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Effect of high-intensity training on peak oxygen uptake and muscular strength after lung transplantation: A randomized controlled trial

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BACKGROUND: Peak oxygen uptake (VO_{2peak}) remains low after lung transplantation (LTx). We evaluated the effect of high-intensity interval training (HIIT) on VO_{2peak}, muscular strength, health-related quality of life (HRQOL), pulmonary function, and physical function after LTx.
METHODS: In this randomized controlled trial, 54 participants were enrolled from 6 to 60 months after LTx. The HIIT group ($n = 25$) followed a supervised HIIT program, consisting of endurance and strength trainings 3 times a week for 20 weeks. The control group ($n = 29$) received usual care. The primary outcome was a change in VO_{2peak} measured by cardiopulmonary exercise testing. The secondary outcomes were changes in 1-repetition maximum (1RM) for arm press and leg press, HRQOL (36-Item Short-Form Health Survey [SF-36]), pulmonary function (forced expiratory volume in 1 sec, diffusing capacity of the lungs for carbon monoxide), and physical function (1RM in handgrip, 15-sec stair run, and 30-sec chair stand).
RESULTS: A total of 46 participants completed the study, including 23 of 25 in the intervention group. For the primary outcome, the intention-to-treat analysis revealed a non-significant between-group difference for change in VO_{2peak} of 0.7 ml/(kg.min) (95% CI = −0.3, 1.8) ($p = 0.17$). The between-group differences for 1RM arm press and leg press and mental aspect of SF-36 were 4.9 kg (95% CI = −0.1, 9.9) ($p = 0.05$), 11.6 kg (95% CI = 0.1, 23.0) ($p < 0.05$), and 5.7 kg (95% CI = 0.9, 10.4) ($p = 0.02$), respectively. There were no between-group differences in pulmonary function or physical function. When excluding participants with an attendance of <70% ($n = 16$), the between-group difference for VO_{2peak} was 1.2 ml/(kg.min) (95% CI = 0.1, 2.4) ($p = 0.032$).
CONCLUSIONS: HIIT improved muscular strength and HRQOL but did not improve VO_{2peak} more than usual care after LTx. However, with acceptable adherence, HIIT appears to have beneficial effects on VO_{2peak}.
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Lung transplantation (LTx) is a lifesaving treatment for many patients with terminal lung disease. Although life expectancy improves after LTx in appropriately selected patients, poor cardiorespiratory fitness and muscle weakness are persistent and common after LTx despite normalization of pulmonary function. Prolonged inactivity before LTx and muscle dysfunction associated with the use of immunosuppressive drugs have been suggested as causes for this.[1−3]

Strong associations between peak oxygen uptake (VO_{2peak}) and mortality have been shown in the general population,[4,5] in individuals with chronic obstructive pulmonary disease,[6] and in patients after LTx.[7] Muscular strength, which has been inversely associated with all-cause mortality after adjustment for VO_{2peak},[8] may play a similarly important role.

Typically, structured exercise for LTx recipients involves programs of moderate intensity.[9,10] However, studies in both healthy individuals and several populations with disease have shown that VO_{2peak} and muscular strength can be improved more effectively by high-intensity exercise training.[11,12] High-intensity interval training (HIIT) improves VO_{2peak} and muscular strength after heart transplantation,[13] and in those who have survived cancer, mixed-mode HIIT interventions consisting of both aerobic and strength training have been shown to be the most effective in improving aerobic fitness.[12] The effects of such training in LTx recipients are unknown. Previous studies among LTx recipients have varied with respect to both chosen end-points and observed effects of exercise training.[9,14]

Given the possible benefits of mixed-mode HIIT, we conducted a randomized controlled trial to evaluate the efficacy of high-intensity endurance and strength training in LTx recipients from 6 months to 5 years after transplantation. The primary outcome was a change in cardiorespiratory fitness, measured as VO_{2peak}. Additional outcomes were changes in upper and lower muscular strength, health-related quality of life (HRQOL), pulmonary function, and physical function. We hypothesized that HIIT would improve cardiorespiratory fitness and muscular strength more than usual care.

Methods

Study design and participants

This study was a single-center, randomized controlled, two-armed trial, comparing a mixed-mode HIIT program with usual care among adult LTx recipients from 6 to 60 months after surgery. We have previously reported the factors associated with cardiorespiratory fitness in this population in a cross-sectional analysis limited to baseline data.[15] This study reports the primary outcome of the trial. Recruitment, randomization, and data collection took place at Oslo University Hospital, Rikshospitalet, Norway, between September 2017 and January 2019. Eligible participants were aged ≥18 years with stable medical conditions in the opinion of the enrolling investigator. Exclusion criteria included inability to complete a symptom-limited maximal cardiopulmonary exercise test (CPET) on a treadmill or participation in another ongoing study. All participants underwent baseline testing; thereafter, they were randomly assigned to either mixed-mode HIIT or usual care in a 1:1 ratio. The randomization was performed in blocks with varying block sizes (4−6 subjects) without any stratification. All patients undergoing LTx at our institution receive triple-drug immunosuppression consisting of tacrolimus or cyclosporine, mycophenolate mofetil, and prednisolone. The long-term maintenance dosage for prednisolone, beginning at >6 months after LTx, is 7.5 mg daily.

