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Do pulmonary and extrapulmonary features differ among cystic fibrosis, primary ciliary dyskinesia, and healthy children?

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Abstract

Background: Primary ciliary dyskinesia (PCD) is generally likened to cystic fibrosis (CF) due to similarities in impaired mucociliary clearance and some other symptoms. The aim of our study was to investigate pulmonary and extrapulmonary characteristics of children with CF and PCD since no studies have addressed respiratory muscle strength in children with PCD and to compare the results to those obtained from healthy age-matched controls.

Methods: Pulmonary and extrapulmonary characteristics were assessed by 6-min walk test, spirometry, maximum inspiratory and expiratory pressure measurements, and knee extensor strength test in the children with CF, PCD, and healthy controls.

Results: Children with PCD and CF had similar PFT results, except forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) which was lower in PCD ($p = .04$). Maximum inspiratory pressure (MIP) value was lower in the children with CF compared with the healthy controls ($p = .016$), MEP value of the children with PCD was worse than those with CF and healthy controls ($p = .013$ and $p = .013$), respectively. 6-min walk test (6MWT) distance of the children with CF was lower than their healthy counterparts ($p = .003$). Knee extensor muscle strength differed among the children with PCD, CF, and healthy control groups, but post hoc test failed to show statistical significance ($p = .010$).

Conclusion: Children with CF and PCD had some impairments in pulmonary functions, respiratory muscle strength, functional capacity, and peripheral muscle strength compared with healthy children. However, the unique characteristics of each disease should be considered during physiotherapy assessment and treatment. The clinicians may especially focus on the respiratory and peripheral muscle strength of the children with PCD.

KEYWORDS

cystic fibrosis, functional capacity, lung function, muscle strength, primary ciliary dyskinesia, respiratory muscle strength

1 | INTRODUCTION

In both primary ciliary dyskinesia (PCD) and cystic fibrosis (CF), the pathogenesis involves impaired mucociliary clearance that leads to intermittent or chronic sino-broncho-pulmonary infections.[1,2] Despite similarities in pathophysiology, outcomes differ between the two diseases, for example, the sputum concentrations differ between subjects with CF and PCD.[3] In addition, the radiologic distribution of lung disease is predominantly seen in middle and lower lobes in subjects with PCD while upper lobes are more impaired in subjects with CF.[1,4] Differences in lower airway pathogens and chronic colonization between PCD and CF are likely to reflect impaired mucociliary clearance, which is a primary defect in PCD but a secondary defect in CF. Besides, the children with PCD have a disadvantage compared with CF because of the late diagnosis which is made after the airway epithelium is already impaired and pulmonary function has deteriorated.[3,5]

In addition to comparisons of pulmonary aspects, the other related symptoms, such as exercise capacity and muscle function, are impaired in both CF and PCD. However, there is no consensus about the origin of the functional limitation in CF and PCD; whether it is a result of the cardiorespiratory system′s inability to meet metabolic demands or the intrinsic abnormalities in the muscle itself. It is shown that CF and PCD have abnormal muscle metabolism caused by different mechanisms, but this does not rule out the possible interaction between respiratory disease and muscle function.[6] Subjects with PCD and CF exhibit lower aerobic fitness compared with healthy children and young adult subjects,[7,8] but there is no consensus regarding the effect of severity of CF and PCD on functional capacity. PCD is generally considered a less severe disease than CF; however, a 1-year follow-up study presents a similar decline on exercise capacity in both the age-matched children with PCD and CF.[9] On the other hand, aerobic fitness is closely related to the respiratory muscle function, and there are conflicting results regarding respiratory muscle strength, which is reported as diminished, normal, or even increased in subjects with CF.[10–14] Since no studies have addressed respiratory muscle strength in children with PCD, there is no comparison of this data between children with CF and PCD in the literature.

