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The Role of Computed Tomography in Monitoring Patients with Cystic Fibrosis

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Summary

Cystic fibrosis is the most common lethal autosomal recessive disorder in the Caucasian population. Although the survival rate in patients constantly improves, lung damage is still the major cause of morbidity and mortality in patients with cystic fibrosis.

In clinical practice, evaluation of patients' pulmonary state is made by combination of monitoring of lung function and more directly by assessing the lung structure in imaging studies. Studies showed that computed tomography findings are more sensitive as compared to the pulmonary function tests.

Computed tomography can identify a wide range of morphological abnormalities in patients with cystic fibrosis, such as bronchiectasis (which is progressive, irreversible and probably the most relevant structural change in cystic fibrosis) peribronchial thickening, mucous plugging and many other disorders that occur in the course of the disease. Computed tomography has a crucial role in the assessment of pulmonary damage over time, detecting complications and monitoring treatment effects in patients with cystic fibrosis.

MeSH Keywords: Bronchiectasis • Cystic Fibrosis • Tomography, X-Ray Computed

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Background

Cystic fibrosis (CF) is the most common lethal autosomal recessive disorder in the Caucasian population. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. The product of this gene is a chloride ion channel, which regulates the components of respiratory, digestive and reproductive system secretions. Malfunctioning of this protein causes these secretions become more viscous and difficult to clear [2].

Although cystic fibrosis is a multisystem disease, lung damage is the major cause of morbidity and mortality in patients with CF [3]. The viscous secretion in the respiratory tract leads to impaired airway clearance, bacterial colonization and chronic inflammation, which result in irreversible lung damage.

During last decades a large progress in cystic fibrosis diagnostics and treatment strategies has been made [4]. One of the reasons of this improvement is a large step forward in imaging technics. The aim of this paper is to present the role of computed tomography in estimating and monitoring the course of CF lung disease severity and treatment effects.

Computed Tomography in Lung Damage Assessment in Patients with Cystic Fibrosis

According to Cystic Fibrosis Papers of the Year 2012 the most important outcome measures in CF studies are changes in pulmonary function and rate of pulmonary exacerbations, although radiographic changes on CT scans are increasingly important [5]. Therefore, in clinical practice, the evaluation of patients' pulmonary state is made by combination of monitoring of lung function and more directly by assessing the lung structure in imaging studies.

Until 1990s, the chest x-ray had been the main imaging method used to control pulmonary morphological changes in CF. The first articles describing the application of computed tomography in patients with cystic fibrosis were

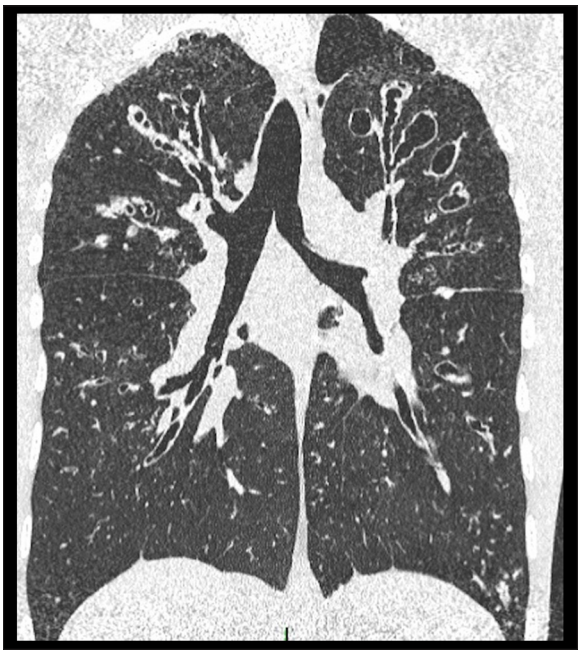

Figure 1. HRCT. MPR – reconstruction. Widespread bilateral bronchiectasis mostly advanced in the upper lobes with peribronchial thickening and mucus plugging in the right upper lobe.

published in the 1980s [7]. Comparisons to chest radiography proved that CT is a more accurate and sensitive method to monitor lung structure. Nowadays it is regarded as the gold standard for the identification of airways and lung parenchymal structural changes in CF [8].