The study was conducted in accordance with the Helsinki Declaration, approved by the Regional Committee for Medical and Health Research Ethics (REK South East, No. 2017/399), and was registered in ClinicalTrials.gov (NCT03155074). All participants provided written informed consent before enrollment.

Measurements

Experienced exercise physiologists, assisted by master students from the Norwegian School of Sports Sciences, performed before and after measurements in the presence of a medical doctor. Participants were asked to complete a questionnaire before and after the intervention regarding demographics and exercise habits.

CPET

All participants performed a maximal symptom-limited CPET on a treadmill (TechnoGym Runrace, Forli, Italy) using a modified Balke protocol.[16] The speed was set to 1.8, 2.8, 3.8, or 4.8 km/hour depending on the participant's judgment of fitness level. The incline was set to 4% and increased by 2% every minute. If a participant reached the maximal incline of 20%, the speed was increased by 0.5 km/hour until exhaustion. Gas exchange and ventilation were directly measured breath-by-breath and averaged over 30-sec intervals (Vyntus CPX Metabolic Cart, CareFusion Corporation, Hoechberg, Germany). VO_{2peak} was defined as the highest oxygen consumption value sampled over 30-sec interval, and reference values were calculated according to the protocol given by Edvardsen et al[17]. Measurements of percutaneous oxygen saturation, blood pressure, and a 12-lead electrocardiogram (Custo cardio 100, Custo Med, Ottobrunn, Germany) were conducted at rest and throughout the test. Perceived exertion was rated by Borg 6–20 scale,[18] and blood lactate concentration was measured with a capillary blood sample obtained within 60 sec after test termination.

One-repetition maximum testing

Muscular strength was measured by 1-repetition maximum (RM) (1RM) in the leg (Cybex International Inc., Medway, MA) and arm press (Technogym Element +, Gambettona, Italia). The 1RM testing started with a short warm-up. Thereafter, the load was increased until 1RM was reached, with 3-minute breaks between each single repetition. To assure that the same sitting position and technique were used for testing before and after the intervention, the equipment settings and foot placement were carefully measured.

1RM handgrip strength was measured for the dominant hand with a hand-held dynamometer (Baseline 90 kg, Chattanooga, TN). The best of 3 attempts was recorded.

HRQOL

The Medical Outcomes 36-Item Short-Form Health Survey (SF-36) was used to evaluate HRQOL. A total of 8 sub-scales were aggregated into 2 summary scores: the Physical Component Summary and the Mental Component Summary. The summary scores are based on data for the US general population and standardized to a mean of 50 ± 10, where higher scores indicate better HRQOL.[19]

Pulmonary function

Spirometry and measurement of diffusing capacity of the lungs for carbon monoxide (DL_{CO}) (Vyntus, CareFusion Corporation, Hoechberg, Germany) were conducted according to the American Thoracic Society/European Respiratory Society task force guidelines.[20,21] Reference values were calculated using the global lung initiative equations for spirometry and DL_{CO}.[22,23]

Physical function

Physical function was assessed by maximal stair run and chair stand test.[24] For the maximal stair run test, the participant was asked to climb the stairs as fast as possible for 15 sec without holding the railing. The number of steps was counted. The chair stand test required the participants to stand up from and sit down on an armless chair as many times as possible for 30 sec.

Training intervention

Participants randomized to the exercise group (EG) were prescribed supervised mixed-mode HIIT 3 times a week for 20 consecutive weeks. The sessions were individually tailored and instructed by a certified personal trainer and/or a physical therapist at a fitness center close to the participant's home. Each session was estimated to last for 60 minutes and consisted of a cardiovascular warm-up, HIIT, and strength training. During the first 4 weeks, the patients were introduced to the program while focusing on safety, technique, and familiarization. The endurance intensity and strength load were then continuously increased. The main exercise mode during the interval training was uphill walking on a treadmill. The interval protocol consisted of 4-minute exercise bouts at 85%–95% of maximum heart rate, with 2 minutes of active recovery in between. Modifications to the duration of the exercise bouts were allowed if the participant were struggling to maintain the activity for 4 minutes.[25,26] The strength training was performed after the interval training and included 3 sets of 6–12RM by leg press, arm press, back extension, and seated row using stationary machine weights. Instructors were given a training program, including an exercise log to be filled out for each completed session. In addition, all participants registered their daily physical activity in a personal training diary. They were also asked to log events causing interruption of scheduled training sessions. Missed sessions were not rescheduled unless the absence was planned owing to holidays or medical appointments.

Usual care

Participants in the control group (CG) were asked to follow the hospital's general recommendation for maintaining regular physical activity but otherwise received only standard post-transplant medical follow-up care per our institution's protocol.

