Elucidating progression of early cystic fibrosis lung disease

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Widespread implementation of newborn screening has allowed early diagnosis and disease detection in infants with cystic fibrosis (CF). Early surveillance has shown that pulmonary infection and inflammation occur early in life, and are associated with the development of structural disease as well as lung function decline in childhood [1, 2]. With the advent of disease-modifying therapies for CF, and evidence of their efficacy in adults and adolescents [3], there is a need for sensitive outcome measures to monitor efficacy and safety of these therapies in infancy.

In this issue of the *European Respiratory Journal*, DAVIES *et al.* [4] from the London Cystic Fibrosis Collaboration (LCFC) extend their follow-up of a newborn-screened CF cohort and contemporaneous controls to 2 years of age. This prospective, longitudinal, observational study presents infant lung function outcomes from 62 infants with CF diagnosed following newborn screening and 34 healthy controls at the 2 year follow up visit. This study follows previous publications from this group that reported infant lung function outcomes in the same cohort at 3 months and 1 year of age [5, 6]. The authors report that at 2 years of age, group means for lung clearance index (LCI) and plethysmographic functional residual capacity z-scores were significantly higher in children with CF compared with healthy controls, while forced expiratory volume in 0.5 s ($FEV_{0.5}$) z-scores were not different between groups. In addition, no child had an abnormal LCI or $FEV_{0.5}$ on all test occasions, which the authors report to preclude the ability to identify "high-risk" children using these techniques.

Of the tests included in this study, LCI appears to be the most sensitive marker of early lung disease. In children with CF, LCI values were 0.81 z-scores higher compared with healthy controls at 2 years, and group means for LCI were also significantly higher than controls at both 3 months and 1 year of age. However, in this cohort, abnormal LCI values at 3 months or 1 year were not associated with abnormal LCI values at 2 years. Data from both the LCFC and Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST CF) cohorts suggest that LCI in the first 2 years of life does not correlate well with structural damage on chest CT [7, 8]. Overall, structural changes in this age group were mild. LCI abnormalities detected at a given test occasion in infancy may reflect ventilation inhomogeneity based on mucus plugging and/or airway inflammatory changes that may be transient and resolve with treatment. Indeed, treatment of pulmonary exacerbations with antibiotic therapy in older children with CF resulted in significant improvements in both LCI and mucus plugging scores on chest magnetic

resonance imaging (MRI) [9], suggesting that LCI is an important measure of reversible disease manifestations in early life.

The results of the study by DAVIES et al. [4] are encouraging for families and clinicians for children with CF. Overall impairments in lung function during infancy appear to be relatively mild and transient. In a previous publication, the authors showed that structural abnormalities on chest CT at 1 year of age were also mild [8]. However, treatment of these infants was adjusted throughout the first 2 years of life and the treating clinician was not necessarily blinded to the lung function results, so it remains unclear whether the results are confounded by the introduction of therapies that led to recovery of lung function in individual patients. This is also reflected by the fact that only nine (15%) out of 61 patients with CF had abnormal LCI at age 2 years. This is in sharp contrast to a previous publication from this group, whereby LCI values were abnormal in 35 (73%) out of 48 patients with CF at age 4 years [10]. Whether this is due to diagnosis by newborn screening, earlier and more intensive monitoring (e.g. lung function) or rapid disease progression during the preschool years is not yet known.

These data raise questions as to whether infant lung function tests are relatively insensitive to detect abnormalities in early CF lung disease or are whether these children are actually healthy in terms of lung physiology. Many studies have now shown that lower respiratory tract infection and inflammatory events can occur in the first months of life in infants with CF [11–14]. Presumably, these events can result in airway mucus obstruction, gas trapping, airway narrowing and/or airway remodelling, all of which could cause reversible or irreversible changes in lung physiology and lung structure. Chest computed tomography data in the AREST CF cohort has shown that structural lung abnormalities persist and progress over 1 year in the majority of young children with CF [15]. However, this study included children up to 6 years of age, and therefore we still don't know exactly how structural disease progresses in the first 2 years of life and how this influences lung physiology. Future studies that longitudinally track infant lung function with matched functional and structural MRI will likely provide important insights into early changes in ventilation and perfusion in CF lung disease.

Does this mean that we do not have to be concerned about progressive lung function decline in this age group? While no child had abnormal lung function on each parameter at every study visit, there were only 31% of infants with CF who had completely normal lung function at every visit. The long-term significance of an abnormal test result at one or two time points is currently unknown. However, longitudinal tracking of LCI in infancy suggests that those who have a lower respiratory tract infection in the first months of life have significantly higher trajectory for LCI over the first 2 years of life than those without a detected pulmonary infection [16]. In addition, longitudinal studies from the LCFC and AREST CF groups have shown that forced expiratory volumes measured in infancy track to school age in children with CF [1, 17]. Therefore, clinical trials in young children with mild CF lung disease may need to be performed over a period of time long enough to capture disease progression and 2 years may not be sufficient.

There are some limitations to the study by DAVIES et al. [4]. As with many other observational studies involving sedation and complex methodologies, data were only collected annually and, therefore, we do not have information regarding the natural variability or responses to treatment of these lung function indices in infants with CF. In addition, while this study provides highly useful information regarding the progression of lung function during the first 2 years of life, this study was not designed to determine whether infant lung function could be used as an endpoint in clinical trials.

Technically, it is important to note that these measurements were performed using custom-made research equipment and custom software that are only available in specialised research centres. The use of sedation during lung function measurements may over- or underestimate ventilation inhomogeneity due to the loss of muscle tone and dynamic control of breathing, and most importantly, this might be different in health and disease. Recent data from the SCILD (Swiss CF Infant Lung Development) cohort, in which infant lung function measurements are performed without the use of sedation, suggests that the size of LCI differences between infants with CF and healthy controls is more or less similar in natural sleep [18].

In this study, the proportion of children who had Pseudomonas isolated by 2 years of age was high at 52%, increasing steadily from 3% at 3 months and 35% at 1 year. Infection status was determined from cough swabs, which were collected every 2–3 months or whenever symptomatic, and from the BAL at 1 year of age. It is possible that the high prevalence of pseudomonas at 2 years of age was due to prophylactic antistaphylococcal treatment, which started at diagnosis and continued throughout infancy to 2 years of age as part of the standardised treatment protocol. As such, translation of results to children with CF not treated prophylactically with antistaphylococcal antibiotics needs to be done cautiously.

A major advantage of the LCFC cohort over previous infant surveillance studies is the recruitment and longitudinal follow-up of contemporaneous healthy control infants. The lack of recruitment of healthy controls in the AREST CF programme has affected the interpretation for forced expiratory volumes in one study [19]. However, the healthy reference data used to generate the z-scores for LCI, while derived using equivalent equipment and software, were collected across three different international research centres with reported centre differences [20]. The standard deviation for the healthy control infants in this study was 0.6 z-scores, compared with the expected 1 z-score standard deviation. Therefore, interpretation of z-score values for LCI using these equations has some limitations.

Overall, the data presented by DAVIES *et al.* [4] provide important insights into the respiratory health of infants with CF in the era of newborn screening. The findings from the LCFC that newborn-screened infants being followed up regularly have relatively mild and transient lung function deficits in the first 2 years of life are encouraging for families and treating physicians. Additionally, these studies provide important insights into the utility of infant lung function techniques to detect and monitor early and mild lung disease. The long-term implications of these transient lung function deficits in the first 2 years of life are currently unknown, and the longitudinal follow-up of these infants to the preschool and school years is widely anticipated.

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