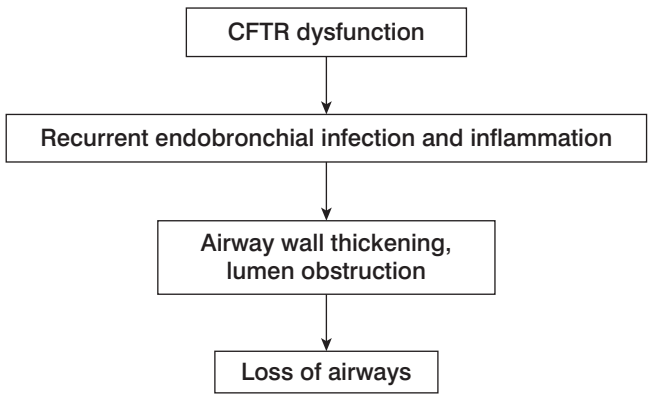
4.6 Small airways disease

Author: Jean-Marc Fellrath

1. INTRODUCTION

- Small airways are defined as any non alveolated and noncartilaginous airway that has an internal diameter of ≤ 2 mm.
- Several observations support the development, very early in the course of CF lung disease, of significant abnormalities in the small airways, leading to the concept that they may be the area of initial pathology. The main mechanism of small airways disease is depicted in **Figure 1**.
- As the small airways account only for a small proportion of total airway resistance and there is significant functional respiratory reserve, their obstruction and loss can remain silent for a long time. Thus, once spirometry becomes abnormal and significant symptoms occur, irreversible histological damage is already present.

Figure 1: Mechanism of small airways disease in CF



2. METHODS OF ASSESSING SMALL AIRWAY ABNORMALITIES

2.1 Respiratory function tests

- FEV_1 is the most important item to assess both the severity of lung disease and its course over time in patients aged > 5 years. However, it has a very poor sensitivity for capturing small airway abnormalities.
- Flows at lower volume, such as $FEF_{25-75\%}$ or $FEF_{75\%}$, are more sensitive but have higher variability. Their reduction, which occurs early in CF, while FEV_1 and FVC are still normal, cannot be explained by this variability. Thus, currently, $FEF_{25-75\%}$ and $FEF_{75\%}$ can be considered

the most appropriate spirometric items for capturing small airways abnormalities but only when an obstructive syndrome is not present yet (i.e. early stages of CF lung disease).

- An alternative method used to detect small airways abnormalities is to compare TLC measured by body plethysmography and by the helium dilution technique. The difference in TLC between these techniques reflects the volume of gas trapping.
- Another functional method for detecting and monitoring small airways disease in CF is the lung clearance index (LCI), a measure of ventilation inhomogeneity determined during multiple breath washout (MBW). LCI is only available in some CF centers in Switzerland.
  - LCI can be measured during tidal breathing, requires minimal cooperation and coordination. This technique is thus suitable for children aged < 5 years.
  - As for $FEF_{25-75\%}$ or $FEF_{75\%}$, LCI measurement is presently appropriate in adult CF patients only at an early stage of lung disease **(see also Chapter "*Pulmonary disease: clinical evaluation*")**.

2.2 Chest HRCT scan

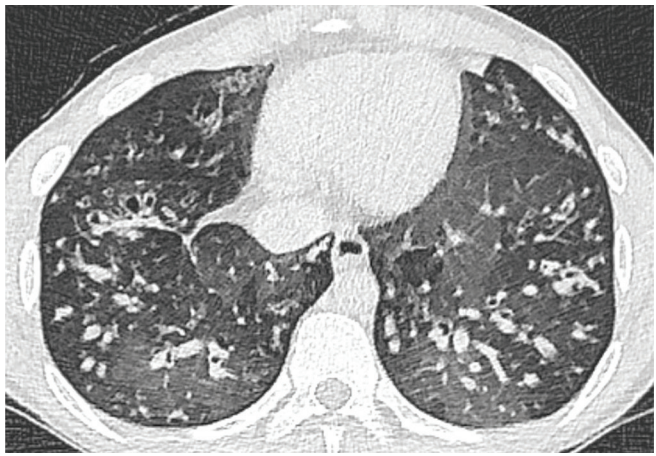
- High resolution CT (HRCT) scan is the most sensitive imaging method to date for detecting significant changes in small airways. This technique requires radiation, although the administered doses are decreasing over time with newer machines and dose-adjusted protocols. Characteristic signs of small airways disease found in chest HRCT scan are summarized in **Table 1** and **Figure 2**.
- Several studies demonstrate that the small airways abnormalities change over the time:
  - air trapping (mosaic attenuation) is the most frequent abnormality in younger and mildly affected patients.
  - bronchiectasis becomes the most frequent pattern in older and severely affected patients.