Outcomes

The primary outcome was a change in cardiorespiratory fitness, defined as the difference in directly measured VO_{2peak} between before intervention and after intervention. The secondary outcomes included before intervention and after intervention changes in muscular strength (1RM arm press and leg press, 1RM handgrip), pulmonary function (forced expiratory volume in 1 sec [FEV_1], maximal voluntary ventilation, and DL_{CO}), physical function (15-sec stair run and 30-sec chair stand), and HRQOL (SF-36 Physical Component Summary and Mental Component Summary).

Statistics

Descriptive statistics are reported as mean ± SD. Power analysis with an alpha level of 0.05, power of 0.80, and a primary outcome/smallest clinical worth effect size in VO_{2peak} of 3.5 ml/(kg. min), assuming an SD of 3.4, yielded a sample size estimation of 15 participants in each group. Data from an analogous randomized controlled trial utilizing HIIT in patients with lung cancer after surgery were used to estimate the expected smallest clinical worth effect size, including SD for VO_{2peak}.[25]

The between-group differences in the outcome variables from baseline to follow-up were assessed by analysis of covariance, adjusted for baseline scores. Per-protocol analyses were also performed for change in VO_{2peak}, muscular strength, and HRQOL. Participants attending ≥70% of the planned sessions were included in these analyses.

Pearson's correlation coefficients and univariate and multivariable linear regression (hierarchical, enter method) were used to assess associations between clinical characteristics, adherence to training, and the percentage change in VO_{2peak}. A negligible correlation was defined as $r < 0.30$, a low correlation as $r = 0.30$–0.49, a moderate correlation as r = 0.50–0.69, a high correlation as r = 0.70–0.89, and a very high correlation as $r \geq 0.90$.[27] A *p*-value < 0.05 was considered statistically significant.

All analyses were performed using SPSS, version 25.0 (IBM Statistics, Chicago, IL).

Results

Baseline characteristics are reported in Table 1 and were similar for both groups. Owing to leukopenia, 1 participant did not take mycophenolate mofetil, and 3 participants received a reduced prednisolone dosage of 5 mg/day at baseline testing. A total of 54 participants (27 women, aged 50 ± 15 years) were included and randomized to either the EG ($n = 25$) or CG ($n = 29$) (Figure 1). A total of 2 participants in the EG and 6 participants in the CG did not complete follow-up testing (Figure 1). One of these participants died of chronic lung allograft rejection, which was assessed as unrelated to the study.

Adherence, feasibility, and safety to exercise

In total, 846 of 1,260 planned exercise sessions were completed. The average exercise intensity was 93 ± 9% of peak heart rate, during the uphill interval. The average attendance was 40 ± 13 sessions (73%, ranging from 0% to 100%). A total of 16 of 25 participants (64%) in the EG attended ≥70% of the prescribed sessions and met the criteria for inclusion in the per-protocol analysis. There were, in total, 46 treatment interruptions (missing ≥3 consecutive sessions), of which 5 were permanent. The reasons for missing sessions were illness (48%), vacation/holidays (14%), musculoskeletal pain (7%), absence of instructor (4%), and work related (3%). In 24% of the missed sessions, no reason was given. No adverse events

Table 1 Baseline Characteristics for Participants by Group Assignment

Characteristics	HIIT ($n = 25$)	CG ($n = 29$)
Age, years	52.3 ± 11.9	51.1 ± 13.5
Female sex, *n* (%)	14 (56)	13 (45)
BMI, kg/m^2	25.3 ± 4.4	26.8 ± 3.7
Hemoglobin, mg/dl	12.2 ± 1.3	12.6 ± 1.7
Time since LTx (months)	30.2 ± 16.6	26.6 ± 15.7
Comorbidities		
CLAD, *n* (%)	5 (20)	2 (7)
Hyperlipidemia, *n* (%)	7 (28)	7 (24)
Hypertension, *n* (%)	8 (32)	14 (48)
Diabetes, *n* (%)	1 (4)	1 (3)
Renal insufficiency, *n* (%)	13 (52)	13 (45)
Native lung disease		
COPD, *n* (%)	12 (48)	12 (41)
Interstitial lung disease, *n* (%)	8 (32)	7 (24)
Pulmonary hypertension, *n* (%)	1 (4)	5 (17)
Cystic fibrosis, *n* (%)	2 (8)	0 (0)
Acute respiratory distress syndrome, *n* (%)	0 (0)	2 (7)
GvHD after stem-cell transplantation, *n* (%)	1 (4)	1 (3)
Lymphangioleiomyomatosis, *n* (%)	1 (4)	1 (3)
Systemic sclerosis, *n* (%)	0 (0)	1 (3)
Immunosuppression		
Cyclosporine, *n* (%)	18 (72)	17 (59)
Tacroliums, *n* (%)	7 (28)	12 (41)
Mycophenolate mofetil, *n* (%)	24 (99)	29 (100)
Prednisolone (7.5 mg/day), *n* (%)	22 (88)	29 (100)
Pulmonary function		
FEV_1, liter	2.51 ± 0.67	2.66 ± 0.79
FEV_1, % of predicted	81 ± 26	81 ± 25
FVC, liter	3.54 ± 0.65	3.67 ± 1.02
FVC, % of predicted	89 ± 18	89 ± 23
DL_{CO}, mmol/(min.kPa)	6.17 ± 1.40	6.47 ± 1.52
DL_{CO}, % predicted	76 ± 18	77 ± 17
Baseline performance on study outcomes		
VO_{2peak}, ml/(kg.min)	22.2 ± 7.0	22.1 ± 7.0
VO_{2peak}, % of predicted	65 ± 17	63 ± 15
Leg press, kg	104.8 ± 36.5	118.9 ± 31.5
Arm press, kg	43.2 ± 16.0	52.8 ± 24.3
SF-36 Physical Component Score	48.8 ± 8.9	48.0 ± 10.3
SF-36 Mental Component Score	47.8 ± 10.2	52.8 ± 7.7

