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PhD THESIS

IMPLICATIONS OF THE LUNG CLEARANCE INDEX IN PULMONARY FUNCTION EVALUATION IN CYSTIC FIBROSIS PATIENTS

A B S T R A C T

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ABSTRACT

The topic chosen for this doctoral thesis addresses an important field of research - the evaluation of lung function using the lung clearance index in children with cystic fibrosis, where international research is still in its infancy, being a topic less studied so far.

This research topic is not only current at international level, but also the first national approach of its kind, combining current research activities with important involvement in medical practice and scientific research.

The aim of this paper is to evaluate the lung ventilation inhomogeneity of patients with cystic fibrosis by determining the lung clearance index and its correlation with spirometry parameters and lung structural deterioration. We also aim to identify potential factors such as genotype, nutritional status, chronic infections, the presence of complications such as hepatopathy and diabetes associated with cystic fibrosis, which may prolong the lung clearance index.

This thesis is concepted from two part: the general part and the specific part. In the general part I presented general notions about what is cystic fibrosis, about its genetics and clinical signs and symptoms. There is a whole chapter about cystic fibrosis lung disease and how to treat it, and also another chapter about what do we use so far in order to diagnose cystic fibrosis lung disease.

Cystic fibrosis (CF), the most common, potentially lethal, monogenic disorder of the Caucasian population, is clinically characterized by an impressive polymorphism, with pulmonary and gastrointestinal implications. Even if the life expectancy of CF patients has increased in recent years, the mortality rate is almost constant mainly due to the progressive deterioration of lung function.

Although the molecular basis of this pathology is currently known, there are still many debates about when and how the first lung changes occur, especially due to the heterogeneous nature of lung deterioration in this population. It is estimated that by the age of 8 months, almost half of infants with CF have a degree of lung deterioration, which cannot be detected by standard assessment methods.

Identifying these early changes in lung function is absolutely necessary to institute aggressive treatment in order to try to prevent future irreversible lung damage.

Assessing the degree of lung damage (structural and functional) is an essential part of CF patients' care. The goal is to identify early changes and institute appropriate treatment.

Functional assessment of lung status is not representative for the structural or anatomical deterioration of the lung. Airways obstruction is progressive, as demonstrated by spirometry, but lung function can be preserved in normal parameters. Evidences have shown that bronchiectasis cannot be detected by spirometry.

Most infants with CF are asymptomatic, however they do have asymptomatic structural lung changes evidenced by high-resolution computed tomography.

Currently, the computed tomography represents "the gold standard" in evaluation of cystic fibrosis lung disease.

A special score, the modified Bhalla score, was created to assess the degree of lung damage using CT. This score assesses the degree and extent of bronchiectasis, thickening of the bronchial wall and the formation of mucus plug, with the appearance of atelectasis and / or consolidation and air capture.

But pulmonary computed tomography is an irradiated method and guidelines recommend the use of it starting with the age of 3 and then every 2 years or earlier if the patient's clinic status recommend it.

The ideal lung function test for preschool children should be one applicable to any age, so that longitudinal studies can monitor the subject from infancy to adulthood; it must be an easy-to-perform test, sensitive enough to detect changes with growth and to clearly distinguish between health and illness.

It is the most widely used method of assessing lung function. It is aimed especially at patients older than 6 years and who can perform the technique correctly. To perform this technique the patient must perform a maximum inspiration followed by a maximum expiration, repeating this maneuver several times until obtaining the flow-volume curve.

Detecting obstruction using FEV_1 as a parameter has traditionally been used to monitor lung function in CF patients and is still recognized as a good predictor of outcome in cases with moderate to severe lung damage. The discrepancy is given by the fact that, the functional evaluation of the lung status is not representative for the structural or anatomical deterioration of the lung.

Spirometry remains a difficult technique for preschool patients and is contraindicated in patients with cystic fibrosis who are in exacerbation or who have an acute respiratory pathology, regardless of their age.

In 1952 Ward S. Fowler described a method of measuring nitrogen clearance curves in healthy patients and those with cardio-respiratory disease to quantify the "inequality of gas distribution".

Pathological process that affects the peripheral airways will cause an increase in the heterogeneity of pulmonary diffusion. There are several mechanisms that contribute to the alteration of this homogeneity. Airway narrowing, due to factors such as mucus retention, inflammation and alteration of the airway wall structure.

