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Research Article

Lung Clearance Index and Exercise Capacity among Children with Cystic Fibrosis (Cf) and Non-Cf Bronchiectasis Over A Two Year Period

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Abstract

Background: There has been limited experience on the progression of lung disease, assessed by exercise limitation and lung clearance index (LCI), among children with bronchiectasis.

Aim: To compare progression of lung disease assessed with LCI and exercise capacity among children with bronchiectasis.

Method: Fourteen stable CF patients and 13 stable children with non-CF bronchiectasis and comparable FEV_1 were assessed with HRCT, maximal incremental cardiopulmonary exercise testing (CPET) and Multiple Breath Washout (MBW) over a two-year period.

Results: Fourteen patients with CF (mean age 14.09 years, mean FEV_1:81.46%) and 13 patients with non-CF bronchiectasis (mean age 13.05 years, mean FEV_1:76.6%), participated in the study. LCI was comparable among CF and NCFB patients (LCI: 10.11 and LCI: 9.72, respectively, $p = 0.707$). VE/VO_2 and VE/VCO_2 were significantly impaired among the CF group compared to patients with NCFB (p: 0.001 and p: 0.002, respectively). FEV_1 % predicted improved significantly over the two-year period among patients with NCFB ($p < 0.05$), while VE/VO_2 and VE/VCO_2 deteriorated significantly ($p < 0.05$). LCI, VE/VO_2 and VE/VCO_2 deteriorated significantly in the CF group, ($p < 0.05$).

Conclusions: Despite comparable FEV_1 values, patients with CF seem to have more impaired gas exchange, compared with patients with non-CF bronchiectasis. Aggressive treatment may improve lung function among patients with non-CF bronchiectasis, while ventilation inhomogeneity deteriorates among patients with CF over a two-year period.

Keywords: *Cystic Fibrosis; Non-CF Bronchiectasis; Lung Clearance Index; Exercise Limitation; Exercise Capacity; Ventilation Inhomogeneity*

Introduction

Bronchectasis, a heterogenous group of conditions that refers to non-reversible dilation of the bronchi wall, has drawn increased interest among researchers and clinicians over the past years. Advances in the understanding of these conditions' epidemiology and pathophysiology suggest that early identification of disease progression along with a proper intervention can be crucial in maintaining an overall good quality of life status for these patients [1-3].

Bronchectasis may be due either to cystic fibrosis (CF) or a heterogenous group of diseases (non cystic fibrosis bronchectasis-NCFB) with most common cause being primary ciliary dyskinesia (PCD). Patients with bronchiectasis present with different symptoms which vary from persistent productive cough and daily sputum to recurrent respiratory infections [4,5] that eventually lead to the deterioration of lung function. Spirometry, which traditionally has been used to evaluate lung function, hasn't been proved that sensitive in monitoring early disease progression either in CF [6,7] or PCD patients [8]. Recently, Lung Clearance index (LCI) has been shown to be a surrogate marker of early structural lung damage in patients with bronchiectasis either of CF [9] or NCF origin [3,10].

British Thoracic Society suggests that all patients with cystic fibrosis should undergo exercise testing every year to fully evaluate their exercise capacity [11]. However, in children with non-cystic fibrosis bronchiectasis an annual exercise testing isn't recommended and is only suggested to be part of a rehabilitation program in adults [12]. No studies of Exercise Testing as a tool in detecting and monitoring lung damage in NCFB patients exist.

The aim of this study was to compare progression of lung disease assessed with LCI and exercise capacity among children with CF and non-CF bronchiectasis.

Material and Methods

Study Subjects

Fourteen CF patients and 13 patients with non-CF bronchiectasis (NCFB) were recruited. All patients were of Caucasian origin. Age, weight, height and BMI were recorded. Bronchiectasis were confirmed with chest HRCT and scored with the modified Bhalla score [13,14]. Five out of the thirteen NCFB patients were diagnosed with Primary Ciliary Disease (PCD), while the etiology of bronchiectasis was not defined for the others. CF patients were following their treatment whereas NCFB patients were started on regular treatment with hypertonic nebulized saline.