Abbreviations: BMI, body mass index; CG, control group; CLAD, chronic allograft dysfunction; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity in the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; GvHD, graft vs host disease; HIIT, high-intensity interval training; LTx, lung transplantation; SF-36, 36-Item Short-Form Health Survey; VO_{2peak}, peak oxygen uptake.

Data are presented as mean ± SD or *n* (%).

were reported during the exercise training, but 4 participants reported exercise-related musculoskeletal pain.

In the CG, 11 participants reported exercising regularly 2–3 times per week, and 5 participants reported exercising at least 4 times per week.

Training effects

Intention-to-treat analyses for primary and secondary outcomes are presented in Table 2 and Figure 2. For the primary outcome, there was no between-group difference for change in VO_{2peak}; the observed change was 1.4 ± 1.8 ml/(kg.min) in the EG and 0.7 ± 1.7 ml/(kg.min) in the CG ($p = 0.169$). Of note, whereas most participants ($n = 43$, 80%) increased or maintained their VO_{2peak} during the intervention, 5 participants in the EG and 6 participants in the CG decreased their VO_{2peak}. In the EG, 2 participants had chronic lung allograft dysfunction (CLAD), and 2 participants suffered from chronic pain. In the CG, 1 participant had recurrent respiratory infections, 1 had progression of systemic sclerosis, and 1 suffered a myocardial infarction during the study. For the remaining 4 participants who experienced a loss of fitness, no complications were reported.

For the change in leg press, there was a significant between-group difference, with an increase of 14.7 ± 20.0 kg in the EG and 2.8 ± 17.2 kg in the CG ($p = 0.047$). The change for arm press was 5.2 ± 9.3 kg in the EG and 0.2 ± 6.2 kg in the CG ($p = 0.053$). There was a significant difference for the change in the SF-36 Mental Component Summary Score, with an increase (improvement) of 3.6 ± 7.4 in the EG vs a decrease of −3.4 ± 5.9 in the CG ($p = 0.020$).

Per-protocol analyses for change in VO_{2peak}, 1RM arm press and leg press, and HRQOL are reported in Table 3. In the per-protocol analysis, there was a significantly greater change in VO_{2peak} in the EG (1.9 ± 1.7 ml/[kg.min] vs 0.7 ± 1.7 ml/[kg.min], $p = 0.032$). Significantly greater changes were also observed for 1RM arm press and leg press as well as for the SF-36 mental component.

Factors associated with change in VO_{2peak}

For the EG, there was a strong correlation between change in VO_{2peak} and time since LTx, with longer elapsed time because LTx associated with smaller changes in VO_{2peak}. The estimated change in VO_{2peak} was 4.6% less for every year from LTx. In addition, a moderate correlation between change in VO_{2peak} and baseline FEV_1 was observed, with higher FEV_1 being associated with larger changes in VO_{2peak} (Figure 3). In the multiple linear regression analysis, sex, age, time since LTx, and FEV_1 explained 60% of the variability in VO_{2peak}. Time since LTx was independently associated with change in VO_{2peak} (Table 4).

Given the correlation between change in VO_{2peak} and time since LTx, we performed a post-hoc sub-group analysis to investigate whether this was due to natural recovery. When including only participants who had undergone LTx <2 years ago (HIIT group: $n = 10$, CG: $n = 11$), there was a

