

CASE REPORT

High-intensity interval training in an adolescent with cystic fibrosis: A physiological perspective

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ABSTRACT

Nutritional, musculoskeletal, and/or ventilatory status can lead to a decreased exercise capacity in children with cystic fibrosis (CF). Exercise training is already part of the usual care; however, the “optimal” intensity and volume of exercise training to improve exercise capacity is still unknown. Six weeks of high-intensity interval training (HIT) for a patient with CF with a ventilatory limitation was evaluated by a cardiopulmonary exercise test (CPET). Peak oxygen uptake and peak workload increased 19% and 16%, respectively, and there was a rise in peak ventilation from 50 L/min to 75 L/min, with an increase in both breathing depth and respiratory rate. A relative short period of HIT resulted in a significant increase in exercise capacity. In patients with CF, HIT might be an effective and efficient training regimen, especially in CF patients with a ventilatory limitation. Further research is necessary to investigate whether HIT is a better alternative than traditional aerobic training programs especially in ventilatory limited patients with CF.

INTRODUCTION

Cystic fibrosis (CF) is a common genetic disease in the Caucasian population with an incidence of 1 in every 2,500 Caucasians live births (Slieker et al, 2005). CF is a multisystem disorder that affects the digestive system, sweat glands, and the reproductive tract; however, progressive lung disease continues to be the major cause of mortality (Slieker et al, 2005). Deteriorating nutritional, musculoskeletal, and ventilatory status can lead to a decreased exercise capacity compared to healthy peers (deMeer, Gulmans, and van Der Laag, 1999). A decreased exercise capacity often leads to inactivity, which in turn may result in further deconditioning thereby creating a vicious cycle (Hebestreit et al, 2006). In contrast, higher levels of aerobic exercise capacity in patients with cystic fibrosis are associated with a significantly

lower mortality risk (Nixon, Orenstein, Kelsey, and Doershuk, 1992).

Patients with CF have thick mucus secretions as a result from a mutation in the CF transmembrane regulator (CFTR) (Welsh and Fick, 1987) and often develop a chronic infection of the respiratory tract that can lead to a respiratory insufficiency and eventual respiratory failure (Gibson, Burns, and Ramsey, 2003). Patients with CF receive regularly physical therapy as a part of their treatment. The aim of physical therapy is to help mobilizing mucus by choosing proper airway clearance techniques and enhancing physical fitness and improving exercise capacity (Bradley and Moran, 2008; Bradley, Moran, and Elborn, 2006).

The “optimal” intensity of exercise training to improve exercise capacity efficiently and effectively depends on the individual goals of each patient. If the patient wishes to increase the ability to sustain current physical performance, low to moderate-intensity training is likely to be sufficient. If the goal is to increase the ability to perform tasks that are above the current level of capacity, higher intensity training is likely to give superior training results than traditional endurance training. To perform high-intensity exercise,

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interval training (HIT) seems appropriate. HIT involves significant anaerobic energy utilization and, therefore, is believed to better mimic the physiological requirements of activities of daily living (i.e., activities of short duration) (Butcher and Jones, 2006). Furthermore, HIT has been proven to provide comparable physiological adaptations as in endurance training, while placing a lower toll on the respiratory system (Burgomaster et al, 2005; Gibala, 2007). It thus combines the benefits of aerobic and anaerobic training with significant results in children with CF (Klijn et al, 2004).

Another factor that determines the optimal intensity of training is the relative contribution of ventilatory limitation to exercise tolerance. Ventilatory limitation reflects the relationship of ventilatory demand to ventilatory capacity and has traditionally been evaluated by the ventilatory reserve (Cerny, Pullano, and Cropp, 1982). Ventilatory limitation may be partly caused by the increased oxygen demand of the respiratory muscles and partly by a pulmonary obstruction that has led to a relative alveolar hypoventilation and oxygen desaturation (Klijn et al, 2003b; Lands, Heigenhauser, and Jones, 1992). This case study describes from a physiological perspective the effects of HIT on exercise capacity and ventilatory response in a patient with CF.