Study design

All study participants underwent chest HRCT to determine the extent and severity of structural damages of the lungs. They also performed spirometry, CPET and MBW in order to have their lung function and exercise capacity fully assessed. All patients were re-evaluated with HRCT, spirometry, CPET and MBW, two years later.

The study was approved by the local ethics committee and informed consent was obtained from the patients or their guardians if the patients were under 18 years.

Methods

Anthropometry

Height and weight were measured in light clothing, and body mass index (BMI) was calculated.

Spirometry

Forced vital capacity (FVC), forced expiratory volume in on second (FEV1), and forced expiratory flow at 50% of FVC (FEF50) were measured using standard spirometry following the ATS/ERS guidelines. No beta-2 agonists were used 24 hours before spirometry. Data were expressed in %predicted using the normative data from the Global Lung Function Initiative software (GLI 2012, Global Lung Function Initiative Task Force, available at: http://www.lungfunction.org/)

Multiple-Breath-Washout

MBW measurements were performed with a flow, volume and molecular mass measurement analyzer (EXHALYZER D, Ecomedics,

Switzerland), according to ERS/ ATS Consensus Guidelines [15]. LCI is defined as the number of FRC lung turnovers (TO: Cumulated Expired Volume divided by the Functional Residual Capacity (FRC)) required to reduce end-tidal N_2 concentration to 1/40 of the starting concentration, which accounts to 2.5% of the initial one. A pulmonary disease resulting in uneven ventilation distribution, prolongs the duration of the washout, thus elevate the LCI. FRC expresses the remaining air in the lungs at the end of expiration which is in direct relevance with the airway opening [16,17].

Cardiopulmonary Exercise Testing

All children performed a CPET on a cycle ergometer (Ergoline, Vmax Series V.20-1, Sensor medics). Cardiology parameters were also measured (cardiograph model Corina, S.N. 101164361, Cardiosoft software V5.15). A continuous incremental cycle protocol to volitional fatigue was used; after baseline measurements for 2 minutes and a warm-up period of 3 minutes cycling with 20 W, work load was increased by 10 watt every two minutes until volitional fatigue and should keep the exercise time within the recommended 8-12 min[18] . Patient's heart rate over 85% of maximum predicted [19] along with Respiratory equivalence ratio (RER) over 1.05 [20] were used as indicators of a maximal test. The following parameters were measured: peak oxygen uptake (VO_2peak), ventilator equivalent ratios for oxygen and carbon dioxide at peak exercise (VE/VO_2, VE/VCO_2), anaerobic threshold (AT), breathing reserve at peak exercise (BR%), dead space to exhaled volume ratio (VD/VT). VO_2peak % predicted was calculated using the Orenstein gender specific equations [21], which have often been used in cystic fibrosis [18,22,23]. Breathing reserve was calculated as: MVV– VE/MVV (MVV = maximal voluntary ventilation; (MVV = 35 x FEV_1); VE= maximum exercise ventilation). Anaerobic threshold (AT) was determined by the Sensor Medics software, using the VCO_2/VO_2 plot.

Chest HRCT

HRCT scans were performed employing an (Asteion) Toshiba CT scanner. Slices measuring 1.5 mm were obtained at 10mm intervals during suspended respiration in supine position. Additional expiratory scans were obtained in older cooperative children at 20 mm intervals. Each CT scan was scored using the "Bhalla" scoring system by an experienced radiologist; the modified Bhalla score shows high inter-observer reproducibility and sensitivity [13,14]. The following changes were evaluated: severity and extent of bronchiectasis, severity of peribronchial thickening, generation of bronchial division involved, extent of mucus plugging, sacculation or abscess formation, bullae, emphysema, atelectasis and consolidation. Higher values of the Bhalla score indicate more severe lung disease.