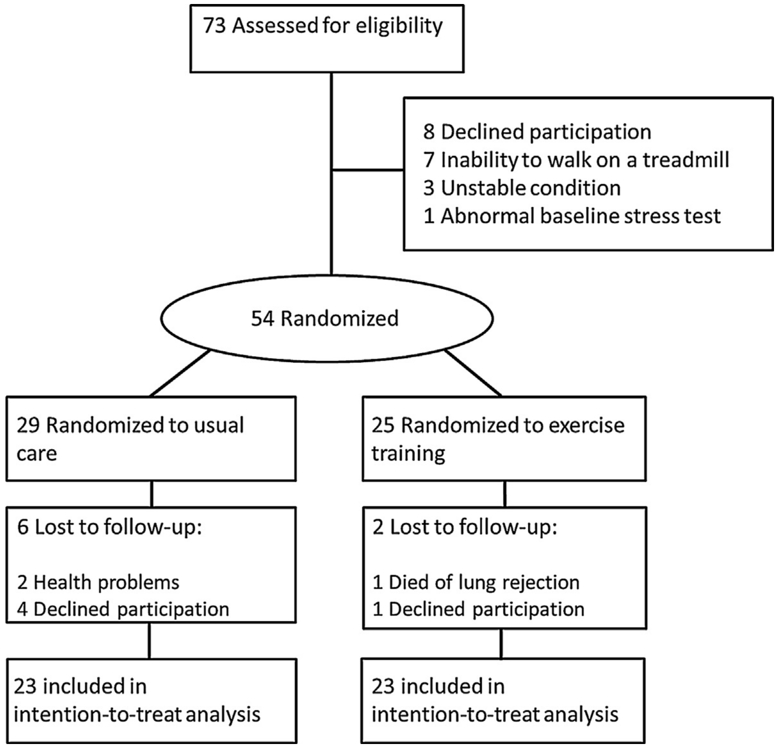

Figure 1 Flow chart of trial participation.

significant between-group difference in change in VO_{2peak} of 1.9 (95% CI = 0.7, 3.1) ml/(kg.min) ($p = 0.004$).

Discussion

This randomized controlled trial investigated the effects of mixed-mode HIIT on physical fitness after LTx. Whereas no overall effect of HIIT on VO_{2peak} was observed, there was a clear benefit of HIIT on cardiorespiratory fitness among participants who adhered to the exercise intervention. In addition, HIIT led to significant improvements in muscular strength, demonstrated by a significant increase of 11% in 1RM leg press. The benefits of HIIT among LTx recipients appear to be greatest if the intervention is undertaken within 2 years after LTx, suggesting that HIIT may help speed recovery.

Table 2 Intention-to-Treat Analyses on the Effect of Mixed-Mode HIIT on Primary and Secondary Outcomes

Intention-to-treat analyses	EG ($n = 23$)		CG ($n = 23$)		Between-group difference (95% CI)[a]	*p*-value[a]
	Before	After	Before	After		
Cardiorespiratory fitness						
VO_{2peak}, liter/min	1.6 ± 0.3	1.7 ± 0.4	1.7 ± 0.5	1.8 ± 0.5	0.02 (−0.07, 0.11)	0.680
VO_{2peak}, ml/(kg.min)	22.6 ± 7.0	24.1 ± 7.6	23.2 ± 7.3	24.0 ± 7.2	0.7 (−0.3, 1.8)	0.169
Muscular strength						
1RM leg press, kg	104.1 ± 31.2	118.8 ± 36.0	110.0 ± 27.0	112.9 ± 30.9	11.6 (0.1, 23.0)	0.047
1RM arm press, kg	44.4 ± 15.9	49.6 ± 20.4	51.8 ± 26.3	52.0 ± 25.1	4.9 (−0.1, 9.9)	0.053
Hand grip, kg	34.2 ± 11.3	35.7 ± 12.2	33.9 ± 12.0	34.3 ± 11.9	0.9 (−1.5, 3.3)	0.459
Physical functioning						
Chair stand, *n*	11.8 ± 2.7	13.5 ± 3.1	11.9 ± 2.7	13.6 ± 2.8	0.2 (−0.7, 1.1)	0.691
Stair run, sec	32.7 ± 8.4	34.4 ± 9.2	32.4 ± 8.9	33.8 ± 9.4	0.2 (−1.7, 2.0)	0.791
Pulmonary function						
FEV_1, liter	2.5 ± 0.7	2.5 ± 0.6	2.6 ± 0.8	2.5 ± 0.7	0.04 (−0.09, 0.16)	0.545
DL_{CO}, mmol/(min.kPa)	6.2 ± 1.4	6.1 ± 1.4	6.4 ± 1.5	6.4 ± 1.4	−0.02 (−0.31, 0.26)	0.868
HRQOL						
SF-36 MCS	47.1 ± 10.3	50.6 ± 9.2	54.0 ± 7.1	50.7 ± 10.9	5.7 (0.9, 10.4)	0.020
SF- 36 PCS	48.6 ± 8.3	48.4 ± 8.7	51.5 ± 6.9	52.3 ± 6.4	−1.7 (−5.1, 1.8)	0.328

Abbreviations: 1RM, 1-repetition maximum; ANCOVA, analysis of covariance; CG, control group; DL_{CO}, diffusion capacity in the lungs for carbon monoxide; EG, exercise group; FEV_1, forced expiratory volume in 1 sec; HIIT, high-intensity interval training; HRQOL, health-related quality of life; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score; SF-36, 36-Item Short-Form Health Survey; VO_{2peak}, peak oxygen uptake.

[a]ANCOVA analyses adjusting for baseline scores. Data are presented as mean ± SD.

