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Respiratory impedance in children with cystic fibrosis using forced oscillations in clinic

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ABSTRACT

Background: Measurement of lung function is an important component of clinical management in cystic fibrosis (CF) but has been difficult in young children. This study aimed to characterise the utility of the forced oscillation technique to measure lung function in preschool-age children with CF in a routine clinical setting.

Methods: Lung function was assessed in 56 young children (2–7 years) with CF. Resistance and reactance at 6, 8 and 10Hz (Rrs6, Rrs8, Rrs10, Xrs6, Xrs8 and Xrs10, respectively) were measured and expressed as Z scores. Children were classified as asymptomatic or symptomatic based on an administered respiratory questionnaire and physical examination at the time of testing. Between-test repeatability was assessed in 25 children.

Results: Measuring lung function using FOT was feasible in the CF clinic. Children with CF, as a group, had Z-scores for Rrs6 ($p<0.001$), Rrs8 ($p<0.001$), Rrs10 ($p<0.001$), Xrs6 ($p<0.001$) and Xrs8 ($p=0.02$) significantly different from zero. Children with current symptoms had significantly decreased Xrs ($p<0.05$) and increased Rrs6 ($p=0.02$) compared to asymptomatic children.

Conclusion: Measuring lung function with FOT is feasible in young children with CF in a clinical setting. The technique has the potential to improve our knowledge on early CF lung disease.

Word count: 198

INTRODUCTION

Onset of lung disease in cystic fibrosis (CF) occurs early in life with changes in lung structure [1,2] and function [3-6] as well as the presence of inflammation and infection [3,5-7] in otherwise asymptomatic infants. During the preschool years structural changes and abnormalities due to CF have been identified using high resolution computed tomography (HRCT) [1,8,9]. Measurement of lung function is an integral component of the clinical management of older children and adults. Spirometry is commonly used in older children to predict pulmonary exacerbations or to track responses to therapy; however alternative techniques are required for routine use in younger children.

Alterations in the respiratory function of young children with CF have been demonstrated using the interrupter technique [10-12], multiple breath washout method [13-14] and impulse oscillations [12,15]. The forced oscillation technique (FOT) is a practical method to monitor pulmonary function in young children requiring minimal patient co-operation [16,17]. It provides information about both respiratory system resistance (Rrs) and apparent stiffness (reactance; Xrs) that can not be obtained using either the interrupter or multiple breath washout techniques. The use of a FOT technique that employs pseudorandom noise (PRN) as a forcing signal may provide different information on respiratory dysfunction compared to impulse oscillation (IOS), a variation of the FOT that uses an intermittent pressure impulse [18]. This study focuses on PRN oscillatory signal and will be referred to as FOT unless otherwise stated.

Studies utilising the FOT in healthy young children have demonstrated that, at frequencies less than 10 Hz , measurements of Rrs and Xrs are repeatable with a mean coefficient of variation (CV) of <10.2% and <20.5%, respectively and a standard deviation between two measurements over a 15 minute period of <1.3 hPa.s/L and <1.0 hPa.s/L, respectively [19-21]. However, in children with respiratory diseases repeatability might be different and has not been studies yet in children with CF.

This study aims to determine the utility of using FOT to measure respiratory function of a young CF population during a routine clinical setting.

METHODS

Patients

Fifty six children between the ages of 2 and 7 years with CF, who underwent pulmonary function testing as part of their clinical assessment at Princess Margaret Hospital for Children, Perth, Australia, participated in the study. Diagnosis of CF was determined through new born screening in 56% of patients, respiratory symptoms in 9% and failure to thrive, meconium ileus or family history in the remaining 35%. Diagnosis of CF was confirmed by sweat test [22]. Parents gave written consent for their children to participate in the study and the study was approved by the ethics committee of Princess Margaret Hospital for Children.

Protocol

Assessment of the children, including height and weight measurements, was performed on the day of respiratory function tests. Children were classified as being

currently symptomatic or asymptomatic at the time of consult through a validated administered questionnaire to parents with clinician comments [23]. Children were classified as currently symptomatic if a parent reported cough, sputum production or a current cold or had signs of a lower respiratory tract infection detected by a paediatric respiratory physician. Children were classified as asymptomatic if free of respiratory symptoms and abnormal respiratory signs at time of investigation.