Statistical Analysis

Descriptive statistics were used to describe the study population. MBW, CPET, spirometric parameters as well as the total Bhalla score of patients were expressed as mean and standard deviation (sd). Independent samples t-test was used to compare different baseline parameters between partial groups of study population. The change of MBW, CPET, spirometric, parameters and Bhalla score over the 2-year period was evaluated with the Paired-T test criterion. A p-value < 0.05 was considered statistically significant for all analyses. Statistical analysis was performed with the statistical package SPSS for Windows version 20.0 (SPSS IBM SPSS Statistics 20, USA).

Results

Fourteen patients with NCFB and 13 patients with CF participated in the study. Population and lung function characteristics are shown on Table 1. Mean age, weight, height, BMI and FEV_1 were comparable ($p > 0.05$) between patients of both groups.

Baseline mean (SD) Bhalla score was comparable in NCF and CF group, [9.67(4.80) vs. 8.33 (5.25), respectively]. Mean (SD) FEV_1% was [76.60 (22.38) vs. 81.46 (11.88)], mean (sd) LCI was [9.72 (2.22) vs. 10.11 (2.83)] and mean (SD) VO2 Peak was [83.00 (21.23) vs. 77.31 (12.85)] in NCF and CF group, respectively. FEV_1%, VO_2 Peak and LCI were comparable in NCF and CF group ($p > 0.5$). Respiratory equivalents for oxygen and carbon dioxide at peak exercise showed statistically significant difference between NCFB and CF patients [VE/VO_2: 27.60 (1.51) vs. 33.00 (4.58), $p = 0.001$; and VE/VCO_2: 29.00 (2.11) vs. 33.62 (4.09), $p = 0.002$, respectively] (Table 1).

	NCFB	CF	
	Mean (sd)	Mean (sd)	p
Age	13.05 (4.55)	14.09 (5.16)	0.591
Weight	42.56 (17.03)	44.89 (13.48)	0.702
Height	149.15 (19.27)	151.85 (12.10)	0.673
BMI	18.42 (3.59)	19.08 (3.21)	0.621
LCI	9.72 (2.22)	10.11 (2.83)	0.707
FEV_1%	76.60 (22.38)	81.46 (11.88)	0.509
VO_2Peak%	83.00 (22.39)	77.31 (12.85)	0.485
VE/VO_2	27.60 (1.51)	33.00 (4.58)	0.001*
VE/VCO_2	29.00 (2.11)	33.62 (4.09)	0.002*
Bhalla score	9.67 (4.80)	8.33 (5.25)	0.557

Table 1: *Anthropometric and baseline lung function characteristics of the Patients with CF and non-CF bronchiectasis.*

**Level of significance p < 0.05.*

Over a two year period, FEV_1 was improved among NCFB patients from 76.60% to 84.40%, p = 0.029, while FEV1 remained stable among CF patients (p: 0.424). VE/VO_2 and VE/VCO_2 deteriorated significantly in both the NCFB and CF group (p < 0.05). Finally, LCI remained stable among patients with NCFB and deteriorated significantly among patients with CF (p < 0.001).

		Baseline	Follow up	
		Mean (sd)	Mean (sd)	p
LCI	CF	10.11 (2.83)	12.85 (4.01)	0.0001*
	NCFB	9.72 (2.22)	9.25 (2.18)	0.582
VO_2 peak (L)	CF	1.47 (0.36)	1.66 (0.38)	0.135
	NCFB	1.93 (0.70)	2.05 (0.47)	0.462
VO_2 peak %	CF	77.31 (12.85)	71.38 (18.36)	0.313
	NCFB	83.00 (22.39)	77.80 (14.54)	0.177
VO_2max (L)	CF	34.22 (8.71)	33.55 (7.37)	0.808
	NCFB	39.55 (7.97)	37.12 (5.66)	0.349
VO_2 max%	CF	74.23 (17.08)	73.00 (17.01)	0.830
	NCFB	84.30 (18.92)	80.90 (13.25)	0.552
AT(%VO_2peak)	CF	43.50 (14.29)	40.75 (12.31)	0.552
	NCFB	45.44 (15.71)	40.89 (8.57)	0.434
BR (%)	CF	33.62 (18.76)	21.92 (27.27)	0.108
	NCFB	30.10 (21.89)	29.90 (16.78)	0.979
VE (L/min)	CF	51.24 (12.18)	63.25 (15.12)	0.020*
	NCFB	56.64 (19.49)	71.76 (17.21)	0.045*
VD/VT(peak exercise)	CF	0.07 (0.08)	0.14 (0.04)	0.011*
	NCFB	0.11 (0.03)	0.13 (0.03)	0.032*