In spite of all these differences mentioned above, the management of PCD is based on the clinical practice borrowed from the evidence-based management of CF.[15] Since airway clearance techniques and physiotherapy approaches are suggested for both PCD and CF, understanding the differences and requirements of these diseases may increase the success of treatment modalities and improve the quality of life in these patients.[16] So, our study aims to investigate the pulmonary function, respiratory and peripheral muscle strength, and functional capacity of children with CF and PCD and to compare the results among patient groups and healthy age- and gender-matched controls. Our hypothesis is that since the chronic lung inflammation does not affect children with CF and PCD on an equal basis, the pulmonary or extrapulmonary features may differ between these two diseases.

2 | METHODS

2.1 | Study design and study population

The subjects referred from the outpatient clinic of the Division of Pediatric Chest Diseases to the Department of Cardiopulmonary Physiotherapy and Rehabilitation of Bezmialem Vakif University were included in the study via simple random sampling according to the following selection criteria. Inclusion criteria were being 6–18 years of age and being diagnosed with CF or PCD. The diagnosis of CF was made using genetic and sweat testing according to the guidelines.[2,17,18] As for the diagnosis of PCD, PICADAR score was used after the presence of other respiratory diseases were excluded.[19] The subjects who were unable to perform the tests because of mental or physical disability and because of prior cardiovascular disease, acute exacerbation, or hospitalization history in the previous month were excluded. One hundred and thirty-six subjects (88 were CF and 48 were PCD) in the registry of our university hospital′s "Outpatient Clinic of the Pediatric Chest Disease" were assessed for eligibility by a pediatric pulmonologist. From this cohort, 31 subjects with CF, 28 subjects with PCD, and 25 healthy age- and gender-matched controls having no prior disease were allocated to this prospective study between December 2019 and February 2020. The flow diagram of the study is shown in Figure 1.

The study was approved by the Human Research Ethics Committee of Bezmialem Vakif University (Protocol number: 18/353) and performed in accordance with the Declaration of Helsinki. The study was registered to ClinicalTrial.Gov website with the registration number of NCT04161313. Written informed consent was obtained from the parents and the guardians of each child.

2.2 | Testing procedure

The demographic characteristics of subjects were recorded using a standard form. The information regarding the age at diagnosis, number of exacerbations in the previous year, genotype, pancreatic insufficiency, liver disease, medications, and *Pseudomonas aeruginosa* colonization were collected from the patient files. The number of bronchiectatic lobes was determined according to the reports of last year computed tomography.

Participants performed spirometry (except healthy controls), maximum inspiratory (MIP) and expiratory (MEP) pressure measurements, knee extensor strength test, and 6-min walk test (6MWT), respectively.

Pulmonary functions were assessed by using a spirometer (COSMED Pony FX, COSMED) in compliance with the guideline of the American Thoracic Society and European Respiratory Society.[20] The reference equations were used for predicted values of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25–75}$).[21]