Inequality of ventilation affects the overall efficiency of the gas mixture in the lungs and can be measured by tracking the elimination of a control gas during tidal respiration. In a pathological process, this elimination process will last longer, requiring a bigger number of breaths.

The lung clearance index (LCI) is a sensitive marker of lung function assessment and is the cumulative expiratory volume required to remove an inert gas from the lungs, related to functional residual capacity (FRC). This method is based on the multiple breath washout (MBW) technique and can be performed by children of different age because it requires minimal effort. The most used gas is nitrogen (N2) which can be eliminated from the lungs by multiple breaths with pure oxygen (100% O2).

The determination of the lung clearance index is currently considered in Europe the gold standard for the early detection of lung disease in children under 5 years. However, it is a method of evaluating pre-school patients used in few specialized centers. This topic is in line with current standards and requirements of the European research area in the field and has great potential for international visibility, thus meeting the current goals of the research strategy of University of Medicine and Pharmacy “Victor Babes” Timisoara for permanent growth of research excellence.

Numerous studies have demonstrated the usefulness of LCI in detecting impaired lung function faster than spirometry (expressed by FEV_1) in preschool and school-age children. Moreover, an increased LCI in preschool is associated with an increased LCI in adolescence and significant structural lung changes on computed tomography.

The special part represents all the research I have made and how I did it in order to be able to establish conclusions and give recommendations for a better use of the lung clearance index.

This study was conducted at the 2nd Pediatric Clinic and at the National Cystic Fibrosis Center Timisoara, within the Pius Branzeu Timisoara County Emergency Clinical Hospital, between 2017 and 2021. 56 patients, who agreed to participate in this study and were able to perform spirometry and multiple breath washout technique, were enrolled.

The design of this study is observational and allowed the analysis of patient data obtained during their periodical investigations. Data from this thesis were published this year in an article entitled “The Relation between Vitamin D Level and Lung Clearance Index in Cystic Fibrosis-A Pilot Study”. This is the first article about the use of lung clearance index, as a tool for evaluating lung function in Romania, and also is the first article ever published who approach the relation between vitamin D and lung ventilation inhomogeneity.

56 patients were enrolled in the study, all of them being able to perform spirometry and multiple breath washout technique.

In the first part of the Results, I described the study group and all the parameters which have been evaluated for this thesis: age, gender, genotype, nutritional status, microbiological profile, associated co-morbidities as cystic fibrosis liver disease and related diabetes, vitamin D and inflammatory status. We also evaluated patients’ cystic fibrosis lung disease with spirometry, lung computed tomography and lung ultrasound. All patients have lung deterioration diagnosed by CT, but not all this deterioration were detected by spirometry or by lung ultrasound. In the second part of the Results, I have evaluated the lung clearance index and its relation with all parameters described above.

Moreover, I compered the multiple breath washout technique with the others methods available for the evaluation of cystic fibrosis lung disease. Strong correlations were obtained between LCI value and Bhalla score, respectively LUS score.

Lung clearance index has a strong correlation with CT score, better the spirometry, being a more useful tool to estimate lung structure deterioration and therefore we can reduce to use of CT exposure. It also can be used to evaluate if a

patient is in exacerbation and identifies patients with lung ventilation inhomogeneity, even when the spirometry is normal.

Lung disease is progressive in cystic fibrosis and this can be confirmed by the value of LCI which is significantly higher in older then in younger patients.

At last, but not the least, through this research I was able to identify risk factors for lung ventilation inhomogeneity. Some of them cannot be prevented or treated, as gender or genotype, but the others risk factors can be both prevented and treated: malnutrition, vitamin D deficiency, chronic pulmonary infection and chronic inflammation.

Lung clearance index implies an easier technique than spirometry, and this is a very important aspect for patients, especially the younger ones. It is also a non-irradiating technique which can be repeated as often as necessary and easier to interpretate. Is widely used in Europe as a reference method to evaluate lung function and the response to the new modulatory therapy, and at least for the next years represents the future in evaluation of lung ventilation inhomogeneity, and not only for patients with cystic fibrosis.

