Monitoring early stage lung disease in cystic fibrosis

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Abstract

Purpose

Early stage lung disease has long been synonymous with infancy and childhood. As diagnosis happens earlier and conventional management improves, we are seeing larger proportions of people with CF in adolescence and even adulthood with well-preserved lung health. The availability of highly effective CFTR modulator drugs for a large proportion of the CF population will impact even further. Transitioning into adult care with 'normal' lung function will become more common.

However, it is crucial that we are not blasé about this phase, which sets the scene for future lung health. It is well-recognised that lung function assessed by spirometry is insensitive to 'early' changes occurring in the distal, small airways. Much of our learning has come from studies in infants and young children, which have allowed assessment and optimisation of alternative forms of monitoring.

Recent findings

Here, as a group of paediatric and adult CF specialists, we review the evidence base for sensitive physiological testing based on multibreath washout, lung imaging, exercise and activity monitoring, assessment of infection and quality of life measures.

Summary

We seek to emphasise the importance of further work in these areas, as outcome measures become widely applicable to a growing CF population.

Keywords Cystic fibrosis, Lung clearance index, Computerised Tomography, Magnetic resonance imaging, Outcome measures

Introduction

The term 'early stage' lung disease in cystic fibrosis (CF) has long been synonymous with 'early life', i.e. infancy and childhood. However, as diagnosis is increasingly made with newborn screening (NBS) and as both conventional and mutation-based therapies advance, this term will become relevant also to increasing numbers of older people with (pw)CF. In our opinion, the use of the term 'mild' is inappropriate and may lead to complacency and under-treatment; many early stage changes are not insubstantial. They are, however, more challenging to detect. Sensitive methods to assess early stage lung disease are required to track clinical progression, guide management and detect efficacy (or harm) in clinical trials. Here, we describe current clinical challenges and highlight some of the paths forward.

Predicted impacts of highly effective CFTR modulators.

The last decade has witnessed a paradigm shift in treatment for CF. Whereas previously, all therapies targeted the *consequences* of CFTR dysfunction (mucus composition and accumulation, infection), CFTR modulators target the *CFTR protein itself*, restoring function as an ion channel (1). Ivacaftor has demonstrated substantial durability (2), with a slowing in loss of lung function, fewer exacerbations, improvements in nutrition and quality of life. Most accept that even complete restoration of CFTR function will not reverse established, structural lung damage. However, commencement at an early-moderate stage may substantially slow the development of lung disease, or even prevent its onset. Indeed, restoration of pancreatic exocrine function, previously considered irreversible, has been now been seen in children starting ivacaftor (3-5). As we write, the European Medicines Agency (EMA) has approved the latest such drug (elexacaftor/ tezacaftor/ ivacaftor; Kaftrio). The acute impacts of this combination, in pwCF possessing either 1 (6) or 2 (7) copies of the F508del mutation (~85% of global population) are substantial, at least as good or exceeding those with ivacaftor. Trials in 6-11 year old children are underway (Clinicaltrials.gov NCT04043806) and are planned for younger age groups. The

widespread uptake of these highly effective modulator therapies (HEMT) will change the face of CF dramatically.

What we have learned from disease monitoring in early life

Most infants and many children with CF are asymptomatic from the chest point of view. Detection of lung disease in this group poses several challenges: the requirement for highly sensitive tests, the child's small size and their inability/ unwillingness to co-operate. Conventional spirometry is not possible early in life. Specialist labs have developed techniques to measure volumes/ flows, although they are largely applied on a research basis. They include the raised volume rapid thoracoabdominal compression technique (RVRTC), plethysmography, and multiple breath washout (MBW, see later). Two key research collaborations have monitored the development of CF lung disease from infancy: the Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF), and the London Cystic Fibrosis Collaboration (LCFC)(8-12). LCFC infants diagnosed by NBS had abnormal $FEV_{0.5}$ at 3 months of age (9), which improved over the first year (10). Aged 2, there was no significant difference between healthy controls and CF (13). This contrasts with a dramatic decline in infant lung function over this period in AREST-CF (8, 11). Possible explanations for this difference remain to be resolved (14).

