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Effects of chest physiotherapy and aerobic exercise training on physical fitness in young children with cystic fibrosis

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Abstract

Background: Cystic fibrosis is a multisystem disease where the main problems are existing in the respiratory system. Aerobic exercise programs are effective in increasing physical fitness and muscle endurance in addition to chest physiotherapy.

Objective: The aim of this study was to evaluate the effects of chest physiotherapy and aerobic exercise training on physical fitness in young children with cystic fibrosis.

Methods: Sixteen patients with cystic fibrosis, between the ages 5-13 years, were included in this study. All children were assessed at the beginning and at the end of 6 week of the training. Modified Bruce protocol was used for assessing the cardiovascular endurance. The sit-up test was used to evaluate the dynamic endurance of abdominal muscles, standing long jump was used to test power, sit and reach, trunk lateral flexion, trunk hyperextension, trunk rotation and forward bending tests were used to assess flexibility, 20 m shuttle run test and 10-step stair climbing tests were used to assess power and agility. All patients received chest physiotherapy and aerobic training, three days a week for six weeks. Active cycle of breathing technique and aerobic exercise training program on a treadmill were applied.

Results: By evaluating the results of the training, positive progressions in all parameters except 20 m shuttle run and 10 stairs climbing tests were observed (p < 0.05). Active cycle of breathing techniques were used together with exercise training in clinically stable cystic fibrosis patients increases thoracic mobility (p < 0.05) and the physical fitness parameters such as muscle endurance, strength and speed (p < 0.05). Comparison of the results in sit and reach and forward bending tests were not significant (p > 0.05).

Conclusion: It is thought that in addition to medical approaches to the systems affected, the active cycle of breathing techniques along with aerobic training helps to enhance the aerobic performance, thoracic mobility and improves physical fitness in children with cystic fibrosis.

Keywords: Cystic fibrosis, physical fitness, aerobic exercise, training

Background

Cystic fibrosis is a multisystem disease where the main problems are existing in the respiratory system [1]. Most common problems requiring help in these patients are excessive bronchial secretion, decreased exercise tolerance and feeling of breathlessness [2,3]. Aerobic exercise programs are effective in increasing physical fitness

and muscle endurance in addition to chest physiotherapy [4]. It is therefore important to provide pulmonary rehabilitation programs in addition to regular medical treatment to increase the quality of life and prolong survival in children with cystic fibrosis.

Several studies have demonstrated favorable effects of exercise programs in children and adults with cystic fibrosis [5,6]. Specifically, an increase in physical activity was associated with an improvement in exercise capacity, stabilization and improvement in lung function and a higher quality of life [5,6].

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There are some studies which support that peripheral muscle strength, as a physical fitness parameter, can be affected in children with cystic fibrosis [7,8]. Aerobic exercise training in addition to chest physiotherapy is a vital component of the rehabilitation program of cystic fibrosis patients. Exercise is known to increase cardiorespiratory fitness and muscle endurance, decrease the feeling of shortness of breath and support a feeling of wellness [2,9]. It was reported that aerobic exercise increases forced expiration and sputum clearance in children with cystic fibrosis. This has led to an improvement in the clinical state, exercise tolerance, cardiovascular fitness and muscular endurance, together with a decreased sensation of breathlessness [10-12].

Cystic fibrosis patients who were included in an aerobic exercise program (walking and running) three days a week for three weeks at 70% of the maximum heart rate showed increase in respiratory muscle endurance and improvement in aerobic performance [12].

In the literature, the data showing the changes created by active cycle of breathing techniques and aerobic exercise training in children with cystic fibrosis on physical fitness parameters are inadequate and generally from the adult patients with cystic fibrosis. The aim of this study was to evaluate the effects of active cycle of breathing techniques and aerobic exercise training on physical fitness in young children with cystic fibrosis.