Patients with CF may present a wide range of pulmonary abnormalities, which can be seen on CT scans, such as: bronchiectasis, peribronchial thickening, mucus plugging, sacculations, abscesses, bullae, emphysema, air trapping, hyperinflation, collapse, consolidation, mosaic perfusion, ground-glass opacities, acinar nodules, alveolar consolidation, thickening of interlobular and intralobular septa (Figures 1–3). Bronchiectasis, peribronchial thickening and mucus plugging are the most frequent abnormalities. It was confirmed in the study by de Jong et al. [9], where CT scans of 25 patients with CF were retrospectively assessed. The prevalence of bronchiectasis was 76%, peribronchial thickening 85% and mucus plugging 79%.

Bronchiectasis, which is a permanent enlargement of bronchi caused by a chronic inflammation, is regarded as a cardinal structural sign in later stages of CF (Figure 4). In the study by Stick [12] computed tomography and bronchoalveolar lavage were performed with anesthesia on 96 children with CF. The incidence and extent of bronchiectasis were observed to increase with age. Furthermore, the presence of bronchiectasis was reported to correlate well with pathophysiological risk factors such as inflammation and infection.

Mucus plugging is a total or partial obstruction of the bronchial lumen caused by an abnormal composition of the epithelial lining fluid. In the study by de Jong [13] the evaluation of the CT scans and the pulmonary function tests (PFT) was made at the starting point and after 2 or 3

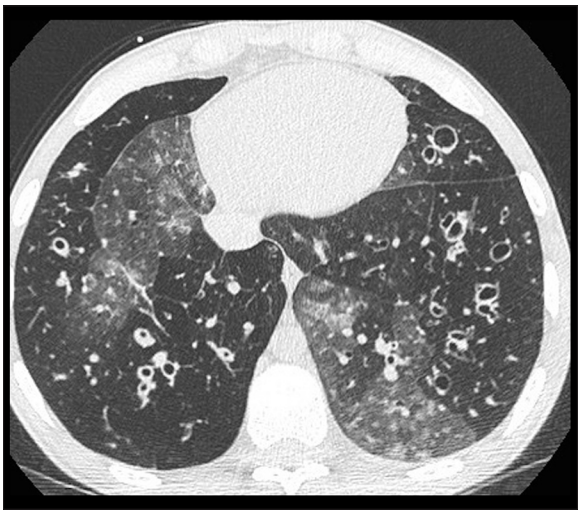

Figure 2. HRCT. Axial image presents coexisting ground-glass opacities, bronchiectasis, centrilobular nodules, peribronchial and septal thickening.

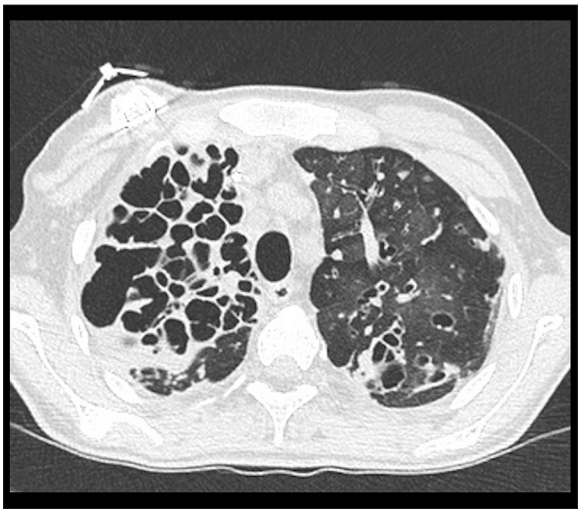

Figure 3. HRCT. Axial image. Severe cystic bronchiectasis in the right upper lobe with areas of fibrosis. Mosaic attenuation in the left upper lobe most likely due to air trapping.

years. The abnormalities that worsened significantly were mucus plugging and the severity, extent and peripheral extension of bronchiectasis. The largest annual progression was observed in the peripheral bronchiectasis score. On the basis of this observation authors suggested that selective assessment of bronchiectasis and mucus plugging might be more efficient and reproducible than complex assessment of other CF morphological features and could be used as an outcome measure in clinical studies.

Airway wall thickening is another important morphological sign that appears in the course of cystic fibrosis. These changes begin very early in life; airways in minimally symptomatic infants and young children with CF were found to have thicker walls as compared to normal control infants [12].