VE/VO_2 (peak exercise)	CF	33.00 (4.58)	35.54 (6.19)	0.008*
	NCFB	27.60 (1.51)	31.80 (3.74)	0.002*
VE/VCO_2 (peak exercise)	CF	33.62 (4.09)	35.43 (3.13)	0.012*
	NCFB	29.00 (2.11)	31.80 (3.74)	0.041*
FEV1 (L)	CF	2.32 (0.54)	2.37 (0.57)	0.710
	NCFB	2.49 (0.94)	3.01 (0.76)	0.002
FEV_1 %	CF	81.46 (11.88)	78.77 (16.22)	0.424
	NCFB	76.60 (22.38)	84.40 (15.72)	0.029*
FVC (L)	CF	2.68 (0.67)	3.09 (0.58)	0.009*
	NCFB	3.02 (1.03)	3.68 (0.84)	0.006*
FVC %	CF	86.23 (10.10)	88.15 (12.73)	0.456
	NCFB	54.90 (22.75)	94.00 (14.48)	0.063
Bhalla score	CF	8.20 (5.71)	9.00 (4.62)	0.223
	NCFB	9.00 (4.66)	8.63 (4.37)	0.285

Table 2: *Change of lung function parameters in a 2-year interval.*

**Level of significance $p < 0.05$.*

Discussion

The main finding of this study was that LCI and CPET parameters provide additional information to spirometry and HRCT on the progression of lung disease. This is the first study to examine the course of LCI and CPET parameters in a two-year period both in CF and NCFB patients.

Bronchectasis refers to a pathological, non-reversible dilation of the bronci wall [22,24]. Even though bronchectasis are caused by many factors, the dilation mechanism stays the same. At first, mostly due to an infection or inflammation, airways are blocked. Host immune response to recurrent microorganism intrusions leads to the destruction of the ciliated epithelium and thus, difficulty in clearance of the secretions. Secretions that are not cleared remain in the airways and lead to a vicious cycle of chronic bacterial infection and persistent inflammatory response; that induces the destruction of the bronchi wall and the induction of nonreversible dilations which are called bronchectasis [4,25-28]. At first, peripheral bronchi and secondly large airways are impaired. Monitoring lung disease and especially detecting early damages is therefore crucial in order to escalate treatment and prevent further deterioration [27]. The gold standard method of monitoring lung disease either in CF or NCFB has been HRCT [29,30]. HRCT can detect early damages and its changes can be quantified by using Bhalla [31] or Brody [32] scores.

LCI reflects peripheral airway damage that may lead to air trapping and airway remodeling. It has been shown to be a surrogate marker in monitoring lung disease either in NCFB or CF patients [9,10]. Many studies have shown promising results for LCI either in detecting early lung damages [9,33,34] or in monitoring disease progression [35,36].

Whereas LCI has been proved to be a surrogate marker of disease detection and progression, no data exist in CPET and its parameters as a tool to monitor lung disease progression among patients with bronchiectasis. Cardiopulmonary exercise testing has been used to assess quality of life and disease prognosis both in CF and NCFB patients. Peak oxygen uptake correlates strongly with exercise capacity, prognosis and quality of life. [22,37-40] However, CPET provides some other parameters that may add more clues in the patient's assessment. Increased VE/VO_2 and VE/VCO_2 values during peak exercise reflect hyperventilation due to inadequate gas exchange [41]. Thus, the lower these values in peak exercise are, the more capable the patient's lungs are in exchanging gases.

