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Interval versus constant-load exercise training in adults with Cystic Fibrosis

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Key words: Cystic Fibrosis; Pulmonary Rehabilitation; Interval Exercise; Physical Activity

Abstract

Background: The efficacy of interval exercise (IE) compared to constant-load exercise (CLE) training remains unsettled in adults with Cystic Fibrosis (CF).

Methods: Twenty-four adults with CF were randomised to 30-min IE (100% peak work capacity (WRpeak) for 30-s alternated with 40% WRpeak for 30-s; n=12) or 30-min CLE (70% WRpeak; n=12) training, 3 times weekly, for 12 weeks. Isometric quadriceps muscle strength was assessed using a strain gauge Myometer.

Results: The magnitude of improvement in quadriceps muscle strength was greater (p=0.037) in the IE (by 32±13 Nm) compared to the CLE (by 23±12 Nm) groups. Maximum inspiratory and expiratory mouth pressures were significantly improved only in the IE group (by 30±10 cmH_2O; p=0.009 and 13±4 cmH_2O; p=0.007, respectively). Arterial oxygen saturation during training was higher (p=0.002) for IE (94±1%) compared to CLE (91±1%), whereas dyspnoea scores were lower (p=0.001) for IE (3.8±0.7) compared to CLE (5.9±0.8)

Conclusions: IE is superior to CLE in improving peripheral and respiratory muscle strength and preferable to CLE because it is associated with lower exercise-induced arterial oxygen desaturation and breathlessness.

Highlights

- Interval improves more than continuous training peripheral and respiratory muscle strength in adults with CF
- Improvements in aerobic capacity are comparable following interval and continuous training in adults with CF
- There is less oxygen desaturation and breathlessness with interval than continuous exercise in adults with CF
- Application of interval is preferable to continuous exercise for rehabilitation in adults with CF

1. Introduction

Cystic fibrosis (CF) is the most common inherited life-threatening disease worldwide. Although there is still no cure for CF, life expectancy for people with CF continues to increase; median life expectancy is estimated to be 47 years [Cystic_Fibrosis_Trust 2018]. The effects of highly-effective CFTR modulators (Kaftrio®) are anticipated to improve this further [Middleton, et al. 2019,Heijerman, et al. 2019]. CF places a substantial burden on patients beyond conventional costs and has significant societal implications with quality of life (QoL) being considerably lower than in the general population [Angelis, et al. 2015].

People with CF exhibit lower aerobic exercise capacity [Pastré, et al. 2014] and greater muscle dysfunction compared to age-matched healthy individuals [Gruet, et al. 2016,Gruet, et al. 2010]. The reasons responsible for this are complex and multifactorial and include ventilatory and gas exchange abnormalities [Pastré, et al. 2014,Perpati, et al. 2010] and peripheral muscle abnormalities [Gruet, et al. 2017]. Indeed, lower peripheral muscle strength in people with CF compared to age-matched healthy individuals is well documented [Arikan, et al. 2015] and associated with reduced peak oxygen consumption ($\dot{V}O_2$), peak power output and six minute walking distance [Gruet, et al. 2017,Troosters, et al. 2009]. Some studies demonstrated a reduction in maximal muscle strength that correlated with decreased exercise tolerance in both children and adults with CF [Troosters, et al. 2009,Sahlberg, et al. 2005,de Meer, et al. 1999].

Likewise, muscle fibre abnormalities are also reported in this population alongside reduced muscle perfusion during exercise [Rodriguez-Miguelez, et al. 2020], impaired cellular energy metabolism [Joseloff, et al. 2014] and loss of fat-free mass secondary to systemic inflammation [King, et al. 2014], oxidative stress and use of corticosteroids [Gruet, et al. 2017].

There is evidence that high levels of physical activity in CF are associated with preserved aerobic capacity, lung function, improved QoL and professional achievements [Frangolias, et al. 2003,Hebestreit, et al. 2006,Hind, et al. 2008,Urquhart, et al. 2012]. Conversely, lower levels of aerobic capacity are associated with increased risk for hospitalisations due to a respiratory infection and higher levels of mortality [Nixon, et al. 1992,Pérez, et al. 2014,Pianosi, et al. 2005]. Accordingly, aerobic capacity is as an independent predictor of survival in CF [Nixon, et al. 1992,Pianosi, et al. 2005,Hebestreit, et al. 2019].