Bronchiectasis is considered irreversible, while mucus plugging and peribronchial thickening are reversible CF

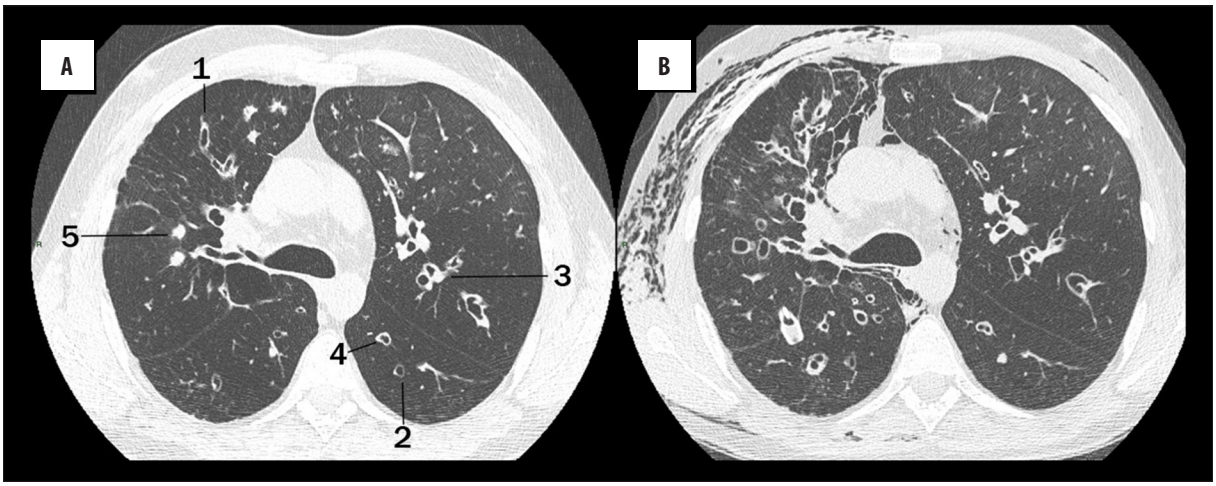

Figure 4. (**A**) The diagnosis of bronchiectasis on inspiratory computed tomography images can be based on the following findings: lack of normal tapering of the bronchial lumen (1), visibility of airways in the peripheral lung (2) and lumen of the bronchi larger than the lumen of the accompanying pulmonary artery (3), which can be observed as a signet-ring sign. These images also show other CF signs: airway wall thickening (4) and mucus plugging (5). (**A, B**) HRCT scans present progression of the disease tracked by computed tomography in a 28-year-old man. The interval between (**A**) and (**B**) examination was two years. A substantial progression of bronchiectasis and airway wall thickening coexisting with complications in the course of the disease such as subcutaneous emphysema and pneumomediastinum.

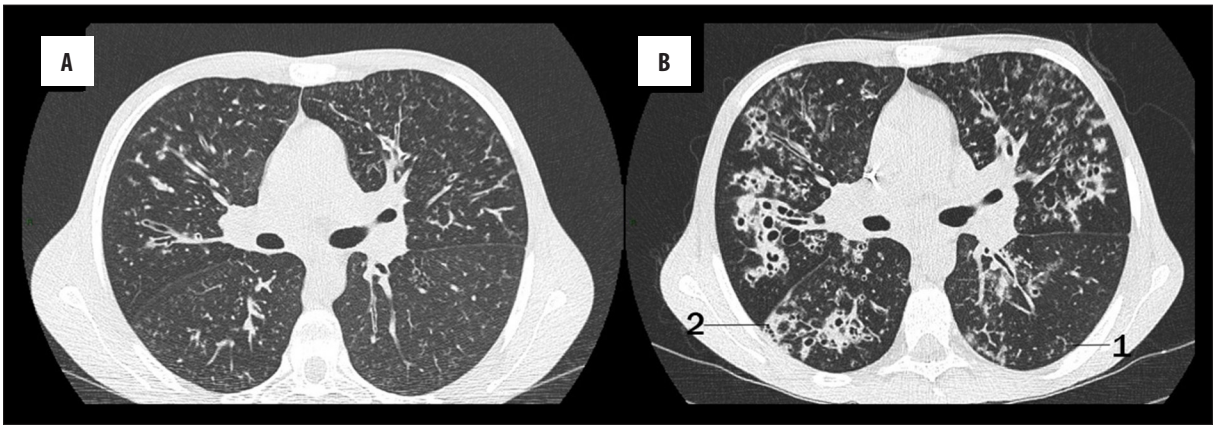

Figure 5. Significant deterioration of the HRCT images observed during exacerbation. The interval between examination (**A**) and (**B**) was two months. In addition to worsening of bronchiectasis and airway wall thickening, the image (**B**) showed substantial progression of mucus plugging, which in the smaller peripheral airways is observed as the "tree-in-bud" sign (1). It represents dilated and mucus-filled centrilobular bronchioles. On image B also small consolidation regions can be observed (2).