Both groups have evaluated the role of chest CT in early CF life. Aged 1 year, LCFC NBS infants showed only mild abnormalities on the CF-CT Brody II system (15, 16). This may reflect true minimal lung disease or an insensitive scoring system. The Perth-Rotterdam Annotated Grid Morphometric Analysis for CF (PRAGMA-CF) scoring system was developed to detect the mildest abnormalities on chest CT and be more discriminative than CF-CT (17). AREST-CF reported a 20% prevalence for bronchiectasis and 58% for air trapping at 1 year of age in NBS infants (18), but the mean extent of bronchiectasis was only 0.2% of the lung. Novel methods of quantifying structural lung abnormalities (such as counting airway segments (19)), or automated approaches to quantitative measurement of air

trapping will further help to elucidate the relationship between structure and function outcomes in CF and will be applicable at all ages.

Detection of neutrophilic inflammation is a prognostic marker for lung disease in the early years. AREST-CF reported the association between free neutrophil elastase (NE) activity at 3 months and bronchiectasis from one year of age (20). Repeated detection of free NE is associated with worse CT outcomes (21). They also reported an association between detectable NE in bronchoalveolar lavage (BAL) at 3 months of age and isolation of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and significantly lower lung function during the first 2 years of life (11). In the NBS LCFC cohort, inflammation and current/ prior infection was associated with only mild abnormalities on chest CT and lung function at 1 year of age (22). Ongoing follow up of these cohorts will determine the importance of these outcomes in later childhood and adolescence.

Sensitive physiology testing: MBW and Lung Clearance Index

MBW tests have emerged over the last decade as a highly sensitive method of identifying early changes in obstructive airways diseases, and particularly in CF (23). MBW involves tidal breathing to washout an inert tracer gas, typically either exogenous sulphur hexafluoride (SF_6) or resident nitrogen, the latter washed out by 100% oxygen. The washout starts after a relaxed expiration, with the lung at functional residual capacity (FRC). The simplest and most commonly used derived measure is lung clearance index (LCI) (24), the total breath volume required to wash the inert gas out to $1/40^{th}$ of its starting concentration, expressed as multiples of the FRC. Lung disease in CF is patchy and uneven; more diseased lung regions are less well ventilated and wash tracer gas out more slowly. A high LCI is thus a marker of more significant lung disease.

LCI sensitively detects early CF airway abnormalities from infants to adults (25) even those with normal spirometry (26-31). It can be measured in very young children with high rates of success (32). It is possible in infants, though requires different approaches (27, 33, 34). LCI tracks CF lung disease more

sensitively than spirometry, changing with inflammation and improving with treatment (35-40). Significant pulmonary infection is associated with increased LCI (25, 38, 41-43) and an accelerated rate of progression (43, 44). For disease monitoring, a strength of LCI is that the upper limit of normal remains very stable, including during adolescence (45-47) facilitating assessment of longitudinal change (48). In stable preschool and school age children with CF, LCI has a repeatability of +/- 25% baseline LCI (49-51), worse than in healthy subjects or in adults with CF, but comparable to spirometry (52).

The challenges of measuring lung function in infants described above make LCI well-suited to this population. The AREST-CF cohort showed normal or impaired LCI in the first 6 months of life with deterioration thereafter in children with a history of pulmonary infections (43). The London group reported that NBS infants with increased or normal LCI tracked to one (10), but not to two, years of age.(13, 44). The LCFC have recently reported the association between preschool and adolescent LCI in a clinically diagnosed cohort (10, 53) Longer term follow-up of these cohorts will help inform the predictive value of very early assessments in NBS populations.

There are, as with all physiological measurements, some important challenges in measuring LCI. In infants sedation is usually required (43, 54). In younger children, success is the norm above around 3 years old, but requires a controlled environment and an experienced team (32). Testing takes longer than spirometry, placing limitations on scale up to routine clinical use (55, 56).

In clinical trials recruiting children with well-preserved baseline FEV_1, LCI has allowed demonstration of efficacy; examples include RhDNase, dual-combination CFTR modulator therapies and nebulised hypertonic saline (57-62). Procedures have been standardised across CF trial networks globally for one MBW technique, which is being increasingly adopted into paediatric (63) and adult studies. LCI may also possess sufficient sensitivity to be used in future trials of additional therapies once HEMT is standard of care and incremental improvements are anticipated to be small.

Inversely, LCI is less reliable in more severe disease or pulmonary exacerbations (36, 37). In more advanced disease, duration of tests can also be unacceptably long. There are also important

differences between measurement systems and tracer gases; results are not comparable between different technologies (56, 64, 65).