CASE DESCRIPTION

Participant

A 16-year-old female, diagnosed with CF (positive sweat test and mutation analysis) in her first year of age, has since been treated at the Children's Hospital, University Medical Center. She is known with several related medical conditions: CF-related liver disease, *Pseudomonas aeruginosa* and *Mycobacterium* abscesses in her lungs and since 2005 an allergic bronchopulmonary aspergillosis (ABPA). Informed consent was obtained from the parents and from the child.

During an outpatient clinic visit she complained of increased fatigue and shortness of breath during field hockey. She lost a considerable amount of weight (4 kg) over a period of 3 months. At the last annual checkup, 1 month earlier, her height and weight were both slightly below average (height=163.5 cm, 22nd percentile; weight = 49.3 kg 15th percentile). Her lung function had dropped significantly, from a forced expiratory volume in 1 second (FEV₁) of 2.12 L (73% of predicted) to an FEV₁ of 1.41 L (49% of predicted) and an FEV₁/Forced Vital Capacity (FVC) of 83% of predicted to an FEV₁/FVC of 63% of predicted, at her last annually check-up visit, with increased air trapping (Residual Volume/Total Lung Capacity of 51% of predicted). After the lung function testing and physical examinations, she

was put on a prescription of Cefazidime[®] and Tobramycin[®] 3 weeks intravenously at home, because she was suspected of an infection leading to exacerbation of her pulmonary condition. Before and after starting intravenously treatment, a cardiopulmonary exercise test (CPET) was performed according to ATS-guidelines as described below to evaluate her exercise performance before and after this antibiotic treatment (Ross, 2003).

Cardiopulmonary exercise testing

CPET were performed by using an electronically braked cycle ergometer (Lode Examiner; Lode, Groningen, The Netherlands). After assessment of baseline cardiopulmonary values during a 3-minute rest period, the test started and the participant pedaled between 60 and 80 revolutions per minute against a 20 W load. Thereafter, the workload was increased by a constant increment of 20 W · min⁻¹ intervals. During the CPET, strong verbal encouragement was given by the test-leader until the patient stopped because of voluntary exhaustion. Heart rate (HR) was monitored by three-lead ECG (Hewlett-Packard, Amstelveen, The Netherlands) and oxygen saturation (SpO₂%) by pulse oximetry (Nellcor 200 E; Nellcor, Breda, The Netherlands).

During the exercise tests, participants breathed continuously through a facemask (Hans Rudolph Inc, Kansas City, MO) and breath-by-breath respiratory gas analysis and volume measurements were performed with a flowmeter (Triple V volume transducer) and gas analyzers for oxygen (O₂) and carbon dioxide (CO₂) (Jaeger Oxycon Pro, Cardinal Health, Houten, The Netherlands). V_E, VO₂, carbon dioxide output (VCO₂), and the respiratory exchange ratio (RER) were calculated from conventional equations. Output from the flowmeter and gas analyzers were averaged at 10-second intervals and stored for further use.

Effort was considered to be at a maximal level when the participants showed clinical signs of intense effort and were unable to maintain the required pedaling speed and when at least one of the following criteria was met: 1) heart rate (HR_{peak} > 95% (210 age); 2) respiratory exchange ratio (RER_{peak} of >1.00); and 3) the presence of a VO₂-plateau in the final minutes of testing (Bar-Or and Rowland, 2004).

VO_{2peak} and the V_E that occurred at peak exercise (V_{Epeak}) were taken as the average value for the last 30 seconds during the CPET. Ventilatory threshold (VT) was defined if the participant demonstrated at least one of the following: 1) RER>1.0; 2) increase in ventilatory equivalents for oxygen (VE/VO₂) without simultaneous increase in ventilatory equivalents for carbon dioxide (VE/VCO₂); and/or 3) disappearance

of the linear relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ (Sritippayawan et al, 2008).

Intervention

The main goal was to increase her exercise capacity through HIT. This training regimen will put the least strain on her respiratory system, while still providing many of the physiological benefits of aerobic exercise in her locomotor muscles (Baquet et al, 2004). HIT is primarily powered by anaerobic metabolism, which means that her peripheral muscles are more challenged (Ratel et al, 2004). To monitor the effect of HIT on exercise capacity, a second CPET was scheduled after the intervention to see if her exercise capacity really had increased. The program was designed on the basis of a study by Gibala et al (2006), who showed that HIT can lead to improvements typically associated with endurance training, while increasing anaerobic power as well. Several studies have shown that anaerobic exercise programs can have positive effects on aerobic fitness as well (Gibala et al, 2006; Klijn et al, 2004; Ratel et al, 2004).