Exercise training positively affects the respiratory function (FEV_1 and FVC) in people with CF [Kriemler, et al. 2013,Schneiderman-Walker, et al. 2000] and reduces the rate of decline in respiratory function following the completion of a pulmonary rehabilitation program [Bradley and Moran 2008,Hebestreit, et al. 2010]. A Cochrane review [Radtke, et al. 2017], which performed a

quantitative analysis of 8 randomised controlled exercise training studies, highlighted the need for high-quality randomised controlled trials to comprehensively assess the benefits of recommended exercise programmes in people with CF. However, there were a number of limitations highlighted in the Cochrane review [Radtke, et al. 2017]. Firstly, there was marked heterogeneity in the interventions across the studies. Both home- and hospital-based training programmes, of varying duration, with differing exercise modalities were included. There were also methodological differences between the studies reviewed. Not all studies had a control group [Urquhart, et al. 2012,Schneiderman-Walker, et al. 2000,Hebestreit, et al. 2010,Radtke, et al. 2017,Beaudoin, et al. 2017,Moorcroft, et al. 2004,Rovedder, et al. 2014], whereas sample sizes were inadequate, thereby resulting in underpowered studies [Radtke, et al. 2017]. The Cochrane review concluded that the evidence base acted as a mandate for further well-conducted clinical trials to be performed in this area [Radtke, et al. 2017].

Unfortunately, exercise training in this population is challenging due to limitations presented by the impaired respiratory function. Low arterial oxygen saturation during constant-load exercise (CLE) does not allow people with CF to exercise at high intensities long enough to achieve the required physiological adaptations [Gruber, et al. 2014]. However, in severe chronic obstructive pulmonary disease (COPD), high intensity interval exercise (IE) is sustainable as patients exercise without severe exercise-induced arterial oxygen desaturation and/or breathlessness [Vogiatzis, et al. 2002]. In addition, high intensity IE leads to augmented stimulus to the peripheral muscles without severe exercise-induced arterial oxygen desaturation and breathlessness in COPD [Maltais, et al. 2014], and thus it may be appropriate for people with CF [Sawyer, et al. 2020a].

Gruber and colleagues proposed that IE training is a suitable alternative training modality, which allows people with CF with reduced diffusion capacity for carbon monoxide to exercise without severe oxygen desaturation and breathlessness [Gruber, et al. 2014]. Furthermore, 8 weeks of low-volume IE was recently compared to usual care and shown to be well tolerated by people with CF producing gains in exercise capacity and self-reported physical function [Sawyer, et al. 2020b]. In addition, eight weeks of high-intensity IE in people with CF accelerated $\dot{V}O_2$ kinetics (reflecting improved muscle oxidative metabolism) and increased time to exhaustion, thereby providing evidence that people with CF may benefit from this type of exercise [Reuveny, et al. 2020]. An early case study by Hulzebos and colleagues reported that in an adolescent with CF high intensity interval exercise was beneficial in improving aerobic capacity and exercise tolerance [Hulzebos, et al. 2011]. Moreover, one session of high intensity interval exercise has previously been found to cause lower inflammatory and growth factor response compared to one session of moderate intensity continuous exercise in children with CF [Nguyen, et al. 2012]. However, to the best of our

knowledge there are no studies comparing the efficacy of high intensity IE training to the widely implemented moderate CLE training in adults with CF.

The aim of this study was, therefore, to investigate whether IE training was more efficacious than CLE training in improving exercise capacity and peripheral muscle strength. Given that IE leads to augmented stimulus to the peripheral muscles [Maltais, et al. 2014,Sloth, et al. 2013,MacDougall, et al. 1998,Burgomaster, et al. 2007] it was reasoned that the improvement in lower body muscle strength, will be greater following high intensity IE training compared to moderate intensity CLE training.

2. Materials and Methods

2.1 Study design

This study was a prospective, single centre, two parallel-groups, randomised controlled trial (RCT) with 1:1 individual allocation comparing IE to CLE training. The design of the study and flow of adults with CF is presented in Figure 1. All participants had been diagnosed with CF by the medical team on the basis of clinical history and documentation of the presence of a CFTR mutation in both alleles of the CFTR gene and/or a positive sweat chloride test. Participants' clinical condition was stable in the month prior to the initiation of a hospital-based supervised pulmonary rehabilitation (PR) program. Exclusion criteria included participation in another clinical trial, pregnancy, transplant listing, or clinical cor pulmonale. No change in the medical treatment was made during the duration of the PR program. Participants underwent a structured, outpatient, supervised hospital-based PR program for 12 weeks with a frequency of 3 training sessions per week. Participants were randomized either to high-intensity IE training or to moderate intensity CLE training by independent staff within our institution. Anthropometric, respiratory and exercise function data are shown in Table 1. Exercise training interventions were balanced to provide the same overall training workload (IE training: cycling for 30 sec, initially aiming at 100% of peak work capacity (WRpeak) alternated with 30 sec of active recovery at 40% of WRpeak for 30 minutes; CLE training: initially aiming at 70% WRpeak for 30 minutes of cycling). Assessment including pulmonary function, exercise capacity, daily physical activity levels, peripheral and respiratory muscle strength and quality of life, were performed at baseline and following completion of the PR programme. Once per week, prior the exercise training session, participants performed airway clearance during a respiratory physiotherapy session, supervised by a respiratory physiotherapist. Informed written consent was obtained from all participants. The investigations were carried out

following the rules of the Declaration of Helsinki of 1975 and the study was approved by the University Hospital Ethics Committee (Protocol ID-18367).

