Respiratory Function in Children with Nephrotic Syndrome: Comparative evaluation of Impulse Oscillometry and Spirometry

Fatih Kilci[1], Z. Seda Uyan[2], Mehtap Çelakil[3], Kenan Doğan[1], Kenan Bek[3]

1- Kocaeli University Faculty of Medicine Department of Pediatrics

2- Koç University Faculty of Medicine Department of Pediatrics Division of Pediatric Pulmonology

3- Kocaeli University Faculty of Medicine Department of Pediatrics Division of Pediatric Nephrology

Abstract

Aim: To evaluate the respiratory functions of children with nephrotic syndrome (NS) by IOS and its correlation with spirometry.

Methods: Fifty-five NS patients aged 3–18 years were included as the study group and 40 healthy children of the same age formed the control group. Patients were divided into nephrotic phase (first attack and relapse) and remission. Demographic, anthropometric and laboratory data of the children were recorded. Respiratory functions were evaluated by IOS and spirometry. Children over 6 years old performed both IOS and spirometry while children under 6 years performed only IOS.

Results: The R (R5%, R10%, R5-20) and AX and Z5% values of IOS in patients with nephrotic phase were higher than remission patients and control group while spirometry indices of FEV1%, FEV1/FVC, PEF% and MEF25-75% were lower. FEV1% showed negative correlation with R5%, R10%, R15%, X10% and X15% results, FEV1/FVC% showed negative correlation with R5%, R5-20 and X15% results, FVC showed negative correlation with X10% results, MEF25-75% showed negative correlation with, R5%, R10%, R5-20, X15%, F res, Z5% and AX results.

Conclusion: Our study demonstrated that respiratory functions measured by IOS and spirometry were affected at the time of nephrotic phase in NS patients. And IOS, a novel method easily applicable even in small children, is a valuable and reliable tool to detect this condition; given its good correlation with spirometry.

Keywords

Nephrotic syndrome, Respiratory functions, Spirometry, Impulse Oscillometry

1 | INTRODUCTION

The lungs are considered to be protected from generalized edema in nephrotic patients thanks to very low net filtration pressure at alveolar level which is defined as "lung-safety factor" seemingly unique to respiratory system[1]. Along with this, high interstitial compliance of the lung capable of harboring large volume of fluid without significant pressure increase also contributes to prevention of water accumulation in alveoli during hypoalbuminemia [1,2]. Absence or rarity of symptomatic pulmonary edema even in severe cases of nephrotic syndrome (NS) seems to support this knowledge. However, this does not mean that lungs are totally spared in conditions with increased extracellular fluid with no relevant changes in respiratory functions at all. Current evidence through impedance and ultrasound studies indicates that asymptomatic lung congestion does exist in hypoalbuminemia states [1]. But data regarding changes in respiratory function in nephrotic children are limited and solely provided by a few conventional spirometric studies [3].

Because of the need for great patient cooperation, spirometric tests are not applicable in small children. However, since the impulse oscillometry (IOS) is a forced oscillation method requiring only passive cooperation of the patient, it can be easily performed even in infants. This new noninvasive method measures the lung impedance defined through the parameters of resistance (R) and reactance (X) [4-6]. It is used for diagnosis, follow-up and assessment of disease severity and treatment response. It can also differentiate between pulmonary resistance, frequency dependence and resistance to pulmonary reactivity providing more detailed data about peripheral and central airway problems of the lungs than conventional spirometry [7].

Given the fact that idiopathic NS mostly affects children below 5 years of age, IOS may be more appropriate to use in these patients than spirometry. In this study, we aimed to evaluate the respiratory function of children with NS aged 3-18 years with IOS and spirometry in order to document how respiratory function tests are influenced–even at subclinical level- during hypoalbuminemia and generalized edema. Our second objective was to compare the IOS with conventional spirometry, to see the validity and reliability of this new noninvasive tool in nephrotic children.

2 | METHODS

This prospective cross-sectional study was conducted by Departments of Pediatric Nephrology and Pediatric Pulmonology at Kocaeli University. The study protocol was approved by the Kocaeli University Medical School Ethics Committee (2018/25). Written informed consent was obtained from the parents of all children.

2.1 | Study group

Fifty- five patients between the ages of 3 and 18 years who were followed up with a diagnosis of NS by Kocaeli University Pediatric Nephrology Department were enrolled in the study group. The diagnosis of NS was based on the International Study of Kidney Disease in Children (ISKDC) which defined NS as massive proteinuria leading to hypoalbuminemia, edema and hyperlipidemia [2].