Before starting the training program she performed a steep ramp test on a bicycle ergometer to determine the "maximum short-time exercise capacity" (MSEC) (Meyer et al, 1996). After 3 minutes of unloaded pedaling, every 10 seconds the work rate was increased by 25 watts (W). The test was stopped at the moment she could not maintain 60 revolutions per minute (rpm). Her achieved maximum work load (MSEC) was 225 W. This MSEC test was repeated every 2 weeks to adjust the training intensity accordingly. Based on the results of the steep ramp test, we determined the optimal workload for training. Training frequency was set at three times per week for 6 weeks. Each training session consisted of 10–20 intervals, alternating between 30 seconds of high intensity (50–90% MSEC) pedaling and a 60-second recovery period (25% MSEC) as previously described by Meyer et al (1997). Pedaling was done at a rate

between 60 and 80 rpm. After 6 weeks a CPET was performed to check for improvements. During each training session the Borg scale was used to substantiate her subjective feelings during training and to measure the level of peripheral fatigue and dyspnea (Borg, 1982). To ensure that she was constantly challenged, the training program was progressively more demanding per week interval. By increasing both intensity and duration of the training it was expected that she would improve throughout the entire 6 weeks. The training program is described in Table 1. Besides the HIT training program, she continued her usual medications and maintained her caloric intake. CPET was also repeated after 6 weeks of HIT.

OUTCOMES

The baseline characteristics before and after 3 weeks of intravenously Ceftazidime® and Tobramycine® at home and after the 6-week HIT program are shown in Table 2. The three exercise tests were well-tolerated and fulfilled the criteria for performing a maximal CPET. The adherence to the exercise training program was good with a mean attendance rate of 90%. Reasons for absence were holidays.

At the end of the 3-week intravenous treatment her weight had increased from 49.3 kg to 50.0 kg; no increase was found for height. Increase in pulmonary function for FEV_1 was 13% and FEV_1/FVC of 14%, RV/TLC decreased with 11%. Her CPET were symptom-limited as she stopped due to fatigued legs, which was represented by a score of 9 on the Borg scale (Borg, 1982).

On the first CPET her $\dot{V}O_{2peak}$ was 1.54 L/min (70% of predicted), corrected for weight ($\dot{V}O_{2peak/kg}$) 31.3 mL/kg/min (80% of predicted). Peak workload was 163 watt (75% of predicted), corrected for weight ($W_{peak/kg}$) 3.3 watt/kg (86% of predicted) with a ventilatory threshold (VT) of 54% of $\dot{V}O_{2peak}$ predicted. Peak heart rate (HR_{peak}) was 171 beats per minute (89% of

TABLE 1 Training intervention

| Week | Low intensity (%MSEC) | Duration (sec) | High intensity (%MSEC) | Duration (sec) | Intervals (number) | Supplemental O_2 (L/min) |
|------|-----------------------|----------------|------------------------|----------------|--------------------|----------------------------|
| 1 | 30 | 60 | 50 | 30 | 10 | 3 |
| 2 | 30 | 60 | 60 | 30 | 12 | 3 |
| 3 | 30 | 60 | 70 | 30 | 14 | 3 |
| 4 | 30 | 60 | 80 | 30 | 16 | 3 |
| 5 | 30 | 60 | 90 | 30 | 18 | 3 |
| 6 | 30 | 60 | 90 | 30 | 20 | 3 |

