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ORIGINAL ARTICLE

Use of lung clearance index to assess the response to intravenous treatment in cystic fibrosis

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Abstract

Background: Progressive lung disease is the main cause of clinical deterioration and mortality in cystic fibrosis (CF) patients. Being able to assess the effectiveness of interventions is very significant.

Objectives: To assess the response to intravenous (IV) treatment among CF patients, using forced expired volume in 1st second (FEV_1) and Lung Clearance Index (LCI) as outcome measures and to compare the effect of IV treatment on lung function and LCI between CF children being treated on a regular basis, or in case of a pulmonary exacerbation.

Subjects and Methods: Thirty-two CF patients (15 males) with mean age 9.90 (range: 2-23) years, performed spirometry and multiple breath washout (MBW) before and one month after IV antibiotic treatment. Nineteen patients received a course of elective treatment (group A) and 13 received IV antibiotic regimens for an acute exacerbation (group B).

Results: Statistically significant differences after treatment were seen in LCI ($p \leq 0.001$), and Forced Expiratory Flow (FEF) z-scores ($p<0.05$). FEV_1 did not change significantly after drug intervention. Dividing patients into two groups, only LCI showed significant change ($p<0.05$), when treatment was administered on a regular basis. Patients being treated for an acute pulmonary exacerbation showed significant improvement in most of the lung function parameters: LCI ($p=0.0001$), FEV_1% ($p=0.05$), FEV_1 z-score ($p=0.033$) and FEF_{25-75} ($p=0.046$). The mean LCI difference was significantly greater in group B compared to group A ($p=0.001$).

Conclusion: LCI is more sensitive marker than FEV_1 to assess the effect of IV antibiotic treatment among CF children. IV antibiotics are more effective on lung function parameters, when they are administered for an acute exacerbation, than when they are given on a regular basis. Hippokratia 2015, 19 (1): 47-52.

Keywords: cystic fibrosis, lung clearance index, pulmonary exacerbation, intravenous treatment, evaluation of intervention

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Introduction

Chronic lung disease is the most serious clinical expression of Cystic Fibrosis (CF) and the major cause of morbidity and mortality among CF patients[1]. Evaluation of pulmonary function is an essential part of clinical care for detection of the disease response to treatment[2].

Forced expired volume in the 1st second (FEV_1) has traditionally been used to monitor lung function in CF patients and is still recognized as a good predictor of outcome in cases with moderate-to-severe CF lung disease[3,4]. However, FEV_1 measurement has two significant disadvantages. First, spirometry is difficult to be performed by preschoolers and infants, because it requires special cooperation[5,6]. Second, several clinical trials showed that the majority of young children with CF tend to have FEV_1 values within the normal range at early school age[7-9], while 30% of CF patients with normal spirometric parameters have already structural damages on high resolution computed tomography (HRCT)[10-12].

Multiple breath washout method (MBW) is a non-invasive and safe test for assessing ventilation inhomogeneity. Lung clearance index (LCI), a common index of uneven ventilation distribution, has recently been proposed as a sensitive marker for the detection of early pulmonary changes in CF[13-15] and has strongly been associated with structural changes on HRCT[12,16]. Moreover, LCI seems to be a stronger functional predictor of disease progress than FEV_1[14,15]. A significant advantage of LCI measurement is that it can be feasible from early age to adulthood and is independent of age, weight, height and sex, with an exception for infants[17-19]. There are a few studies addressing the role of LCI as an index for the effectiveness of therapeutic interventions in CF patients. In two studies LCI was used to examine the clinical response to intravenous (IV) antibiotic therapy among CF children

during an acute pulmonary exacerbation[20,21].

The aim of this study was to compare the effectiveness of IV treatment on LCI and FEV_1 when it is administered on a regular basis, versus during an acute pulmonary exacerbation.

