Structure Function Correlates - CT or lung function tests, or both

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RUNNING TITLE: CT or PFTs, or both?

KEY-WORDS: Cystic Fibrosis, High-Resolution CT, Inert gas washout, Pulmonary function, Spirometry, Ventilation inhomogeneity.
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Early diagnosis and regular follow-up of the course of the disease, and the effects of interventions using sensitive and reliable objective measures, are necessary in progressive paediatric lung diseases for which effective therapies are available. Cystic fibrosis (CF) lung disease is an important example of such a disease and will therefore be discussed in this paper.

Despite the lack of a permanent cure for CF lung disease, quality of life and life expectancy have improved markedly over the last decades (1), but progressive lung disease remains the major cause of morbidity and premature death. Evidence strongly supports the view that CF lung disease begins in early life in most cases. While the lung structure of a newborn child with CF is normal (2), lower respiratory tract infection and inflammation are frequently seen in the first year of life, even before clinical manifestations of lung disease appear (3, 4).

Reduced mucociliary clearance, infection and an exaggerated inflammatory response cause bronchiolar and bronchial obstruction by epithelial destruction, mucus plugging and airway wall thickening. Untreated, these events result in a self-perpetuating progressive disease of recurrent or chronic endobronchial infections, persistent inflammation and destruction of the airways (bronchiectasis), and later in the course, destruction also of the lung parenchyma (5).

Today, such structural changes can be identified at an early stage using high-quality CT images of the chest in infants and in children with CF with minimal clinical signs or symptoms of lung involvement (6, 7, 8). These structural abnormalities will eventually be reflected in abnormal lung function findings. Depending on the sensitivity of the methods used and the monitoring intervals, the lag time between the occurrence of structural aberrations and their diagnosis will vary significantly. Ideally, close monitoring of infection, inflammation, lung structure and function with sensitive and patient friendly methods should be included in all CF follow-up programmes, in order to effectively prevent or delay structural damage. Ten or 20 years ago, therapeutic options for CF were limited and CF lung disease was thought to have a rather similar progressive course in most subjects, so there was little need for sophisticated monitoring methods that could allow for individualization of treatment efforts. Today the situation is completely different with rapid development of new modes of treatment including new inhaled antibiotics, anti-inflammatory agents, substances targeting the CFTR itself or the chloride channel, and even gene therapy.

It is obvious today that disease severity and the course of CF lung disease vary greatly among patients, with some young patients relatively free of lung involvement, while others suffer from chronic lung infection and severe bronchiectasis, and may require advanced interventions. It is also appreciated that CF lung disease is heterogeneously distributed among lung regions (9). It has been known for some time that the disease process generally starts in the peripheral airways (10, 11), and that the peripheral airways are important determinants of overall airway function even in advanced disease (12). These developments and insights have led to a demand for more sensitive methods than plain chest radiographs and spirometry for assessing lung structure and airway function in CF, which can be applied in all age groups.

Chest radiographs are conventionally used to monitor CF lung disease in addition to spirometry. They are inexpensive, easy to perform even in unsedated young children, and involve little radiation, but they are relatively insensitive to structural changes in CF compared to chest CT (13, 14), especially bronchiectasis, for which CT is a gold standard (15). Spirometry (forced expiratory volume in one second; FEV₁) is still the most commonly used method for monitoring of CF lung disease in the clinic and is thought to be a good predictor of outcome in patients with moderate to severe CF lung disease (16).

More
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aggressive treatment and closer monitoring of early CF lung disease over the last two decades have resulted in many school-age children with CF who manifest normal FEV1 (17). Other children show a slow rate of progression of decrement in FEV1 (18, 19), although it is likely that significant progression of lung disease is not always reflected in spirometric measurements. Another limitation of spirometry is that reliable forced expiratory manoeuvres are difficult to obtain in children under the age of 5 years, and testing of infants and pre-school children is mostly restricted to specialist laboratories. More sensitive lung function testing methods that can be applied easily in all age groups have therefore been sought after.

