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Exercise Performance and Breathing Patterns in Cystic Fibrosis

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1. Introduction

Cystic fibrosis (CF) patients often experience exercise limitations. Although exercise capacity in CF patients has been extensively investigated over the past 15 years, factors contributing to exercise limitation in such patients have not been fully characterized.

The prognostic value of various exercise indices is considered in numerous clinical studies. However, whether exercise rehabilitation programs will improve the long term prognosis for CF patients remains controversial.

2. Cardiopulmonary exercise testing (CPET): Physiology of exercise

Ventilation, pulmonary gas transfer, cardiac output and peripheral blood flow, all increase in response to the metabolic demands of working muscles.

The pattern of breathing can be described by the following equation:

$$V_E = V_T \times f_b \quad (1)$$

where V_E is pulmonary ventilation, V_T the tidal volume (the volume of air inhaled and exhaled during one respiratory cycle) and f_b the frequency of breathing. In normal subjects during exercise the increase in V_E is achieved by increases in V_T at low and moderate work load, up to 50-60% of vital capacity (Jones and Rebuck, 1979). This is achieved by gradual increases in end inspiratory lung volume to about 80% of total lung capacity (TLC) and reductions in end expiratory volume to about 40% of TLC (Cotes, 1979).

At higher exercise intensity the increase of ventilation is achieved through rise in frequency of breathing. Obviously, in smaller lung volumes, like in children, the f_b commonly seen is at higher levels, not rare up to 60 br/min.

Furthermore, the breathing pattern during exercise includes additional variables, as inspiratory flow (V_I) and the duty cycle (T_i / T_{tot}). In these terms, the above mentioned equation could be written as:

$$V_E = V_I \times T_i / T_{tot} \times 60 / f_b \quad (2)$$

Also, the V_D / V_T ratio (physiological dead space) normally is 25 to 35% at rest and in exercise falls to 5 to 20%, due to V_T increase (Jones et al., 1966).

Oxygen consumption depends on work rate levels. The characteristics of oxygen uptake kinetics (VO_2) differ with exercise intensity (Webb and Dodd, 1995). When exercise is performed at a given work rate below lactate threshold (LT) there is a linear dynamic relationship between VO_2 and the work rate. When exercise is performed at work rate above LT, the VO_2 kinetics become more complex and there is an additional slow component either drives to the max VO_2 levels (VO_2 max) or delay steady state VO_2 (then the highest VO_2 value is characterized as VO_2 peak) (Xu and Rhodes, 1999).

Also, in healthy population, cardiac output (Q) during exercise is linearly related to oxygen uptake (Smith et al., 1988, Wasseman et al., 1997). It is important to note that at low exercise intensity (up to 30% of VO_2 max) approximately 50% of energy demands covered by carbohydrates as the other 50% use lipids as source of energy (Borsheim and Bahr, 2003). At higher exercise levels, the energy sources used remain under investigation.

The anaerobic threshold (AT) is the point reached during exercise of increasing intensity, at which aerobic processes give way to anaerobic processes. At this point oxygen intake is unable to meet energy needs and for additional work the energy provided by anaerobic glycolysis. There are various methods have been used to estimate the AT, like measurement of lactate production in plasma accompanies increase in ventilation or measurements of carbon dioxide output and ventilation as indicators of blood lactate increases (Wasserman, 1987, 1994, Zoladz et al 1998).

$VO_2 t / \text{slope}$ is an index expresses the oxygen debt and used to describe the early phase of recovery after exercise. $VO_2 t / \text{slope}$ has been evaluated in congestive heart failure, chronic obstructive pulmonary disease, cystic fibrosis, beta thalassaemia etc. (Nanas, 1999,2009, Vogiatzis 2005, Pouliou 2001, Koike, 1995). In healthy subjects all these changes during exercise, express their ability for a normal response to exercise. However, in this adaptive capacity should be taken into account some factors affect it like gender, age and physical activity.

CPET is an important tool for evaluation of exercise performance in healthy individuals and additionally utilized in clinical practice to assess a patient's level of intolerance to exercise and the possible underlying causes for this.