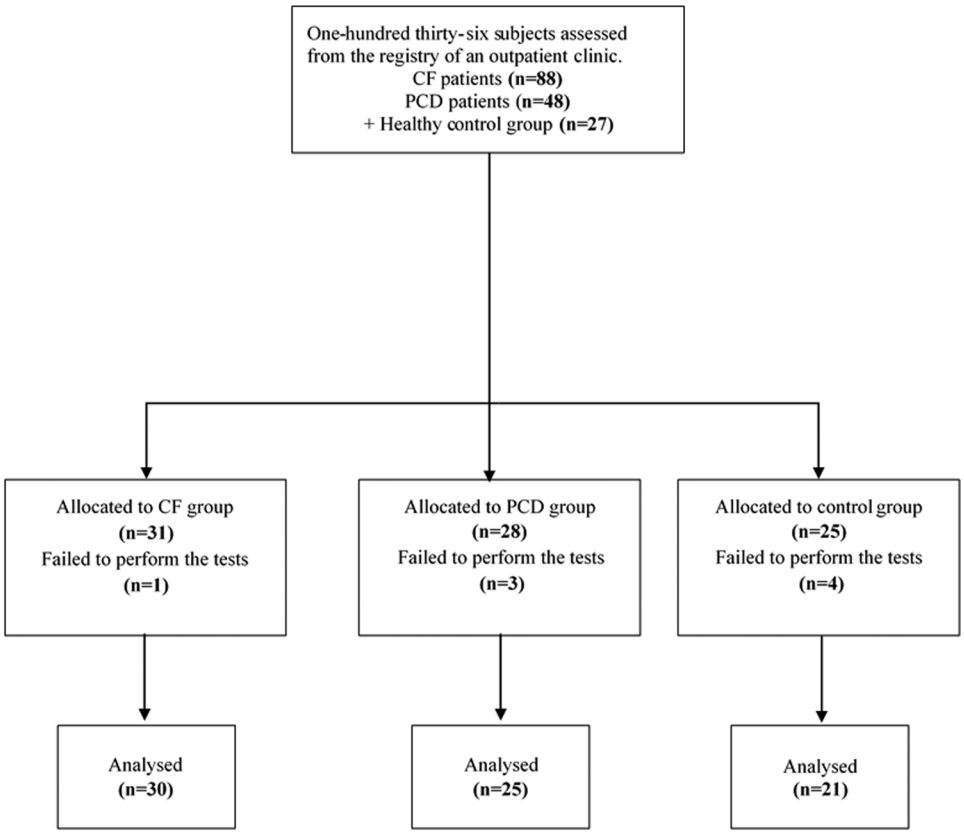

FIGURE 1 Flow diagram of study design. CF, cystic fibrosis; PCD, primary ciliary dyskinesia

MIP and MEP were determined using a mouth pressure meter (MicroRPM, MicroMedical).[22] The maximum value of three efforts, which vary by less than 5%, was accepted as MIP and MEP values of subjects. The subjects had a rest for about 1 min between each test.

The knee extensor strength test was evaluated using a MicroFet 2 hand-held dynamometer (Hogan Health Industries Inc.) with the break method. The maximum value of three consecutive measurements was recorded as the knee extensor strength. Subjects were allowed to rest for about 1 min between efforts.

The functional capacity was evaluated using 6MWT according to the guideline.[23] Patients were instructed to walk as fast as possible between two cones in a 30 m corridor and the walking distance in 6 min was recorded.

2.3 | Sample size and statistical analysis

The statistical procedure was carried out using SPSS software (Version 16.0; SPSS). The normality of all variables was analyzed using the Kolmogorov–Smirnov test. One-way analysis of variance or Kruskal–Wallis tests were used for between-group comparisons according to the distribution of the dependent variables. Independent samples *t* test or Mann–Whitney *U* test was performed to compare spirometric parameters between CF and PCD groups. The effect size was calculated using Cohen's definition (d_{Cohen}). We considered that an effect size less than 0.2 was negligible, between 0.2 and 0.5 was small, between 0.5 and 0.8 was moderate, and equal to or greater than 0.8 was large. *p* value of less than .05 was considered statistically significant. The sample size estimation was calculated depending on 6MWT scores and minimally 17 number of subjects for each group achieved a power equal to 0.80 with a probability d_{Cohen} of type I error equal to .05.[14]

3 | RESULTS

Thirty subjects with CF, 25 subjects with PCD, and 21 healthy age- and gender-matched controls completed the assessments (Figure 1).

The demographic and clinical characteristics of CF, PCD, and control groups are presented in Table 1. The demographical data were similar among three groups. The clinical characteristics such as age of diagnosis, number of exacerbations in the previous year, number of bronchiectatic lobes, and *P. aeruginosa* colonization were compared between CF and PCD groups. Children with CF were diagnosed earlier compared with the children with PCD ($p < .001$). Number of exacerbations in the previous year and *P. aeruginosa* colonization were found statistically higher in the CF group ($p = .030$ and $p = .013$, respectively). The genetic and sweat test had been applied to 24 and 30 subjects of CF, respectively. F508del homozygous ($n = 5$), F508del heterozygous ($n = 4$), N1303K