The patients were divided according to phase of NS as follows: nephrotic phase (first attack and relapse) and remission. We defined the patients at the time of diagnosis as first attack. Patients with a negative or spot urine protein (mg / dL) / creatinine (mg / dL) ratio of <0.2 and serum albumin levels above 3.5 g / dL with urine dipstick on three consecutive days were considered in remission. Patients who developed new nephrotic proteinuria after remission were defined as relapse [2].

Patients with respiratory symptoms, desaturation, allergic disease and patients in remission who received low-dose steroid therapy at last one month were excluded from the study.

2.2 | Control group

The control group consisted of 40 children between the ages of 3 and 18 years without respiratory tract disease. Inclusion criteria for the control group were as follows: absence of personal or familial history of wheezing or asthma, personal or familial allergic rhinitis or eczema, exposure to cigarette smoke at home, history of premature birth or low birth weight, cardiac disease, obesity or muscle disease, connective tissue disease, malignancy, upper respiratory tract infection within the last 15 days and presence of normal growth and development.

2.3 | Study Design

Physical examination of all patients was performed at each control and disease stage (nephrotic phase or remission) was determined. Anthropometric measurements (weight, height and body mass index) and standard deviation scores were recorded according to reference tables [8]. Serum albumin and spot urine protein / creatinine levels of the nephrotic phase patients were recorded. Oxygen saturation was measured by pulse oximetry using a finger probe.

2.4 | Pulmonary function tests

Before the test, the patients' height and weight were measured with a Desis brand height-weight meter, computerized data entry with the date of birth and gender data was performed. Children over 6 years old performed both IOS and spirometry while children under 6 performed only IOS. Pulmonary function tests were performed before the patients were given steroid or immunosuppressive therapy.

2.5 | Impulse oscillometry

IOS (Jaeger Masterscreen, Wurzburg, Germany) was used to measure the input impedance of the respiratory system. A pneumotachograph was calibrated with a special 3-L metal syringe daily. Before this process, data regarding hygrometer and room temperature and humidity were recorded. Before applying IOS, each child was informed about the procedure and was told to breathe normally during the test. The IOS test was performed using a nose clip while the child was in the sitting position, the neck was slightly extended and breathing was normal. The chin and cheeks were stabilized manually by the investigator during the measurement. For measurements, 30 sec of regular respiration without sudden changes (coughing, swallowing, vocalization, or breath holding) was considered sufficient and at least three maneuvers were performed. The best test results were recorded. Resistance (R), which is the energy required to propagate the pressure wave through the airways and reactance (X), which reflects the viscoelastic properties of the respiratory system at 5, 10, 15, and 20 Hz (kPa/(L/s)) and their percent predicted were recorded. Also, pulmonary impedance (Z) which consists of resistance and reactance parameters and the area of reactance (AX), which represents a summation of reactance values below resonance frequency were measured. The test, 0.6 at 5 Hz, and 0.8 at 10 Hz on the section of “coherence” was considered appropriate. We measured percentage of predicted R, X, F res, Z, and AX values at 5–20 Hz frequency

levels using IOS, and statistical analyses were performed on these values. Predicted values for IOS parameters were calculated according to the reference equations[9].

2.6 | Spirometry

To participants who were able to adapt to spirometry, first IOS was applied, then spirometry was performed on the Flowhandy ZAN100 spirometer. Spirometry was performed by closing the nose with a clip while the patient was sitting upright. The best value of a minimum of the three adequate measurements was taken. Values of FEV1, FVC, FEV1 / FVC, PEF and MEF25-75 measured by spirometry were recorded according to the criteria of the American Thoracic Society and ERS [10]. Predicted spirometry values were calculated according to GLI 2012 reference standards[11.] Statistical analyses were performed on percentage of predicted values. Spirometry results of children who could not adapt to spirometry were not included in the study.