Pulmonary infection data were obtained from the most recent bronchoalveolar lavage performed as part of the routine annual assessment. Infection data was not used for 10 children as BAL visit was more than one year before FOT, or children had not undergone a BAL.

Pulmonary function was first attempted at 2 years of age and at every subsequent 3 monthly clinic visit in order to familiarise the children with the FOT. Once children could produce at least three technically acceptable measurements in a single test session measurements were recorded and retained.

Forced Oscillation Technique

Forced oscillatory measurements were performed according to European Respiratory Society recommendations [16] and as previously described by our group [21]. Measurements of respiratory system input impedance (Zrs) were obtained using a commercially available device (I2M, Chess Medical, Ghent, Belgium) based on the research equipment prototype described by Landser *et al* [17]. Briefly, a loudspeaker generated pseudo-random noise forcing signal, containing integer-multiple frequencies between 2 and 48 Hz was applied at the mouth of the child via a

mouthpiece containing a 0.1μm pore bacterial filter (SureGard; BirdHealthcare, Australia). Mouth pressure and flow were recorded for 8 s per measurement at the airway opening and Zrs spectra calculated from both the inspiratory and expiratory signals. The equipment accuracy was verified daily using known impedance and the Zrs spectra were corrected for the impedance characteristics of the mouthpiece and the bacterial filter.

The patient sat upright, wearing a nose clip breathing quietly through the mouthpiece. To minimise upper airway shunting the patient's cheeks and lower jaw were supported by a technician. Children had a minimum of 3 and maximum of 7 measurements collected. Measurements were considered technically inadequate and excluded if 3 or more individual frequencies had coherence <0.95, if leak occurred around the mouth piece or if physical artefacts such as a cough, swallow or glottis closure were detected. Technically acceptable corrected Zrs spectra were analysed and average resistance (Rrs) and reactance (Xrs) at 6, 8 and 10 Hz recorded. We aimed to obtain a within-test variability of Rrs of less than 10%. However, individual measurements and the subsequent averaged Zrs data were not excluded if this criterion was not met.

To determine the between-test repeatability, a second set of measurements was recorded 15 minutes after the first set in a sub group of children (n=25).

Statistical analysis

Data are expressed as mean (± standard deviation (SD)) and were normally distributed unless otherwise stated. Differences between symptom groups was analysed with

Mann-Whitney Rank Sum Test. Coefficient of repeatability (CR) (1.96*SD of difference between 2 measurements) was calculated for tests performed 15 minutes apart according to the methods of Bland and Altman [24] and comparison between symptom groups analysed using an independent t-test.

Baseline respiratory function (Rrs and Xrs) was expressed as Z-scores, calculated from reference values derived from local population of 158 healthy preschool-children, aged 2 to 7 years, in whom respiratory impedance was measured using an identical FOT protocol [21]. This group of healthy children did not have doctor diagnosed or parentally reported wheeze or asthma at any time of their life and no acute respiratory infections within the past 3 weeks and is described in detail elsewhere [21]. Z-score were not calculated in children with CF who were shorter than 92 cm as this was the lower limit in the healthy population. Bartlett's Test [25] was used to test whether children with CF had altered respiratory function from the healthy reference population. All statistical analyses were performed using SPSS for Windows 11.5 (SPSS inc., Chicago, IL, 2002).

RESULTS

Details of the study population are given in table 1. There were no significant differences in age, height or weight between children classified as currently asymptomatic or currently symptomatic.

Table 1: Patient demographics of the cystic fibrosis population.

	Total CF group	Asymptomatic	Symptomatic

n	56	26	30
Gender (male/female)	25/31	13/13	12/18
Age (years)	4.3 ± 1.2 (2.4 – 6.9)	4.0 ± 1.1 (2.5 – 6.6)	4.5 ± 1.2 (2.4 – 6.9)
Height (cm)	102.0 ± 9.8 (86 – 127)	101.0 ± 10.4 (86 – 127)	102.9 ± 9.4 (86 – 123)
Weight (kg)	16.8 ± 3.8 (10.7 – 27.0)	16.5 ± 4.0 (10.7 – 26.0)	17.0 ± 3.6 (10.9 – 27.0)
Genotype			
ΔF508 Homozygous	31	14	17
ΔF508 Heterozygous	24	11	13
Other	1	1	0
Microbiology*			
Pseudomonas aeruginosa	2	1	1
Staphylococcus aureus	5	1	4
Haemophilus influenzae	4	2	2
Mixed oral flora	8	3	5
Isolated colonies	10	5	5
No detectable bacteria	19	12	7
Not available	10	3	7

Values shown are mean ± SD (range); *results from last bronchoalveolar lavage, pathogen identifed as >104cfu/ml., isolated pathogen identified as <104cfu/ml.