2.2 Respiratory function assessment

Standard spirometry was performed with a metabolic cart (Vmax Encore 22: Sensor Medics, Yorba Linda, CA, United States) using the "fast inspiratory manoeuvre" [D'Angelo, et al. 1994]. Maximum static inspiratory (PImax) and expiratory (PEmax) mouth pressures were measured with a plastic semi-rigid flanged mouthpiece fitted to a metallic stem incorporating a 3-way tap, manufactured according to the design of Ringqvist [Koulouris, et al. 1988,Ringqvist 1966]. Static lung volumes were determined by the multiple nitrogen washout technique (Vmax Encore 22 apparatus) [Darling, et al. 1940]. The diffusing capacity for carbon monoxide (DL_{CO}) via the single-breath technique was also determined (Vmax Encore 22 apparatus) [Macintyre, et al. 2005]. Predicted values for spirometry, static lung volumes, and DL_{CO} were from the European Community for Coal and Steel [ERS 1993].

2.3 Peripheral muscle strength, body mass composition and quality of life

Prior to the onset and following completion of the 12-week PR program all participants were assessed for quadriceps isometric muscle strength with a strain gauge Myometer (MIE, Medical Research ltd, Leeds, UK). Furthermore, body mass composition was assessed with the method of bio-impedance (Maltron BF-907, Maltron International, UK). The Cystic Fibrosis-Questionnaire-Revised (CFQ-R) was used to assess quality of life [Quittner, et al. 2009].

2.4 Incremental cycle-ergometer exercise test

Participants performed a ramp incremental exercise protocol on the cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, CA, USA). The work rate increments were determined according to the equations reported by the ERS statement on standardisation of CPET in chronic lung diseases [Radtke, et al. 2019]. The exercise protocol was as follows: after 3-min of baseline measurements and 3-min of unloaded pedalling, the work rate was increased by 5-10 W every 1-min to the limit of tolerance. During each test arterial oxygen saturation (SpO2%) was obtained by a portable pulse oximeter (Nonin 8600, Nonin medical, Plymouth, USA). The modified Borg 1-10 scale [Borg 1982] was used to rate the magnitude of perceived dyspnoea and leg discomfort every 2-min throughout the test and at the end of exercise.

2.5 Functional capacity

The 6-min walk test (6-MWT) was performed according to the instructions of the American Thoracic Society, i.e.: the maximum distance walked by each patient on an 18-meter hospital

corridor in 6 minutes was assessed [Holland, et al. 2014]. Intensity of dyspnoea and leg discomfort were assessed by the modified Borg 1-10 scale [Borg 1982], whereas heart rate (HR) and SpO_2% were recorded every minute and at the end of 6-MWT. In those participants in whom SpO_2 fell below 88% during the test, O_2 was supplemented at a rate of 1.5 to 2.0 L/min.

2.6 Daily physical activity

Daily physical activity was assessed for 7 days one week prior and one week following the completion of the PR program, using a triaxial accelerometer (SenseWear Armband; Bodymedia, Pittsburgh, Pennsylvania, USA) placed on their upper arm for at least 8 hours a day, during the waking hours, with the exception of swimming or showering/bathing, for a period of seven consecutive days. Participants with a minimum of 4 valid days (including weekends), counting only days with at least 480 minutes of wearing time during waking hours (as defined from 08:00 am to 10:00 pm) were contained in the analysis [Demeyer, et al. 2014].

2.7 Exercise training protocols

The PR program involved supervised exercise training, 3 times per week, for 12 weeks, allowing at least one rest day between the training sessions. Exercise training was performed on electromagnetically braked cycle ergometers (Cateye Ergociser, ECI600; Osaka Japan). Participants were randomized either to 30-min high-intensity IE (initially aiming to 100% WRpeak for 30 sec alternated with 40% WRpeak for 30 sec) or 30-min moderate intensity CLE (initially aiming to 70% WRpeak). The above training design allowed the interventions to be balanced and thus, provide the same initial overall training workload in both groups as previously described [Vogiatzis, et al. 2002]. Accordingly, the average initial training workload for both IE and CLE groups was set to correspond to 70% WRpeak. During each training session dyspnoea and leg discomfort were recorded on the modified 1-10 Borg scale [Borg 1982], whereas HR and SpO_2% were continuously monitored by a pulse oximeter (Nonin 8600). Based on symptoms of breathlessness the exercise intensity was increased on a weekly basis by 5-10% of the baseline WRpeak in both IE and CLE groups as previously described [Vogiatzis, et al. 2002]. Oxygen was supplemented during exercise training to those participants experiencing a drop in SpO_2 below 90% at a rate of 1.5-2.0 L/min. The PR program was multidisciplinary including respiratory physiotherapy, nutritional advice, and psychological support.

