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Review

Multi-modality monitoring of cystic fibrosis lung disease: The role of chest computed tomography

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EDUCATIONAL AIMS

The reader will come to appreciate that:

- Lung structure and function require complimentary modes of assessment
- The monitoring of bronchiectasis optimally involves sequential computerized tomography scans
- Current protocols for computerized tomography scanning involve minimized doses of irradiation, equivalent to approximately one third to half of a year's background radiation exposure per scan.

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SUMMARY

Cystic fibrosis [CF] lung disease is characterized by progressive bronchiectasis and small airways disease. To monitor CF lung disease traditionally spirometry has been the most important modality. In addition to spirometry chest radiography was used to monitor progression of structural lung abnormalities. However, the importance of chest radiography in disease management has been limited due to its poor sensitivity and specificity to detect disease progression. Over the last decade chest CT has become the gold standard for monitoring the severity and progression of bronchiectasis. Small airways disease can be monitored using spirometry, multiple breath washout techniques, and chest CT. In modern CF-care a multi-modality approach is needed to monitor CF lung disease and to personalize treatment for the needs of the patient. When state-of-the-art low dose bi-annual chest CT protocols are used radiation risk is considered to be low. In between chest CT imaging, physiologic measures are important to obtain for monitoring. Stratification of monitoring protocols based on the risk profile of the patient can help us in the future to better care for people with CF.

PATHOGENESIS OF CYSTIC FIBROSIS LUNG DISEASE

At birth, the lungs and airways of the infant with CF are normal. Peripheral airway inflammation and infection occur early in life; thereby, contributing to defective mucociliary clearance and progressive structural lung damage that ultimately leads to respiratory failure. To monitor the presence and evolution of CF lung disease multiple modalities are used including symptom monitoring, sputum or deep pharyngeal cultures, spirometry, multiple breath washout and imaging techniques. The most important components of CF lung disease that eventually result in respiratory failure are bronchiectasis coupled with small airways disease.[1,2] The development of these structural abnormalities begins during infancy.[3–5] Since bronchiectasis and small airways disease are important determinants for disease progression, these pathologic findings should be closely monitored

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starting in infancy with the aim of preventing or slowing irreversible abnormalities. In this article we will focus on the role of chest CT in multiple modality monitoring of CF lung disease.

GENOTYPE-PHENOTYPE CORRELATION

Over the past 10 years, investigators have improved their understanding of the types of genetic mutations leading to a defective CF Transmembrane Regulator protein. Certain classes of gene mutations are associated with a more severe course of the disease.[6] However, these associations only account for large groups of patients. Between individuals with the same mutation, large phenotypic variability is often observed.[7] Unfortunately, we are currently unable to predict, using validated bio-markers, the risk profile for developing progressive lung disease within the individual. This type of personalized model is the way of the future and is needed to personalize treatment and monitoring. Until these personalized models are available, the clinician must use current tools to detect and monitor relevant features of CF lung disease. Using these tools, treatment is tailored to the individual needs of the patient. This monitoring strategy is often viewed as 'one size fits all' and remains so until personalized medicine becomes a reality within the CF population.

HETEROGENEITY OF CF LUNG DISEASE

CF lung disease is heterogeneous. Not only is there a wide variation in severity of CF lung disease between patients, but also within the lungs of a single patient.[8,9] On chest CT normal lung tissue can be adjacent to lung tissue with end-stage structural changes. The severity of structural changes has been demonstrated to be associated with increased airway inflammation.[9] Furthermore, it has been shown that different regions of the lung can host different microorganisms.[10] Awareness of the heterogeneous nature of CF lung disease is important for clinicians. For example, when executing a diagnostic bronchoscopy multiple regions need to be sampled to reduce the chance of missing localized disease. When only small volumes of the lung are involved in active disease this might easily remain unnoticed. As such, patients with localized disease may have normal exercise tolerance since sufficient functioning lung tissue is present. When examining a patient lung auscultation can be normal over most of the thorax. Careful auscultation of the complete thorax is needed since abnormal auscultation may only be present in a small area. Similarly, normal spirometry does not exclude severe local disease.[8,11] A sufficiently large percentage of diseased lung parenchyma may need to be affected before an abnormality is detected by routine spirometry. Therefore, when imaging the lung it is important to evaluate all areas of the lung. Imaging techniques that give adequate 3-D information are chest Computed Tomography (CT) and chest magnetic resonance imaging (MRI).