Repeatability

Between-measurement repeatability of Rrs and Xrs are shown in table 2.

Table 2: Between-measurement repeatabillity of resistance and reactance in young chilren with cystic fibrosis.

	Mean difference ± SD	Percent difference ± SD(%)	Coefficient of Repeatability
Rrs6	0.18 ± 1.25	2.0 ± 11.2	±2.46
Rrs8	0.18 ± 1.08	2.0 ± 10.1	±2.12
Rrs10	0.27 ± 1.07	2.6 ± 10.6	±2.10
Xrs6	-0.16 ± 0.70	4.7 ± 18.1	±1.36
Xrs8	-0.28 ± 0.67	9.5 ± 27.2	±1.31
Xrs10	-0.34 ± 0.74	12.7 ± 29.8	±1.45

No systematic bias in between-test repeatability for Rrs or Xrs was observed (figure 1). Absolute and relative differences in lung function between-tests were not dependent on mean lung function, height or age using univariate modelling. The CR between tests was <2.5 hPa.s/L for Rrs and <1.5 hPa.s/L for Xrs, equating to a difference of <3% for Rrs and <13% for Xrs (table 2). Repeatability was not affected by the presence of respiratory symptoms (data not shown).

Figure 1: Bland Altman plots for resistance (Rrs) and reactance (Xrs) at 6Hz showing mean difference (—) with limits of agreement (---) for two sets of forced oscillation

measurements made 15 minutes apart in children with cystic fibrosis. Measurements made in the absence (○) or presence (●) of respiratory symptoms are shown.

Respiratory Function

Z-scores were calculated in 53 children (of 56 children) with a height >92cm. The distribution of respiratory function in children with CF related to the healthy reference population is shown in figure 2. Technically acceptable measurements were obtained, on average, after 2 to 3 visits. As a group, children with CF had significantly increased Rrs compared to the healthy reference population with z-scores for Rrs6 ($p<0.001$), Rrs8 ($p<0.001$) and Rrs10 ($p<0.001$) significantly different from zero (table 3). Even when children were classified asymptomatic (n=24) at the time of testing, Z-score Rrs8 ($p<0.02$) and Rrs10 ($p<0.05$) was significantly increased from zero.

When compared to the healthy population the Z-scores for Xrs in children with CF as a group were significantly different from zero at Xrs6 ($p<0.001$) and Xrs8 ($p=0.01$) but not Xrs10 ($p=0.09$) (table 3). These differences were primarily due to the children who were symptomatic at the time of testing (Table 3).

Figure 2: Distribution of resistance (○) and reactance (Δ) at 8Hz of 56 children with cystic fibrosis, when asymptomatic (open symbols) or symptomatic (closed symbols), compared to healthy reference population. Measurements of mean (—) and 95% confidence intervals (---) of regression of the healthy reference population are shown.

Table 3: Z score respiratory resistance and reactance using the forced oscillation technique in children with cystic fibrosis as a group, and when asymptomatic and symptomatic.

	Whole population	Asymptomatic	Symptomatic	Asymptomatic v^{s} symptomatic (p value)
n	53	24	29	
Rrs6	0.64 ± 1.05†	0.26 ± 0.82	0.95 ± 1.12†	0.02
Rrs8	0.73 ± 1.05†	0.46 ± 0.92*	0.96 ± 1.11†	0.09
Rrs10	0.63 ± 1.07†	0.41 ± 0.92^{f}	0.82 ± 1.16†	0.17
Xrs6	-0.71 ± 1.16†	-0.27 ± 0.90	-1.08 ± 1.25†	0.01
Xrs8	-0.52 ± 1.41‡	-0.09 ±1.15	-0.87 ± 1.53‡	0.05
Xrs10	-0.30 ± 1.26	0.15 ± 0.93	-0.67 ± 1.39‡	0.02

Data shown as mean ± SD; p values are compared to healthy children; $^{\dagger}p<0.001$; $^{\ddagger}p<0.01$; $^{*}p<0.02$; $^{f}p<0.05$

DISCUSSION

In the present study we measured respiratory function in 56 young children with CF using the FOT in a routine clinical setting and demonstrated that these children had an increased Rrs and reduced Xrs compared to a healthy reference population [21]. The test was easy to perform and feasible within the clinical setting. Children with current symptoms had increased Rrs6 and lower Xrs (6-10Hz) compared to children who were asymptomatic at the time of testing. The between-test repeatability in young children with CF was similar to that previously reported in healthy preschool aged children [21].