During the test, patients are subjected to symptom-limited incremental exercise and breath by breath monitoring of cardiopulmonary variables mentioned above (VO_2 , V_E , VCO_2 , f_b , $VO_2 t / \text{slope}$, HR, Q etc). Moreover they undergo assessment of perceptual responses (eg dyspnea, leg fatigue), measurements of arterial oxygen desaturation, lung volumes and muscle pressures. The incremental exercise period should last 10 – 12 minutes. The measures are reproducible and useful for diagnostic and prognostic purposes (Jones, 1997).

3. Ventilatory response and oxygen kinetics during maximal exercise and early recovery in patients with cystic fibrosis (CF)

One of the earliest observed abnormalities of pulmonary function in CF is an increase in the physiological dead space related to disease severity (Godfrey et al., 1971). This high resting

ratio increases further with exercise due to a limited V_T and severe mismatching of ventilation and perfusion (Cerny et al 1982). Ventilation is higher for a given workload.

When Forced Expiratory Volume in first second (FEV_1) is $> 60\%$, the CF patients can exercise almost as the healthy population, while patients with severe disease have limited capacity to increase their tidal volume during exercise and in order to maintain alveolar ventilation they heighten f_b .

As airways obstruction progresses the tidal expiratory flow limitation (EFL), accompanied by decreased inspiratory time (T_i) and lower inspiratory time to total respiratory cycle time (T_i / T_{tot}), leads to raised f_b and essentially to air trapping. EFL has been associated with chronic dynamic hyperinflation during tidal breathing where end-expiratory lung volume is greater than the relaxation volume of the respiratory system.

This dynamic hyperinflation affects the function of respiratory muscles by diaphragm flattening and shortening of the auxiliary and intercostals muscles. Inspiratory muscles overworked on large volumes become unable to pay off the oxygen debt and with exercise progress will fatigue prematurely (Hirsch et al., 1989, Coates et al., 1988).

Oxygen uptake kinetics are slowed in cystic fibrosis. During exercise, ventilation rises in a linear fashion until oxygen consumption reaches a level of 60-70% of VO_2 max, but in CF patients the VO_2 max usually is not reached and at earlier point the oxygen supply becomes inadequate to meet demand and begins anaerobic metabolism and lactic acid accumulation. The recovery is also slower, as it expressed by increased VO_2 t / slope (Webb and Dodd, 1995, Pouliou et al, 2001, Perpati et al., 2010).

The mechanisms causing prolonged oxygen kinetics on early phase of exercise recovery, has not been fully understood although has been observed in deconditioning, heart failure, COPD and CF. A possible cause is a slow recovery of energy stores of the peripheral skeletal muscles (Harris et al., 1976). In the muscles of patients with chronic respiratory impairment the oxidative phosphorylation impaired and there is an early activation of anaerobic glycolysis. Another mechanism that should be considered in the prolonged VO_2 recovery is the oxygen cost of breathing. In CF patients there is a basic physiologic defect leading to enlarged dead space and it is present even in the most mildly affected patients. Progressive airway obstruction reduces vital capacity resulting in V_T limitation. In compensation, decreased inspiratory time and increased end-expiratory volume are observed in order to preserve adequate inspiratory and expiratory flow rates. Airway obstruction causes prolongation of expiratory flow rate and in association with the increased breathing frequency results in air trapping. The work and oxygen cost of breathing are increased at high lung volumes and finally exercise is discontinued.

Studies to assess cardiac output in CF patients during steady state exercise found that cardiac function did not influence exercise performance. Although a limitation in diastolic reserve has been observed and there is a rapid rise in the heart rate, the cardiovascular responses are relatively normal for a given workload. However there are some recent data conclude that in CF patients with severe disease, CF related diabetes and older CF patients there is abnormal haemodynamic response to exercise (Hull et al., 2011). As for gas exchange abnormalities, it has been demonstrated that in patients with mild to moderate disease oxygen desaturation is not present during exercise.