In the present study patients with CF and NCFB were examined. CF patients were following their treatment whereas NCFB patients were started on regular treatment with hypertonic nebulized saline. Both groups of patients demonstrated similar values concerning demographic characteristics and FEV_1%, LCI and Bhalla score at baseline (Table 1). Peak oxygen uptake (VO_2Peak) did not differ significantly between the two groups. Edwards et al, found that NCFB along with CF patients did not differ in exercise capacity [42]. CF patients presented worse respiratory equivalents for oxygen and carbon dioxide at peak exercise than Non- CF ones both at baseline and in two-year time.

In a two-year period, LCI and some CPET parameters deteriorated significantly among CF patients. LCI was the parameter that deteriorated more significantly, among the tests performed ($p = 0.0001$, Table 2). Exercise testing parameters VE/VO_2, VE/VCO_2, VE and VD/VT also deteriorated significantly. Kraemer., *et al*. reported that LCI can predict lung function deterioration in CF patients and Fuchs., *et al.* along with Liou., *et al*. concluded that it can be sensitive in monitoring lung disease and correlates well with CT findings [13,43,44]. After two years, CF patients demonstrated greater ventilation inhomogeneity and peripheral airway damages without however presenting any difference in their spirometry. The fact that in our study LCI deteriorated more significantly than other parameters examined, indicates that LCI can provide more efficient data in monitoring progressive lung disease in a two-year period. Moreover, the fact that significantly deteriorated VE/VO_2, VE/VCO_2, VE and VD/VT values were found after two years, reveal that the patients' progressive lung disease started affecting their performance during maximal exercise causing increased dead space and elevated ventilation.

Regular inhaled hypertonic saline was opted as treatment among NCFB patients. FEV1 was improved over the two-year period among NCFB patients ($p = 0.029$). This comes in accordance with the findings of Chang., *et al*. who suggested that early intervention and treatment in NCFB patients leads to overall improvement [2]. Apart from that, NCFB patients showed non- significant changes in LCI and Bhalla score values over the two years, while VD/VT, VE/VO_2, VE/VCO_2 deteriorated significantly. Green., *et al*. found that patients with PCD presented ventilation inhomogeneity in comparison to healthy ones [45]. Our findings suggest that despite the treatment, a more inadequate gas exchange over time that can cause hyperventilation still existed in NCFB patients indicating disease progression.

Different parameters in both groups changed significantly over the two-year period, indicating different mechanisms of disease progression. NCFB patients deteriorated more significantly concerning respiratory equivalents VE/VO_2, VE/VCO_2 hinting to a more inadequate gas exchange over time that can cause hyperventilation. And this comes in accordance to current literature that has suggested different mechanisms of disease progression over the two groups of conditions [3].

Conclusion

Our findings suggest that exercise testing and LCI are valuable markers that provide useful information for the overall evaluation and progression of lung disease among patients with CF and NCFB. To our knowledge this is the first study in literature that examines these markers in both groups over a two-year period. However, more studies in larger cohorts need to be conducted in order to come to final conclusions.

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EH, VA and JT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EH, VA, AK and JT contributed substantially to the study design, data analysis and interpretation. PV, MK and VA performed the MBW measurements, while FK and AK performed the CPET measurements. VG performed Bhalla scoring of the HRCT scans. All the authors contributed to the writing of the manuscript. EH and JT reviewed and edited the manuscript. EH and JT are guarantors.

Ethics approval

Aristotle University of Thessaloniki Medical School Ethics Committee (IRB file No. 1/8-11-2012).

Competing interests

None declared.

Conflict of interest statement

All authors would like to confirm that there is nothing to declare.

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