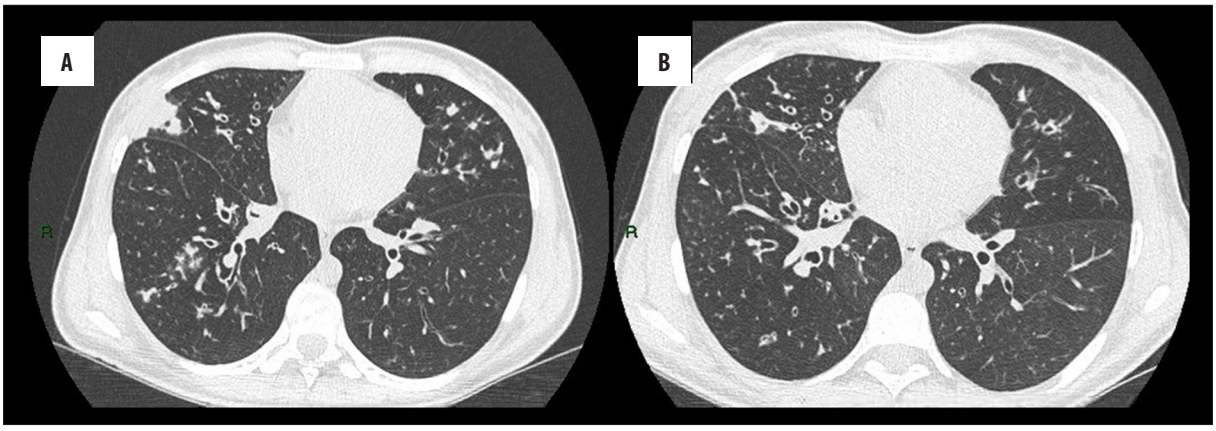

Figure 6. HRCT. Axial image A presents bronchiectasis with peribronchial thickening. Some of the bronchi are filled with mucus. Additionally, image (**A**) depicts inflammatory subsegmental and peribronchial consolidations. Follow-up HRCT image in picture (**B**) reveals partial resorption of the inflammatory consolidations and mucus plugs.

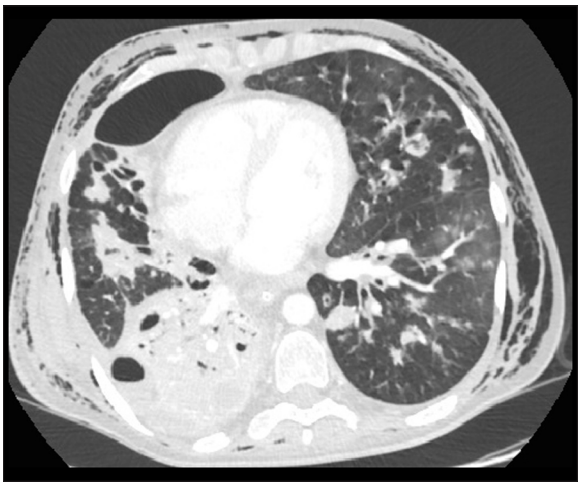

Figure 7. Axial chest CT image after contrast injection depicts complications in the course of CF. Subcutaneous emphysema, right-sided pneumothorax coexisting with right lower lobe atelectasis and widespread consolidation regions in both lungs.

features [14]. They were observed to increase during exacerbation and decrease after exacerbation treatment. Estimating these two features instead of all CF symptoms can be useful during monitoring of treatment effects [15] (Figures 5, 6).

Air trapping on expiratory scans is another important cystic fibrosis sign, because it reflects structural abnormalities of the peripheral airways [16]. Structural abnormalities of small airways found in necropsy specimens include: dilatation of respiratory bronchioles and alveolar ducts, bronchiolar scarring and stenosis, destructive emphysema [17]. Airways measuring below 1 mm cannot be visualized directly on CT scans, but regional air trapping, which is an indirect symptom of small airway disease can be detected on expiratory HRCT images as areas of low attenuation in comparison to regions with normal attenuation [18]. Trapped air is observed very often and early among patients with CF [19].