TABLE 1 The demographic and clinical characteristics of all groups

	CF Group (n = 30)	PCD Group (n = 25)	Control Group (n = 21)	*p* Value
Boys	15 (50%)	13 (52%)	11 (52.4%)	.98
Girls	15 (50%)	12 (48%)	10 (47.6%)	
Age (years)	11.4 ± 2.1	12.5 ± 3.5	11.0 ± 3.4	.18
Height (cm)	140.3 ± 14.0	132.9 ± 18.7	144.5 ± 16.8	.28
Weight (kg)	36.1 ± 13.4	32.3 ± 13.4	41.9 ± 17.8	.44
Body mass index (kg/m^2)	17.9 ± 3.0	18.6 ± 3.7	19.0 ± 4.7	.37
Body mass index (percentile)	47.2 ± 31.1	42.2 ± 33.2	56.8 ± 30.6	.31
Age at diagnosis (month)	4.5 ± 2.3	60.1 ± 22.5		<.001
Number of exacerbations in previous year	2.2 ± 2.9	0.8 ± 1.2		.03
Number of bronchiectatic lobes				
One lob	7 (23%)	4 (16%)		.607
Two lobes	9 (30%)	11 (44%)		
Three or more lobes	9 (30%)	9 (36%)		
Pseudomonas aeruginosa colonization	11 (37%)	2 (8%)		.013

Note: Values are expressed as mean ± *SD* or *n* (%).

Abbreviations: CF, cystic fibrosis; PCD, primary ciliary dyskinesia.

homozygous (*n* = 2), E92K homozygous (*n* = 2), E92K heterozygous (*n* = 1), R347P homozygous (*n* = 1), G542X homozygous (*n* = 1), G85E homozygous (*n* = 1), R1070Q homozygous (*n* = 1), 2183AA− >G homozygous (*n* = 1), 1531C/T heterozygous (*n* = 1), 621+1G− >T homozygous (*n* = 1), 3755delG homozygous (*n* = 1), R334W heterozygous (*n* = 1) mutations were identified in gene analysis. Two mutations were identified in two children, and no mutations could be found in three children. All subjects with PCD and 80% of subjects with CF had chest computed tomography in the preceding year. The degree of bronchiectasis was shown according to the number of affected lobes in Table 1. According to patient recordings, 25 subjects (83.3%) had pancreatic insufficiency and 3 subjects (10%) were diagnosed with liver disease in the CF group. Eleven children with CF (36,6%) and 22 children with PCD (88%) had bronchodilator therapy. Nine children with CF (30%) used hypertonic saline and all children with CF-inhaled dornase alpha as the mucolytics. All subjects were performing oscillatory positive pressure device and postural drainage with percussion in daily home physiotherapy program for airway clearance.

The spirometric parameters did not show a statistically significant difference between CF and PCD subjects except FEF_{25-75} ($p = .04$). The ratio of subjects who had lower than 80% FEV_1 was 58% in CF subjects and 66% in PCD subjects ($p > .05$). FEF_{25-75} value of PCD subjects was distinctly less than CF subjects ($p = .04$; $d_{cohen} = 0.86$; Table 2).

There were statistically significant differences among groups in terms of MIP and MEP values ($p = .02$ and $p = .005$, respectively). These differences were based on the changes between CF and healthy subjects, and between PCD and healthy subjects in MIP and MEP, respectively. CF group had a statistically lower score than the control group for 6MWT distance ($p = .003$). Knee extensor muscle strength was different among CF, PCD, and healthy group, but post hoc analysis failed to show a significant difference ($p = .01$; Table 3).

4 | DISCUSSION

Although CF is a systemic disease and PCD is not, in regard to lung disease, our study showed that the children with CF and PCD had similar pulmonary function results except forced mid-expiratory flow, which was significantly lower in the children with PCD.