Patients and Methods

A total of 20 clinically stable children between the ages 5-13 were included in the study. The subjects had been diagnosed with cystic fibrosis in Hacettepe University Medical Faculty Department of Child Pulmonary Diseases by clinical findings consistent with cystic fibrosis and a sweat chloride value above 60 mEq/L on two measurements or cystic fibrosis-relevant mutations on both alleles of the CFTR gene, an age of \geq 13, a forced expiratory volume in 1s (FEV1) of \geq 35%, and the ability to perform physical activity. The criteria for inclusion were the following: clinically stable, no medical contraindications for exercise testing and participating in an exercise training program. Home medication (inhaled or oral antibiotics, bronchodilators, pancreatic enzyme supplements, and vitamins) was continued unchanged throughout the time of study. Exclusion criteria were non-cystic fibrosis related chronic disease and cystic fibrosis related conditions posing an increased risk to the patient when exercising. The scope and aim of the study were explained to the children participating in the study and their families and written informed consent was obtained. All procedures were in accordance with the current revision of the Helsinki Declaration [13].

Four patients were excluded from the study at the base line assessment due to a FEV1 below 35%. No patients were excluded for any other exclusion criteria.

All assessments were done by a single qualified physiotherapist and all the evaluation was done by a single pediatric pulmonologist. Exercise training and chest physiotherapy was done by another qualified physiotherapist.

The Schwachman scoring system [14] was used to determine the disease severity, clinical course and therefore the prognosis in cystic fibrosis cases while the Chrispin and Norman radiological scoring system was used to evaluate radiological changes [15].

All cases were evaluated before the physiotherapy program and after 6 weeks. The chest circumference was measured at three different points to evaluate the thoracic mobility.

The progressive multilevel treadmill test was done using modified Bruce, which is an incremental protocol, to determine the cardiovascular endurance of children with cystic [16]. The Enraf-Nonius (The Netherlands) treadmill was used for the test. The first two stages of the Modified Bruce Test are performed at a 1.7 mph and 0% grade and 1.7 mph and 5% grade, and the third stage corresponds to the first stage of the Standard Bruce Test protocol which continues as 1.7 mph 10% grade, 2.5 mph 12% grade, 3.4 mph 145 grade. Per stage takes 3 minutes.

The sit-up test was used to evaluate the dynamic endurance of abdominal muscles [17-19]. The standing long jump was used to test the power [17-19]. The sit and reach, trunk lateral flexion, trunk hyperextension, trunk rotation and forward bending tests were used to assess flexibility in patients with cystic fibrosis [17-20].

The subject was asked to run a 20 m distance as fast as possible in the 20 m shuttle run test. The running time was recorded with a chronometer [17,19].

The 10-step stair climbing test consisted of asking the subjects to climb the stairs without skipping any steps and using one foot for each step and descend without stopping and the duration was recorded. The height of the step was standardized as 15 cm.

Patients were trained three times a week for six weeks. At each visit they underwent the active cycle of breathing techniques and aerobic exercise training program on the treadmill. The exercise training was on the treadmill using 75-80% of the maximum heart rate for 30 min. The workload during the training was obtained by using the heart rate, blood pressure, electrocardiography (ECG) changes and clinical symptoms for each individual. The active cycle of breathing techniques was repeated three times for each pulmonary segment. The active cycle of breathing techniques and posture exercises were combined with breathing and taught to the

families as a home program. There was no exacerbation during the study.

The data was expressed as mean \pm standard deviation, The Wilcoxon test was used to compare the values before and after the physiotherapy program [21]. The significance level was accepted as p < 0.05.

Results

The physical and clinical characteristics of the children included in the study are presented in table 1. Ten subjects were good, three mild and three were moderate according to their Shwachman scores as shown in table 1. The parameters related to the treadmill test such as blood pressure, heart rate, inclination and average speed is given in table 2.

There was a statistically significant increase after the treatment in chest circumference from subcostal, epigastric and axillary regions and the sit-up, standing long jump, right lateral flexion, left lateral flexion, right rotation, left rotation, trunk hyperextension, 20 m shuttle run, and 10-step stair climbing tests compared to the pre-treatment state as shown in tables 3 and 4 (p < 0.05). No statistically significant difference was obtained in sit and reach and forward bending test (p > 0.05).