2.8 Statistics

Verification of sample size was based on the study of Salvadurai and colleagues [Selvadurai, et al. 2002] comparing resistance training to usual care (no training) in people with CF. Based on the mean difference in quadriceps muscle strength of 25 Nm between resistance and usual care groups, and a standard deviation (SD) of 21 Nm, an alpha significance level of 0.05 (2-sided) and 80% power, a minimum sample size of 11 participants per group was calculated to be sufficient to detect significant differences in quadriceps muscle strength between IE and CLE training groups. To compensate for possible attrition at 30%, a total sample size of 28 participants was recruited.

Randomisation into IE and CLE training groups was stratified at baseline by lung function (FEV_1: < 40% predicted or ≥40% predicted) and peak work rate (WRpeak: <70 watts or ≥70 watts) using a block size of 4. Normal distribution of the data was checked with the Shapiro-Wilk test. Data were expressed as mean (SEM) unless otherwise stated. Comparisons of baseline characteristics were made using independent t-test. Two-way ANOVA with repeated measures was applied to detect differences between the two groups across different time points. The LSD post hoc correction method was used where appropriate. A p value <0.05 was considered significant. Statistical analysis was performed using IBM SPSS 22 statistical software.

3. Results

The effects of the IE and CLE training programmes on body composition, respiratory function and exercise capacity are presented in Table 2. Quadriceps muscle strength was significantly improved only in the IE group (by 32±13 Nm; p=0.024), whereas a trend for greater muscle strength was detected in the CLE group (by 23±12 Nm; p=0.072) (Table 2) (Figure 2a). The magnitude of improvement in quadriceps muscle strength was, therefore, greater in the IE group (p=0.037).

Following completion of the PR program cycle-ergometer WRpeak was significantly improved both in the IE Group (by 21%; p=0.001) and in the CLE Group (by 17%; p=0.001) (Figure 2b). The magnitude of improvement was not different between groups for WRpeak. $\dot{V}O_2$ peak was improved in both IE (by 12%) and CLE (by 11%) groups (Table 2), albeit without reaching the level of statistical significance.

The 6-min walk distance was significantly improved in the IE Group (by 45±28 m; p=0.001) and in the CLE Group (by 48±35 m; p=0.001) with improvements exceeding the minimal clinical important difference [Bhatia, et al. 2020] in both groups (Table 2) (Figure 2c).

PEmax and PImax were significantly improved only in the IE group (by 30±10 cmH_2O; p=0.009 and 13±4 cmH_2O; p=0.007, respectively) (Table 2). Hence, the magnitude of improvement in PEmax and PImax was greater in the IE (p=0.033) compared to the CLE (p=0.043) group.

Following the IE training programme, steps per day increased by a clinically important margin (by 1255±1058 steps/day; p=0.257) [Demeyer, et al. 2016] and accompanied by an increase in activity time (by 40.8±17.9 min/day; p=0.041) (Figure 3a & 3b). In contrast, steps per day decreased in the CLE group (by 1005±1131 steps/day; p=0.390 (Figure 3b), whereas activity time was not altered in the CLE group (p=0.827) (Figure 3a). The magnitude of improvement in steps/day was significantly greater in the IE compared to CLE group (by 2260±1442 steps/day; p=0.048), whilst there was a trend for greater activity time in favour of the IE group (by 36.6±20.5 min/day; p=0.114).

The CFQ-R was improved in both groups only for the domains of "physical functioning" (IE Group: by 11.8±3.6; p=0.004, CLE group: by 6.8±3.6; p=0.072) and "body image" (IE Group: by 5.6±2.5, p= 0.037; CLE Group: by 6.6±2.5, p=0.015).

Average SPO_2% during the 12-week PR programme was higher (p=0.002) for IE (94±1%) compared to the CLE (91±1%), whereas dyspnoea scores were lower (p=0.001) for IE (3.8±0.7) compared to CLE (5.9±0.8) (Figure 4). The relative increase of training intensity from the first to the last week of training was greater (p=0.035) for IE (by 87%) compared to CLE (by 70%) training modalities (Figure 5).