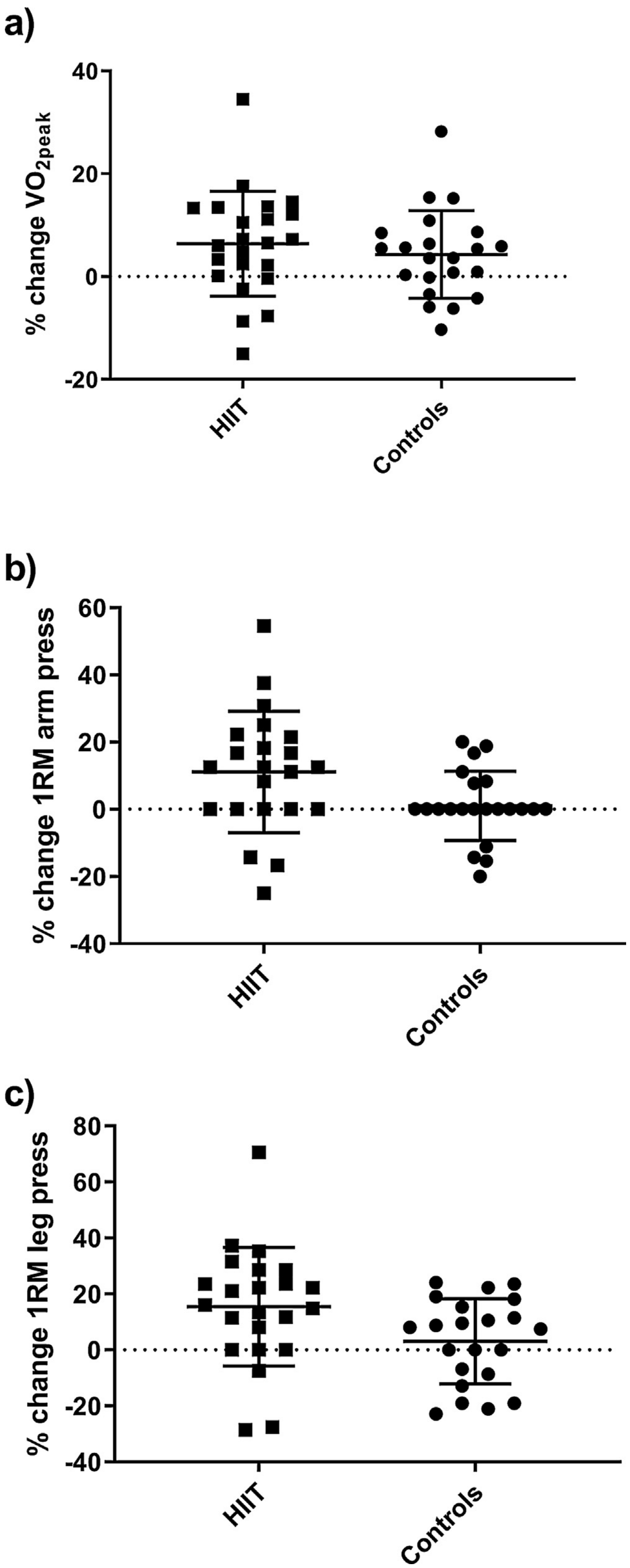

Figure 2 Percentage change in (a) VO_{2peak} and (b, c) 1RM for arm press and leg press after 20 weeks of HIIT and controls. 1RM, 1-repetition maximum; HIIT, high-intensity interval training; VO_{2peak}, peak oxygen uptake.

To our knowledge, no other studies have investigated the effect of mixed-mode HIIT in a randomized controlled trial after LTx. However, one study by Langer et al[28] investigated the effects of a supervised 12-week endurance training and resistance training program at moderate intensity. Consistent with our findings, they found beneficial effects on muscular strength and HRQOL but no effect on VO_{2peak} compared with a CG receiving activity counseling. Significant effects of exercise training on VO_{2peak} have been found in previous non-randomized controlled trials.[29−31] However, these uncontrolled studies were not able to separate the effects of exercise training with the natural recovery process after LTx.

Although there was no significant increase in VO_{2peak} in the intention-to-treat analysis, the per-protocol analysis revealed a larger and significant increase in the EG. The per-protocol analysis reflects the effects of HIIT when undertaken with acceptable adherence and suggests that highly motivated LTx recipients capable of completing 20 weeks of mixed-mode HIIT may indeed increase their VO_{2peak}. Several factors may contribute to the lack of effect in the overall study population, including (1) sub-optimal adherence to training and training intensity, (2) ventilatory limitation to exercise, or (3) effects of immunosuppressive drugs. Exploratory analyses suggest that lung function and the timing of the intervention relative to LTx itself may be of importance.

Most participants in the EG discontinued the exercise program either temporarily or permanently at some point during the intervention mainly because of infections and musculoskeletal pain. This is not surprising in a highly deconditioned patient group treated with immunosuppressive drugs and must be taken into account when prescribing exercise training. Importantly, there was no indication that the EG had more infections than the CG. Furthermore, self-reported exercise habits revealed a physically active CG, where a large majority exercised at least twice a week. This may have caused an underestimation of the exercise effects.