Material and Method

Subjects

This was a prospective study that recruited CF children followed up at the CF centre of the 3rd pediatric department of Aristotle University of Thessaloniki from October 2011 to October 2012. All children were colonized with pseudomonas aeruginosa and were admitted in order IV antibiotics to be administered for two weeks, either because of an exacerbation, or on regular basis. All participants were of Caucasian origin. Height, weight and body mass index (BMI)) were recorded and the Shwachman - Kulczycki (SK) score was calculated to assess the severity of the disease[22]. A total of 34 eligible children with CF were recruited; 32 subjects completed the study (two children were excluded from the analysis, because of poor cooperation during MBW measurement). Nineteen patients received a course of elective treatment (group A), while thirteen received IV antibiotics due to an acute exacerbation (group B). This study was approved by the Ethical Committee of Aristotle University of Thessaloniki.

Table 1. Demographics and clinical data of the 32 cystic fibrosis patients, that were evaluated with spirometry and multiple breath washout before and one month after intravenous antibiotic treatment.

Population characteristics	Mean (range) or N (%)
Number of patients	32 (15 male, 17 female)
Age (years)	9.90 (2 - 23)
Height (cm)	128.88 (83 - 171)
(z-score)	-0.74 (-4.27 - 1.00)
Weight (kg)	30.18 (11.00 - 61.80)
(z-score)	-0.36 (-3.91 - 3.59)
BMI	16.94 (11.56 - 23.09)
(z-score)	-0.08 (-3.35 - 4.25)
Shwachman – Kulczycki score	65.97 (32.00 - 90.00)
ΔF508 homozygous	12 (37.5%)
Pseudomonas aeruginosa colonized	32 (100%)
Pancreatic insufficient	31 (96.8%)

BMI: body mass index.

Study design

All patients received a course of two anti-pseudomonal antibiotics for 14 days. Spirometry and MBW tests were performed on the first day of hospitalization. Height and weight were measured and z-scores were calculated using World Health Organization anthropometric software (WHO anthro plus). The presence of pulmonary exacerbation on admission was defined, according to Fuchs *et al* criteria, modified by Bilton *et al*[23-24]. All patients were reevaluated one month later with spirometry and MBW.

Spirometry was performed according to ATS/ERS standards[25] using an electronic spirometer (Vitalograph 2120, Vitalograph Ltd Ennis, Ireland). Forced Vital Capacity (FVC), FEV_1 and Forced Expiratory Flow 25-75 (FEF_{25-75}) were calculated. The results were expressed as percentage predicted and z-scores, which were calculated, using the Global Lung Function Initiative software (GLI 2012, Global Lung Function Initiative Task Force, available at: http://www.lungfunction.org/). MBW measurements were performed according to ATS/ERS standards[26] using an ultrasonic flow measuring system for measuring flow, volume and molecular mass (EXHALYZER D, Ecomedics, Switzerland).

Statistical analysis

Descriptive statistics were used to describe the study population. Normality was determined using the Kolmogorov-Smirnov test. Differences in lung function parameters before and after antibiotic treatment were analyzed using paired t-tests. P values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS for Windows version 19.0 (SPSS IBM SPSS Statistics 19, USA).

Results

A total of 34 eligible children with CF receiving IV treatment were initially recruited, but two of them were excluded from the analysis, because of poor cooperation during MBW measurements. MBW measurement was performed by 32 subjects and spirometry by 23 (the rest were unable to achieve a satisfactory effort because of their young age), before and one month after IV treatment. The demographic and anthropometric characteristics of the 32 patients that participated in the study are shown in Table 1. The mean (range) age at admission was 9.90 (range: 2-23) years. Baseline spirometry was consistent with moderate impairment, with a mean (range) FEV_1% predicted of 83.43 (30.4-124.0), (Table 2).

Statistically significant differences after treatment were seen in LCI ($p<0.001$) and FEF z-scores ($p<0.05$), while FEV_1 did not change significantly after drug intervention ($p=0.859$). LCI decreased by a mean of 1.77 lung turnovers, a 15% change ($p=0.0001$), improving in 29 of 32 patients. FEF_{25-75} z-score improved by 0.44, a 36% change ($p=0.048$) (Table 2).

