Interval exercise training in cystic fibrosis — Effects on exercise capacity in severely affected adults

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Abstract

The aims of the present study were to investigate the effects of IT on lung function power (P) and oxygen uptake (VO2) at peak performance (peak) and ventilatory anaerobic threshold (VAT) in CF patients who were unable to participate in a standard exercise program (SEP) and to compare these IT responses with corresponding effects in CF patients performing SEP. 20 patients (FEV1 25.5 ± 7.5%; pred; SpO2 > 90% at rest or P lower than 0.3 W/kg) who were unable to participate in SEP were allocated to IT (5 × 20 min weekly). 23 patients (FEV1 31.6 ± 4.2%; p < 0.05) did 5 × 45 min per week of SEP. Lung function remained unchanged in both groups. VO2peak and PVAT increased in both groups (p < 0.05). However, only after the SEP an increase in Ppeak (p < 0.05) and only after IT a higher VO2VAT (p < 0.05) were found. Compared to SEP, IT improved submaximal exercise capacity to a greater extent whereas responsiveness on peak performance was higher in SEP. This seems to indicate a specific potential of IT for positive peripheral muscular adaptations in spite of diminishing potential of pulmonary improvement. IT represents an alternative, effective and safe training regimen with patients with CF and severe lung disease, with a greater potential than SEP.

Keywords: Exercise capacity; Interval training; Responsiveness; Severely affected subjects

1. Introduction

There is growing consensus that exercise in subjects with cystic fibrosis (CF) may yield improvements in measures of exercise capacity, lung function and quality of life [1–5]. Physical inactivity may accelerate the severity of disease [6]. Exercise capacity, expressed as peak oxygen uptake (VO2peak) has been found to be one of the best predictors of survival in subjects with CF. Those subjects with a higher VO2peak related to age and gender specific predicted VO2peak (%pred) have a better prognosis than those with a lower VO2peak (%pred) [7].

Most exercise programs in which subjects with CF were involved used prolonged low intensity aerobic exercise training, strength training, training of coordination and flexibility, or a combination of these. Some of the exercise programs were part of a multidisciplinary treatment regimen during an in-patient rehabilitation program, while others were designed as supervised or non-supervised home exercise programs [2,8–12]. Mode, duration, frequency and intensity in most exercise programs were similar to exercise recommendations for healthy persons [13].

High intensity interval exercise training (IT) consists of numerous sets of repetitive short bouts of high intensity exercise alternating with bouts of low exercise intensity exercise (“active recovery”) or short periods of passive rest. Subsequent IT sets are separated by longer periods of passive rest. IT has been shown to be an effective stimulus to working muscles with minimal cardiac or pulmonary strain [14]. In non-specifically trained healthy persons and subjects with chronic obstructive pulmonary disease (COPD), IT had a...
greater effect on exercise capacity than prolonged constant power low intensity training [15,16]. Furthermore, studies have demonstrated beneficial effects on mental health, dyspnea, economy of locomotion and health related quality of life following IT in COPD and chronic heart failure, including patients on a heart transplant waiting list [14,15,17–19].

However, little is known about the effects of IT on peak and submaximal exercise capacity in CF. One single case study [20] reported an increase of VO₂peak and peak workload (Wpeak) of 19% and 16% respectively in an adolescent patient with CF after IT. In a small group of subjects with CF awaiting lung transplantation IT showed improvements in VO₂peak and peak power of 6.7% and 6.9% [21].

Therefore the aim of the present study was a) to investigate the effects of IT on peak and submaximal exercise capacity and lung function in severely affected subjects with CF referred to a six-week inpatient rehabilitation course who were unable to participate in a standard exercise training program including prolonged constant power low intensity exercise (SEP) due to significant oxyhemoglobin de-saturation at rest and/or very low power and b) to compare these IT responses with the effects of SEP in subjects with CF who did not have severe de-saturation at rest or with very low power exercises.