Table 1: Signs of small airways disease in CF patients obtained by a chest HRCT scan

Airways with diameter < 1 mm cannot be visualized directly, however, **thickening of bronchiolar walls** due to inflammation and **lumen dilatation** makes small airways visible.
An early sign of small airways disease is lobular or segmental parenchymal inhomogeneity referred to as **mosaic pattern** – the darker areas are abnormal and represent narrowing or obliteration of the bronchioles, air trapping and underperfusion – mosaic pattern is well apparent on expiratory scans. – air trapping has been observed in up to 75 % of young sedated CF children using the controlled ventilation technique
Mucus plugging of small airways is common and easily visualized with HRCT. Usually, dilated small airways filled with secretions or with peribronchiolar inflammation generate micronodular centrilobular opacities called **tree-in-bud pattern**

Figure 2: Examples of small airways disease in chest CT scans 1) thickening of bronchiolar walls, lumen dilatation and air-trapping with mosaic pattern, 2) tree-in-bud [a. centrilobular nodules, b. maximum intensity projection (MIP) facilitates visualization]

1)



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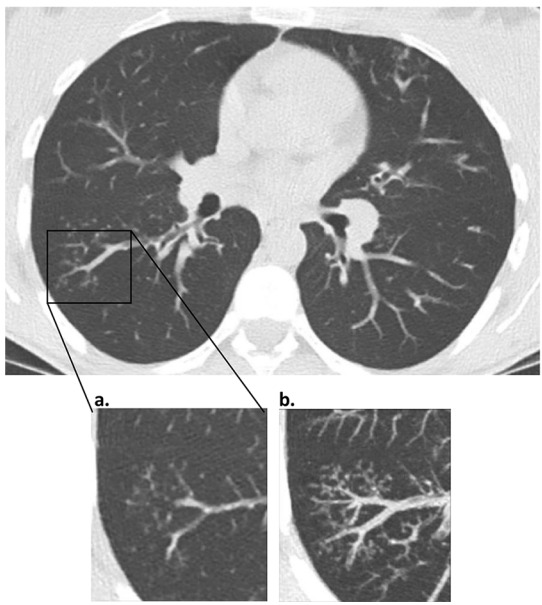


2.3 Thoracic MRI

- The relative new technique of magnetic resonance imaging with hyperpolarized noble gas such as helium-3 allows visualization of ventilated airspaces.
- The lack of exposure to radiation is a considerable advantage.
- Air trapping and decreased perfusion in areas of airways obstruction could be visualized with this technology probably with higher sensitivity when compared with HRCT, nuclear medicine or pulmonary function tests.
- Thoracic MRI is currently and routinely used for CF children in some Swiss centers but not yet for adults (at the time of writing this is a subject of ongoing research).

3. AGGRAVATING FACTORS

- Infectious bronchiolitis, mainly due to viruses, may be responsible for small airways disease associated with a rapid decline of FEV_1 and gas exchange abnormalities.

4. TREATMENT

- The concept that a more efficient delivery of a medication to the small airways may translate into better functional and clinical outcomes is very attractive. Early therapeutic intervention targeting the small airways might slow the progression of small airways disease and thus prevent the inevitable progression of CF lung disease.
- During the course of lung disease in CF, exacerbation of small airways disease may occur with failure to respond to usual treatments including antibiotics.
- No clear recommendations exist on the optimal treatment for CF patients with small airways disease but in case of an associated clinical deterioration, based on some case-studies, and our own experience, some suggestions can be made:
  - **Inhaled treatment:** rhDNase and osmotic agents delivered via a nebulizer producing smaller size particles was shown to result in significant improvements in flows at lower lung volume.
    a) rhDNase once a day (e.g. in the evening) and hypertonic saline 3-6% once a day (e.g. in the morning), if well tolerated, can be tried.
    b) rhDNase twice a day
  - **Corticosteroids:**
    – Prednisone 0.5-1 mg/kg may be tried in case of a rapid decline of FEV_1 thought to be due to deteriorating small airways disease or infectious bronchiolitis. Dose tapering should follow over weeks or sometimes months depending on FEV_1. Potential side-effects of systemic corticosteroids must be evaluated, prevented, and carefully followed.
    – In case of severe deterioration of small airways disease, demonstrated by spirometry and chest HRCT scan, methyl-prednisolone 1g IV daily for 3 days has been shown to increase lung function significantly.
  - **Other anti-inflammatory compounds:**
    – Azithromycin if not already used, may be added even in patients not colonized with *Pseudomonas aeruginosa.* This treatment should also be considered in adult

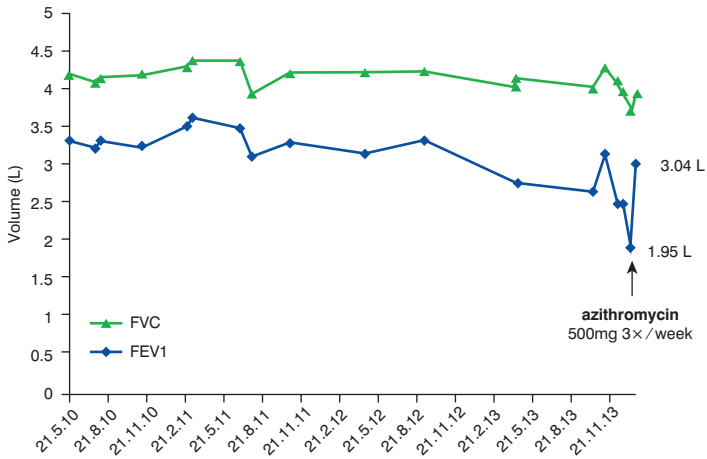
CF patients with early stage lung disease suffering from infectious bronchiolitis (e.g. **Figure 3**). Regimens used:

a) daily regimen: 250 mg per day OR

b) weekly regimen: 250-500 mg /3 times a week (the 500mg dose for patients >40kg)

– High dose ibuprofen is not recommended in adult CF patients because of minor clinical benefit and potential serious side-effects.

Figure 3: Example of a 22 year-old CF patient with small airways disease due to infectious bronchiolitis. Evolution of lung function following initiation of azithromycin.



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