Forced Oscillation for Monitoring Children with Cystic Fibrosis

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Cystic fibrosis (CF) is a multi-system genetic disease with a considerable burden of morbidity that is mainly attributed to respiratory health deterioration. Forced oscillation technique (FOT) requires minimal cooperation from the patient as it is effort-independent. All it needs is resting tidal breathing through a mouthpiece while sound waves of different frequencies are superimposed through a loudspeaker. It has been used mainly for monitoring patients with asthma but is increasingly being applied in patients with CF.

Keywords: cystic fibrosis ; forced oscillation ; oscillometry ; spirometry

1. Introduction

Cystic fibrosis (CF) is a multi-system genetic disease with a considerable burden of morbidity that is mainly attributed to respiratory health deterioration. Mortality is not negligible and is attributed mainly to lung disease progression and respiratory complications. Therefore, monitoring of respiratory health of patients with CF, during both clinical stability and respiratory exacerbations, is mandatory. Spirometry is the most commonly applied method for monitoring lung function of school-aged children, adolescents, and adults with CF [1][2]. An inherent limitation of spirometry is that it requires a patient's cooperation and therefore is usually not applicable in children younger than 6 years old. Therefore, other modalities of lung function assessment such as forced oscillation technique [3] and breath washout [4] have been explored in preschool-aged children as well as in older children and adolescents.

2. Forced Oscillation for Monitoring Children with Cystic Fibrosis

2.1. Forced Oscillation Technique-Background

FOT was initially described by Dubois in 1956 [5]. Since then, several FOT variants were developed regarding measurement patterns, oscillation frequencies and assessment principles. More recently, the impulse oscillometry technique (IOS) was developed, which generates pressure oscillations at a standard square pressure wave, at a frequency of 5 Hz from which all other applied frequencies are derived using spectral analysis.

FOT measures the airway impedance (denoted as Zrs) which is comprised of two components: the real part, which is the resistance (denoted as Rrs), and the imaginary part, which is the reactance (denoted as Xrs). The resistance is the in-phase component of respiratory impedance which reflects the relationship between the applied pressure and the resultant flow. The reactance is the out-of phase component of impedance and encompasses the capacitive and inertive properties of the lung [3][6].

The resistance represents the total respiratory system resistive properties (extrathoracic and intrathoracic airways, lung parenchyma, and chest wall). The resistance at low frequencies (i.e., 5 Hz) reflects the total airway resistance while the resistance at high frequencies (i.e., 20 Hz) reflects large airway resistance, as high-frequency sounds do not reach the small airways. The difference between resistance at 5 Hz and resistance at 20 Hz reflects the small airway resistance.

The reactance comprises the inertia of the air column to move which is positive in sign, and the capacitance of the lung which reflects the elasticity of the lung and is negative in sign. For both technical and physiological reasons oscillometry results are most often reported as the resistance and reactance at 5 Hz (Rrs5 and Xrs5, respectively), and the resistance and reactance at 20 Hz (Rrs20, Xrs20, respectively), although the results from other frequencies may also be reported.

The frequency at which the reactance crosses zero is called resonant frequency (denoted as Fres). At this point, the capacitive properties are equal and opposite to the inertive forces. Below this frequency capacitive properties are dominant whereas above this frequency inertive properties dominate [6].

Another important measurement of oscillometry is AX which represents the sum of all reactance components at all frequencies before the resonant frequency. It reflects the total area that capacitance is dominant reflecting the elastic properties of the lung [7].

2.2. Feasibility and Reliability

In healthy children, the oscillation technique is feasible even from the age of three years, as there is no need for an expiratory maneuver, as in spirometry. The within-test variation, as it was demonstrated by Hall et al. in healthy children, is satisfactory; it is higher in children who have their serial attempts without any rest in between [8]. Concerning the short-term repeatability within 15 min, the relative mean difference was 2% for all FOT variables except for reactance, which showed a relative mean difference of 3.8%.

The feasibility was also assessed in children with CF. Kerby et al. evaluated spirometry and forced oscillation in children with CF and healthy controls aged 36 to 60 months [9]. Acceptability rates did not differ between patients and controls, and between males and females, for each age range. They were higher compared to those of spirometry. The overall acceptability rate was 70% for FOT among children with CF and 72% among healthy controls. However, for children with CF aged between three and four years, the acceptability rate was as low as 40%. The intraclass correlation coefficient (ICC) for two-week interval reproducibility was moderate for resistance and reactance but lower to the respective ICC for spirometric measurements at the same interval. Higher ICC was found in another study [10] in children with CF and healthy controls; however, the age range was 6–14 years, and therefore, this difference could be attributed to the different age range from the study of Kerby et al. [9]