2.7 | Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 23.0 (SPSS, Chicago, IL). Categorical variables were presented as n (%). Normality was tested using the Shapiro-Wilk test. Data are presented as mean ± SD for parametric data and median (range or interquartile range [IQR]) for non-parametric data. Student's t-test was used for comparison of parametric variables, and Mann-Whitney U test was used for non-parametric data. Correlation between continuous variables was analyzed with Spearman Correlation Analysis. A value of $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

98 (58 patients and 40 healthy children) children were enrolled in the study. After the examination three patients were excluded the study. Two of them had respiratory symptoms (pneumonia, pleural effusion, desaturation) during the nephrotic period and one of them had an allergic disease. None of the 55 patients included in the study had respiratory complaints or examination findings. Demographic and anthropometric data of children are presented in Table 1. There was no difference between groups in terms of demographic characteristics and anthropometric measurements. ($P > 0.05$).

3.2| Pulmonary function test results

Of the 60 children who were older than 6 years, 45 could perform spirometry and 15 were not able to perform repeated forced expiration maneuvers needed for spirometry.

IOS was administered to 55 patients with NS and 40 healthy children. All of them completed the IOS test successfully. In total, 45 children (30 patients and 15 controls) underwent spirometry with measurement of percent predicted FEV1%, FVC%, FEV1/FVC%, PEF% and MEF25–75%.

While serum albumin levels of first-attack patients were statistically lower than patients with relapse, there was no significant difference between the spot urine protein/creatinine values of the two groups. We did not find any significant difference between the IOS and spirometry parameters of children with nephrotic syndrome at first attack and relapse (Table 2).

Percent predicted values of R5, R10, R5-20, AX and Z5 were higher in children with nephrotic phase compared with remission phase patients and control group. No statistically significant difference was found between the IOS data of children with nephrotic syndrome in the remission period and children in the control group (Table 3).

Spirometric indices of FEV1%, FEV1/FVC%, PEF% and MEF25-75% were lower in nephrotic phase patients than controls. PEF% and MEF25-75% values of nephrotic phase patients were lower than remission patients' values. When spirometry values of the patients in remission and control group were compared, no difference was found (Table 4).

3.3| Correlation of IOS and spirometry

In our study, the correlation between percent predicted spirometric results and percent predicted IOS results of patients were evaluated. FEV1% showed negative correlation with percent predicted R5%, R10%, R15%, X10% and X15% results, FEV1/FVC% showed negative correlation with percent predicted R5%, R5-20 and X15% results, FVC showed negative correlation with percent predicted X10% results, MEF25-75% showed negative correlation with percent predicted R5%, R10%, R5-20, X15%, F res, Z5 and AX results. No significant correlation was found between the PEF% parameter measured by spirometry and any IOS parameter (Table 5).

4 | DISCUSSION

Edema, a major symptom in children with nephrotic syndrome, may not always be present in the lungs. However, the absence of edema may not mean that there is no lung involvement. Although the lungs are protected from widespread edema in children with NS, there is no study showing whether respiratory functions are affected.

Conventional spirometric tests have an important role in detecting pediatric airway problems, for both determining disease severity and monitoring. In order to achieve the optimum result of conventional spirometry, repetitive implementations are needed along with sufficient time for explaining the procedure to get the maximal patient cooperation [12,13]. In a study conducted in children aged 3-5 years, the spirometry was reported to be inapplicable and even in selected patients with very good control, acceptable test performance was attained only in 55% of the children [12]. In our study, while none of the children under the age of 6 tried to do spirometry, 75% of the children over the age of 6 who tried to perform spirometry were able to complete the test satisfactorily.

To overcome these limitations, various studies were carried out to develop new methods to measure lung function especially in young children such as plethysmography, respiratory inductance plethysmography, interrupter technique (Rint) and forced oscillation techniques. However, most of these methods cannot be used in young children due to applicability problems [14].

At this stage; forced oscillation techniques applicable during normal tidal respiration, requiring minimal patient co-operation, has been introduced in young children. IOS is one of these techniques defined by Dubois et al 50 years ago that allows passive measurement of

lung mechanics. Measurements are made during normal tidal breathing with only passive cooperation of the patient [4].

There are many studies showing that IOS is an effective method to evaluate airway pathologies in small children, especially in asthma, both for diagnosis and disease monitoring[15-17]. A study comparing the spirometry and IOS results of asthmatic children both basally and at exacerbations revealed similar spirometric indices in both group other than small difference in FEV1/FVC% while there was a significant difference between the R5Hz, R5-20Hz and AX values of the parameters examined with IOS [18].