CT examination is also essential in detecting CF complications, for example pneumothorax, atelectasis or pneumonia (Figure 7).

Computed Tomography in Clinical Status Assessment in Patients with Cystic Fibrosis

Studies showed that CT scans enable the assessment of pulmonary damage over time in patients with cystic fibrosis. Furthermore, CT findings occurred to be more sensitive as compared to the pulmonary function tests [22,23]. In the study by de Jong [22], 48 children had high-resolution computed tomography (HRCT) scans and pulmonary function tests (PFT) at the beginning of the study and were revaluated after 2 years. The progression of the lung damage was observed on the HRCT scans, while lung function parameters assessed by spirometry and body pletysmography remained stable or in some cases improved. Moreover, in many patients with normal PFT parameters substantial damage could be observed on CT scans. Therefore, authors suggested that PFT in some cases fails to reveal the beginning and early progression of lung disease in CF and using PFT as a tool to treatment effect assessment may underestimate them.

It is also worth mentioning that severity of changes in lungs observed in CT was found to correlate with severity of the inflammation process determined by inflammatory parameters in bronchoalveolar lavage (BAL) fluid in very young children with CF [24]. It was proved that the regions with more severe structural damage had higher inflammatory markers in the BAL fluid.

The importance of computed tomography in cystic fibrosis was also confirmed by the studies which showed that changes in HRCT correlate with true outcomes in CF. The first study which showed such a correlation was the study by Brody [25]. CT scan and PFT were carried out at baseline and at the end of the study after 2 years. During a 2-year period, the history of exacerbations was recorded. PFT and HRCT results collected at the beginning of the study correlated with the number of respiratory tract exacerbations.

In order to quantify in a systematic fashion the CT findings, specific tools such as scoring systems were developed. In early 1990s the first article presenting CT scoring system for CF was published by Bhalla et al. [26]. Since then many other scoring systems have been developed [9]. Bronchiectasis and mucus plugging are given the highest weighting in almost all scoring systems, as they are regarded as the hallmarks of CF. To date it has not been established which scoring system has the highest sensitivity to track clinically relevant changes. Nowadays, when CT in used not only to monitor the status of patients with CF but also in clinical trials, the consensus about the most appropriate scoring system is needed in order to systematize the results across centers.

Scanning Techniques

In clinical practice there are two types of CT scanning protocols to choose from: high-resolution CT (HRCT) imaging, in which scans of 0.5–1.5-mm thickness are performed at 0.5–2-cm intervals at the end of inspiration, and next limited, spaced (e.g. obtained at the level of the aortic arch, carina, the inferior edge of the right hilum, and 2 cm above the right diaphragm) HRCT slices are obtained for expiratory scans; and total spiral CT imaging of the entire lung for inspiration and expiration images [27].

HRCT is obtained with lower radiation doses compared with complete spiral CT protocols, but it is more time-consuming in comparison to spiral CT scanning and provides only a limited view of the axial plane. Another disadvantage is that serial HRCT sometimes fails to obtain anatomically-matched airways and regions of the parenchyma. On the other hand, spiral CT scanning enables more accurate matching of lung regions in follow-up studies and provides 3D assessment of lung structure, but it requires higher radiation doses with lower resolution compared to HRCT. Low-dose strategies (100 kVp and 20–40 mAs) in CT scanning protocols allow to obtain comprehensive assessment

of CF lung disease with radiation exposure reduced to 0.2–0.3 mSv in HRCT and 1.5 mSv in spiral CT scanning [27]. The overall risk connected to routine usage of CT in patients with CF has been discussed by Kuo W et al. [28] and assessed as small. Authors also emphasized the fact that in CF, which is a life-limiting disease, there is a lower risk of radiation-induced cancer. Nevertheless, the radiation dose should always be as low as reasonably achievable and each CT examination should be justified.

Conclusions

Computed tomography in combination with pulmonary function tests is commonly used for the evaluation of cystic fibrosis progression in individual patients. In clinical practice it is essential to control individual response to a specific therapy in order to estimate the adequacy of the treatment the patient is given. Because of limitations of PFT, CT has been used more often recently to closely monitor therapeutic effects. Nowadays, CT has a crucial role in monitoring morphological changes and detecting lung complications in patients with cystic fibrosis.

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