Today the task is to develop treatment strategies aimed at stopping progression of pulmonary disease before irreversible changes occur. Chest CT scans will be an integral part of such approaches, both in clinical research studies and in routine follow-ups. Scans can be performed as thin (1 mm) axial slices taken every 10 mm (high resolution CT; HR CT scans) or full volume (helical) scans. The chest scanning is generally performed at full inspiration. In addition, expiratory scans may be taken near residual volume (RV). In infant studies, scans are commonly taken at maximal inspiration, and expiratory scans may be taken at functional residual capacity (FRC) (7). To give information that is useful in research studies or for standardized follow-ups, CT images must be interpreted and reported in a meaningful way. Bhalla and co-workers introduced a scoring system for HRCT images in 1991 (20), and several other scoring systems based on this have been developed subsequently. They generally take into account airway pathology (airway wall thickening, bronchiectasis, mucus plugging, nodules) and parenchymal pathology (air trapping, consolidation, bullae, and septal thickening). The distribution and extent of the changes in different lung lobes or segments are scored, and a total score is given. De Jong and co-workers compared five different scoring systems in CF patients and concluded that all were reproducible, robust, correlated well, and showed significant correlations with FEV1 in a cross-sectional study (21). However, they expressed doubt that these systems would be adopted in routine clinical work because they may require 15 minutes of the radiologist’s time to score. On the other hand, less qualified staff might be trained to score images accurately with good reproducibility. There is also concern that these scoring systems may have insufficient resolution and reproducibility in patients with only minor pathology. Nevertheless, scored CT images in CF are not only more sensitive than spirometry to diagnose pathology in subjects with mild CF lung disease (22) but they also detect progression of lung disease more sensitively (23). HRCT scores have been shown to correlate with clinical status in CF subjects (24), and to improve after treatment of an exacerbation (25, 26). A study of CF children younger that 5 years demonstrated superiority of HRCT to chest radiographs in showing improvement after 100 days of treatment with inhaled recombinant human DNase (27).

Advantages of CT in CF monitoring compared to standard lung function tests include superior sensitivity, and anatomical localization of pathological processes. This reflects the heterogeneity of distribution of disease and gives the opportunity to guide physiotherapy or surgical interventions. In contrast, conventional lung function tests do not account for the non-uniformity of disease distribution, yielding only a global value. Resolution of CT images is still limited, however, and pathological changes in airways with a diameter less than 1 or 2 mm can rarely be identified with scanners currently in clinical use. Peripheral airway obstruction is therefore diagnosed indirectly as air trapping, *i.e.* regions with low attenuation on expiratory images taken near RV, or in infants at passive FRC (7). High quality CT scans can be performed even in infants, either during general anaesthesia or under sedation with chloral hydrate, allowing for control of the lung volume at which images are taken (6, 7).
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The future direction of chest CT scanning is towards automated quantitative analyses of images based on full-lung scans. This will not only speed up interpretation and reporting, but may also allow for direct comparisons over time of processes in different specific airways. Quantitative measurements can already be done of airway wall thickness and luminal area, even in infants (7, 28).

Radiation dosage is an increasing concern with increasing life expectancy in CF and the greater vulnerability of young children to radiation (29). Efforts to reduce radiation dosage from the scanners include protocols with a minimal number of slices, optimized intervals between scans, and limited use in infants and young children. Some of these efforts are in conflict with the ambition to monitor lung disease closely. It is now reasonable to achieve CT protocols that cause a radiation dose equivalent to only about 10 standard chest radiograph studies. Modern multi-detector scanners may provide protocols that yield better resolution with no greater radiation than currently.

Because CF lung disease is thought to start in the peripheral airways, is non-uniformly distributed, and may involve only a limited region of the lung initially, tests of overall airway function such as spirometry are not expected to be sensitive in mild CF lung disease. Even maximal expiratory flows at 50 or 25 of the vital capacity (MEF\textsubscript{50}; MEF\textsubscript{25}) have limited usefulness as they are heavily dependent on collaboration and maximal efforts, and show marked variability. Despite the relative insensitivity of spirometry, impaired airway function has been shown even in asymptomatic infants with CF in specialized centres using the raised volume rapid thoraco-abdominal compression (RVRTC) method (30, 31). In 3 to 6 year old clinically stable children with CF trained to perform spirometry, abnormal results were found compared to normative data obtained in children of the same age, and impairment correlated significantly with the Brasfield chest radiograph scores (32). These reports show that spirometry can indeed be used to diagnose lung involvement even in apparently non-symptomatic young children, and also probably to monitor disease progression in specialized centres. The RVRTC method is, however, invasive in the sense that the lungs are “pumped” up to a pressure of 20 or 30 cm H\textsubscript{2}O after which the thorax and abdomen are compressed by an inflatable vest. The ratio of the residual volume to the total lung capacity (RV/TLC) has been shown to correlate with amount of air trapping on CT scans (33). The RV/TLC ratio has been measured in infants in a few specialized centres (34) but is used routinely in school age patients and adults. The test requires good collaboration in children may show marked variability and is not very useful at the individual level. Little is known about the feasibility and reproducibility of such methods in non-specialized CF centres. In order to gain a wider acceptance among parents and users, tests are required that are less invasive and less complicated to perform.