To the best of our knowledge, there are no studies on the measurement of lung function of nephrotic children by IOS and/or spirometric methods. However, in adult nephrotic patients some spirometry studies do exist. For example, in a study conducted by Balaji et al., comparing 25 adult patients with NS and end stage renal disease with controls; lower spirometric results were reported in patients. The authors had attributed this result to pulmonary edema and uremia [19]. In our study, respiratory functions were evaluated in the frequency of 5-10-15-20Hz of IOS in 55 children with NS and 40 healthy controls. Resistance, reactance, resonance frequency, impedance and reactance area were measured.

NS is characterized by a sudden onset, edema is the main presenting symptom. Although relapsed patients present with recurrence of massive proteinuria, edema is often accompanied [2]. In the present study, there was more intense edema in first attack than relapse in terms of serum albumin levels (1,7 g/dl vs 2.08 g/dl, p=.004) there was no difference between the spot urine protein/creatinine levels (p=>0,5). We did not find any difference in respiratory parameters with both IOS and spirometry between these groups. We attribute the equally impaired respiratory function of both groups to the relapse patients who had massive proteinuria as well as those in the first attack.

In the nephrotic phase, the values of R5%, R10%, R5-20Hz, X15%, Z5% and AX were higher than the control group, indicating distal airway involvement in nephrotic children during active disease. In diseases causing obstruction in distal airways, a frequency-dependent increase in resistance is observed. At low frequencies, such as R5Hz, the pressure waves spread towards the lung periphery, while at the higher frequencies such as R20Hz, the more proximal resistance is measured. Reactance decreases in distal obstructions; because of the narrowed airways, the proximal airways are detected as distal airways and the signals are returned. In our study, the increase in R5% values was higher in patients at nephrotic phase compared to the remission and control group, and the difference from R5 to R20 was gradually decreased. High frequency oscillations (R15, 20Hz and X15, X20Hz) provide

information about the central airways. In our study, no significant difference was found in the high frequency oscillatory R and X values of the patient and control groups; which is a finding indicating the central airways being spared. This small and distal airway involvement we showed in children with nephrotic syndrome in our study can be associated with both airway diameter and gravity. It can be thought that the diameter towards the distal becomes smaller and the interstitial fluid will accumulate more due to gravity-dependent edema, especially for the basal lung areas.

The spirometric findings in our study were similar to the literature. Similar to the results of Balaji et al., FEV1%, FEV1 / FVC%, PEF% and MEF25-75% of the patients in the nephrotic phase were lower than the control group. These findings were in consistent with distal and small airways obstruction and in parallel with IOS results of patients in the nephrotic phase. Spirometry and IOS parameters of 23 patients in remission period were compared with control group. No difference was found between the two groups. It was thought that the patients in remission had similar results with the control group probably due to the recovery of the tissue fluid dynamics secondary to resolution of hypoalbuminemia.

There are studies in the literature evaluating the correlation between IOS and spirometry. In a study by Song TW et al. in children with asthma over 7 years of age, the spirometric parameters of FEV1% and PEF% were shown to be correlated with Z and R5,10,20,35Hz and FVC to Z, R10,20,35 Hz. The correlation between the parameter MEF25-75% with any IOS parameter could not be shown [20]. In another study conducted in our center, lung function of 49 patients (mean age years SD: 7.75±3.55) with cystic fibrosis (CF) was evaluated with IOS and spirometry, and IOS was shown to be able to detect altered lung function in children with CF. Correlation of IOS and spirometry was also evaluated in the same study. FEV1% was correlated with R (5-10 Hz), X (5,10,15Hz), F res, Z and AX. FVC % was correlated with X (10-15 Hz), F res and AX. MEF25-75 was correlated with all IOS values except R15 and R20 [21]. In our study, IOS and spirometry parameters of the participants were evaluated, and similar to the previous studies FEV1% showed correlation with R% (5-10-15 Hz) and X% (10-15 Hz). FVC% was correlated with X10%. FEV1/FVC was correlated with R5%, R5-20 and X15%. MEF 25-75 was correlated with R% (5,10,5-20 Hz), X15%, F res, Z5% and AX. The IOS parameter showing a significant relationship with the PEF% value was not determined.

To the best of our knowledge, in this study, we have shown for the first time in the literature that respiratory functions are affected in the pattern of distal airway obstruction in

children with nephrotic syndrome. For the clinical significance or consequences of this finding, studies with larger patient groups are needed. Another important result is the significant correlation between IOS and the conventional spirometry supporting the hypothesis that IOS, as a novel method, can be a reliable tool in children to evaluate respiratory function and it may even be superior to spirometry in small children.

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