



Aberrant small airways function relates to asthma severity in young children



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ABSTRACT

Background: Frequency dependence of resistance (R5–20) assessed by impulse oscillometry (IOS) is suggested to be a measure of small airways. Small airways involvement during induced bronchoconstriction has been shown to reflect severity of asthma in adults.

Objective: Our aim was to evaluate if methacholine (Mch) induced changes in R5–20 are associated with the severity of exercise induced bronchoconstriction (EIB) in young children.

Methods: A total of 109 children aged 3–8 years were studied, 95 with obstructive symptoms and 14 in good health, to assess small airways function during a Mch challenge. R5–20 and other IOS resistance and reactance parameters were measured at baseline and after the Mch challenge. In a standardized exercise test, the children were grouped according to the severity of EIB expressed as the percentage increase in resistance at 5 Hz ($\Delta R5$) after exercise, indicating either no EIB ($\Delta R5 < 40\%$, $n = 84$), moderate EIB ($\Delta R5 40–80\%$, $n = 13$) and severe EIB ($\Delta R5 > 80\%$, $n = 12$).

Results: The baseline R5–20 was not associated with the severity of EIB, but during Mch induced bronchoconstriction the change in R5–20 was significantly higher in children with severe EIB (2.61 fold increase) than in children with moderate EIB (1.48) or no EIB (1.74, $p = 0.036$). No significant associations were found in changes of other IOS parameters. The children with severe EIB also used more short-acting beta-agonists during the past two months than the other two groups ($p < 0.001$).

Conclusion: Frequency dependence of resistance (R5–20) measured by IOS during the Mch induced bronchoconstriction and more frequent use of beta-agonists are associated with severe EIB in young children.

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1. Introduction

Attention has recently been targeted at the role of peripheral airways in asthma control and pathogenesis [1]. Small airways obstruction has been associated with nocturnal asthma, exercise induced asthma, difficult-to-treat asthma, recurrent exacerbations, fatal asthma and responses to inhaled corticosteroids [2]. Although the distal airways make up more than 90% of the total lung volume,

they are difficult to evaluate using conventional lung function measurements [1].

Individual responses to bronchoconstrictors such as methacholine (Mch) vary among patients with asthma [3]. Studies in adult asthmatics have shown that Mch induced changes in forced vital capacity, which is thought to reflect airway closure due to small airways dysfunction, are related to the severity of asthma, frequency of symptoms and steroid requirements [4]. However, similar studies of the importance of small airways dysfunction in children with asthma are so far lacking. In children with poorly controlled asthma, symptoms are often triggered by exercise. Exercise induced bronchoconstriction (EIB) is closely related to airway inflammation [5], and the severity of EIB can be graded by the lung function changes after exercise [6]. Exercise induced asthma symptoms have previously been linked to small airways dysfunction in adults [7].

It has been suggested that impulse oscillometry (IOS) can be used to assess both central and peripheral airways obstruction

Abbreviation: EIB, exercise induced bronchoconstriction; IOS, impulse oscillometry; Mch, methacholine; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; R5–20, difference between R5 and R20; X5, respiratory system reactance at 5 Hz; X10, respiratory system reactance at 10 Hz; AX, reactance area; HR, heart rate; SPT, skin prick test; SABA, short-acting beta-agonist; PD40R5, provocative dose to induce 40% increase in R5.

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[8,9]. Frequency dependence of resistance may reflect peripheral airways, as early models of respiratory mechanics predicted frequency dependent behaviour of resistance and compliance in lungs with heterogeneities in time constants [10]. More recent models have suggested that respiratory resistance and reactance are sensitive to parallel heterogeneity in airway diameter and this is characterized by randomly closed or nearly closed airways [11]. A number of oscillometric parameters are thought to reflect such changes in the small airways, including R5–20, the difference between the respiratory resistance at 5 (R5) and 20 Hz (R20) [12], as well as reactance at 5 Hz (X5) and the area delineated from the curve of the negative component of reactance (AX) [8,13].

Since oscillometric parameters may be sensitive to airway heterogeneity and closure, we aimed to evaluate if IOS changes previously suggested to reflect small airways dysfunction appear during bronchoconstriction in children with obstructive symptoms. We applied an experimental design by using a standardized Mch provocation in order to induce bronchoconstriction, and the parameter of special interest was the frequency dependence of resistance, expressed as R5–20. Secondly, we investigated whether the IOS pattern suggesting involvement of small airways during bronchoconstriction is associated with clinical expression of asthma in these children. The severity of asthma was assessed by the magnitude of EIB during exercise test and the use of beta-agonists. We hypothesised that frequency dependence of resistance (R5–20) may detect small airways dysfunction during Mch induced bronchoconstriction in young children and that this pattern is reflected by the severity of the obstructive disorder.