Patients were divided into two groups. Group A consisted of 19 patients who had scheduled admission for IV antibiotics and group B consisted of 13 patients that were treated for an acute pulmonary exacerbation. The mean LCI was decreased significantly by 6% ($p=0.018$) among patients of group A (Figure 1). On the contrary, spirometric parameters showed no statistically significant changes in this group (Table 2). Patients of group B showed significant improvement in most of the lung function parameters; mean LCI decreased by 26% ($p=0.0001$) improving in 12 to 13 patients (Figure 1). FEV_1% increased significantly by 10.36% ($p=0.05$) and FEF_{25-75} increased by 28.5% ($p=0.046$), (Table 2). Five out of 12 patients (42%) of group A, and 7 out of 11 patients (64%) of group B showed improvement in both LCI and FEV_1 values. Forty-two percent (42%) of group A and 36% of group B showed improvement only in LCI, but not in FEV_1 (Figure 2). The mean LCI difference was significantly greater in

group B compared to group A (p=0.001).

Discussion

This study demonstrates that LCI is more sensitive index than FEV_1 to assess the effectiveness of IV antibiotic treatment in CF patients. Significant difference has been shown in LCI as a result of a course of IV treatment in the whole group of patients, while FEV_1 did not change significantly. Moreover, this is the first study in which LCI was used as an index to compare the effectiveness of IV treatment between two groups: CF children being treated on a regular basis (group A) and children being treated in case of a pulmonary exacerbation (group B). Current data showed that LCI improved more significantly (p<0.001) after treating an acute exacerbation compared to the improvement after scheduled IV treatment (p<0.05).

Progressive obstructive lung disease is the main cause that results in frequent admissions and shortens life expectancy in most CF patients. FEV_1 has been used as an outcome measure of different interventions and is recognized as a good predictor in subjects with moderate-to-severe CF lung disease[3]. FEV_1 is influenced by many factors including the resistance and mechanical properties of the airways, total lung capacity, the elastic recoil pressure of the lungs, and muscular strength. In early stages of the disease normal FEV_1 values are usually found, while structural damages have already been developed[13,27-28]. FEF_{25-75} reflects the flow in small airways[29] and is more sensitive than FEV_1 for detecting structural damages in small airways[12].

Over the last decade, an increased interest for MBW method has been noted among CF patients. LCI is the most common reported index of ventilation inhomogeneity obtained from the MBW test[20]. There are many studies comparing the sensitivity of LCI versus FEV1 to detect chronic lung disease in early childhood[8,13-14,17,20,27,28,30,31]. LCI has been correlated with the presence and extent of structural lung damages with a sensitivity of 88%[13]. There are a few studies regarding the use of LCI as an outcome measure after therapeutic interventions in CF population. Fuchs *et al*[32] examined if LCI was changed significantly after administrating chest physiotherapy. The effectiveness of hypertonic saline[33-34] and dornase alpha[35] on lung function has been also examined. Davies *et al* assessed the clinical response to ivacaftor with LCI in CF patients aged 6 years or older who had at least one G551D-CFTR allele[36]. There are two studies[20-21] investigating the utility of LCI, as a tool to assess the clinical response to IV antibiotics in CF children for an acute pulmonary exacerbation.

In the present study LCI showed statistically significant improvement after IV treatment (p<0.001). Cystic fibrosis lung disease affects the airways at early stages and eventually progresses to parenchymal destruction. LCI expresses differences in ventilation inhomogeneity among lung units, which may be due to changes in airway resistance or lung compliance. Robinson *et al*, considered as clinical significant an LCI change >5%[21]. Our study showed a mean LCI increase of 15% after administration of IV antibiotics. Spirometric parameters FEV_1, FVC showed no significant improvement, except FEF_{25-75} z-

Table 2. Lung function parameters Pre- and Post-intravenous (IV) antibiotic treatment among the whole group, group A (patients treated on a regular basis) and group B (patients treated due to an acute pulmonary exacerbation).