The first time that exercise limitation in CF patients had been correlated with pulmonary mechanics rather than circulatory factors and hypoxia was in 1971 (Godfrey et al). Later, Browning et al. investigating 11 adult patients with CF showed that there was a correlation between disease severity and respiratory rate during exercise (Browning et al., 1990). Coates et al also found that there is decreased V_T and T_i , don't lead necessary to respiratory failure although there is a carbon dioxide rise at the onset (Coates et al., 1988). Lands et al. in a study with 14 patients found VE max and VO_2 max decreased during exercise without V_E/VO_2 and V_E/VCO_2 difference between patients and healthy controls. In the same study VO_2 max correlated with FEV_1 (Lands et al., 1992). Nixon and Webb confirmed that VO_2 max was statistically significant prognostic index for disease severity and survival (Nixon et al., 1995). Pouliou et al. describe prolonged oxygen kinetics at early recovery in adult patients with CF (Pouliou et al., 2001). Perpati et al. described breathing pattern in CF patients during maximal CPET and evaluated the correlation between resting respiratory variables and exercise capacity in CF participants (Perpati et al., 2010). They investigated 18 adult patients and 11 healthy subjects who underwent pulmonary function test at rest and symptom-limited treadmill CPET. The main ventilatory response indices at rest, peak exercise and recovery, for each group, are presented at Table 1. Patient's ability to increase V_T and V_E was limited in comparison with healthy subjects. CF patients showed similar ability to increase f_b from rest to peak exercise in comparison with healthy subjects, however they exhibited a prolonged rapid breathing after exercise along with shortened inspiratory time. VO_2 peak was lower in patients and in the same group recovery was longer, as it is expressed by lower VO_2/t slope.

	Patients			Healthy subjects		
	Rest	Peak	Recovery	Rest	Peak	Recovery
V_E (lt/min)	12.5 ± 2.4	57.2 ± 19	14.4 ± 6.7	11.3 ± 2	81.3 ± 13.2	20.5 ± 5.8
V_T (lt)	0.56 ± 0.1	1.53 ± 0.6	0.72 ± 0.3	0.57 ± 0.2	1.88 ± 0.4	1.2 ± 0.3
f_b (breaths/min)	23 ± 6	38 ± 9	32 ± 8	19 ± 4	44 ± 8	22 ± 5
T_i (s)	1.2 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	1.5 ± 0.3	0.7 ± 0.1	1 ± 0.2
V_T/T_i (lt/s)	0.5 ± 0.2	1.9 ± 0.6	0.8 ± 0.3	0.4 ± 0.1	2.7 ± 0.4	1.2 ± 0.3
VO_2	4.93 ± 1.8	29.12 ± 7	5.77 ± 3.3	4.03 ± 1.1	35.54 ± 7.3	4.82 ± 1.9
V_D/V_T	0.35 ± 0.2	0.16 ± 0.02	0.19 ± 0.04	0.36 ± 0.2	0.10 ± 0.02	0.16 ± 0.04
V_E/VO_2		25.65 ± 5.5			19.9 ± 5.88	
V_E/VCO_2		28.51 ± 5.3			26.62 ± 3.14	
VO_2/t -slope		0.59 ± 0.25			0.95 ± 0.18	

Table 1. CPET indices at rest, peak exercise and recovery for patients with cystic fibrosis and healthy subjects

4. Factors limiting maximal exercise performance in cystic fibrosis: The role of resting lung function, nutrition and disease severity

As mentioned above, it appears that the role of pulmonary mechanics is crucial to exercise limitation. The resting lung function and thus the disease severity have been associated with exercise performance as it is expressed by VO_2 max and $VO_2 t / slope$.