Following this paper on the implications of the lung clearance index in the evaluation of lung function in the patient with cystic fibrosis, the following conclusions can be drawn regarding the lung clearance index: it is a more sensitive parameter than spirometry in assessing the degree of lung functional impairment and can be used as a marker of lung disease progression. It has a strong correlation with the CT score, the current "gold standard" for assessing the degree of lung damage, and can thus be used as a non-invasive indicator instead of CT, an irradiating method for the patient. It also has a strong correlation with the LUS score. Its sensitivity in increased in detecting lung lesions, but low specificity.

Patients without lung infections have a lower lung clearance index and therefore a better homogeneity of pulmonary ventilation; it can be used as a diagnostic tool for patients in exacerbation. Patients with chronic infections have a higher LCI value than those without any infection, or those without chronic infections.

The presence of comorbidities such as diabetes and hepatopathy associated with cystic fibrosis are risk factors for prolonged LCI.

Male patients and those with the non-homozygous F508del genotype have better lung homogeneity.

Although the patient's weight and height do not appear to influence the LCI value, one percentile of the patient's BMI <50 is a risk factor for altering the homogeneity of pulmonary ventilation.

Low vitamin D levels, <30 ng / ml, are also a risk factor for prolonged LCI.

Chronic inflammation of the lungs also influences in a negative way the degree of inhomogeneity of pulmonary ventilation.

At the end of this conclusions, it might be said that the purpose of this thesis: to evaluate the lung ventilation inhomogeneity of patients with cystic fibrosis by determining the lung clearance index and its correlation with spirometry parameters and lung structural deterioration, has been achieved.

This thesis highlighted that using lung clearance index to evaluate lung function, is not just easier to perform comparative with spirometry, but even a better method the detect incipient lung function deterioration, even in case of patients with normal spirometry. Moreover, it has a very good correlation with “the gold standard” method – pulmonary computed tomography with a 100% sensitivity in detecting moderate and severe lung deterioration and 74% sensitivity in cases with mild deterioration.

Cystic fibrosis lung disease is progressive and although some structural changes exist even from fetal period, they take time to expand and produce severe damage on lung structure. Also, once the lung structure deterioration is produced (bronchiectasis) they won’t cure, at best they can remain still. Lung clearance index might be more sensitive and even more specific for patients being in exacerbation, its value tends to be higher in this situation and after the treatment it can return to initial value.

Lung clearance index can be used as an exacerbation predictor, its value being significantly higher in patients with infections then in cases of patients without infections.

It is not only important to treat but also to prevent. We identified risk factors for ventilation inhomogeneity as: malnutrition, low level of vitamin D, chronic inflammation and chronic infection. With correct prevention and right treatment these factors can be eliminated.

Unfortunately, we identified also some risk factors that cannot be modified: female gender and genotype F508del homozygous. It is important to know these

factors because if they are present, we can aware our patients to pay more attention to those risk factors they can modify.

Presence of associated co-morbidities, as cystic fibrosis liver disease and cystic fibrosis related diabetes, represents also risk factors for pulmonary ventilation inhomogeneity. This in important to know and to start the right treatment as soon as this co-morbidities are diagnosed, in order to help to prevent lung function deterioration.

Lung clearance index is new, good and rare. Not all European hospital benefits of it and in Romania, in Timisoara, at the National Cystic Fibrosis Center is the only hospital where patients can benefit of it.

It comes with some technical-economic disadvantages, and the most important are the consumables: filters and gas tank.

There are still some problems which need to be resolved. One of them, and is an international problem, is the lack of enough healthy control subjects in order to obtain a scale for normal values. It is generally accepted as 7 – the upper normal limit. But there are still discussions if this value is accepted for all types of machines that can perform multiple breath washout technique.

In future, I consider that are a few research ways to go.

First of them will be to perform the test on enough healthy control subjects to be able to establish reference values.

Guidelines recommend to expose children at radiation with computed tomography starting with age of 3. Being able to perform multiple breath washout technique and obtaining the lung clearance index at this group age of patients might be essential for their future lung development, in preventing and treating lung infections.

There are also others lung diseases that might be evaluated with this much easier method than spirometry. One of them is asthma, or patients with recurrent wheezing, bronchial hyperreactivity, but also patients with bronchopulmonary dysplasia or even adults with chronic obstructive pulmonary dysplasia.

More researches need to be done and only time will confirm if lung clearance index will be the next gold standard in evaluation of lung inhomogeneity ventilation.