Lung Function Parameters	Pre IV	Post IV	p	Pre IV	Post IV	p	Pre IV	Post IV	p
	WHOLE GROUP			GROUP A			GROUP B		
LCI	11.57 (3.28)	9.80 (3.02)	0.000¶	10.67 (2.74)	10.02 (2.90)	0.018*	12.87 (3.66)	9.47 (3.28)	0.000¶
FVC (L)	2.14 (0.94)	2.28 (1.04)	NS	2.17 (0.96)	2.29 (1.10)	NS	2.10 (0.95)	2.27 (1.01)	NS
% predicted	86.41 (7.73)	91.11 (1.73)		90.71 (20.60)	92.30 (20.66)	NS	81.72 (13.35)	89.82 (23.79)	NS
z-score	-1.43 (1.62)	-0.99 (1.98)	NS	-1.04 (1.76)	-0.82 (1.76)	NS	-1.86 (1.41)	-1.17 (2.26)	NS
FEV_1 (L)	1.73 (0.75)	1.82 0.79)	NS	1.85 (0.80)	1.86 (0.81)	NS	1.60 (0.70)	1.78 (0.80)	NS
% predicted	83.43 (24.30)	87.94 (26.44)	NS	91.49 (26.59)	90.63 (22.75)	NS	74.64 (18.92)	85.00 (30.83)	0.051*
z-score	-1.82 (1.87)	-1.46 (2.06)	NS	-1.13 (1.96)	-1.17 (1.80)	NS	-2.57 (1.53)	-1.77 (2.37)	0.033*
FEF_{25-75} (L)	2.14 (1.17)	2.40 (1.22)	NS	2.43 (1.26)	2.46 (1.09)	NS	1.82 (1.04)	2.34 (1.40)	0.046*
% predicted	72.89 (36.65)	77.88 (42.81)	NS	85.70 (39.53)	87.02 (36.28)	NS	58.91 (28.70)	67.90 (48.73)	NS
z-score	1.23 (1.93)	1.67 (2.14)	0.048*	1.83 (2.11)	1.95 (2.04)	0.546	0.57 (1.54)	1.35 (2.30)	NS

Data are presented as mean and standard deviation in brackets, Statistical significance: *p<0.05, ¶p<0.01, LCI: Lung Clearance Index, FVC: Forced Vital Capacity, FEV_1:Forced Expiratory Volume in one second, FEF_{25-75}: Forced Expiratory Fow 25-75, NS: non-significant.

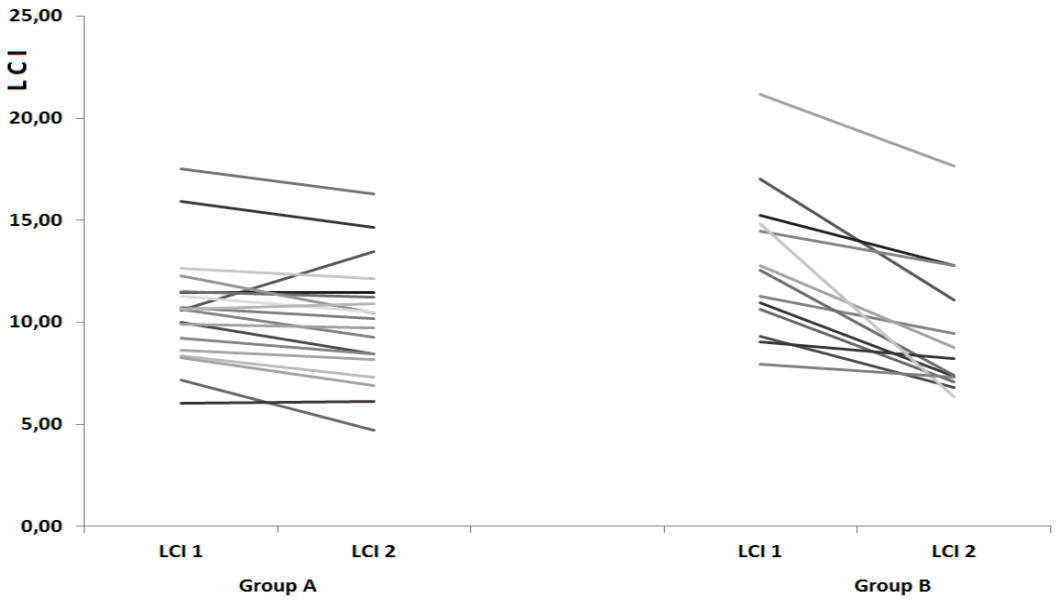

Figure 1. Pre and post IV treatment lung clearance index (LCI) for study's participants divided into two groups; Group A (patients being treated on a regular basis) and Group B (patients being treated for an acute exacerbation).

score that was significantly changed ($p<0.05$). As FEF_{25-75} reflects the small airways resistance, it is an indication of clinical improvement of affected distal airways.