Exercise testing/ activity monitoring

Maximal exercise capacity (VO_2 max) is associated with CF mortality (66-68). Current evidence supports a role in CF in providing prognostic information (death or transplant); its role in early stage CF lung disease is less well established. Furthermore, although recommended as part of standard care from 10 years of age (69, 70), it is not performed in all CF centres. There are limitations e.g. younger participants may not have sufficient leg length or achieve appropriate cadence. Field exercise tests, (6 minute walk (71) and shuttle (72)), may be sub-maximal in health and in mild CF lung disease: the 15-level Modified Shuttle Test (MST) is sub-maximal in 30% of healthy individuals and 6% of adults with CF (73). Further modifications have been developed to address this (73).

Activity monitoring quantifies physical activity undertaken in daily life with questionnaires or, objectively, with wearable sensors. Self-reported physical activity is associated with rate of decline in FEV_1 in CF: those reporting an increase in habitual physical activity over a nine year period had slower lung function loss (74). Similar levels of physical activity have been reported between children/adults with CF and healthy controls, except at very low lung function when those with CF may be less active (75). However, there may be differences in the intensity of activity being undertaken, with school aged children with CF spending less time undertaking strenuous or vigorous activities than controls (75, 76). Other groups have detected a CF-health difference in activity even in mild disease (77).

Advances in Lung imaging

One of the most powerful emerging technologies to measure and track early CF lung disease is magnetic resonance imaging (MRI). Conventional MRI detects protons in lung tissue reading out structure similarly to HRCT. Advanced MR techniques provide high resolution images rivalling CT (78),

and imaging is possible to sixth generation bronchi (79). Neither CT nor MRI can image smaller airways, early disease more distally being identified instead by mucus plugging and gas trapping. The main advantage of structural MRI over CT is radiation-free imaging (80, 81). Multi-centre trials have demonstrated the feasibility of repeated scans (25, 61), and standardised scoring systems are available (82). Numerous additional MR imaging techniques also exist to enhance the data available from proton imaging, or to make use of injectable contrast agents (83). The unique power of MRI however lies in the ability to introduce inhaled contrast (83), such as hyperpolarised helium (He^3) or xenon (Xe^{129}). These provide detailed 3-dimensional representations of breath distribution and can pick out regions affected by airway blockage below the resolution of structural imaging by CT or MRI. He^3-MRI has been shown to be the most sensitive measure of airway obstruction, being abnormal in those with well-preserved spirometry and normal LCI (80). It has also shown disease progression over time despite stable spirometry and stable LCI (31). The detection of ventilation defects however does not tell us specifically what the cause is. For those with normal spirometry, the appearances are typically of multiple small ventilation defects which disappear on deep-breath imaging (84). This suggests small airway obstruction, for instance caused by mucus, which may be amenable to intervention. In those with abnormal FEV_1 however, ≥10% of lung volume is obstructed during tidal breathing, and less reversibility is seen on deep inhalation (84), suggesting a fixed obstruction. Ivacaftor resulted in very marked improvement in ventilation imaging in adults with the G551D mutation (85).

He^3 provides the highest quality ventilation-MR images, but its expense has led to increasing use of Xe^{129}, more widely available and cheaper but possessing a poorer signal-to-noise ratio and potential for short-lived systemic absorption (86). Xenon appears to provide similar information to Helium imaging, is repeatable and able to detect changes over time and in response to intervention (87, 88). It is likely that its practical advantages will lead to Xe being the standard for future long-term studies and clinical trials involving ventilation-MRI.

Hyperpolarised gas-free techniques have developed in parallel and provide both functional and structural information. Oxygen-enhanced MRI is a potentially attractive example, providing a

composite measure of alveolar ventilation, diffusion and perfusion. One study has reported its correlation with spirometry and CT scores in pwCF (89) and a larger studies are ongoing. MRI remains more technically complex and expensive than lung function measurements like LCI, requires sedation for young children, and has only been proposed as a routine annual assessment in highly specialist centres (90). In the short term it is likely to remain restricted to specialist use but could help considerably in the assessment of interventions early in disease progression.