In serial studies there is a significant correlation between these variables and FEV_1 (Moorcroft et al., 1997, Nixon et al., 1992, Pouliou et al., 2001). Moreover, recent data confirm that oxygen uptake at maximal exercise and early recovery are correlated to resting

respiratory variables including inspiratory capacity (IC) and explore its role as predictor of exercise capacity (Perpati et al., 2010). The significant correlations of VO_2 peak and $\text{VO}_2/\text{t-slope}$ to resting lung function are listed in Table 2. In a multivariate stepwise regression analysis, using peak VO_2 as the dependent variable and the pulmonary function test measurements as independent variables respectively, the only significant predictor emerged was IC. $\text{VO}_2/\text{t-slope}$ was also lower in CF patients and showed significant correlation with IC. In a final stepwise regression analysis including all independent variables of the resting pulmonary function tests, the only predictor selected for VO_2 peak and $\text{VO}_2/\text{t-slope}$ was IC (Figure 2).

Parameters	VO_2 peak		$\text{VO}_2/\text{t-slope}$	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
FEV ₁ , % pred	0.575	0.013	0.774	0.0001
FVC, % pred	0.602	0.008	0.663	0.003
FEV ₁ /FVC, %	0.513	0.029	0.678	0.002
IC, ml	0.608	0.007	0.859	0.0001

Table 2. Significant correlations of VO_2 peak and $\text{VO}_2/\text{t-slope}$ to various resting respiratory parameters.

Although pulmonary disease correlates with exercise tolerance, especially in those CF patients with an FEV₁ less than 50% of predicted, nutritional status and muscle function may also play an important role for maintaining anaerobic and aerobic exercise. Several studies with mild or moderate pulmonary disease reported increases in lactate levels and early occurrence of the lactate threshold during incremental exercise, indicating an increase in muscle metabolism and suggesting that peak exercise is not limited by ventilation, but rather by non pulmonary factors that lead to leg fatigue (Moorcroft et al., 2005, Mc Loughlin et al., 1997, Nikolaizik et al., 1998)

In a study included 104 CF who performed progressive cycle ergometry to a symptom limited maximum, the conclusion was that the main factor limiting exercise in mild to moderate disease is peripheral muscle effort (Moorcroft et al., 2005). Reduced muscle performance may be due to poor nutritional status or reduced habitual activity. There are some data to support the hypothesis that the cause is an intrinsic muscle defect.

However, clearly there is a strong relationship between nutrition and muscle function (Elkin et al., 2000). In patients with CF and advanced lung disease, nutritional status plays a significant role in determining exercise capacity but poor nutrition is not correlated with pulmonary function and resting O_2 partial pressure (PaO_2). Malnutrition leads initially to loss of body fat and then to lean tissue wasting and can have adverse metabolic and structural effects on skeletal muscles. Leading to loss of leg muscle mass and decreased respiratory muscle strength, malnutrition can impair exercise performance.

The data of studies exploring the effect of nutritional supplementation on exercise tolerance are controversial. This fact support the hypothesis that exercise limitation in CF patients is the result of multiple combined effects of airways obstruction, nutritional status and metabolic processes.

5. The prognostic value of exercise testing in patients with cystic fibrosis

FEV₁, maximum oxygen consumption (VO₂ peak) during CPET and the Schwachman score (SS) are commonly used to assess functional capacity and disease severity in CF patients. Poulidou et al. explored the relationship between oxygen kinetics during early recovery after maximal CPET and the severity of the disease. They showed that VO₂ t / slope is closely correlated to FEV₁ and SS (Figure 1).