TREATMENT BURDEN OF CF LUNG DISEASE

Treatment should start at an early stage with the aim of preventing irreversible lung damage from occurring.[5,12] To prevent progression of CF lung disease, modification of therapy is often needed. Attention should be focused on adherence to maintenance therapy and therapy competence.[13] In case progression of disease is present and when adherence and therapy competence are deemed sufficient, treatment may need to be intensified. This approach, unfortunately, will increase the burden of therapy.[14,15] Adding drugs to maintenance therapy also means increasing the risk of side-effects related to these drugs. Hence, to intensify treatment robust arguments are needed. For this reason clinicians use a wide spectrum of monitoring tools to determine with sufficient certainty whether CF lung disease is stable, improving or worsening and whether therapeutic modifications are needed.

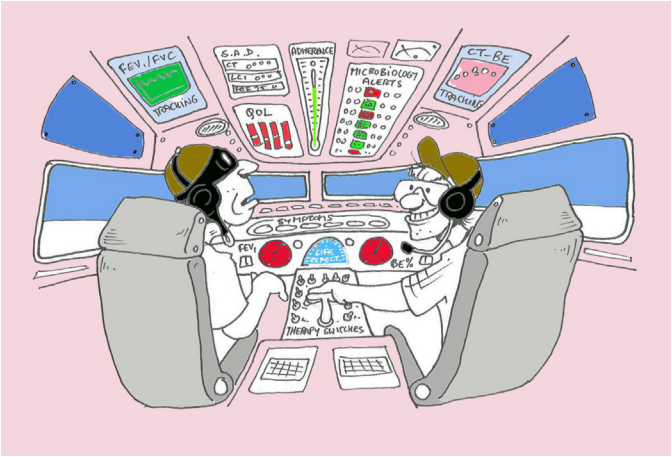

Figure 1. This cartoon shows that physicians responsible for managing CF lung disease are like pilots using readings of different instruments to understand what course CF lung disease is taking. Each instrument has a specific function. All instrument readings are being taken into consideration. In case abnormal readings are observed the pilot will try to understand the big picture by using all available information. Depending on the nature of the problem different therapy switches will be flipped. (Artist: J.C. de Jongste, Photoshop colour staining: Rosaria Macrí).

MULTI MODALITY MONITORING

To monitor the various aspects of CF lung disease multiple modalities are used and each tool evaluates different disease aspects. Clearly, there is not a single modality that is able to capture all relevant aspects of CF lung disease including its heterogeneity, an aspect which only leads to more difficulty in identifying early irreversible abnormalities. The use of multi-modality monitoring is comparable to the instruments in the cockpit used by a pilot to fly a modern airliner (Figure 1). There is a wide array of information delivered by the instruments but also redundancy between the instruments. Using this analogy, the physician/pilot utilizes overlapping information. When a technical problem occurs, such as an increase in symptoms or a clinical deterioration, all instruments are used to identify the exact nature of the problem and determine the best treatment response. The set of instruments used for differing issues will be determined based on the nature of the problem. Furthermore, the most important instrument will vary based on the identified problem. Similarly, CF physicians use the information supplied by multiple monitoring modalities to understand the course of the disease. To do this the clinician should have a firm understanding of the strengths and weaknesses of each modality.

SENSITIVITY AND ACCURACY OF DIAGNOSTIC MODALITIES

Over the past decades the number of modalities used for monitoring has increased. This increase in available tools has required comparisons between modalities to evaluate accuracy, sensitivity, validation status, impact on clinical decision-making, and ideally impact on long-term outcomes. The latter requirement however does not seem to be realistic. Since so many modalities are used for monitoring CF lung disease, it is mostly not feasible to dissect out the contribution of a single observation to the overall long-term outcome of CF lung disease. In addition, monitoring disease does not necessarily lead to a positive impact on disease outcomes. After establishing change in CF lung disease