To ensure high external validity, participants with a broad range of ages, comorbidities, and post-operative complications were included in this study. Ventilatory limitation to exercise (defined as having a low breathing reserve) was observed in some participants at baseline, mainly in participants with CLAD. A total of 5 of the 7 participants with CLAD were allocated to the EG. Patients with ventilatory limitations to exercise cannot be expected to improve their VO_{2peak} as much as patients limited by the cardiovascular system,[32] likely because they are less capable of exercising at a high enough intensity (above 85% of maximum heart rate) to obtain the expected training effects of HIIT.[33] The finding that lower FEV_1 and lower breathing reserve during exercise were associated with a smaller increase in VO_{2peak} supports this.

Immunosuppressive drugs used by all participants are known to affect physical fitness negatively. For example, long-term steroid use may cause myopathy, and cyclosporine

Table 3 Per-Protocol Analyses of Effect of Mixed-Mode HIIT on VO_{2peak}, Muscular Strength, and HRQOL (SF-36)

Per-protocol analyses	EG ($n = 16$)		CG ($n = 23$)		Between-group difference (95% CI)[a]	p-value[a]
	Before	After	Before	After		
VO_{2peak}, ml/(kg.min)	24.2 ± 6.7	26.1 ± 6.8	23.2 ± 7.3	24.0 ± 7.2	1.2 (0.1, 2.4)	0.032
1RM arm press, kg	42.9 ± 16.7	49.5 ± 20.3	51.8 ± 26.3	52.0 ± 25.1	6.1 (1.3, 10.9)	0.014
1RM leg press, kg	103.4 ± 29.7	123.8 ± 33.3	110.0 ± 27.0	112.9 ± 30.9	17.5 (6.6, 28.3)	0.002
SF-36 MCS	46.2 ± 10.0	50.1 ± 9.5	54.0 ± 7.1	50.7 ± 10.9	6.7 (1.6, 11.8)	0.012
SF-36 PCS	49.8 ± 6.1	49.5 ± 6.1	51.5 ± 6.9	52.3 ± 6.4	−1.7 (−5.3, 1.8)	0.319

Abbreviations: 1RM, 1-repetition maximum; ANCOVA, analysis of covariance; CG, control group; EG, exercise group; HIIT, high-intensity interval training; HRQOL, health-related quality of life; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score; SF-36, 36-Item Short-Form Health Survey; VO_{2peak}, peak oxygen uptake.
[a]ANCOVA analyses adjusting for baseline scores. Data are presented as mean ± SD.

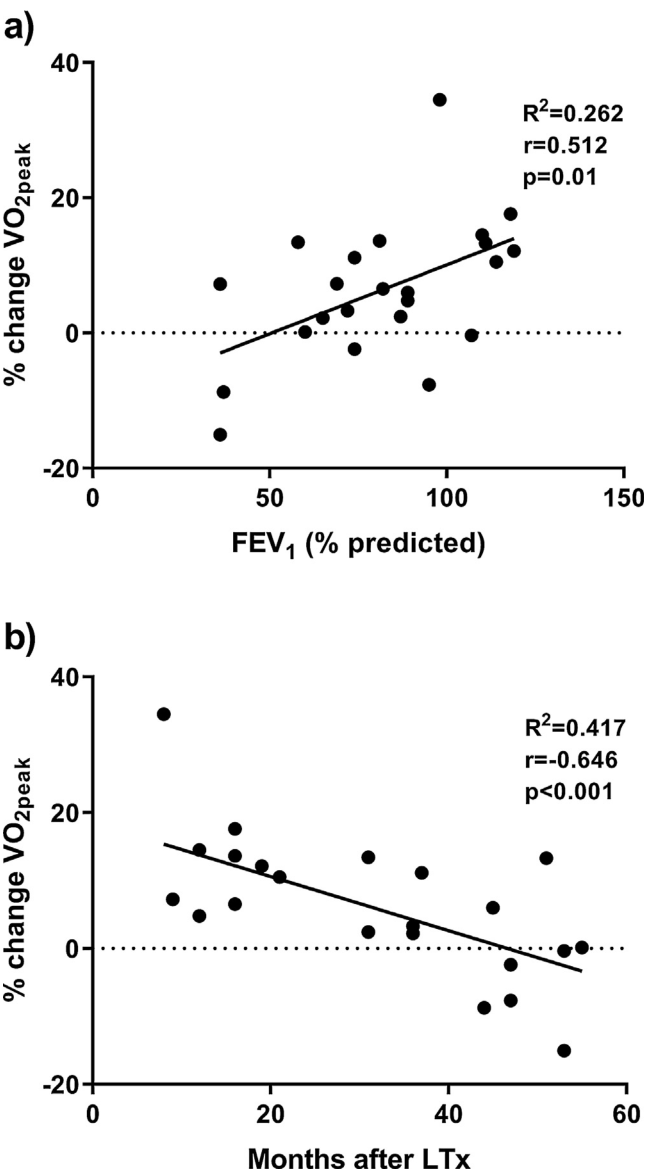

Figure 3 Correlations between percentage change in VO_{2peak} after 20 weeks of HIIT and FEV_1 at (a) baseline and (b) months after LTx. FEV_1, forced expiratory volume in 1 sec; HIIT, high-intensity interval training; LTx, lung transplantation; VO_{2peak}, peak oxygen uptake.