The findings reported above suggest that a combination of methods for monitoring young CF children, including both imaging and lung function testing is possible. CT scans could be performed at the time of diagnosis and subsequently every second or third year, or earlier to guide management decisions when clinical findings or lung function tests indicate progression of disease. Lung function can be tested more frequently, ideally every month in children not requiring sedation. Obviously, modern methods for assessment of airway infection and inflammation should also be included.

Inert gas washout tests have been used since the early 1950’s to assess how well inspired gas is distributed (35) and with the advent of the PC in the 1980s breath-by-breath N\textsubscript{2} washout tests using 100% O\textsubscript{2} were used in pediatric studies (36, 37). These tests are thought to reflect
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peripheral airway function. The lung clearance index is the number of lung volume (FRC) turnovers required to clear the lungs of a tracer gas. This simple tidal breathing test can be performed in children of all age groups, including infants (38, 39, 40) and adults up to age 60 years (41). Interestingly, the LCI shows a similar narrow distribution in normal subjects of all age groups with almost the same upper limit of normality, which greatly facilitates longitudinal studies in individual subjects as well as inter-individual comparisons. The LCI has been shown to discriminate better than any other lung function test between CF subjects and healthy controls from the age of 3 years into middle age (39, 40, 41). In infants it showed similar discriminative capacity as the RVRTC method in the only study published so far. The LCI appears to be an important predictor of the further course of CF lung disease (42). The relationship of LCI to other lung function tests longitudinally in CF patients has not been reported. Although promising, more studies are needed before its definite role in monitoring of established CF can be determined. In a recent study in 44 children and adolescents up to 18 years of age with CF, it was shown that the LCI correlated significantly better with HRCT scores than spirometry (43). The study showed that practically all subjects with abnormal CT scores also had a raised LCI, i.e. a normal LCI indicates the absence of structural lung damage. Interestingly, an elevated LCI was seen in some patients with normal CT scores suggesting that the method may even be more sensitive than HRCT. Taken together these studies suggest that the inert gas washout method may be useful when monitoring subjects with emerging CF lung disease. Once the LCI has risen above normal, more advanced diagnostic measures such as CT could be used to confirm or reject progression and to guide management. Surprisingly, only one system for inert gas washout is commercially available today, despite world-wide interest in the method among clinicians and researchers.

Today’s aggressive approach towards early CF lung disease and the demand for clinical studies of new therapeutic options in a limited number of patients with mild disease require more sensitive and immediate outcome measures. Thus, conventional outcome measures such as clinical symptoms, survival or FEV₁ are not particularly useful. It has been suggested that valid outcome surrogates must be biologically plausible, must reflect disease severity, must improve rapidly with effective treatment, and must correlate with true clinical outcomes (44). It may be difficult to prove the validity of new surrogate markers with respect to all these criteria. In addition, the surrogates should be easy to measure and the methods should patient friendly, ideally non-invasive, inexpensive, and not put the patient at hazard. Realistically, there must be a trade-off when dealing with a life threatening disease such as CF. Frequently performed physiological tests reflecting different aspects of lung function such as inert gas washout and spirometry could be used in combination with a low radiation dose CT protocol performed every two or three years and when lung function tests give a warning signal.

REFERENCES


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43. Gustafsson PM, Pim A de Jong PA, Tiddens HAWM, Lindblad A. Multiple-breath inert gas washout and spirometry vs. structural lung disease in cystic fibrosis. Thorax 2007 Aug 3; [Epub ahead of print].