Challenges with infection surveillance

Real-time awareness of an individual's lower airway infection status allows prompt intervention which may improve long-term outcomes. This is relatively easy in patients with moderate-severe lung disease, most of whom chronically producing sputum. Although sputum culture 'misses' many organisms detectable on molecular analysis (91), the clinical importance of these remains unclear. Most children and an increasing number of adult pwCF do not produce sputum and this will become more common once highly effective CFTR modulators are widely available. Surveillance in this instance relies routinely on less sensitive/ specific 'cough' or throat swabs (92). Induction of sputum with hypertonic saline nebulisation is useful but time-consuming and therefore not frequently repeatable (93). Bronchoalveolar lavage, the 'gold-standard' is invasive, requires general anaesthesia and is largely used when other measures to obtain secretions in a child causing clinical concern have failed. This is an area of unmet clinical need requiring new techniques, likely advanced technology based, to be resolved.

Assessing Quality of Life and psychological health

The CFQ-R is a disease-specific quality of life(QoL) questionnaire, with domains including respiratory symptoms, treatment burden and physical functioning (94); higher scores (better QoL) are associated with less severe lung disease assessed according to FEV_1 (94). Different versions are available: 14yrs+ (CFQ Teen/adult), 6-13 years, and parent. A modified version for parents of children <6 years was

utilised in the Infant Study of Inhaled Saline clinical trial (95, 96). Perrem et al have recently demonstrated the discriminant validity of the parental CFQ-R Respiratory Symptoms domain score which deteriorates with acute respiratory events in preschool children and improves with treatment (97). The CFQ-R respiratory domain has been used as an outcome in clinical trials including those involving mild lung disease. A clinical trial of ivacaftor in those with preserved spirometry (>90% predicted FEV_1) met its primary endpoint of significant improvement in LCI but did not detect a significant difference in the change in the CFQ-R respiratory domain score between treatment and placebo groups (98). It is likely that this tool is insufficiently sensitive in early stage disease and alternatives are required.

Looking to the future

The population with CF is growing as survival improves. Modern care, including early diagnosis with NBS has incrementally improved lung health and the widespread use of highly effective modulator drugs will impact this hugely. Never has there been a more pressing need for tools to monitor disease in patients at the earlier stages of CF severity. Drugs will continue to be needed, but the testing of these will become more complex if being applied on top of HEMT (99). Measures such as those discussed above will be needed as trial outcomes and require standardisation and a robust evidence base.

In the second quarter of 2020, the CF clinical community, our patients and their families adapted rapidly to the acute health threat of the global covid-19 pandemic. Home monitoring, to date an area of pilot research and feasibility studies, became a necessity, with video-consultations, hand-held spirometers and weighing scale provision becoming widespread. The impact of these essential measures on data quality, longer term outcomes and emotional well-being requires assessment, but it seems likely that we will use the experience gained to establish new ways of working once the heat of the pandemic has cooled. Personalised care, particularly as population health improves with HEMT, is likely to involve fewer in-person clinic visits and a reduced need for hospitalisation. We urgently

need to establish a robust infrastructure with appropriately trained teams, suitable IT capacity and information governance structures to deliver this. Advances in technology including wearables, adherence aids and point-of-care and breath-based infection diagnostics are encouraging. Implementation of any of these needs to decrease rather than add to the burden of care for pwCF (100, 101) and mandates assessment in partnership with the patient community.

Conclusions

The health of people with CF has been improving over recent decades. The introduction of highly effective CFTR modulator drugs will have further beneficial impact. Whilst this is hugely encouraging, it does present some challenges with regard to tracking lung disease. The absence of a measurable defect in spirometry does not indicate the absence of inflammation, infection and remodelling. Paediatric respiratory medicine has grappled with the requirement for more sensitive measuring tools for many years , providing much experience upon which we can build. An evidence base is building for lung clearance index and progress is also being made with imaging modalities; those free of radiation, whilst some way behind CT, may enable frequent assessment. Further work is needed in these, and other areas. In order that these assessments in themselves do not add to the burden of management already experienced by people with CF, we advocate a partnership approach with patient representative organisations and lay experts.

Key points

- Early stage lung disease is increasingly present in adolescents and adults with CF and will become more common with the advent of highly effective modulator therapy for a majority of patients

- Conventional spirometry is unhelpful in monitoring this stage of disease, mandating the use of more sensitive tools

- Experience built in paediatric centres with sensitive physiology testing and imaging is providing a useful foundation for optimisation of newer approaches to lung disease monitoring

Acknowledgement

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