2. Methods

2.1. Study subjects

109 rehabilitation clinic CF inpatients volunteered for this study. Inclusion criteria were 1) FEV₁ < 40% pred., 2) stability of disease throughout the study period, and 3) no acute exacerbation during the 4 weeks prior to the in-patient program. Exclusion criteria were 1) untreated CF-related diabetes, 2) clinical evidence of exercise limiting cardiac, neurological or musculo-skeletal problems, 3) intravenous antibiotic therapy during the 4 weeks prior to the program, or 4) ventilatory anaerobic threshold (VAT) not detectable. 66 subjects had to be excluded by having one or more of these exclusion criteria. The remaining forty-three subjects were referred to a six week in-patient rehabilitation course (Table 1). All patients, parents or guardians signed an informed consent form approved by the Ethics Committee of the Medical Chamber of Schleswig-Holstein.

2.2. Study design

At admission (T1) and at discharge (T2), all participants underwent a complete medical examination which included measurement of lung function, exercise capacity, height and bodyweight and a resting ECG (only at baseline). Exercise capacity was determined by an incremental exercise test. The participants were allocated into training groups according to results of oxygen saturation (SpO₂) during incremental exercise testing. Subjects who de-saturated (SpO₂ < 90%) at very low power (≤ 0.3 W/kg) or had a SpO₂ ≤ 90% at rest were allocated to IT. The other participants were assigned to SEP. Prior to beginning IT, the IT group performed an additional Steep Ramp Test (SRT) to determine the exercise intensity of IT [14].

2.3. Testing

SpO₂ was measured using pulse oximetry with a finger sensor (Nellcor Oxynmax N 550, Nellcor Puritan Bennett, Pleasanton, CA, USA). Forced Expiratory Volume in 1 s (FEV₁, % pred), and Vital Capacity (VC % pred) were measured by spirometry (Master screen, Jaeger, Wuerzburg, Germany) according to recommended techniques, and values were expressed as a percentage of age, sex and anthropometry related to normal values [22]. Body composition was measured using the bioelectrical impedance analysis system (BIA) (Data input, Darmstadt Germany).

Cardio-pulmonary exercise testing (CPET) was performed on an electro-magnetically braked cycle ergometer (Examiner, Lode B.V. Groningen, The Netherlands). Gas exchange and ventilatory measures were recorded breath by breath (Master Screen CPX, Viasys Healthcare GmbH, Hoechberg, Germany). After a period of rest (3 min) and after a 3 min phase of unloaded cycling, power was increased every minute by 10–20 W (Godfrey protocol) depending on the patient’s height and physical fitness [23]. Participants were encouraged to make a maximal effort, and the test was continued until the subject could no longer maintain a pedaling cadence of 60 rpm or SpO₂ was <85%. To specify the Ventilatory Anaerobic Threshold (VAT), the excess carbon dioxide method (ExCO₂), and the modified V-Slope method were used [24]. Heart rate (HR) was measured continuously using 12 lead ECG.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>IT (n = 20)</th>
<th>SEP (n = 23)</th>
<th>ANOVA</th>
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<tr>
<td></td>
<td>Mean ± SD T1</td>
<td>Mean ± SD T2</td>
<td>Mean ± SD T1</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>26.4 ± 7.5</td>
<td>26.3 ± 9.9</td>
<td>26.3 ± 9.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.0 ± 7.3</td>
<td>169.1 ± 8.2</td>
<td>169.1 ± 8.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>48.7 ± 6.1</td>
<td>49.3 ± 5.6</td>
<td>52.5 ± 6.3</td>
</tr>
<tr>
<td>BMI</td>
<td>17.1 ± 2.1</td>
<td>17.5 ± 2.1</td>
<td>18.3 ± 2.0</td>
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<tr>
<td>Fat-free mass (kg)</td>
<td>38.6 ± 5.2</td>
<td>39.4 ± 5.2</td>
<td>41.7 ± 5.8</td>
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<tr>
<td>FEV₁ (% pred)</td>
<td>25.5 ± 7.5***</td>
<td>24.4 ± 6.9**</td>
<td>31.6 ± 4.2</td>
</tr>
<tr>
<td>VC (% pred)</td>
<td>38.0 ± 10.0***</td>
<td>36.8 ± 10.2***</td>
<td>52.9 ± 8.4</td>
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</table>

Abbreviation as described in text; T1 = baseline, T2 = end of program T = time, EP = exercise program, IT = interval-training, SEP = standard exercise program.