Pseudomonas aeruginosa is the most common isolated pathogen from the sputum cultures in CF patients, associated with recurrent pulmonary infections, leading to irreversible structural damages. CF patients chronically colonized with *Pseudomonas aeruginosa* are usually treated with IV courses of antibiotics in order to maintain their lung function and improve their quality of life[37]. There are two main strategies to treat CF patients with chronic pseudomonas aeruginosa infection; the elective one (administering courses of IV antibiotics on a regular basis) and the symptomatic treatment (treating the acute pulmonary exacerbations). A recent systematic review in Cochrane database[38] explored whether an elective vs.

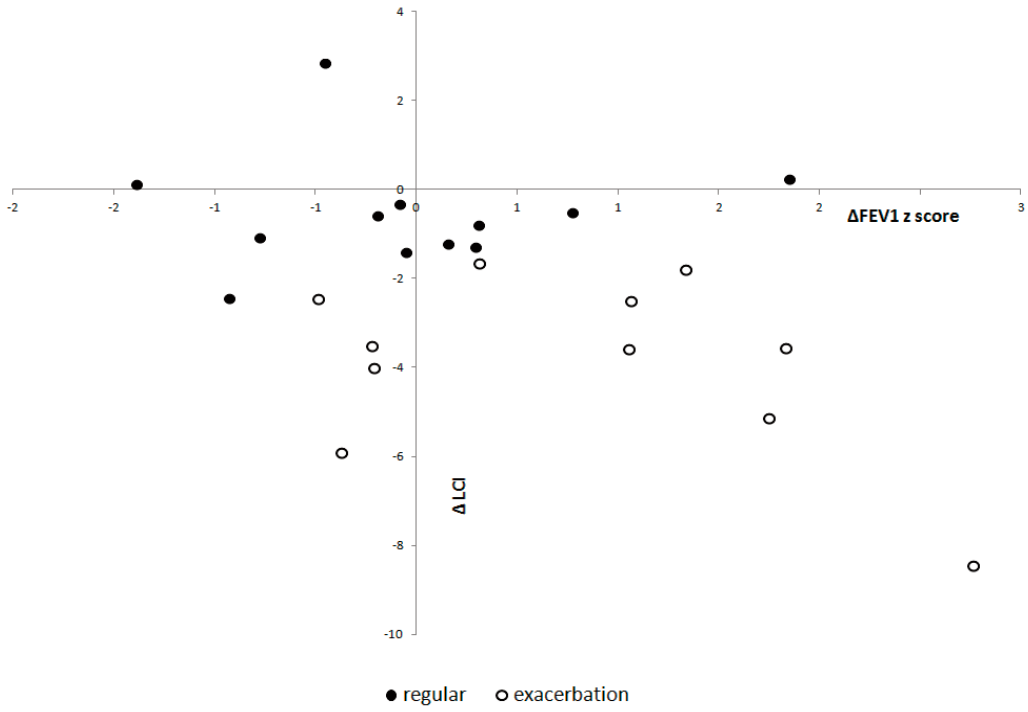

Figure 2. Correlation between the change in lung clearance index (LCI) and the change in forced expired volume in 1st second % predicted (FEV_1%) among patients being treated either on a regular basis (●) or in case of an acute pulmonary exacerbation (○).

symptomatic intravenous antibiotic treatment results in an improvement in clinical status and survival rates. There was only one[39] multicenter study that compared elective vs. symptomatic IV antibiotics using as an outcome measure the improvement in lung function after a 3-year-period. They did not observe significant advantage of regular elective antibiotic treatment over symptomatic treatment, either in relation to clinical improvement, or to survival.

