Sensitive markers to detect progression of lung disease in children with cystic fibrosis

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Shareable abstract (@ERSpublications)
LCI detects progression of lung disease in children with CF. Preschool LCI is a strong predictor of lung disease in older children with CF. However, factors influencing progression remain diverse and are not comparable between different patient cohorts. https://bit.ly/2MCeJTW

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Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene with consecutive functional impairment of the CFTR anion channel in various epithelia, leading to reduced chloride secretion and increased viscosity of epithelial secretions with impaired mucociliary clearance in the airways [1]. This inherited basic defect is already present before birth, leading to organ manifestations such as exocrine pancreatic insufficiency in ∼85% or meconium ileus in ∼10% at birth [2, 3]. In contrast to these gastrointestinal manifestations, the lungs are structurally normal at birth [4]. Today, the majority of patients die in young adulthood due to chronic CF lung disease, which starts in the first months of life. Early onset of CF lung disease was demonstrated by bronchoalveolar lavage and chest computed tomography studies showing neutrophilic inflammation and structural changes in infants diagnosed following newborn screening (NBS) at the age of ∼4 months [5]. However, less invasive end-points are desirable for studies on the natural history of early disease progression, and as clinical study end-points and diagnostic tools. A better understanding of the onset and early progression of CF lung disease is essential, as it has recently been shown that early inflammation determines the extent of bronchiectasis at the age of 5 years [6]. Improved understanding and close follow-up of early CF lung disease could contribute to the development of new therapies to prevent and/or delay irreversible lung damage [7].

Investigation of infants and preschool children with noninvasive end-points is challenging, *i.e.* the traditional measurement of forced expiratory volume in 1 s necessitates forced breathing manoeuvres, limiting its feasibility in this age group with naturally reduced cooperation. This limitation is overcome by multiple-breath washout (MBW) as a lung function technique that determines homogeneity of lung ventilation. Narrowing of the airways due to (inflammatory) thickening of the bronchial walls and/or intraluminal mucus plugging leads to an inhomogeneous ventilation. The lung clearance index (LCI) as measure of ventilation homogeneity indicates the number of lung turnovers necessary to clear a tracer gas from the lungs [8–11]. Since the measurement is performed in tidal breathing, it requires very little cooperation and can be carried out from infancy onwards, allowing a continuous evaluation of lung function from birth [9, 12–18]. In addition to feasibility of MBW in preschool children, LCI was shown to be more sensitive than spirometry to detect early lung disease, but also responses to therapy in adults with more advanced CF lung disease [9, 12–16, 19].

In this context, two studies in this issue of the *European Respiratory Journal* investigated the ability of the LCI to track early CF lung disease and aimed to identify factors that influence the trajectories of the LCI [20, 21]. In the first study, Stanojevic *et al.* [20] followed their previously investigated preschool cohort of children with CF and healthy controls for another 24 months during early school age years. While LCI worsened during the 12-month observation period in preschool children with CF, it remained rather stable during the age of 5 to 10 years [20]. In the second study, Frauchiger *et al.* [21] included children with CF

of a comparable age, but they also investigated adolescents up to 18 years of age. In this study, the LCI was stable during preschool years and started to rise in the early school age years with the biggest increase in adolescence [21]. The authors argue that these differences may be due to inherent differences of their cohorts (diagnosis following NBS *versus* symptoms) or MBW settings (research *versus* clinical). However, two other factors may have contributed even more to these differences. 1) Clinicians were blinded to MBW results in the study by Stanojevic *et al.* [20] but not in the study by Frauchiger *et al.* [21], which could have led to an intensified treatment if LCI increases in children from the latter cohort. 2) CFTR modulators became available during the observation period in North America with up to 30% of study participants on modulator therapy at the end of the observation period. Therefore, the different trajectories of LCI in these cohorts may already reflect long-term efficacy of modulator therapy.

Stanojevic *et al.* [20] identified preschool LCI and deterioration of preschool LCI as main influencing factors of the first school-age LCI. This underlines the importance of the preschool years when lung disease seems to be modifiable and effective therapies initiated at that time-point could have a long lasting impact on CF lung disease [18, 22]. However, they could not determine any factor that modified an individual patient's school age trajectory [20]. An acute increase in LCI (but not a change in LCI slope) could be observed at times when a respiratory pathogen was detected or antibiotic therapy was given [20]. Again, the picture was different in the study of Frauchiger *et al.* [21], who identified presence of pulmonary exacerbations, CF-related diabetes or allergic bronchopulmonary aspergillosis, and colonisation with *Pseudomonas aeruginosa* or *Aspergillus fumigatus* during the study as risk factors for a steeper deterioration in LCI [21]. Interestingly, a new acquisition of one of these pathogens was associated with a steeper increase in the LCI slope compared to the time before colonisation, but not with an acute change in LCI [21]. But even in the absence of these identified risk factors, LCI increased over the time of the observation period as demonstrated by the analysis after adjustment for these factors, highlighting the progressive natural course of disease [21].

Both of these studies were performed at sites highly experienced in MBW and underline that this technique can be integrated in the assessment of children with CF [20, 21]. The number of visits performed in two representative cohorts of children with CF over long time-periods is impressive. These studies add to our understanding of the natural course of early lung disease in CF while the differences in the results of the two studies highlight that this course may be influenced by a number of risk factors, but also by early therapeutic interventions [20, 21]. The early years of patients with CF are a window of opportunity to set the course for CF lung disease. To elucidate the reasons for the differences in LCI slopes in the different age groups between the studies, it may be helpful to combine the lung function test with an independent, sensitive outcome measurement like lung imaging in future studies on the course of early CF lung disease [23].

Conflict of Interest: M. Stahl has nothing to disclose.

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