*Between groups: unpaired t-test: * p < 0.05, ** p < 0.01, *** p < 0.001; †within groups: Wilcoxon test: † p < 0.05, †† p < 0.01, ††† p < 0.001.
VO2peak (ml/min/kg) and Peak power (Ppeak in W/kg) were defined as the highest power achieved before terminating the test. Peak gas exchange and peak ventilatory measures were specified as the highest value during the final 30 s before stopping the test. The metabolic cart was calibrated using 3.0 l syringe and gases of known concentration (O2: 21.0%, CO2: 5.0%, N2: 74%) before each exercise test.

The SRT, additionally performed by the IT group only, was a treadmill test (modified Balke-protocol). As proposed by Meyer et al. [14] this test had a substantially higher increase in power per minute than the original Balke-protocol or the CPET cycle ergometer test described above. After familiarizing with the treadmill and a warm-up phase of 2 min (speed 4 km/h, grade 0%) the workload was increased every 20 s by 2.5% grade with constant velocity (4 km/h) until exhaustion. During the SRT all subjects received supplemental oxygen via nasal cannula. The maximum inclination (power) achieved during SRT is called “maximum short-time exercise capacity (MSEC)” [14] and is primarily determined by early onset of peripheral muscle fatigue. The training intensity of the “high intensity phases” of the IT was set at 50% of MSEC treadmill inclination.

2.4. In-patient program

IT or SEP was part of a multidisciplinary treatment regimen during the rehabilitation course. In addition all subjects received daily intensive chest physiotherapy and a high energy diet with nutritional supplements according to disease severity and nutritional status, psychosocial support and a disease specific educational program. Depending on subjects’ disease and mucus production, frequency and duration of daily chest physiotherapy varied between 30 and 60 min (once or twice per day) under the supervision of an experienced physiotherapist.

3. Exercise training

3.1. Interval-training

An IT program with a work-recovery ratio of 1:2 was designed to apply physical stress that can improve exercise capacity without high lactate accumulation or cardiac or pulmonary strain [14,15,17]. Thus, in the present study a work-recovery ratio of 30 s work phase to 60 s active recovery phase was chosen. In more severely de-conditioned participants as indicated by inability to sustain this pattern, the IT work-recovery ratio was changed to 20 s work phase to 60 s recovery phase.

The IT treadmill program was performed at the individual’s comfortable continuous walking speed, between 3 and 4 km/h lasting 16 min, 5 times weekly and consisted of ten intervals of 20 or 30 s high intensity bouts at 50% of maximal grade achieved during SRT, followed by 60 s active recovery phases at 0% grade treadmill inclination. Supplemental oxygen was administered to reach a hemoglobin oxygen saturation of more than 90% during exercise training. The SRT was repeated every 2 weeks to adjust 50% MSEC according to potential individual changes in MSEC.

3.2. Standard exercise program

Participants exercised 5 times weekly for 6 weeks. All training sessions lasted 45 min and consisted of different sport activities depending on participants’ fitness level (prolonged endurance exercise in terms of walking or Nordic-Walking complemented by ball games, stretching, balance training, and resistance training). All sessions were supervised by a specially trained and experienced sport-therapist. The training intensity during endurance training was set at a HR corresponding to 80–90% of VO2VAT equivalent to 60–75% VO2peak and monitored with a portable heart rate monitor (Polar Electro, Finland).

3.3. Statistical analysis

Statistical analysis was carried out using SPSS for windows (version 17.0; SPSS Chicago, IL). All data are given as mean ± standard deviation (SD). The effects of IT and SEP were analyzed using repeated-measures of variance with “time” as within-factor and “exercise program” as between factor after testing for normal distribution. Post hoc analyses to identify differences between and with in subject effects were performed using unpaired and paired t-tests. The level of significance was set at p < 0.05.