4. Discussion

The main findings of this study indicate that IE training is i) superior to CLE training in improving peripheral and respiratory muscle strength and ii) equally effective to CLE training in improving peak exercise tolerance, functional and aerobic capacities alongside domains of QoL in adults with CF. Application of IE in the pulmonary rehabilitation setting might be preferable to CLE because it is associated with lower exercise-induced arterial oxygen desaturation and breathlessness, thereby allowing greater weekly increments in exercise intensity throughout the PR programme.

In patients with COPD as well as in healthy individuals, high intensity IE compared to moderate intensity CLE training is associated with greater phenotypical adaptations within the locomotor muscles that are manifested by greater changes in muscle fibre size [De Brandt, et al. 2016,Simoes and Vogiatzis 2018]. In the present study IE afforded work of maximal intensity to be performed with a relatively low perception of breathlessness, thereby facilitating greater weekly increments in work intensity throughout the exercise training programme (Figures 4 & 5). In contrast, the weekly increments in work intensity achieved during the CLE training programme were likely constrained by intolerable symptoms of breathlessness (Figure 4). Therefore, the significantly greater improvement in peripheral muscle strength most likely reflects greater muscle fibre hypertrophy in the IE training group secondary to greater increments in the work training intensity.

Inspiratory and expiratory muscle strength was significantly improved in the IE group only. Previous studies provide conflicting evidence in regards to the effect of whole body exercise training on respiratory muscle strength. The study by Santana-Sosa and colleagues did not report any improvements in respiratory muscle strength following an eight-week training program including both aerobic and resistance exercise training [Santana Sosa, et al. 2012]. However, a subsequent study conducted by the same group reported that respiratory muscle strength (PImax) was improved following eight weeks of resistance and aerobic training alongside inspiratory muscle training in children with CF [Santana-Sosa, et al. 2014]. In healthy people high intensity exercise training has shown to improve respiratory muscle strength [Dunham and Harms 2012]. The effects observed with inspiratory muscle training in children with CF [Santana-Sosa, et al. 2014] and in healthy adults following high-intensity inspiratory muscle training [Enright, et al. 2006] are consistent with those observed in this study, demonstrating that the stimulus for inducing respiratory muscle adaptations requires high-intensity work. This further justifies the significantly greater improvement in inspiratory and expiratory muscle strength observed following IE compared with CLE training, which was likely due to greater demand placed on the respiratory muscles during the intense bouts of IE training.

An annual increase in $\dot{V}O_2$ peak by 2.3 ml/kg/min relative to baseline fitness is required to prevent a clinically important drop in prognostic stratification [Radtke, et al. 2017,Burgomaster, et al. 2007]. The mean increase in $\dot{V}O_2$ peak in both IE and CLE training groups was similar to that reported from two small randomised controlled trials in similar populations with comparable to the present study interventions [Sloth, et al. 2013,Santana Sosa, et al. 2012]. In the present study the improvement in $\dot{V}O_2$ peak (2.8 ml/kg/min) following IE training was above what is considered as clinically important improvement in $\dot{V}O_2$ peak ([Radtke, et al. 2017]. As aerobic capacity is considered an independent predictor of survival in people with CF [Bradley and Moran 2008,Radtke, et al. 2017,Burgomaster, et al. 2007] it is reasonable to suggest that IE training may be applied in the PR setting because besides the significant improvements in peripheral and respiratory muscle strength it is associated with clinically important improvements in $\dot{V}O_2$ peak.

Interestingly, the aforementioned physiological adaptations following IE training were accompanied by significantly greater changes in steps/day compared to the CLE training programme. The significant improvement in peripheral muscle strength alongside the improvement in $\dot{V}O_2$ peak most likely allowed participants in the IE group to achieve greater levels of daily physical activity compared to CLE group. Our findings are in accordance with previously reported data in COPD patients performing IE training as part of a PR programme [Louvaris, et al. 2016]. Kriemler et al. reported a significant increase in counts per minute following a 3-month CLE training programme compared to usual care [Kriemler, et al. 2013], whereas Salvadurai et al. reported no differences between CLE training and usual care following hospital discharge [Selvadurai, et al. 2002]. Moreover, following 12 weeks of CLE training combined with resistance exercise training there were no differences either in daily steps [Beaudoin, et al. 2017] or in the intensity of movement [Hebestreit, et al. 2010]. In the present study the training intensity in the IE group, reached 150% of baseline WRpeak at the end of the programme, which was significantly greater compared to other studies [Kriemler, et al. 2013,Hebestreit, et al. 2010,Beaudoin, et al. 2017,Selvadurai, et al. 2002].