has been shown to affect muscle metabolism.[34,35] Interestingly, similar studies among heart transplant recipients using the same drugs have shown excellent results in improving VO_{2peak}.[13,36] However, it must be taken into account that LTx recipients may have received large cumulative doses of steroids before transplantation, which may not be comparable with the cumulative doses of heart transplant recipients.

Despite the positive effect on muscular strength, there was no significant increase in physical HRQOL as measured by the SF-36 Physical Component Summary Score. By contrast, mixed-mode HIIT had a positive effect on the SF-36 Mental Component Summary Score. This may be related to the increased attention and close follow-up of the EG or a feeling of well-being after exercise training. However, as the CG had a high Mental Component Summary Score above the normal value at baseline, a ceiling effect for this group must have been taken into consideration, which may have led to a biased between-group difference.

Interestingly, participants starting the exercise intervention within 2 years ($n = 10$) after LTx had a significantly larger increase in VO_{2peak} than those receiving usual care ($n = 11$). Moreover, change in VO_{2peak} was negatively associated with time since transplantation, independent of age, sex, and FEV_1. These findings suggest that mixed-mode HIIT, as relatively early intervention, may increase VO_{2peak} and speed recovery after LTx. However, such sub-group analyses are primarily hypothesis-generating and should be interpreted with caution. Further trials of HIIT specifically targeted to the early post-LTx period are needed.

Limitations

The study was not blinded, which may have led to bias. For this reason, we evaluated typical end criteria after CPET carefully and measured the blood lactate concentration, which showed no difference in the effort during CPET between the groups after the intervention except for the respiratory exchange ratio, which was lower in the EG (refer to supplementary material available online at www.jhltonline.org). Another limitation to this study was the small sample size. The sample size may have been too small to detect effects or associations of secondary outcomes.

Table 4 Univariate and Multiple Linear Regression Analysis Using Percentage Change in VO_{2peak} as Dependent Variable in the EG ($n = 23$)

Variables	Univariate linear regression				Multiple linear regression $R^2 = 0.595$		
	Unadjusted (ß)	95 % CI	R^2	p-value	Adjusted (ß)[a]	95 % CI	p-value
Sex, female	7.9	−0.5, 16.3	0.154	0.064	5.1	−4.0, 14.1	0.253
Age, years	0.1	−0.2, 0.5	0.026	0.466	−0.01	−0.3, 0.3	0.929
BMI, kg/m^2	−0.3	−1.8, 1.2	0.007	0.699	—	—	—
Time since LTx, months	−0.4	−0.6, −0.2	0.417	0.001	−0.4	−0.6, -0.1	0.003
1RM arm press at baseline, kg	−0.3	−0.6, −0.01	0.184	0.007[b]	—	—	—
1RM leg press at baseline, kg	−0.1	−0.3, −0.003	0.178	0.045[b]	—	—	—
FEV_1 % of predicted	0.2	0.05, 0.36	0.263	0.012	0.1	−0.1, 0.3	0.340
VO_{2peak} % of predicted at the baseline	0.1	−0.2, 0.4	0.032	0.414	—	—	—
VE/VCO_2 slope	0.1	−1.0, 1.2	0.003	0.800	—	—	—
O_2-pulse % of predicted	0.2	−0.2, 0.5	0.054	0.286	—	—	—
Use of β-blockers	7.3	−14.6, 29.3	0.023	0.493	—	—	—
Hb, g/dl	−0.9	−4.2, 2.5	0.014	0.597	—	—	—
Attended training sessions, n	0.3	−0.01, 0.6	0.171	0.056	—	—	—

Abbreviations: 1RM, 1-repetition-maximum; BMI, body mass index; CO_2, carbon dioxide; EG, exercise group; FEV_1, forced expiratory volume in 1 sec; Hb, hemoglobin; LTx, lung transplantation; O_2-pulse, indirect indicator of cardiac stroke volume, calculated by the ratio; VE, ventilation efficiency of oxygen consumption to heart rate; VCO_2, VE relative to CO_2 production; VO_{2peak}, peak oxygen uptake.

[a]Adjusted for all variables.

[b]Non-significant after adjusting for sex and age.

Conclusions

In conclusion, mixed-mode HIIT improved muscular strength but not VO_{2peak} after LTx. Strength training in particular appears to be beneficial for patients after LTx. High-intensity exercise training initiated early (<2 years) after transplantation with acceptable adherence appears to have beneficial effects on VO_{2peak} following LTx.

Disclosure statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org/.

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