TABLE 2 Pre/Postintervention measurements

| | Baseline | Postintravenous intervention | Posttraining intervention |
|--|---------------|------------------------------|---------------------------|
| Anthropometry | | | |
| Height (cm) | 163.5 | 163.5 | 163.5 |
| Weight (kg) | 49.3 | 50.0 | 51.8 |
| Exercise response | | | |
| HR _{peak} (bpm) | 171 | 172 | 171 |
| RER _{peak} | 1.18 | 1.20 | 1.23 |
| Borg score (leg fatigue) | 9 | 9 | 9 |
| Borg score (dyspnoe) | 9 | 9 | 6 |
| Lung functions | | | |
| FEV ₁ /FVC % | 63 | 78 | 83 |
| FEV ₁ % of predicted | 49 | 62 | 73 |
| RV % TLC | 51 | 40 | 35 |
| Ventilation | | | |
| VE (L/min) (% predicted) | 50 L (66) | 64 L (86) | 75 L (100) |
| TV (L) | 0.98 | 1.3 | 1.3 |
| BF (bpm) | 51 | 53 | 57 |
| TV/VC (%) | 44 | 47 | 46 |
| VE/VO _{2VT} | 26.5 | 28.7 | 29.6 |
| VE/VCO _{2VT} | 30.0 | 29.3 | 30.9 |
| VD/TV (%) | 27 | 25 | 23 |
| Resting SpO ₂ (%) | 96 | 98 | 96 |
| Exercise SpO ₂ (%) | 83 | 89 | 90 |
| Exercise capacity | | | |
| W _{peak} (watt) (%predicted) | 163 watt (75) | 165 watt (77) | 200 watt (93) |
| W _{peak} /kg (%) | 3.3 (86) | 3.3 (86) | 3.9 (100) |
| VO _{2peak} L/min (%predicted) | 1.54 (70) | 1.59 (76) | 1.96 (89) |
| VO _{2peak} /kg mL/kg/min (%predicted) | 31.3 (80) | 31.8 (81) | 37.8 (96) |
| VT (% VO _{2peak} predicted) | 54 | 55 | 68 |

HR: heart rate; RER: respiratory exchange ratio; FEV₁: forced expiratory flow in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; VE: minute ventilation; TV: tidal volume; VO₂: maximal oxygen uptake; VCO₂: maximal CO₂ production; VD: death volume; SpO₂: oxygen saturation; W: work rate; VT: ventilatory threshold.

predicted), with a peak respiratory exchange ratio (RER_{peak}) of 1.18 (96% of predicted) (Table 2).

VE_{peak} was 50 L/min with an FEV₁ of 1.41 L resulting in a ventilatory reserve (VR) = $[1 - (VE_{\max}/MVV_{\text{predicted}})] \times 100\%$ of -3% (normal >15%; ATS criteria) (ATS/ACCP, 2003). End-tidal CO₂ pressure

TABLE 3 List of the abbreviations

| | |
|------------------------------------|------------------|
| Tidal Volume | TV |
| Vital Capacity | VC |
| Residual Volume | RV |
| Forced Expiratory Flow in 1 second | FEV ₁ |
| Forced Vital Capacity | FVC |
| Total Lung Capacity | TLC |
| High-Intensity Interval Training | HIT |
| Cardio Pulmonary Exercise Testing | CPET |
| Heart Rate | HR |
| Respiratory Exchange Ratio | RER |
| Maximal Short Exercise Capacity | MSEC |

(PETCO₂) increased from 4.0 to 6.0 KPa, while the ratio of dead space to tidal volume (VD/VT) increased from 18% in rest to 27% during exercise, which is indicative of a dynamic hyperinflation and an inability to adequately expire CO₂. The efficiency of ventilation for O₂ (VE/VO₂) was 26.5 and for CO₂ (VE/VCO₂) was 30.0. SpO_{2,ss} decreased during the test from 95% at rest to 83% at maximal exercise (Table 3).

After the 3-week intravenous treatment, pulmonary function tests improved and exercise capacity showed little improvements in VO_{2peak} (1%), VO_{2peak}/kg (1%), and W_{peak} (2%), and watt/kg (0%).

On the basis of her first symptom-limited CPET, we concluded that her aerobic capacity (VO_{2peak}/kg) was more affected than her total work capacity (W_{peak}/kg); that is, she was able to perform additional work using anaerobic energy sources, which might be a compensation mechanism for the reduced oxygen flow to the muscles (Klijn et al, 2003a). In addition, during exercise she rapidly desaturated (after 6.30 minutes her SpO₂ dropped < 90%), which is likely a primary factor of her low ventilatory reserve capacity (hypoventilation). These results are in line with the assumption that ventilatory limitation occurs during maximal exercise based on an elevated ratio of (VE_{peak}) to maximal voluntary ventilation (MVV) at end exercise, whereas arterial hypoxemia has been implicated as a significant limiting factor during maximal exercise in this patient (ventilation/perfusion mismatch) (McKone, Barry, Fitzgerald, and Gallagher, 2005).