4. Results

Age, height, weight and BMI, and fat-free mass were similar in both groups. From T1 to T2, body and fat-free-mass increased (p < 0.05) irrespective of group allocation (Table 1). VC and FEV1 were lower (p < 0.01) in the IT than in the SEP group and remained stable throughout both interventions.

In both training groups, VO2peak, VO2peak related to bodyweight (relVO2peak), VE and O2-Pulsepeak increased (p < 0.05) from T1 to T2 (Table 2). Ppeak and relPpeak showed an identical main effect (p < 0.05). However corresponding post hoc effects could only be verified in the SEP group which was combined with consistent lower Ppeak in the IT group and interaction between training effects and group effect in the Ppeak measures (Table 2). HRpeak remained unaffected by the factors group and training (Table 2).

PVAT, relPVAT, VEVAT and O2-PulseVAT increased in both intervention groups (p < 0.05). Also VO2VAT showed an identical main effect (p < 0.05; Table 3). However, corresponding post hoc effects in VO2VAT and relVO2VAT could only be verified in the IT group (p < 0.05; Table 3). HRVAT remained unaffected by the factors group and training (Table 3).

5. Discussion

The major findings of the present study were that in severely affected and de-conditioned patients with CF who are unable to participate in SEP, the present IT program was an effective and safe strategy to improve exercise capacity.

The present results extended a recent single case study [20] reporting improvements in VO2peak and Ppeak of 19% and 16%, and in VO2 at VAT by 13% in a 16 year old female subject with CF, suggesting that IT might be an effective training
Average peak exercise parameters at baseline and end of the exercise program.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>IT (n = 20)</th>
<th>Mean ± SD T1</th>
<th>Mean ± SD T2</th>
<th>SEP (n = 23)</th>
<th>Mean ± SD T1</th>
<th>Mean ± SD T2</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (ml/min)</td>
<td>978.6 ± 154.6</td>
<td>1097.0 ± 258.5</td>
<td>1107.4 ± 315.7</td>
<td>1311.1 ± 376.9</td>
<td>p &lt; 0.001</td>
<td>p = 0.130</td>
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<tr>
<td>VO2peak (ml/kg/min)</td>
<td>20.9 ± 4.2</td>
<td>23.4 ± 6.9</td>
<td>21.3 ± 6.5</td>
<td>24.6 ± 6.8</td>
<td>p &lt; 0.001</td>
<td>p = 0.324</td>
<td></td>
</tr>
<tr>
<td>Ppeak (Watt)</td>
<td>53.4 ± 8.3</td>
<td>63.8 ± 9.3</td>
<td>68.9 ± 25.9</td>
<td>80.0 ± 28.5</td>
<td>p &lt; 0.001</td>
<td>p = 0.86</td>
<td></td>
</tr>
<tr>
<td>Ppeak (Watt/kg)</td>
<td>1.1 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.4</td>
<td>1.6 ± 0.5</td>
<td>p = 0.005</td>
<td>p = 0.74</td>
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<tr>
<td>VE (l/min)</td>
<td>30.4 ± 5.6</td>
<td>34.1 ± 7.5</td>
<td>37.1 ± 10.1</td>
<td>43.7 ± 12.0</td>
<td>p &lt; 0.001</td>
<td>p = 0.143</td>
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<tr>
<td>HRpeak (b/min)</td>
<td>141.7 ± 15.5</td>
<td>145.9 ± 20.9</td>
<td>152.0 ± 14.2</td>
<td>156.2 ± 18.0</td>
<td>p = 072</td>
<td>p = 0.804</td>
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</tr>
</tbody>
</table>

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Between groups: unpaired t-test: * = p < 0.05, ** = p < 0.01, *** = p < 0.001; within groups: Wilcoxon test: † = p < 0.05, †† = p < 0.01, ††† = p < 0.001.

regimen to improve cardio-pulmonary fitness in patients with CF. This patient was younger had a higher FEV1 (73% of predicted) than our IT group and was able to participate in demanding physical activities (field hockey). The latter may explain why the above improvements in peak performance measures were higher, but not why improvements at VAT were lower than those seen in the present study.