We investigated the impact of IV treatment on lung function among children and adolescents with CF in a short period of time. Group A showed significant improvement only in LCI ($p=0.018$). Among group B patients both spirometric and MBW parameters improved significantly: LCI ($p<0.0001$), FEV_1 % and FEV_1 z-score ($p<0.05$). Sanders *et al*[40] showed that 23% of CF patients didn't manage to recover to baseline FEV_1 after a pulmonary exacerbation. In the current study half the patients showed an improvement in their spirometric parameters one month after treatment and 52% of group B showed an increase in FEV_1, after administration of IV antibiotics for their pulmonary exacerbation. MBW inhomogeneity indices showed more significant difference than spirometric parameters. A percentage of 42% of patients from group A and 64% of patients from group B showed improvement in both LCI and FEV_1. Although LCI was improved in both groups after therapeutic intervention, the mean LCI difference was statistically more significant for group B ($p=0.001$). Although lung volumes have been widely used as an outcome measure in CF[3-4,41], uneven ventilation distribution seems to be a more sensitive predictor of CF lung disease after treatment interventions. Having more significant difference after IV intervention proves MBW indices more sensitive to detect both, pulmonary damage during acute pulmonary exacerbation and response to treatment.

In conclusion, LCI that represents uneven ventilation distribution in CF lungs is more sensitive marker than FEV_1 to assess the effectiveness of IV antibiotic treatment among CF children colonized with *pseudomonas aeruginosa*. A significant treatment effect on most of lung function parameters after IV treatment of an acute pulmonary exacerbation was observed. This finding indicates that administrating IV antibiotic regimens is more effective on FEV_1 and LCI, when it is given in case of an exacerbation in comparison to administration on a regular basis.

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Conflict of interest

None.

References:

1. Ramsey B. Management of pulmonary disease in patients with cystic fibrosis. N Engl J Med. 1996; 335: 179-188.
2. Suri R, Metcalfe C, Lees B, Grieve R, Flather M, Normand C, et al. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. Lancet. 2001; 358: 1316-1321.
3. Aurora P, Wade A, Whitmore P, Whitehead B. A model for predicting life expectancy of children with cystic fibrosis. Eur Respir J. 2000; 16: 1056-1060.
4. Hayllar KM, Williams SG, Wise AE, Pouria S, Lombard M, Hodson ME, et al. A prognostic model for the prediction of survival in cystic fibrosis. Thorax. 1997; 52: 313-317.
5. Eigen H, Bieler H, Grant D, Christoph K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. Am J Respir Crit Care Med. 2001; 163: 619-623.
6. Stocks J, Sly PD, Morris MG, Frey U. Standards for infant respiratory function testing: what(ever) next? Eur Respir J. 2000; 16: 581-584.
7. Aurora P, Bush A, Gustafsson P, Oliver C, Wallis C, Price J, et al. Multiple-breath washout as a marker of lung disease in preschool children with cystic fibrosis. Am J Respir Crit Care Med. 2005; 171: 249-256.
8. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, et al. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. Am J Respir Crit Care Med. 2011; 183: 752-758.
9. Kozlowska WJ, Bush A, Wade A, Aurora P, Carr SB, Castle RA, et al. Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. Am J Respir Crit Care Med. 2008; 178: 42-49.
10. de Jong PA, Lindblad A, Rubin L, Hop WC, de Jongste JC, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax. 2006; 61: 80-85.
11. de Jong PA, Nakano Y, Lequin MH, Mayo JR, Woods R, Pare PD, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. Eur Respir J. 2004; 23: 93-97.
12. Gustafsson PM, De Jong PA, Tiddens HA, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008; 63: 129-134.
13. Ellemunter H, Fuchs SI, Unsinn KM, Freund MC, Waltner-Romen M, Steinkamp G, et al. Sensitivity of Lung Clearance Index and chest computed tomography in early CF lung disease. Respir Med. 2010; 104: 1834-1842.
14. Gustafsson PM, Aurora P, Lindblad A. Evaluation of ventilation maldistribution as an early indicator of lung disease in children with cystic fibrosis. Eur Respir J. 2003; 22: 972-979.
15. Kraemer R, Blum A, Schibler A, Ammann RA, Gallati S. Ventilation inhomogeneities in relation to standard lung function in patients with cystic fibrosis. Am J Respir Crit Care Med. 2005; 171: 371-378.
16. Owens CM, Aurora P, Stanojevic S, Bush A, Wade A, Oliver C, et al. Lung Clearance Index and HRCT are complementary markers of lung abnormalities in young children with CF. Thorax. 2011; 66: 481-488.
17. Aurora P, Kozlowska W, Stocks J. Gas mixing efficiency from birth to adulthood measured by multiple-breath washout. Respir Physiol Neurobiol. 2005; 148: 125-139.
18. Gustafsson P. Inert gas washout in preschool children. Paediatr Respir Rev. 2005; 6: 239-245.
19. Robinson PD, Goldman MD, Gustafsson PM. Inert gas washout: theoretical background and clinical utility in respiratory disease. Respiration. 2009; 78: 339-355.
20. Horsley AR, Gustafsson PM, Macleod KA, Saunders C, Greening AP, Porteous DJ, et al. Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax. 2008; 63: 135-140.
21. Robinson PD, Cooper P, Van Asperen P, Fitzgerald D, Selvadurai H. Using index of ventilation to assess response to treatment for acute pulmonary exacerbation in children with cystic fibrosis. Pediatr Pulmonol. 2009; 44: 733-742.
22. Stollar F, Adde FV, Cunha MT, Leone C, Rodrigues JC. Shwachman-Kulczycki score still useful to monitor cystic fibrosis severity. Clinics (Sao Paulo). 2011; 66: 979-983.