On the basis of the above findings we considered her to be an appropriate candidate for HIT, because HIT might give her an additional training stimulus at the muscle level, without maximally taxing her ventilatory system during the interval training sessions (Table 1).

After 6 weeks HIT program her lung functions further increased from an FEV₁ of 62% of predicted to an FEV₁ of 73% of predicted with a decreased of the RV/TLC of 35% of predicted. CPET showed

improvements in VO_{2peak} (0.43 L/min; 18%), VO_{2peak}/kg (7.0 mL; 11%), and W_{peak} (35 watt; 16%), and watt/kg (0.6; 14%) (Table 2).

There was also an indication for an increased oxygen delivery to the active muscle tissue; oxygen pulse (VO_{2peak}/HF_{peak}) increased 10.3%. Oxygen extraction in these muscles, as indicated by the $\Delta VO_2/\Delta WR$ relationship, increased 4%, and there was an increased in the VT from 54% to 68% of VO_{2max} predicted (Ross, 2003).

She showed a rise in VE_{peak} from 64 L/min to 75 L/min with an increase in both breathing depth, from a TV/VC of 44% to a TV/VC of 46%, and RR from 51 to 57 breaths per minute. There was no difference in ventilatory efficiency (VE/VO_2 and VE/VCO_2) and the ventilatory reserve capacity decreased from -3% to -14%. During the last CPET her $SpO_2\%$ decreased from 98% at rest to 90% at the end of the test after 11 minutes without saturation below 90%.

Finally, her participation into demanding physical activities (field hockey) increased over time from 10 minutes to 90 minutes.

DISCUSSION

The aim of this case report was to describe the effects of HIT on the exercise capacity in a 16-year-old girl with CF. After 3 weeks of intravenous treatment she showed an improvement in pulmonary functions and only little improvement in exercise capacity. After a 6-week program of HIT training, VO_{2peak} improved by 18% and W_{peak} improved by 16%. These values are much higher than the observed day-to-day errors in cardiopulmonary exercise testing results in our laboratory (Takken, van der Net, and Helders, 2005).

Evidence about the efficacy of physical training in cystic fibrosis is limited by the small size, short duration, and incomplete reporting of most of the studies. Physical training is already part of the care package offered to most people with cystic fibrosis, and there is a lack of evidence to actively discourage this. The benefits obtained from including physical training in a package of care may be influenced by the type of training programme (Bradley and Moran, 2008). Gulmans et al (1999) concluded that an exercise training program in the home can produce beneficial effects on oxygen consumption, muscle force, and perceived competence in children with CF. However, acceptability of the program was low, suggesting that long-term adherence would be poor; hence, other sorts of training need to be identified. Klijn et al (2003b) concluded that anaerobic training has measurable effects on aerobic performance, anaerobic perfor-

mance, and health-related quality of life in children with CF. Therefore, anaerobic training could be an important component of therapeutic programs for CF patients. Further research is needed to assess comprehensively the benefits of exercise programmes in people with cystic fibrosis and the relative benefits of the addition of aerobic vs. anaerobic vs. a combination of both types of physical training to the care of people with cystic fibrosis.

An explanation why the HIT training might improve aerobic fitness as well might be as follows: the HIT intervals might not be 100% anaerobic, and there is a significant contribution from aerobic energy sources. In healthy children and adults, the energy turnover during 30 seconds of all-out exercise, during the Wingate anaerobic test (WAnT), has been estimated as 65% and 80% derived from ATP-CP and anaerobic glycolysis, respectively, and thus highly anaerobic (Beneke et al, 2002; Boas, Danduran, and McColley, 1999). It is interesting that children with CF do not rely on aerobic pathways so much during this 30-second exercise test in comparison with healthy children (32% vs. 35%) (Boas, Danduran, and McColley, 1999). Klijn et al (2003a) have hypothesized that the higher anaerobic capacity in patients with CF might be a compensation mechanism for the impaired oxygen flux from the lungs to the mitochondria. One of the limitations of this case report is that we did not evaluate the effects of the HIT training on anaerobic capacity as measured by the WAnT. The steep ramp test takes quite a bit longer than the WAnT (the baseline test of the current patient took 90 seconds) and can therefore not be considered as an anaerobic test.