Discussion

It was found that active cycle of breathing techniques used together with exercise training in clinically stable young cystic fibrosis patients increases thoracic mobility and the physical fitness parameters such as muscle endurance, strength, flexibility and speed. This study was done in young children with cystic fibrosis in contrast the existing studies which were done in adolescents and adults.

Cystic fibrosis is a disorder that affects many systems and can cause various problems. Respiratory system involvement is expected in all patients and plays a significant role in determining the survival and quality of life in these patients. Pulmonary rehabilitation programs

Table 1 Characteristics of the patients

	Mean ± SD	Min-max
Age (years)	8.25 ± 2.77	5-13
Length (cm)	120.68 ± 15.15	107-153
Weight (kg)	22.17 ± 7.63	15-39
Shwachman Clinical Score	73.93 ± 12.40	47-90
Crispin and Norman Radiologic Score	10.06 ± 5.06	4-20
VC	89.37 ± 13.81	72-107
FEV1 (%)	87.15 ± 13.12	80-109
%FEF ₂₅₋₇₅ (%)	87.25 ± 14.89	61-112

VC- vital capacity, FEV1 (%)- Forced expiratory volume in one second, %FEF $_{25}$ - $_{75}$ (%)- %25-75 of forced expiratory flow.

Datas are presented as mean \pm standart deviation, median (min-max).

Table 2 Heart rate, blood pressure, speed and inclination values of the treadmill test.

	Before training (Mean ± SD)	After training (Mean ± SD)	Р
Speed (km/hr)	6.41 ± 1.22	8.5 ± 0.89	0.030
Inclination (%)	15.50 ± 2.0	18.75 ± 2.05	0.020
Heart rate (beats/min)			
Initial	115.81 ± 14.66	111.68 ± 12.18	0.244
Final	182.43 ± 8.32	179.43 ± 12.15	0.461
Recovery 3. min	122.93 ± 12.79	111.18 ± 11.25	0.007
Recovery 5. min	120.12 ± 11.99	109.50 ± 13.10	0.008
Blood Pressure (mmHg)			
Initial	103.12 ± 9.46	90.31 ± 10.40	0.002
Final	132.50 ± 15.27	126.56 ± 7.23	0.063
Recovery 3. min	101.56 ± 10.60	92.50 ± 12.90	0.025
Recovery 5. min	96.25 ± 8.06	89.37 ± 11.23	0.026

Datas are presented as mean \pm standart deviation, p < 0.05

therefore play a large role besides medical treatment for treating children with cystic fibrosis. The general aims of pulmonary rehabilitation programs are to increase bronchial secretion clearance, exercise tolerance, and quality of life while decreasing the feeling of breathlessness. The control or decrease of these problems require developing a proper rehabilitation program using bronchial drainage, breathing techniques, easier coughing, respiration-improving postures and relaxation techniques [9,22-27].

Exercise is an essential treatment approach for cystic fibrosis patients because of psychosocial support and beneficial effects on the cardiovascular and pulmonary systems. Therefore the number of studies on cystic fibrosis has increased recently [28,29].

Tugay [30] has demonstrated in his study that children with cystic fibrosis scored lower values in sit-ups, sit and reach, forward bending, right and left trunk rotation and trunk hyperextension tests compared with their healthy peers. We concluded that these parameters can be improved with aerobic exercise training and respiratory exercises.

We found a 3 repeat/min increase in the push-up test where we evaluated muscle endurance. There are studies

Table 3 Chest circumference of the patients.