2.3. Correlation of Oscillometry and Spirometry Values in Children with Cystic Fibrosis

Spirometry is considered the gold standard method for the assessment of lung function. Therefore, several studies have evaluated the correlation between spirometry and oscillometry indices in children with CF. In 1997 Lebecque et al. [11] investigated this correlation in both asthmatic and CF children. The Rrs was measured at 10 Hz. According to their findings, FEV1 and Rrs showed concordant results in only 16/45 studied children with CF. They also found that Rrs failed to detect even severe airway obstruction as this was indicated by FEV1. The results were not surprising as CF affects mainly the peripheral airways and this obstruction can be depicted by FEV1 but not by Rrs at 10 Hz (which mainly reflects the large airways resistance). The authors did not use other frequencies nor did they assess reactance or other parameters. Similarly, when different lung function tests were evaluated in children aged 2–8 years with CF, no significant correlation between FEV1 with Xrs and Rrs at 5 Hz was found [12]. A similar study was also conducted later by Moreau et al. [13] in children with CF, aged 4–19 years, that evaluated FOT at the same frequency of 5 Hz. They also did not find any significant correlation between FEV1 and FOT values when the indices were expressed as a percent of predicted values. They only found a significant correlation between raw data. More recently, however, in another study [14] that enrolled 34 children and 5 adults, it was shown that there was a significant negative correlation between FEV1 and Zrs5, Rrs5 and Rrs20 when the indices were expressed either as a percent of the predicted values or as raw data. Xrs5 correlated with FEV1 at a significant level only when raw data were considered.

2.4. Distinguishing Subjects with Cystic Fibrosis from Healthy Controls by Oscillometry

In 1973 Cogswell [15] used the FOT in healthy children, children with asthma, and children with CF. Although the authors did not compare in their analysis the results of healthy and CF children, it was mentioned that many of the children with CF had Rrs within the normal range, although the values tended to increase with age and during exacerbations. In 1985 Solymar et al. [16] studied, among other patients, 13 children with CF and found that only 4 had abnormal Rrs values; the reactance at 2 Hz was the most discriminative variable, as it was abnormal in 6/13 patients. A similar study in 2011 compared preschoolers with CF and healthy controls of the same age and showed that FOT indices were not different between clinically stable CF patients and healthy controls, whereas acceptable measurements for spirometry were lower for children with CF compared to controls [9].

3.5. Oscillometry and Its Association with the Clinical Condition in Subjects with CF

Oscillometry has been evaluated in patients with CF before exacerbation and following a 14-day treatment regimen at the hospital [17]. It was found that there was a significant decrease of absolute values of reactance and resistance at 5 Hz by 22% and 27% respectively and these differences were statistically significant. In contrast, the resistance measured at levels >10 Hz and reactance measured at levels >15 Hz did not show any significant change. There was also a significant increase of FEV1 by 27%. Similarly in 2015 Buchs et al. [18] noticed that there was a significant change of reactance and resistance at 5 Hz by 22% and 13%, respectively, following intravenous antibiotic treatment in patients at exacerbation whilst there was a significant increase of FEV1 by 20%. The higher amplitude of change among FOT variables was observed for Xrs5 and Xrs10.

2.6. Oscillometry and Its Association with Pulmonary Inflammation, Infection, and Structural Lung Disease, in Subjects with CF

Another issue that received the attention of researchers was whether FOT measurements were related to the presence of inflammation and infection markers in bronchoalveolar lavage (BAL) fluid. In a study that included a small number of patients aged younger than 6 years, it was shown that FOT was sensitive at detecting early lung disease, as the latter was defined by the presence of inflammation in BAL fluid [19]. Some years later Ramsey et al. [20] found that the BAL neutrophil count of 184 longitudinally studied children was associated with an increase of Fres z-score and Interleukin 8 with a lower reactance z-score at 8 Hz, whereas neutrophil elastase was not associated with any of the FOT values. They also showed that only the isolation of Haemophilus influenza in the BAL was associated with increased resistance and decreased reactance z-scores at 8 Hz. No association was found between other bacterial pathogens and any FOT parameters. The only structural lung disease that was associated longitudinally with a decrease of reactance z-score at 8 Hz was the presence of air trapping. They concluded that FOT parameters were not sensitive enough to detect the underlying lung disease either cross-sectionally or longitudinally.

3. Conclusions

It becomes evident that the role of oscillometry as a lung function modality for monitoring respiratory status in children and adolescents has not yet been established. More studies are needed in order to evaluate the longitudinal relationship of patients' clinical condition and oscillometry values, as well as the relationship of oscillometry indices with those of spirometry, since the existing studies are, in their majority, of small size and their results are conflicting. In the era of the COVID-19 pandemic, there is an increasing interest in oscillometry, as it is a procedure with lesser aerosol generation compared to spirometry. This is another non-negligible reason for clarifying whether oscillometry can provide useful information for the respiratory status of children and adolescents with CF while on exacerbation or clinical stability.

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