Another explanation why HIT training improves the aerobic fitness is the improvement of the ventilation. In patients with severe chronic obstructive pulmonary diseases the exercise breathing pattern is efficient, after rigorous exercise training, and this is associated with improved exercise tolerance (Casaburi et al, 1997). This training regimen also increased maximum voluntary ventilation while decreasing the ventilatory equivalent during exercise with an increase in peak VO_2 and total physical work (Gimenez et al, 2000).

Several co-interventions could have contributed to the results of this intervention as well. Antibiotic treatment was given 3 weeks intravenously before starting the training program. This had a beneficial effect on the pulmonary infection and consequently on the mucus production. Airway clearance techniques to improve the effectiveness of expectoration and mucus clearance techniques were provided as well and also had positive effects on the lung function. Because she was not admitted in the hospital for the duration of the training program, it is possible that she performed other types of physical activity (e.g., recreational

cycling) that could have elicited or superimposed the effects of the HIT. However, a previous longitudinal study found no effects of the promotion of regular physical activities on exercise capacity (Schneiderman-Walker et al, 2000).

Improved nutritional status may have contributed to the improved exercise capacity as well because the significant weight gain most likely has contributed to an increase of muscle mass and consequently of muscle power (Marcotte et al, 1986a; Marcotte et al, 1986b). However, corrected for body mass, our exercise parameters still showed a significant improvement over time. Finally, a natural course of improvement may not be ruled out as well, because the immunological response to the infection will have positively contributed to the cure of the infection.

Other limitations of this case report are the limited follow-up time of the patient and the inclusion of only aerobic exercise parameters. Future studies should perform a longer follow-up after training. In addition, they should monitor objectively measured physical activity levels in daily life in patients with CF before and after training to see whether the improved exercise capacity is transferred into increased levels of physical activity.

CONCLUSION

HIT involves significant anaerobic energy utilization and, therefore, may better mimic the physiological requirements of activities of daily living. It also has been proven to provide comparable physiological adaptations as endurance training, while placing a lower toll on the respiratory system. The authors believe that in patients with CF, HIT is an effective and efficient training regimen, especially in patients with a ventilatory limitation. Further research is necessary to investigate if HIT is a better alternative than traditional aerobic training programs, especially in ventilatory limited patients with CF.

Intermezzo

The European CF physiotherapist should be involved in the evaluation of patients, providing advice on airways clearance techniques, quality control, and professional development (Kerem, Conway, Elborn, and Heijerman, 2005). In cooperation with the patient and family they should develop an individualized, reasonable, optimal, effective, and efficient physiotherapy regimen. This should take into account all relevant physical and psychosocial factors. Modern physiotherapy in CF is primarily preventative and has to be

incorporated into each patient's daily routine. Therefore, physiotherapy must always be carried out in a way that makes future cooperation possible and encourages adherence. The CF center physiotherapist should assess patients every 1–3 months or at every outpatient clinic visit by 1) carrying out and interpreting the results of pulmonary function tests and respiratory symptoms and signs and exercise capacity; 2) monitoring sputum volume and characteristics and the degree of dyspnea; 3) assessing posture, chest mobility, muscle strength, and endurance; and 4) evaluating treatment quality and adherence. A full-treatment session and an assessment of physical capacity by standard protocols should be carried out as part of the annual review. Full treatments may also be given at the clinic or during home visits. Each individual's physiotherapy program needs to be continuously modified as age, needs, and circumstances change. This may help maximize adherence.

The CF center physiotherapist has an important role in the following:

Inhalation Therapy:

- choice of appropriate inhalation device(s)
- training of the patient/family in its optimal use
- handling, cleaning, and need for servicing and replacement of the device

Airway Clearance Therapy:

- choice of technique(s)
- training of the patient and carers in its optimal use

Physical Education and Exercise:

- providing the patient and family with appropriate and stimulating physical education and exercise programs

Education:

- improving and updating patients', families', and locally involved physiotherapists' knowledge of CF and its treatment

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