WRpeak was significantly improved in both groups. This finding is in concordance with the literature reporting significant changes in peak work capacity following training [Hebestreit, et al. 2010,Sawyer, et al. 2020b]. Furthermore, Sawyer and colleagues recently reported increased exercise capacity by approximately 70 Watts in people with CF following a 10-week high intensity interval training programme compared to the control group [Sawyer, et al. 2020b]. The greater improvement reported by Sawyer and colleagues [Sawyer, et al. 2020b] compared to the present can be explained by the characteristics of their participants as FEV_1 was 66% in the experimental group which is substantially greater to the average FEV_1 of the participants in the present study.

The 6-min walk distance was significantly improved in both groups by a clinically important margin [Bhatia, et al. 2020]. In terms of quality of life, two domains of the CFQ-R were improved in both groups. These domains were “physical functioning” and “body image”. In RCTs comparing combined aerobic and anaerobic training to usual care, no significant differences are reported [Hebestreit, et al. 2010,Beaudoin, et al. 2017,Rovedder, et al. 2014]. In the study by Beaudoin and colleagues, no differences were observed in any single health-related quality of life (HRQoL) outcome between the training and control groups after 12 weeks of training [Beaudoin, et al. 2017]. Hebestreit et al showed that the HRQoL subscale of "subjective health perception" was higher in the training compared to the control group after three to six months of PR [Radtke, et al. 2017]. In the study by Rovedder and colleagues, no differences were found in any single HRQoL domain between the training and control groups in either the CFQ-R or the SF-36 questionnaire after three months of PR [Rovedder, et al. 2014]. The difference between our study and others is likely that exercise training included either supervised aerobic exercise of low intensity [Beaudoin, et al. 2017] or non-supervised home-based exercises [Hebestreit, et al. 2010,Rovedder, et al. 2014].

4.1 Clinical implications

IE training was well tolerated by adults with CF, as it was associated with mild arterial oxygen desaturation and moderate levels of breathlessness. This has the following two important implications. Firstly, adults with CF will be able to achieve true physiological training effects during the limited duration of a PR program, thereby yielding better quality of life and survival. Secondly, adults with CF with low baseline exercise capacity due to progression of the disease will be able to participate in a high-intensity IE training programme and benefit from this programme which would otherwise be unable to achieve such high intensity should they performed CLE training. Accordingly, during the new CFTR modulators era, high intensity interval exercise training can make the most of their new altered physiological function and avoid disease related complications such as increased body fat accumulation.

4.2 Study limitations

This was a small-scale study and therefore, generalisability of the results to clinical practice may be limited. The study represents a pragmatic approach as participants exercised under supervision on one-to-one basis to avoid cross contamination considering that exercise increases ventilation and consequently colonisation and/or infection.

Conclusions

In conclusion, within the pulmonary rehabilitation setting, IE is equally efficacious to CLE in improving functional capacity and aspects of quality of life, but it is superior to CLE in improving peripheral and respiratory muscle strength and daily physical activity levels. Furthermore, IE can be applied to adults with CF with lower breathlessness and arterial oxygen desaturation, thus qualifying as a safe exercise training modality.

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Table 1. Baseline characteristics

	High Intensity IE	**Moderate Intensity CLE**
Gender (M/F)	6/6	7/5
Age (years)	32±10	32±9
Height (m)	1.64±0.06	1.69±0.06
BMI ($kg \cdot m^{-2}$)	21.0±2.1	20.2±1.9
FFMI, $Kg \cdot m^{-2}$	16.7±1.7	16.5±2.0
FEV_1 (% predicted)	45±25	46±19
FVC (% predicted)	64±17	74±21
TLC (% predicted)	65±3	68±17
DL_{CO} (% predicted)	69±15	67±14
WRpeak (watt)	89±56	93±49

Values are presented as mean±SD. IE; interval exercise, CLE; constant load exercise, BMI; body mass index, FFMI; free fat mass index, FEV_1; forced expiratory volume in the 1st second, FVC; forced vital capacity, TLC; total lung capacity, DL_{CO}; diffusing capacity for carbon monoxide, WRpeak; peak work rate.

Table 2. Effects of IE and CLE training on physiological outcomes.

	High Intensity IE		Moderate Intensity CLE	
	Pre	**Post**	**Pre**	**Post**
WRpeak (watt)	89±56	108±60*	93±49	109±59*
$\dot{V}O_2$ peak (ml/kg/min)	24.1±10.7	26.9±11.0*	23.2±8.4	25.7±9.5*
6MWT (meters)	538±70	583±83*	516±57	564±55*
BMI ($kg \cdot m^{-2}$)	21.0±2.1	21.3±1.6	20.2±2.0	20.7±1.9
FFMI ($kg \cdot m^{-2}$)	16.7±1.7	16.8±1.5	16.5±2.0	16.8±1.6
Quadriceps Strength (Nm)	167±58	199±63*	177±54	200±41
PEmax (cmH_2O)	121±23	151±30*	100±58	112±58
PImax (cmH_2O)	-71±27	-84±16*	-66±33	-73±31

Values are presented as mean±SD. WRpeak; peak work rate, $\dot{V}O_2$ peak; peak oxygen uptake, 6MWT; 6-minute walk test, BMI; body mass index, FFMI; free fat mass index, PEmax; maximum expiratory mouth pressure, PImax; maximum inspiratory mouth pressure. *; $p<0.05$ within groups.