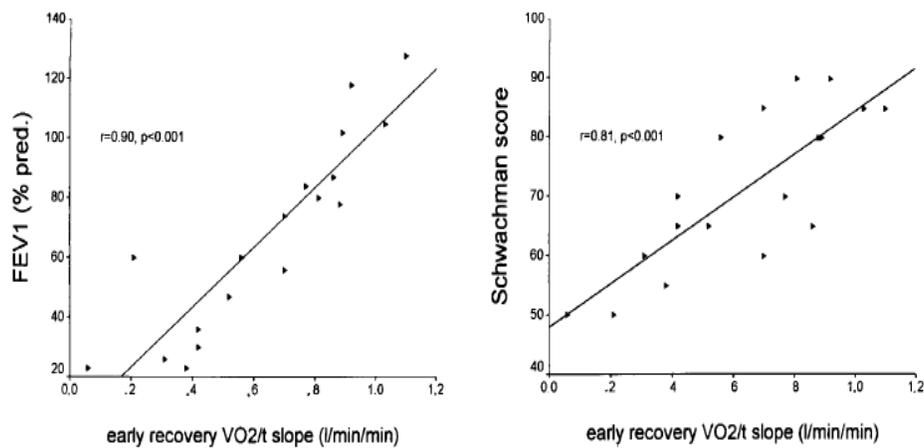


Fig. 1. Correlation between VO₂ t / slope and disease severity.

To the knowledge that resting respiratory variables have a significant correlation to VO₂ peak and to VO₂ t/slope, recent data have been reported about the potential role of IC as of independent predictor of exercise capacity (Perpati et al., 2010).

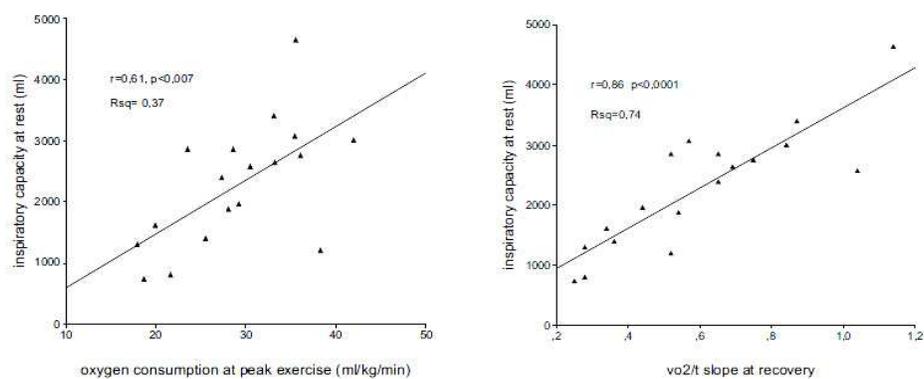


Fig. 2. Correlation between inspiratory capacity and oxygen kinetics at peak exercise and early recovery.

In studies designed to determine the prognostic value of CPET in CF patients higher levels of aerobic fitness are associated with a significantly lower risk of dying. Better aerobic fitness may simply be a marker for less severe illness, however measurement of VO₂ peak appeared to be valuable for predicting prognosis. A multicenter retrospective study analysed 3-year outcomes indicated that there is higher risk of death in patients with lower FEV₁, BMI, diabetes mellitus and higher alveolar arterial gradient for oxygen at peak exercise. Prospective studies needed to confirm the prognostic value of CPET in long term survival and compare its prognostic value with that of FEV₁, especially in patients with mild to moderate disease.

5.1 Submaximal cardiopulmonary exercise testing in cystic fibrosis patients

Submaximal exercise testing is considered a promising exercise capacity testing, especially in patients with limited performance because of fatigue due to disease severity. Submaximal CPET is more tolerable for CF patients as the test is terminated when oxygen uptake approached 75 % of the VO_2 peak. There are a few data showing that VO_2 kinetics during submaximal CPET are a more sensitive index of beneficial effects of exercise training than VO_2 peak and AT in healthy subjects. However, the experience with submaximal CPET in CF patients is generally limited (Hebestreit et al., 2005, Braggion et al., 1989).

In contrast there is a large experience over time with 6 min walk test (6MWT) as a useful tool assessed exercise capacity in patients with CF, mainly for severe disease and children (Gulmans et al., 1996, Nixon et al., 1996, Upton et al., 1988, Butland et al., 1982). The 6MWT is a practical, simple test that measures the maximal distance that a patient can walk at his or her own pace in six minutes. This self paced test is performed in an indoor corridor (or alternatively on a treadmill). The walking course should be 30 m long. The 6MWT provides a global assessment of functional capacity and although it doesn't give specific information and therefore has limited diagnostic capacity, it can be an excellent tool for severe ill patients as it resembles to everyday life activities. Many lung transplant centers use it at the time of assessment prior to transplantation, to determine baseline at start of program, at 6 weeks and every 3 months or to reflect functional changes and after transplantation at 6 weeks, 3 months and formal assessments. This is used in processes of patients referral for transplantation, training protocol design and rehabilitation potential estimation, as severe exercise intolerance could also be a factor precluding transplantation.