However, this finding of the present study was consistent with a previous study where we found an improvement of VO2peak and Ppeak of 6.7% and 6.6% and also higher improvements of 15.5% in VO2 and in relP by 15.7% at the VAT in pre-transplant CF-patients [21]. Additionally, after IT a greater improvement of VO2 at the first ventilatory threshold (VT1) was described than after SEP [25]. The VT1 reflects the workload at which blood lactate levels begin to rise causing an increase in the O2-equivalent [27]. VT1 reflects a lower exercise intensity than the second ventilatory threshold (VT2) detected in the present study. VT2 depicts an increase in the O2-equivalent at higher blood lactate levels [26].

Participants in IT had lower FEV1 and VC values at the beginning and at the end of the program. As in most other lung diseases, CF diminished exercise capacity can be explained by the reduced lung function (specifically by FEV1). However, the range of fitness level for any given lung function level is very wide. Thus, several pathologic factors may have an influence on peak exercise capacity and exercise capacity at VT2. During progressive exercise testing dynamic hyperinflation, air trapping and heightened airways resistance and an increase in dead space ventilation may occur in both groups. However, both factors may be more noticeable in participants of IT leading to an earlier onset of pulmonary limitation and thus stopping the incremental exercise test short after reaching VT2.

Furthermore, arterial hypoxemia may limit maximal exercise capacity in CF. It can result from factors like intrapulmonary shunting, ventilation–perfusion mismatch, elevated venous admixture and alveolar hypoventilation [1,4]. Participants in IT desaturated at very low power or had a SpO2 ≤ 90% at rest. Thus, during exercise arterial hypoxemia may have an adverse effect on maximal exercise capacity as well as on improvement of maximal exercise capacity particularly in the participants of IT.

Safety and effectiveness of IT is of specific interest in the more severely impaired CF-population. Their low exercise capacity and pulmonary constraints allow only short term intermittent efforts, which also reflect their freely chosen pattern of exercise and activities of daily life. The greater improvements of exercise capacity either at VT1 or VT2 may also reflect peripheral muscular adaptations in spite of minimal or diminishing potential for pulmonary improvement [15,18,27]. This may lead to improved ability to adhere to exercise and enhanced physical activity in daily life, known as independent factors of quality of life and prognosis [28].

Despite the increase in VO2peak and Ppeak, no significant overall effect on HRpeak and heart rate at VT2 was found in the present study. The increase in VO2 at peak and VT2 in

**Table 3**

Submaximal Exercise Capacity Parameters at baseline and end of the exercise program.

<table>
<thead>
<tr>
<th></th>
<th>IT (n = 20)</th>
<th>Mean ± SD T1</th>
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<th>SEP (n = 23)</th>
<th>Mean ± SD T1</th>
<th>Mean ± SD T2</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2 (ml/min)</td>
<td>850.8 ± 158.0</td>
<td>1030.4 ± 177.2</td>
<td>836.9 ± 190.6</td>
<td>962.5 ± 203.2</td>
<td>p &lt; 0.001</td>
<td>p = 0.594</td>
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<tr>
<td>VO2 (ml/kg/min)</td>
<td>17.6 ± 3.4</td>
<td>21.9 ± 4.6</td>
<td>16.1 ± 3.0</td>
<td>18.1 ± 3.9</td>
<td>p = 0.001</td>
<td>p = 0.449</td>
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</tr>
<tr>
<td>P (Watt)</td>
<td>41.9 ± 6.9</td>
<td>50.0 ± 7.6</td>
<td>53.8 ± 16.3</td>
<td>63.8 ± 21.1</td>
<td>p = 0.004</td>
<td>p = 0.810</td>
<td></td>
</tr>
<tr>
<td>P (Watt/kg)</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>p = 0.013</td>
<td>p = 0.950</td>
<td></td>
</tr>
<tr>
<td>VE (l/min)</td>
<td>25.2 ± 4.1</td>
<td>30.1 ± 8.1</td>
<td>27.5 ± 5.2</td>
<td>32.5 ± 9.8</td>
<td>p = 0.001</td>
<td>p = 0.667</td>
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</tr>
<tr>
<td>HR (b/min)</td>
<td>130.2 ± 16.4</td>
<td>136.3 ± 18.3</td>
<td>133.4 ± 14.0</td>
<td>137.4 ± 18.6</td>
<td>p = 0.317</td>
<td>p = 0.209</td>
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Between groups: unpaired t-test: * = p < 0.05, ** = p < 0.01, *** = p < 0.001; within groups: Wilcoxon test: † = p < 0.05, †† = p < 0.01, ††† = p < 0.001.
combination with unchanged HR_{peak} and HR at VT2 resulted in a significant improvement of O2-pulse in both training regimes. The O2-Pulse is thought to provide an indirect measure of cardiac stroke volume, and an increase in cardiac stroke volume is a hallmark of improved cardiopulmonary fitness after training programs [29]. Consequently the observed increase in O2-pulse, VO2_{peak} and P_{peak} combined with no change in HR_{peak} and heart rate at VT2 strongly suggests that there is a real improvement in exercise capacity attributable to an increase in stroke volume or/ and utilization of oxygen by skeletal muscles rather than just a potentially higher effort on the post-training test [27].