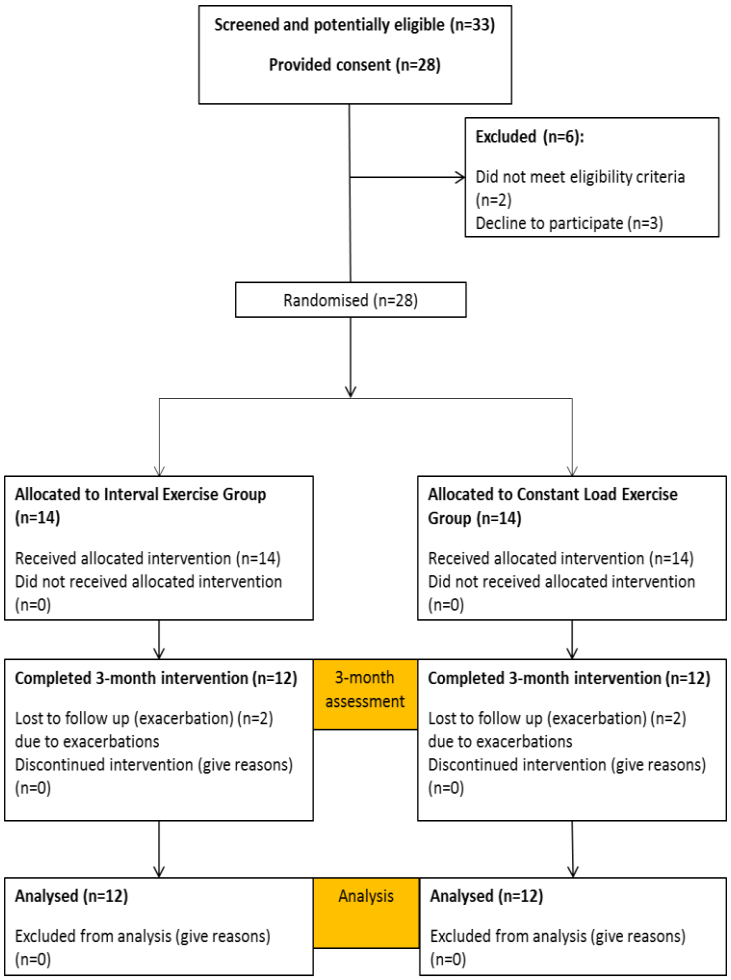

Figure 1. Consolidation Standards of Reporting Trials diagram of the study.

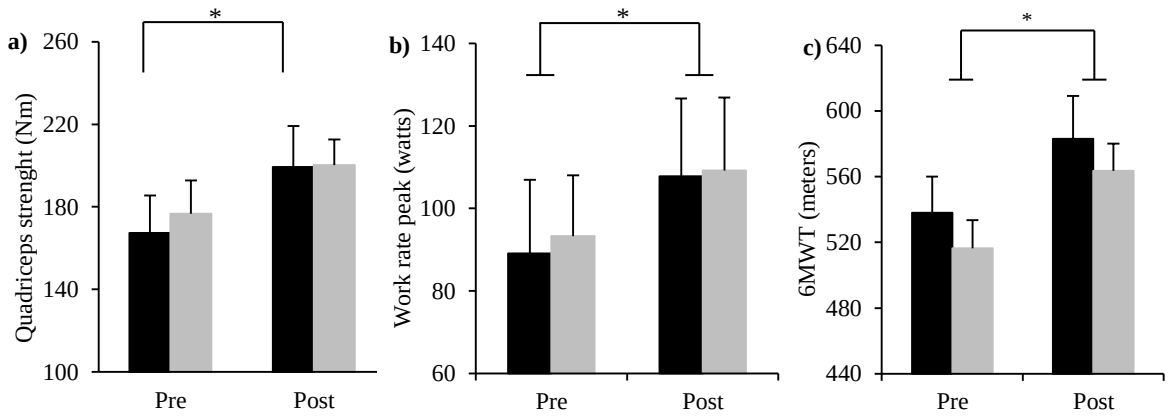

Figure 2. Improvements in: a) quadriceps muscle strength, b) work rate peak and c) 6-minute walk distance (6MWT) following the 12-week pulmonary rehabilitation program. Black bars indicate IE group, grey bars indicate CLE group. *: $p<0.05$ pre- versus post.

