS = mental health score; PHS = physical health score; FVC = forced vital capacity; NYHA = New York Heart Association; FEV_1 = forced expiratory volume in one second; LVAD = left ventricular assist device

[a] = ≤0.01
[b] = ≤0.05
[c] = ≤0.005

Table 3: Cochrane risk of bias summary

	Sequence Generation	Allocation concealment	Blinding (personnel)	Incomplete outcome data	Free of selective outcome reporting	Free from other sources of bias
Hayes et al. [26]	+	+	+	+	+	+
Laoutaris et al. [27]	-	-	+	-	+	+
Ben-Gal et al. [29]	-	-	-	+	+	?
Gloeckl et al. [25]	?	+	+	+	+	+
Manzetti et al. [28]	?	?	?	+	+	+

+ = low risk of bias; ? = Unclear risk of bias; - = High risk of bias

Table 4: Newcastle-Ottawa scale summary

	Selection			Comparability	Outcomes				Score
	1	2	3	1	1	2	3	4	
Dean et al. [30]	a*	a*	a*		a*	a*	b	b*	5
Fonarow et al. [32]	a*	a*	a*		a*	a*	a*	b*	7
Morrone et al. [35]	a*	a*	a*		a*	a*	a*	a*	7
Florian et al. [31]	a*	a*	a*		a*	a*	a*	b*	7
Li et al. [34]	a*	a*	a*		a*	a*	a*	b*	7
Jastrzebski et al. [33]	a*	a*	a*		a*	a*	a*	b*	7

Letters represent answers for the individual questions. One star can be awarded for each numbered item in both the Selection and Outcome categories. A maximum of two stars can be awarded in the Comparability category. See Supplementary File 1 for the scale criteria.

Figure 1: Systematic review search flow