TABLE 2 The pulmonary functions of CF and PCD groups

	CF Group (n = 30)	PCD Group (n = 25)	*p* Value
FVC (% pred)	90.2 ± 18.6	86.7 ± 17.4	.57
FEV_1 (% pred)	79.0 ± 18.2	72.6 ± 15.5	.27
FEV_1/FVC (%)	79.8 ± 9.3	77.6 ± 16.3	.62
PEF (L/s)	75.8 ± 22.3	61.9 ± 28.5	.11
FEF_{25-75} (% pred)	71.0 ± 34.1	45.8 ± 26.7	.04

Note: Values are expressed as mean ± *SD*.

Abbreviations: CF, cystic fibrosis; FEF_{25-75}, forced mid-expiratory flow between 25% and 75%; FEV_1, forced expiratory volume in 1 s; FVC: forced vital capacity; PEF, Peak expiratory flow; PCD, primary ciliary dyskinesia.

TABLE 3 The respiratory muscle strength. Functional capacity and knee extensor muscle strength values of the subjects

	CF Group ($n = 30$)	PCD Group ($n = 25$)	Control Group ($n = 21$)	p Value	Post Hoc p Value		
					CF vs. Control	PCD vs. Control	CF vs. PCD
MIP (cmH_2O)	70.0 ± 16.2	74.8 ± 16.6	83.6 ± 17.3	.02	.02	.25	.91
MEP (cmH_2O)	86.1 ± 14.2	73.6 ± 15.9	87.0 ± 14.7	.005	.99	.01	.01
6MWT distance (m)	538 ± 59	582 ± 65	597 ± 52	.002	.003	.99	.03
Knee extensor muscle strength (kg)	33.5 ± 9.2	26.0 ± 4.7	33.5 ± 11.2	.01	.99	.03	.02

Note: Values are expressed as mean ± *SD*.

Abbreviations: CF, cystic fibrosis; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; 6MWT, 6-min walk test; PCD, primary ciliary dyskinesia.

Inspiratory muscle strength was lower in children with CF compared to the healthy controls, whereas expiratory muscle strength was lowest in children with PCD. The functional capacity of the children with CF was lower compared to PCD and healthy counterparts while the knee extensor muscle strength was lowest in children with PCD. Children with CF were diagnosed earlier and had a higher number of exacerbations in previous year compared to children with PCD. *P. aeruginosa* colonization ratio was also higher in children with CF.

Although CF and PCD are both characterized by bronchial airflow obstruction, the comparative spirometric studies mostly focused on FEV_1, ignoring expiratory flows such as peak expiratory flow (PEF) or FEF_{25-75}. A previous study reported that these two diseases have similar pulmonary function impairments,[3] but a recent one showed that PCD has lower values compared with CF.[9] Irving et al.[24] state that in spirometry, FEF_{25-75} is more sensitive than FEV_1 for demonstrating the condition of small airways which is primarily affected airway in PCD. In our study, we found that FEF_{25-75} was lower in children with PCD compared to CF, which strongly supports this statement. In addition, FEF_{25-75} was below 65% of predicted value in children with PCD which may be defined as abnormal according to Ciprandi et al.[25]

When we analyzed the rest of the spirometric parameters, FEV_1 and FEV_1/FVC of the children with CF and PCD demonstrated obstructive patterns according to the predicted values in our study.[26,27] Decreased expiratory flow rates and velocity were found to be correlated with weak expiratory muscle strength in several cases.[28] In this study, children with CF demonstrated higher MEP, FEV_1, and PEF values compared with children with PCD; however, some of them were not statistically significant. These results may be related to the alterations in mucus properties and cough frequency between the children with CF and PCD, since the expiratory flow and muscle strength alter the magnitude of mucus transport and shear forces on airway surface liquid.[28,29] Radine et al.[30] revealed that cough frequency of subjects with CF was higher than subjects with PCD, which is probably a result of the increased sputum tenacity in CF.[3] Both difficulties in expectoration of the dehydrated sputum and increased number of coughs in a day may constitute a pseudoexpiratory muscle training effect on CF. This assumption may also help explain why children with PCD have decreased MEP compared with healthy and CF subjects.