23. Bilton D, Canny G, Conway S, Dumcius S, Hjelte L, Proesmans M, et al. Pulmonary exacerbation: Towards a definition for use in clinical trials. Report from the EuroCareCF Working Group on outcome parameters in clinical trials. J Cyst Fibros. 2011; 10: S79-S81.
24. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med. 1994; 331: 637-642.
25. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007; 175: 1304-1345.
26. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J. 2013; 41: 507-522.
27. de Jong PA, Nakano Y, Hop WC, Long FR, Coxson HO, Paré PD, et al. Changes in airway dimensions on computed tomography scans of children with cystic fibrosis. Am J Respir Crit Care Med. 2005; 172: 218-224.
28. Lum S, Gustafsson P, Ljungberg H, Hülskamp G, Bush A, Carr SB, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax. 2007; 62: 341-347.
29. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005; 26: 319-338.
30. Aurora P, Gustafsson P, Bush A, Lindblad A, Oliver C, Wallis CE, et al. Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis. Thorax. 2004; 59: 1068-1073.
31. Aurora P, Stanojevic S, Wade A, Oliver C, Kozlowska W, Lum S, et al; London Cystic Fibrosis Collaboration. Lung clearance index at 4 years predicts subsequent lung function in children with cystic fibrosis. Am J Respir Crit Care Med. 2011; 183: 752-758.
32. Fuchs SI, Toussaint S, Edlhaimb B, Ballmann M, Gappa M. Short-term effect of physiotherapy on variability of the lung clearance index in children with cystic fibrosis. Pediatr Pulmonol. 2010; 45: 301-306.
33. Amin R, Subbarao P, Jabar A, Balkovec S, Jensen R, Kerrigan S, et al. Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function. Thorax. 2010; 65: 379-383.
34. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, Davis S, et al. Lung Clearance Index as an Outcome Measure for Clinical Trials in Young Children with Cystic Fibrosis. A Pilot Study Using Inhaled Hypertonic Saline. Am J Respir Crit Care Med.2013; 188: 456-460.
35. Amin R, Subbarao P, Lou W, Jabar A, Balkovec S, Jensen R, et al. The effect of dornase alfa on ventilation inhomogeneity in patients with cystic fibrosis. Eur Respir J. 2011; 37: 806-812.
36. Davies J, Sheridan H, Bell N, Cunningham S, Davis SD, Elborn JS, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013; 1: 630-638.
37. Davidson AGF, Chilvers MA, Lillquist YP. Effects of a Pseudomonas aeruginosa eradication policy in a cystic fibrosis clinic. Curr Opin Pulm Med. 2012; 18: 615-621.
38. Breen L, Aswani N. Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis. Cochrane Database Syst Rev. 2012; 7: CD002767.
39. Elborn JS, Prescott RJ, Stack BHR, Goodchild MC, Bates J, Pantin C, et al. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonasinfection of the lungs. Thorax. 2000; 55: 355-358.
40. Sanders DB, Bittner RCL, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. Failure to Recover to Baseline Pulmonary Function after Cystic Fibrosis Pulmonary Exacerbation.Am J Respir Crit Care Med. 2010; 182: 627-632.
41. Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax. 2001; 56: 746-750.