Between-test Repeatability

The present study characterised the repeatability of between-test measurements over a 15 minute period in a young CF population, with the SD of changes for Rrs (1.07 - 1.25 hPa.s/L) and Xrs (0.67 – 0.74 hPa.s/L) within the ranges of short-term repeatability previously reported in healthy children for Rrs (0.55 – 1.41 hPa.s/L) and Xrs (0.57 – 1.21) [19-21,26,27]. In the present study between-test repeatability was not influenced by symptoms and suggests that in young children with CF, short-term repeatability may not be a function of disease, history or status.

Respiratory Function

As a group, children with CF had significantly worse lung function, with higher Rrs at 6, 8 and 10Hz and lower Xrs at 6 and 8Hz compared to a healthy reference population. However, most children with CF had pulmonary function within the normal range, as defined as being within two standard deviations (±2 Z scores) of the mean of the healthy reference population (Figure 2). These data are consistent with previous reports from children with CF using the interrupter technique [10], multiple breath washout [14] and IOS [12,15]. The fact that the majority of children with CF fall into the normal range is not surprising as, in general, these children had mild disease with less than 5% of children presenting to clinic with respiratory signs of wheeze, crackles or respiratory tract infection. Some children did have abnormal lung function; 13% had Rrs8 and 17% had Xrs8 outside the normal range. This increased to 21% outside normal for both Rrs8 and Xrs8 in children with CF classified as symptomatic. This suggests that measurements outside the normal range may be indicative of clinically relevant disease. As measurements of pulmonary function were performed as part of our routine clinical assessment of children with CF, children

were measured as they presented to the clinic. Lung function testing is used as part of the clinical assessment of children with CF.

Evidence in the literature demonstrates that lung disease in young children with CF begins in the periphery. Structural changes to the parenchyma in CF have been identified in infancy and early childhood using high resolution computed tomography (HRCT) [1,2,9]. Likewise, the presence of inflammation in otherwise asymptomatic children has been reported in young children with CF [3,6,7]. We have previously shown in preschool children with CF the relationship between inflammation and tissue damping, which is reflective of respiratory tissue mechanics [6].

The association between respiratory symptoms and abnormal lung function becomes more apparent in older children with CF, possibly representing the progression of lung disease with age [28]. Studies in infants with CF by Brennan *et al.,*and Ranganathan *et al.,* both reported no associations with the presence or history of respiratory symptoms [5,6]. Although, children in this age group generally have mild lung disease, and in these studies were well enough to undergo general anaesthesia. An association between a history of CF-related symptoms and worsening lung function, measured with the interrupter technique, has been reported in preschool children who were asymptomatic at the time of testing [10]. Although it should be noted that the group children with a history of CF-related symptoms was considerably smaller (n=8), than children without symptoms (n=31) which may affect statistical outcome. The present study measured the respiratory fucntion of children with CF during routine clinic visit as part of the children's clinical assessment. At the time of clinical assessment the present study demonstrated that children with current symptoms had

decreased Xrs (6 – 10Hz) and increased Rrs6 compared to children who were asymptomatic at the time of testing. While this association suggests potential to add to clinical information, longitudinal assessments are required to determine the magnitude of clinically relevant changes in FOT derived variables in individual children.

Conclusion

The present study shows results of lung function measures using FOT in a typical clinic population of preschool children with CF. We have demonstrated that lung function in this group is reduced compared to a healthy reference group and that children with CF with current symptoms have reduced lung function compared to children with CF whom are asymptomatic. Measurements of lung function are an important aid to the clinical management of CF in older children. Further studies are needed to characterise clinically relevant changes in FOT variables and to determine the role of measuring lung function using FOT in the clinical management of preschool children with CF.

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Competing Interests

All authors declare no competing interest.