Dassios et al.[31] suggest that MIP and MEP values of children with CF with no severe lung disease (with no gross hyperinflation and normal pulmonary function) were lower than healthy peers. We found that CF subjects have lower MIP values but similar MEP values compared with healthy controls in our study. Thus, decreased MIP in our CF subjects may be the result of possible hyperinflation. Studies have identified that hyperinflation related to airway obstruction limits the movement of the diaphragm and causes the inspiratory muscle weakness in subjects with CF.[32–34] In addition, to our best knowledge, there is no study comparing the respiratory muscle strength among PCD, CF, and healthy subjects. In our study, subjects with CF and PCD had lower MIP than controls, but only the difference between CF and healthy counterparts was statistically significant.

Functional capacity predicts the risk of hospitalization, morbidity, mortality, and quality of life in chronic respiratory diseases.[35] However, the debate continues to exist whether exercise limitation is based on the cardiorespiratory system′s impairment to meet metabolic demands or intrinsic muscle abnormalities.[6,9,36,37] Wells et al.[6] report that exercise capacity does not differ among CF, PCD, and healthy controls. Similarly, Chetta et al.[14] demonstrate that subjects with CF and healthy peers have similar walking distance in 6MWT. Conversely, several studies report that subjects with CF and PCD demonstrate lower exercise capacity than their healthy counterparts.[7,8] Lower exercise capacity of children with CF in our study may be attributed to the decreased antioxidant capacity which is the result of systemic inflammation and impaired efficiency depending on oxidative damage.[38] The presence of higher number of exacerbations and *P. aeruginosa* colonization ratio in children with CF may also support this assumption.

Assessment of limb muscle strength is clinically important in chronic respiratory disease, since systemic and metabolic effects of inflammation, drugs, impairment in oxygenation, and malnutrition may lead to muscle weakness.[39] In our study, the children with PCD demonstrated the lowest knee extensor muscle strength; however, post hoc analysis failed to show a significant difference. Similar to our results, the literature reports that children with PCD have weaker quadriceps muscles than healthy subjects.[40] A study that investigated muscle metabolism of CF, PCD, and healthy subjects

revealed that even though metabolic demands and exercise capacities of CF, PCD, and healthy peers are similar; subjects with PCD have poorer work outputs, which was supported by the fact that these patients had the greatest muscle strength impairment.[6] For subjects with CF, the severity of the disease is associated with muscle strength, yet the muscle strength of the subjects with milder CF was similar to healthy controls.[41] Likewise, a recent study reports that muscle strength significantly correlates with pulmonary function and also with functional capacity in adults with CF.[42]

The lack of spirometric measurements in healthy children and the assessment physical activity level of the subjects may be considered as a limitation of our study because of its probable role in functional performance. Also, the participants were not selected according to pulmonary functions, especially FEV_1. However, this was intentional since we wanted to take into consideration all spectrum of children with CF and PCD. We believe that this does not pose a problem in terms of the distribution of disease severity in groups, since the ratio of CF and PCD subjects who have FEV_1 under 80% of predicted values were similar. Our study revealed novel findings that may help better understanding the unique features of CF and PCD.

In conclusion, the children with CF and PCD demonstrated some impairments in pulmonary function, respiratory, and peripheral muscle strength and functional capacity compared with healthy children. The findings of our study suggest that the physiotherapy assessment and treatment of children with PCD should not be based on the knowledge obtained from CF studies even if pulmonary functions showed mostly similar patterns with each other. The clinicians may especially focus on the respiratory and peripheral muscle strength of the children with PCD. Some of our results were not in line with the literature. It was probably related to the difference in the severity of chronic respiratory disease and the age range of participants among other studies. In conclusion, PCD and CF have unique features, and pulmonary and extrapulmonary characteristics of these diseases may differ. Such differences should be taken into consideration while evaluating or managing these patient populations.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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REFERENCES