	Before training Mean ± SD	After training Mean ± SD	р
Axillar difference (cm)	3.68 ± 1.74	5.37 ± 2.39	0.003
Epigastric difference (cm)	3.25 ± 1.39	5.81 ± 2.66	0.001
Subcostal difference (cm)	2.84 ± 1.56	5.25 ± 2.14	0.001

Datas are presented as mean \pm standart deviation, p < 0.05

Table 4 Physical fittness parameters

	Before training		After training		z	Р
	Mean	SD	Mean	SD	_	
Sit-ups (times/min)	25.87	7.5	28.25	7.43	-2.274	0.023
Standing long jump (cm)	89.31	29.49	98.37	29.52	-2.986	0.003
Sit and reach (cm)	3.18	3.70	3.81	3.48	-1.349	0.177
Forward bending (cm)	1.5	6.05	3.37	4.78	-1.307	0.191
Right lateral flexion (cm)	11.25	4.62	13.87	4.95	-2.604	0.009
Left lateral flexion (cm)	11.31	4.15	14.25	4.46	-2.950	0.003
Right rotation (cm)	13.50	5.40	15.06	4.55	-2.284	0.022
Left rotation (cm)	13.37	5.56	15.50	4.03	-2.484	0.013
Trunk hyperextantion (cm)	14.62	6.94	17.75	7.83	-3.320	0.001
20 m shuttle run (sn)	5.81	0.98	5.00	1.03	-2.648	0.008
10 step stair climbing (sn)	7.12	1.08	5.50	0.73	-3.477	0.001

SD: Standard deviation, p < 0.05

reporting increased muscle power and endurance with cardiovascular endurance training [31]. This result therefore supports our study. Exercise training on the treadmill is known to have a beneficial effect on increasing lower extremity and body muscle power [32]. We believe that the aerobic exercise program we provided in the study helped to develop muscle endurance. Sahlberg et al. [28], have found a decrease in quadriceps muscle strength and number of sit-ups after cardiovascular endurance training in their study on adult patients with cystic fibrosis. They have provided training to cystic fibrosis patients aged between 16-35, while the ages of the children in our study were between 5-13 years. It is thought that including children with cystic fibrosis in an aerobic exercise program in the early stage is important for developing muscle endurance.

We found that in young children with cystic fibrosis, aerobic exercise program combined with active cycle of breathing techniques increases strength. It is shown that increased cardiovascular endurance is effective in increasing the anaerobic strength of the individuals [33]. We feel that the increased strength of children with cystic fibrosis following the physiotherapy program is related to the aerobic training provided. Even the metabolism in cystic fibrosis is different from their healthy peers; all the children in our study were not severe and younger than the children recruited in other studies. The 20 m shuttle run and 10-step stair climbing tests evaluate both anaerobic power and speed. Exercise training in cystic fibrosis patients has been reported to have beneficial effects on the cardiorespiratory system [34,35]. It is not possible to consider aerobic and anaerobic strength independently as development in one area influences the other [33,36]. We saw that aerobic endurance training also increases anaerobic strength.

The aim of the active cycle of breathing techniques was to increase thoracic expansion. However, posture exercises combined with breathing techniques increased thoracic mobility and therefore body flexibility. Although the age ranges were different, there are two studies supporting our results that aerobic exercise training increases myofibril diameter and length [37,38]. A study showing an increase in flexibility with endurance training also supports our results [34]. We found improvements in all tests in children with cystic fibrosis except for the sit and reach and the forward bending tests. The absence of a difference in only these two flexibility tests may be due to the lack of stretching exercises dedicated to these muscles in the treatment program and the increased muscle tone especially in hamstring groups following the training on treadmill.

There is a study in the literature showing that postural reeducation has improved respiratory muscle strength, thoracic expansion and abdominal mobility [39]. Similarly we found that, active cycle of breathing techniques combined with aerobic training and posture exercises increased thoracic mobility and exercise tolerance in clinically stable cystic fibrosis patients.

One limitation of this study was the low number of children with cystic fibrosis included in the group and the lack of a control group. Future studies may reach comprehensive results using more detailed statistical analyses by increasing the number of children, control group and longitudinal follow up. Also learning effect can be eliminated by using cycle ergometer for the assessment and training on treadmill.

