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Tracking Lung Clearance Index and chest CT in mild cystic fibrosis lung disease over a period of three years

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Summary
Introduction: Lung disease remains the main cause of morbidity and mortality in patients with Cystic Fibrosis (CF). To detect lung disease before clinical symptoms become apparent, sensitive tools are essential. Spirometry is used for monitoring, but the FEV_1 remains frequently normal throughout childhood. The Lung Clearance Index (LCI) calculated from Multiple Breath Washout (MBW) was introduced at the CF centre Innsbruck in 2007 for assessing ventilation inhomogeneity in patients with mild lung disease.

We hypothesized that LCIs in 2007 are of prognostic value for the presence or absence of structural lung changes in later years.
Methods: Between 2007 and 2010 MBW, spirometry and ultra-low-dose HR-CT were prospectively tracked in 36 patients (6–53 years) with a mean FEV_1 $\geq$80% predicted in 2007.
Results: At study start the majority of patients had abnormal CT scores and LCI results. While CT and spirometry remained largely stable throughout the study, LCI results slightly improved but still correlated with CT scores in 2010. LCI results in 2007 correlated with CT scores in 2010 while FEV_1 did not. In 86% the LCI value in 2007 was indicative for the presence or absence of structural lung changes in 2010.

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Conclusion: The LCI is a sensitive tool for detecting and tracking pulmonary changes. Extended structural changes are unlikely if the LCI is normal. The LCI has the potential to be used for monitoring the progression of early CF lung disease and assessing the effect of treatment in both clinical care and research settings.

Introduction

Following considerably intensified treatment strategies over the last decades, life expectancy and quality of life have been greatly improved for patients with Cystic Fibrosis (CF). However, lung disease remains the main cause of morbidity and mortality [1,2]. Detecting early signs of CF lung disease and, where appropriate, earlier onset of treatment may further improve prognosis and outcome [3].

Thus, sensitive methods for monitoring early lung disease in CF are required for both, clinical and research purposes, e.g. the development and evaluation of new treatment strategies that are appropriate to halt progression before irreversible lung damage has occurred [4,5].

Development of bronchiectasis is the most important component of CF lung disease. Thus, computed chest tomography (CT) is the reference method for detecting early and advanced bronchiectasis [6]. CT of the lungs has received increasing attention in recent years particularly for assessing early stages of CF lung disease that are not detectable by conventional spirometry [7–9]. However, there remains concern regarding repeated radiation exposure from routine CT, particularly with respect to the increasing life expectancy of patients with CF [10,11]. Therefore in most countries repeated routine CT is not commonly performed for monitoring. While international efforts for developing a standardized low-dose protocol are still ongoing, in Innsbruck yearly CTs in patients with CF have been performed using an internal ultra-low-dose protocol and a modified Bhalla score for interpretation since 2001.

Conventional lung function tests are routinely performed at least 4 times a year from approximately age 4–5 to assess extent and progression of CF lung disease although the majority of paediatric patients present normal results with a relatively large inter- and intra-individual variability throughout childhood. Most commonly, the forced expiratory volume in one second (FEV_1) is reported for clinical and research purposes. However, there is increasing scientific evidence that FEV_1 has a low sensitivity for detecting early pulmonary disease, since studies demonstrated structural pulmonary changes in patients with normal spirometry [6,8,12]. For early intervention studies, the use of spirometric parameters as outcome parameters would require unrealistically large sample sizes and long study durations because of its low sensitivity and high variability.

Inert gas Multiple Breath Washout (MBW) for assessing ventilation inhomogeneity (VI) is a non-invasive and safe lung function test that has been shown to be sensitive for detecting early pulmonary changes in CF [13–16]. Several indices of ventilation inhomogeneity, such as the Lung Clearance Index (LCI) can be calculated from the washout curves documenting the presence and quantifying the extent of VI. The LCI reflects overall VI within the peripheral and communicating zones of the lungs [17]. In cross-sectional studies the majority of paediatric patients with CF had abnormal LCI results, even in the presence of a normal FEV_1 [13–15,18,19]. In three recent studies the LCI was used as outcome parameter for assessing the effect of inhaled hypertonic saline and Dornase-alpha in young patients with CF [20–22]. Furthermore, LCI had a high sensitivity to detect abnormal imaging results in cross-sectional studies. However this was more obvious in school-age children than in infants [19,23–25]. Implementing longitudinal measurements of LCI into routine lung function testing in CF centres may thus be of clinical and prognostic value and may contribute to reduce radiation exposure, particularly in young patients with CF.

Currently, little is known about the longitudinal course of the LCI and its prognostic value for patients with CF. There is one retrospective [26] and one prospective [3] longitudinal study, tracking spirometry and MBW in paediatric patients beyond infancy. From the prospective data the authors concluded that an abnormal LCI in preschool age predicts any lung function abnormalities in early school age and that a normal LCI in preschool age usually remains normal until school age. To date there are no studies which prospectively track MBW in comparison to CT. At the CF centre in Innsbruck, ultra-low-dose chest CT is performed on a yearly basis in all patients since 2001 and yearly measurement of the LCI was introduced in 2007.

We hypothesized that the LCI would be as sensitive as chest CT in detecting pulmonary changes. In the present study, we prospectively evaluated MBW, spirometry and chest CT over a period of three years in a relatively healthy group of patients with CF who had a normal FEV_1 at study start.

The aim was 1) to investigate the longitudinal course of the LCI in comparison to spirometry and CT and 2) to examine whether LCI results sampled in 2007 are of prognostic value for structural lung abnormalities diagnosed from CT in 2010.

Methods

Study design

This is a prospective, longitudinal observational study in a group of school children, adolescents and few adults with mild CF lung disease. During the study period of three years four test occasions at intervals of approximately one year were aimed pro participant.

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