6. Perspectives in clinical practice: Rehabilitation programs

CF lung disease is often associated with physical inactivity and deconditioning. The effectiveness of exercise training program in CF patients has been studied in randomized controlled trials. The objective change in exercise capacity was reported as an improvement in VO_2 peak in two studies. Also there are studies reported change in peak heart rate, desaturation during exercise and annual decline in FVC at three years. Controversially, there are studies showing no significant differences in peak minute ventilation or annual decline of FEV_1 , although there is a trend for FEV_1 improvement. If exercise training including anaerobic exercises can improve muscle strength and muscle size resulting in weight gain remains also under consideration. Further, in terms of quality of life, positive effects towards perceived feasibility have been noted (Turchetta et al., 2004, Selvadurai et al., 2002, Schneiderman-Walker et al., 2000, Orenstein et al., 1981).

In a recent systematic Cochrane review of trials investigating the effect of exercise training programs on exercise endurance in patients with CF, the authors conclude that there is limited evidence that regular exercise training is associated with improved aerobic and anaerobic capacity, higher pulmonary function and enhanced airway mucus clearance (Bradley, Moran., 2008). Further research is needed to assess relative benefits of rehabilitation program for these patients.

In another review, Williams et al. present general exercise and training recommendations for children and adolescents with CF including cycling, walking, gymnastics and day to day activities for about 30 min, 3-5 times per week intermittently (Williams et al., 2010). For

patients with mild to moderate disease they add activities like swimming, tennis and climbing. In all cases is suggested to avoid activities like bungee-jumping, high diving, scuba diving and hiking in high altitude. The potential risks is associated with more intensive exercise includes dehydration, hypoxemia, hemoptysis, pneumothorax, arrhythmias and fractures in presence of CF related bone disease (Goldbeck et al., 2011).

However, improvements in exercise endurance require individual dosages of training stimuli and vary among individuals.

Prior to transplantation, an individualized pulmonary rehabilitation program is prescribed in order to increase or maintaining mobility and functional capacity, decrease dyspnea and hospitalizations, monitoring oxygen saturation and maintaining morale. Postoperative rehabilitation's goals is safe discharge of functional patients and accelerate recovery in outpatients setting. The training focuses on shoulder range of motion, stretching, strengthening and aerobics to increase endurance (Helm D., 2007).

7. Conclusions

Exercise testing is an important outcome variable in CF patients, correlated with disease severity and survival, exploring the ventilator and cardiac responses to progressively increasing workload and indentifying factors related to this ability for exercise. As there is no perfect test for that, is suggested (Orenstein, 1998) each Cystic Fibrosis Center to adopt the most appropriate for its patients needs and use it consistently.

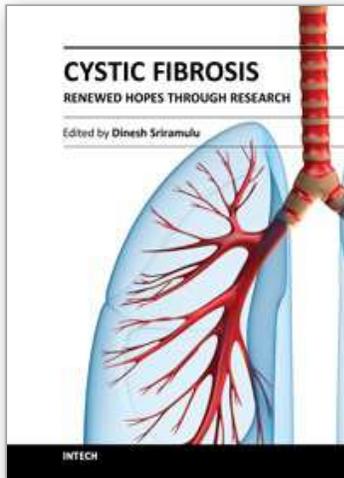
Looking at pulmonary rehabilitation as a program of medical practice implies methods of improvement the patient's functional ability, in terms of medical, mental, emotional and social potential, we will have to explore further the effect of an individualized approach in designed exercise training protocols and encourage physical training as a part of multimodality treatment of CF.

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Cystic Fibrosis - Renewed Hopes Through Research

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Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

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