1. Cohen-Cymberknoh M, Simanovsky N, Hiller N, Hillel AG, Shoseyov D, Kerem E. Differences in disease expression between primary ciliary dyskinesia and cystic fibrosis with and without pancreatic insufficiency. *Chest*. 2014;145(4):738-744.
2. Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153(2):S4-S14.
3. Bush A, Payne D, Pike S, Jenkins G, Henke MO, Rubin BK. Mucus properties in children with primary ciliary dyskinesia: comparison with cystic fibrosis. *Chest*. 2006;129(1):118-123.
4. Jain K, Padley SPG, Goldstraw EJ, et al. Primary ciliary dyskinesia in the paediatric population: range and severity of radiological findings in a cohort of patients receiving tertiary care. *Clin Radiol*. 2007;62(10):986-993.
5. Coren M, Meeks M, Morrison I, Buchdahl R, Bush A. Primary ciliary dyskinesia: age at diagnosis and symptom history. *Acta Paediatr (Stockholm)*. 2002;91(6):667-669.
6. Wells GD, Wilkes DL, Schneiderman JE, et al. Skeletal muscle metabolism in cystic fibrosis and primary ciliary dyskinesia. *Pediatr Res*. 2011;69(1):40-45.
7. Madsen A, Green K, Buchvald F, Hanel B, Nielsen KG. Aerobic fitness in children and young adults with primary ciliary dyskinesia. *PLoS One*. 2013;8(8):e71409.
8. Fielding J, Brantley L, Seigler N, McKie KT, Davison GW, Harris RA. Oxygen uptake kinetics and exercise capacity in children with cystic fibrosis. *Pediatr Pulmonol*. 2015;50(7):647-654.
9. Ring AM, Buchvald FF, Holgersen MG, Green K, Nielsen KG. Fitness and lung function in children with primary ciliary dyskinesia and cystic fibrosis. *Respir Med*. 2018;139:79-85.
10. de Jong W, van Aalderen WMC, Kraan J, Koëter GH, van der Schans CP. Inspiratory muscle training in patients with cystic fibrosis. *Respir Med*. 2001;95(1):31-36.
11. Vendrusculo FM, Heinzmann-Filho JP, Piva TC, Marostica PJ, Donadio MV. Inspiratory muscle strength and endurance in children and adolescents with cystic fibrosis. *Respir Care*. 2016;61(2):184-191.
12. Dunnink MA, Doeleman WR, Trappenburg JCA, de Vries WR. Respiratory muscle strength in stable adolescent and adult patients with cystic fibrosis. *J Cyst Fibros*. 2009;8(1):31-36.
13. Ziegler B, et al. Relationship between nutritional status and maximum inspiratory and expiratory pressures in cystic fibrosis. *Respir Care*. 2008;53(4):442-449.
14. Chetta A, PISI G, ZANINI A, et al. Six-minute walking test in cystic fibrosis adults with mild to moderate lung disease: comparison to healthy subjects. *Respir Med*. 2001;95(12):986-991.
15. Strippoli MPF, Frischer T, Barbato A, et al. Management of primary ciliary dyskinesia in European children: recommendations and clinical practice. *Eur Respir J*. 2012;39(6):1482-1491.
16. Schofield LM, Duff A, Brennan C. Airway clearance techniques for primary ciliary dyskinesia; is the cystic fibrosis literature portable? *Paediatr Respir Rev*. 2018;25:73-77.
17. Barbato A, Frischer T, Kuehni CE, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. *Eur Respir J*. 2009;34(6):1264-1276.
18. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*. 2017;181S:S4-S15.
19. Behan L, Dimitrov BD, Kuehni CE, et al. PICADAR: a diagnostic predictive tool for primary ciliary dyskinesia. *Eur Respir J*. 2016;47(4):1103-1112.
20. Miller MR. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.

21. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. *J Bras Pneumol*. 2007;33(4):397-406.
22. American Thoracic Society/European Respiratory, S. ATS/ERS statement on respiratory muscle testing. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med*. 2002;166(4):518-624.
23. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
24. Irving SJ, Ives A, Davies G, et al. Lung clearance index and high-resolution computed tomography scores in primary ciliary dyskinesia. *Am J Respir Crit Care Med*. 2013;188(5):545-549.
25. Ciprandi G, Capasso M, Tosca M, et al. A forced expiratory flow at 25-75% value <65% of predicted should be considered abnormal: a real-world, cross-sectional study. *Allergy Asthma Proc*. 2012;33(1):e5-e8.
26. Levy ML, Quanjer PH, Rachel B, Cooper BG, Holmes S, Small IR. Diagnostic spirometry in primary care: proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG)1 document, in association with the Association for Respiratory Technology & Physiology (ARTP)2 and Education for Health31. *Prim Care Respir J*. 2009;18(3):130-147. www.gpiag.org.2.www.artp.org.3.www.educationforhealth.org.uk
27. Glady CA, Aaron SD, Lunau M, Clinch J, Dales RE. A spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. *Chest*. 2003;123(6):1939-1946.
28. Kim J, Davenport P, Sapienza C. Effect of expiratory muscle strength training on elderly cough function. *Arch Gerontol Geriatr*. 2009;48(3):361-366.
29. Dwyer TJ, Alison JA, McKeough ZJ, Daviskas E, Bye PTP. Effects of exercise on respiratory flow and sputum properties in patients with cystic fibrosis. *Chest*. 2011;139(4):870-877.
30. Radine A, Werner C, Raidt J, et al. Comparison of nocturnal cough analysis in healthy subjects and in patients with cystic fibrosis and primary ciliary dyskinesia: a prospective observational study. *Respiration*. 2019;97(1):60-69.
31. Dassios T, Katelari A, Doudounakis S, Mantagos S, Dimitriou G. Respiratory muscle function in patients with cystic fibrosis. *Pediatr Pulmonol*. 2013;48(9):865-873.
32. Ionescu AA, Chatham K, Davies CA, Nixon LS, Enright S, Shale DJ. Inspiratory muscle function and body composition in cystic fibrosis. *Am J Respir Crit Care Med*. 1998;158(4):1271-1276.
33. Pradal U, Polese G, Braggion C, et al. Determinants of maximal transdiaphragmatic pressure in adults with cystic fibrosis. *Am J Respir Crit Care Med*. 1994;150(1):167-173.
34. Dekerlegand RL, Hadjiliadis D, Swisher AK, Parrott JS, Heuer AJ, Myslinski MJ. Clinical predictors of inspiratory muscle strength in adults with stable cystic fibrosis: a pilot study. *Cardiopulm Phys Ther J*. 2017;28(4):136-146.
35. Donadio MVF, Heinzmann-Filho JP, Vendrusculo FM, Frasson PXH, Marostica PJC. Six-minute walk test results predict risk of hospitalization for youths with cystic fibrosis: a 5-year follow-up study. *J Pediatr*. 2017;182:204-209. e1.
36. Troosters T, Langer D, Vrijsen B, et al. Skeletal muscle weakness, exercise tolerance, and physical activity in adults with cystic fibrosis. *Eur Respir J*. 2009;33(1):99-106.
37. Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: etiology, clinical implications and response to therapeutic interventions. *J Cyst Fibros*. 2017;16(5):538-552.
38. Hebestreit H, Hebestreit A, Trusen A, Hughson RL. Oxygen uptake kinetics are slowed in cystic fibrosis. *Med Sci Sports Exerc*. 2005;37(1):10-17.
39. MacIntyre NR. Mechanisms of functional loss in patients with chronic lung disease. *Respir Care*. 2008;53(9):1177-1184.
40. Simsek S, Inal-Ince D, Cakmak A, et al. Reduced anaerobic and aerobic performance in children with primary ciliary dyskinesia. *Eur J Pediatr*. 2018;177(5):765-773.
41. Sahlberg ME, Svantesson U, Thomas EMLM, Strandvik B. Muscular strength and function in patients with cystic fibrosis. *Chest*. 2005;127(5):1587-1592.
42. Rovedder PME, Borba GC, Anderle M, et al. Peripheral muscle strength is associated with lung function and functional capacity in patients with cystic fibrosis. *Physiother Res Int*. 2019;24(3):e1771.

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