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Fig 1

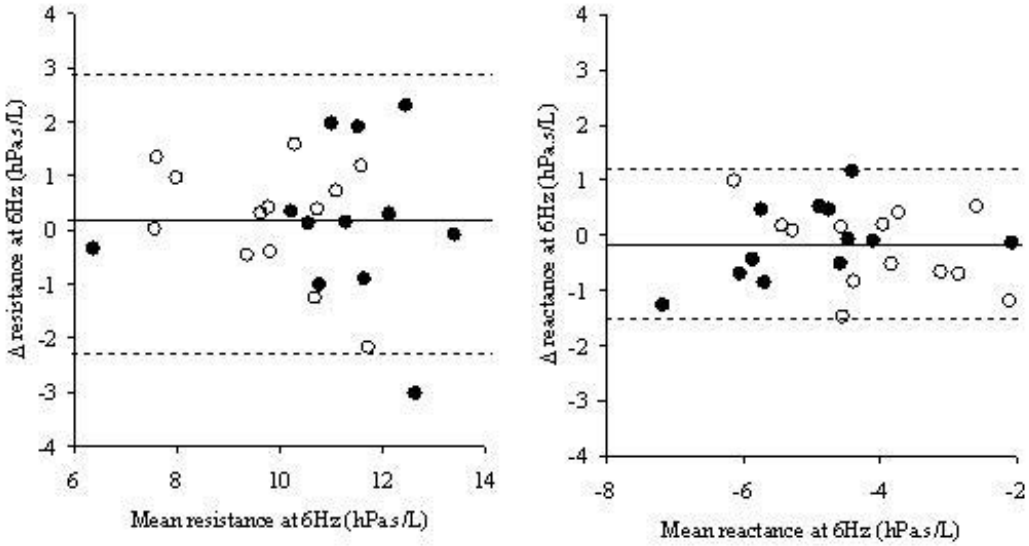
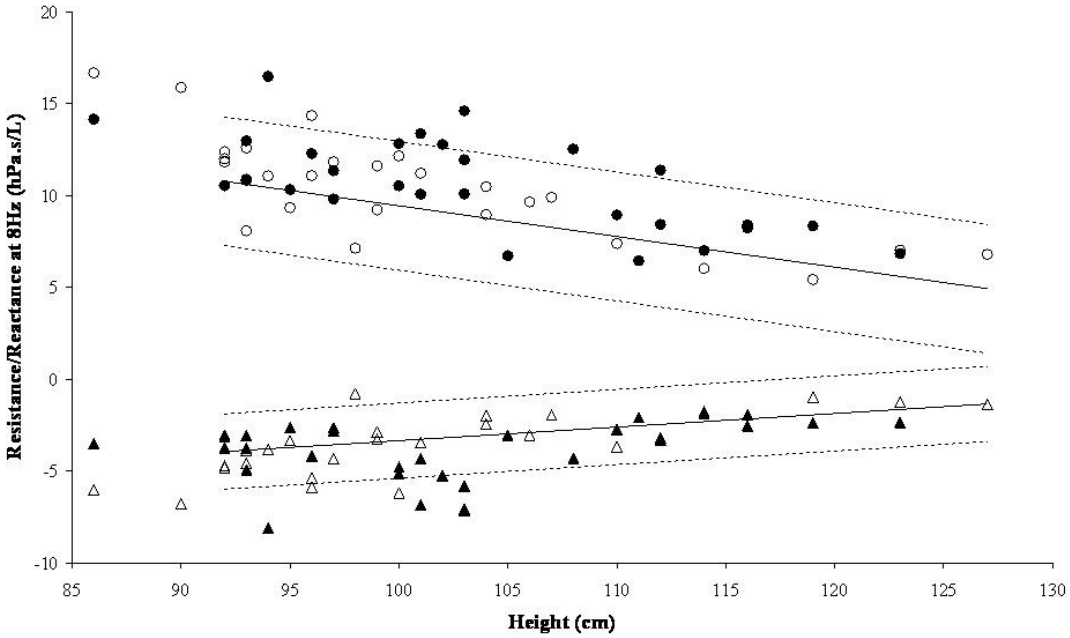

Δ resistance at 6Hz (hPa.s/L)
Mean resistance at 6Hz (hPa.s/L)
Δ reactance at 6Hz (hPa.s/L)
Mean reactance at 6Hz (hPa.s/L)

Fig 2


Resistance/Reactance at 8Hz (hPa.s/L)
Height (cm)
20
15
10
5
0
-5
-10
85
90
95
100
105
110
115
120
125
130