Conclusions

It is thought that in addition to medical approaches to the systems affected, the active cycle of breathing techniques along with aerobic training helps to enhance the aerobic performance, thoracic mobility and improves physical fitness in children with cystic fibrosis.

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Authors' contributions

NT conceived and designed the study. BE was responsible for history taking, clinical examination and implementation of the chest physiotherapy and exercise training for children with cystic fibrosis. He analyzed the data, wrote the manuscript and took part in revision and submission. ID revised the manuscript for important intellectual content and took part in data analysis. UO helped in clinical examination, diagnose of children and selection of the children with cystic fibrosis as well as final revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

- Bradley MJ, Moran FM, Elborn JS: Evidence for physical therapies (airway clearance and physical training) in cystic fibrosis: An overview of five Cochrane systematic reviews. Respir Med 2006, 100:191-201.
- Sandsund CA, Roughton M, Hodson ME, Pryor JA: Musculoskeletal techniques for clinically stable adults with cystic fibrosis: a preliminary randomised controlled trial. *Physiotherapy* 2011, 97(3):209-17.
- Paranjape SM, Barnes LA, Carson KA, von Berg K, Loosen H, Mogayzel PJ Jr.
 Exercise improves lung function and habitual activity in children with cystic fibrosis. J Cyst Fibros 2011.
- Schneiderman-Walker J, Pollock SL, Corey M: A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. J Pediatr 2000, 136:304-310
- Klijn PHC, Oushoorn A, van der Ent CK: Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. Chest 2004, 125:1299-1305.
- Pryor JAP, Prasad SA: Physiotherapy for respiratory and cardiac problems: adults and paediatrics. Edinburgh: Churchill Livingstone; 3 2003.
- De Meer K, Gulmans VAM, van der Laag J: Peripheral muscle weakness and exercise capacity in children with cystic fibrosis. Am J Respir Crit Care Med 1999, 159:748-754.
- 8. Hussey J, Gormley J, Leen G: Peripheral muscle strength in young males with cystic fibrosis. J Cyst Fibros 2002, 1:116-121.
- McIlwaine M: Chest Physical therapy, breathing techniques and exercise in children with CF. Paediatric Respiratory Reviews 2007, 8:8-16.
- Falk M, Kelstrup M, Anderson JB: Improving the ketchup bottle method with positive expiratory pressure PEP in cystic fibrosis. European Journal of Respiratory Diseases 1984, 65(6):423-432.
- De Jong W, van der Schans CP, Mannes GP, van Aalderen WM, Grevink RG, Koeter GH: Relationship between dyspnoea, pulmonary function and exercise capacity in patients with cystic fibrosis. Respir Med 1997, 91(1):41-46.
- Hebestreit H, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, Schenk T. Posselt HG. Kriemler S: Eur Respir J. 3 2010. 35:578-83.
- Rothman KJ: Declaration of Helsinki should be strengthened. BMJ 2000, 321:442-445.
- Shwachman H: Longterm sudy of 105 patients with cystic fibrosis. Am J Dis Child 1958, 96(1):6.
- Chrispin AR, Norman AP: The systematic evaluation of the chest radiograph in cystic fibrosis. Pediatr Radiol 1974, 2(2):101-105.
- Wilmore JH, Costill DL: Physiology of Sport and Exercise. Champaign: USA;
 IL: Human Kinetics, 3 2005.
- 17. Hockey RV: Physical Fitness. Mosby; Boston; 1993.
- Ergun N, Baltacı G: Principals of physiotherapy and rehabilitation in sport injuries. Hacettepe University Physical Therapy and Rehabilitation Highschool Publications, Ofset Foto Press, Ankara 1997.
- Sıpal MC: EUROFİT physical ability tests hand book. Ankara: Hürbilek; 1989.
- Liemohn W: Flexibility Range of Motion. Edited by: Durstine JL, King AC, Painter PL, Roitmen JL. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. USA: A Waverty Company; 1993:.
- 21. Sumbuloglu K. Sumbuloglu V: Biostatistics. Ankara: Hatiboglu: 1998.
- 22. Muammer K, Muammer R: Pulmonary rehabilitation in disabled children and encountered problems. Yeditepe Medical Journal 2009, 3(3):220-6.
- Oberwaldner B, Theissl B, Rucker A, Zach MS: Chest physiotherapy in hospitalized patients with cystic fibrosis: a study of lung function effects and sputum production. Eur Respir J 1991, 4(2):152-158.
- Pryor JA, Webber B: Physiotherapy for cystic fibrosis which technique? Physiotherapy 1992, 78(2):105-108.
- Nowobilski R, Wtoch T, Ptaszewski M, Szczeklik A: Efficacy of physical therapy methods in in airway clearance in patients with chronic obstructive pulmonary disease. Polskie Archiwum Medycyny Wewnetrznej 2010, 120(11):468-477.