Not only increasing disease severity but also lack of time count as relevant barriers for participation in regular physical activity. Therefore an additional advantage of IT is the time efficiency of this exercise training method. Furthermore IT does not only improve VAT but also work economy to a higher extent than prolonged low intensity exercise training [19]. Furthermore, in terms of training experience the patients in the IT group reported to perceive the variable intensity profile of IT motivating and less strenuous than exercising at more or less constant intensity over long lasting periods of training. Therefore IT may have a greater potential of training effects helping to cope better with the physical demands of daily activities than SEP.

Also the SEP participants showed improvements in their maximal and submaximal exercise tolerance, which is consistent with training studies from healthy people after a continuous training program of six week duration [24]. Moreover the results are similar to those found in the literature in CF although the interventions were heterogeneous with respect to duration of exercise training, session duration, specific training modalities disease severity and age [1,2,8,9,11,12,21]. The changes we observed in the current study in SEP in maximal exercise capacity were comparable to improvements we recently found after 4–6 week exercise training in CF regardless of disease severity [2,30]. As long as patients are able to participate in SEP lung function does not seem to be a good predictor for the magnitude of improvement in exercise capacity in CF [30].

The improvement in VO2_{peak} and P_{peak} was superior in SEP compared to IT, supporting the notion that the higher training volume in SEP (5 times/week; 45 min session) could be a key factor for the development of maximal exercise capacity [29]. Another possible explanation could be that the participants in SEP took part in sport activities (e.g. running games, badminton), and physical activities (e.g. cycling, walking) in addition to the regular training program, which was rarely or never happening in participants of IT. The ratio of time spent on exercise and time spent on recovery was maintained during the entire training period. In IT the rate of progression was achieved by increasing training intensity and not by changing the work-time/recovery-time ratio. Partly this was attributed to observations that the very deconditioned patients were not able to sustain IT with shorter recovery phases even after exercise capacity had been increased.

Some limitations of our study should be taken into account in the discussion of the results. Allocation to either IT or SEP was performed using the criteria described above. Consequently, this is a quasi-sample randomization and not a “true randomization”. Therefore, a selection bias cannot be ruled out. Also other physical activities during the in-patient course independent of specific training interventions could have additional training effects which can be quantified neither in the IT nor in the SEP group.

6. Conclusion

The present study showed that IT is an exercise training method which is safe in patients with CF who are unable to participate in SEP. IT is less time consuming than SEP and patients perceived IT as less strenuous compared to constant workload. Compared to SEP, IT improved submaximal exercise capacity to a greater extent than SEP, whereas responsiveness of maximal exercise capacity was higher in the SEP. Overall this seems to indicate a specific potential for positive peripheral muscular adaptations in spite of minimal or diminishing potential of pulmonary improvement. From a practical point of view, IT represents an alternative, effective and safe training regimen with patients with CF and severe lung disease, with a greater potential of training effects helping to cope better with the physical demands of daily activities than SEP.

References