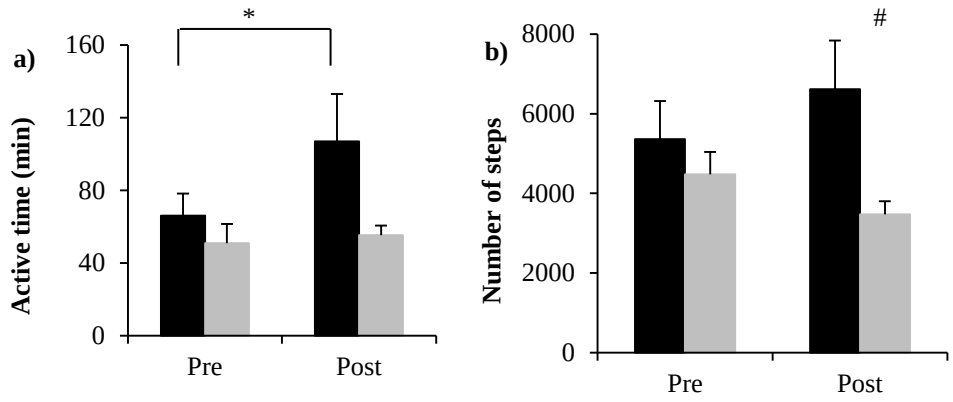

Figure 3. Improvements in a) active time and b) number of steps following the completion of the 12-week pulmonary rehabilitation program. Black bars represent the IE group and grey bars the CLE group. *: $p<0.05$ pre versus post #: $p<0.05$ IE versus CLE post rehabilitation.

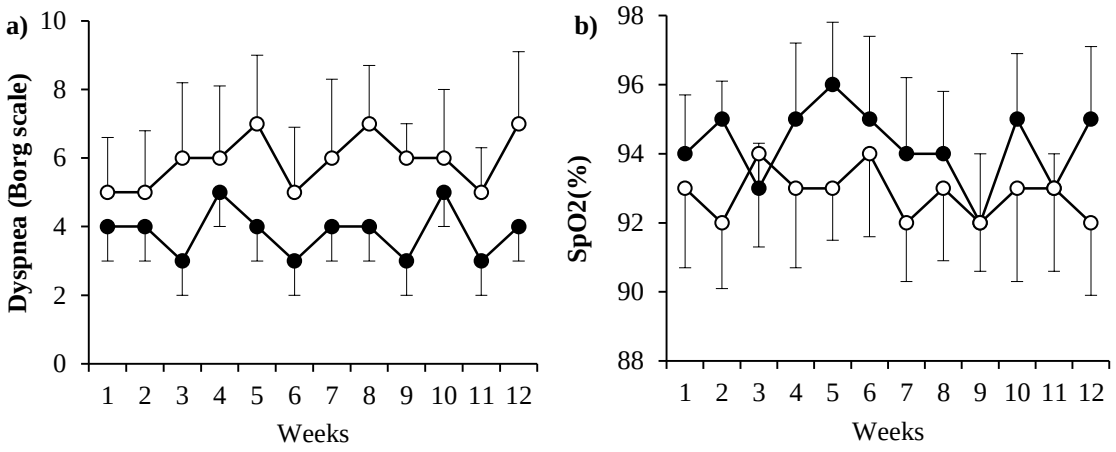

Figure 4. a) Dyspnoea and b) Oxygen saturation during IE training (closed symbols)) and CLE training (open symbols).

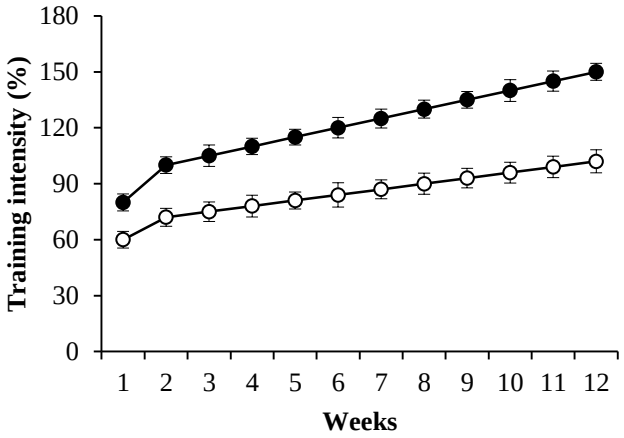

Figure 5. Training intensity during IE training (closed symbols) and CLE (open symbols).