- McCool FD, Rosen MJ: Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest 2006, 129(1):250-259.
- 27. van der Schans CP: Conventional chest physical therapy for obstructive lung disease. *RespirvCare* 2007, **52**(9):1198-1206.
- Wiles DL, Schneiderman JE, Nguyen T: Exercise and physical activity in children with cystic fibrosis. Paediatric Respiratory Reviews 2009, 10(3):105-109.
- Sahlberg M, Svantesson U, Thomas EM, Andersson BAS, Saltin B, Strandvik B: Muscular strength after different types of training in physically active patients with cystic fibrosis. Scand J Med Sci Sports 2008, 18:756-764.
- Tugay U, Arıkan H, Ozcelik U: Pulmonary functions in cystic fibrosis and relationship between body composition and muscle strength. Fizyoter Rehabil 2004, 15(2):47-54.
- Zoeller RF, Riezhman SE, Dabayebeh IM, Goss FL, Robertson RL, Jacobs PL: Relation Between Muscular Strength and Cardiorespiratory Fitness in People With Thoracic-Level Paraplegia. Archives of Physical Medicine and Rehabilitation 2005, 86(7):1441-1446.
- Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP: Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. Pediatr Pulmonol 2002, 33(3):194-200.
- Catai AM, Chacon-Mikahil MP, Martinelli FS, Forti VA, Silva E, Golfetti R, Martins LE, Szrajer JS, Wanderley JS, Lima-Filho EC, Milan LA, Marin-Neto JA, Maciel BC, Gallo-Junior L: Effects of aerobic exercise training on heart rate variability during wakefulness and sleep and cardiorespiratory responses of young and middle-aged healthy men. Braz J Med Biol Res 2002, 35(6):741-52
- Gruber W, Orenstein DM, Braumann KM, Hüls G: Health-related fitness and trainability in children with cystic fibrosis. Pediatr Pulmonol 2008, 43(10):953-964.
- Turchetta A, Salerno T, Lucidi V, Libera F, Cutrera R, Bush A: Usefullness of a program of hospital-supervised physical training in patients with cystic fibrosis. Pediatr Pulmonol 2004, 38(2):115-118.
- Williamsi CA, Benden C, Stevens D, Radtke T: Exercise training in children and adolescents with cystic fibrosis: theory into practice. Int J Pediatr 2010, doi: 10.1155/2010/670640, 1-7.
- Schulter JM, Fitts RH: Shortening velocity and ATPase activity of rat skeletal muscle fibers: effects of endurance training. Am J Physiol Cell Physiol 1994, 266:1699-1713.
- Trappe S, Harber M, Creer A, Gallagher P, Slivka D, Minchev K, Whitsett D: Single muscle fiber adaptations with marathon training. J Appl Physiol 2006. 101:721-727.
- Moreno MA, Catai AM, Teodori RM, Borges BL, Cesar Mde C, Silva E: Effect
 of a muscle stretching program using the Global Postural Reeducation
 method on respiratory muscle strength and thoracoabdominal mobility
 of sedentary young males. J Bras Pneumol 2007, 33(6):679-86.

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