2. Methods

2.1. Patients

A total of 121 children (3–8 years of age) participated in the study. These included 31 children referred to the Skin and Allergy Hospital, part of the Helsinki University Central Hospital group, because of suspected asthma. The mean duration of the symptoms was 11 (range two to 36) months. Twelve of these children (39%) had wheezing, six (19%) had symptoms during exercise and thirteen (42%) had a troublesome cough. We excluded children who had previously been diagnosed with asthma.

A further 61 children came from a former study that evaluated the effect of montelukast on respiratory symptoms and lung function in wheezy infants [14]. They had suffered from persistent or recurrent wheeze and/or dyspnea at the age of six to 24 months with at least one episode being diagnosed by a physician. These children were re-evaluated at the age of three to eight years to assess current lung function and respiratory symptoms.

Fifteen age-matched children who had suffered bronchopulmonary dysplasia (BPD) during the neonatal period were recruited from group's Children's Hospital.

Finally, 14 age-matched healthy subjects who had participated in a study that evaluated the effect of adenoidectomy on respiratory function were recruited [15]. The inclusion criteria were: no signs or symptoms of atopic disease or asthma and successfully performing the free running test and Mch challenge.

If a patient was using asthma control medication at the time of the present study, the medication was stopped four weeks before the lung function measurements were carried out. Lung function tests were performed in a random order during the two-week period and exercise and Mch challenge tests were performed on separate days.

The study was approved by the Ethics Committee of the Helsinki University Central Hospital, Helsinki, Finland and written, informed consent was obtained from the parents of the children.

2.2. Oscillometry

Lung function tests were performed using impulse oscillometry (IOS) and respiratory resistance (R) and reactance (X) at 5 Hz, 10 Hz and 20 Hz were determined as described previously [16]. The frequency dependence of resistance was estimated by calculating the difference between the respiratory resistance at 5 Hz and 20 Hz (R5–20).

2.3. Methacholine challenge

A dosimetric bronchial provocation test modified for preschool children was applied [17]. After baseline measurements of R5, increasing doses of Mch chloride were administered using an automatic, inhalation-synchronised dosimeter (Spira Electro 2, Spira Respiratory Care Centre Ltd, Hämeenlinna, Finland) connected to a calibrated nebuliser (Salter Labs 8900, Arvin, CA). By calculating the number of breaths with nebulised Mch, a rapid dosage scheme with five cumulative dose steps was applied with R5 being remeasured 90 s after each dose inhalation. The procedure was continued until a 40% increase in R5 was observed or the maximum dose of Mch had been administered. The provocative dose of Mch that caused a 40% increase in R5 (PD₄₀R5) was determined from the dose–response curves. At the point of induced bronchoconstriction, the involvement of the small airways was evaluated by calculating the changes in frequency dependence of resistance (R5–20) and reactance (X5 and X10).

2.4. Exercise challenge

The exercise challenge was performed as previously validated outdoor free running test [18]. The children were urged to run for six to eight minutes at a suitable exercise level, so that their heart rate (HR) was kept at approximately 85–90% of their estimated maximum HR. Lung function was measured by IOS at the baseline and at 1, 5, and 10 min after the exercise. An increase of at least 40% in R5 was considered to indicate significant EIB. Finally, the children received a dose of 0.3 mg salbutamol, administered via Babyhaler, and the lung function measurements were repeated 15 min after the inhalation.

2.5. Atopy

Children were screened using skin prick tests (SPT) for aero-allergens (birch, timothy grass, meadow fescue, mugwort, cladosporium herbarum, cat, dog, horse, cow, house dust mite) and foods allergens (egg, milk, fish, wheat, shrimp, peanut).

A positive SPT was defined as a wheal with a diameter of ≥ 3 mm against at least one of the tested allergens.

2.6. Statistical methods

Nonparametric tests were used as the data were not normally distributed. The IOS parameters R5, R20, R5–20, X5 and X10, were compared at baseline and after the methacholine challenge using the Kruskal–Wallis and Mann–Whitney tests. Statistical significance was established at a $P < 0.05$. The data were analysed by using SPSS, version 19.0 (SPSS, Inc, Chigaco, Ill).

3. Results

Selected oscillometry parameters were available for analysis for 109 of the 121 children in the study and their characteristics are presented in Table 1. Based on our previous study of healthy and wheezy preschool children [19], the children were divided into

Table 1

Characteristics and baseline lung function parameters of the study patients.

	All	ET negative	ET 40–80%	ET > 80%	P-value
No of subjects	109	84	13	12	
Males/females, n	64/45	51/33	5/8	8/4	
Age (y), median (range)	6.0 (3.8–8.1)	6.0 (3.8–8.1)	5.8 (4.0–6.6)	5.5 (4.3–6.8)	0.142
Height (cm), median (range)	116 (97–153)	117 (103–153)	114 (97–124)	113 (108–120)	0.059
Atopy, n (%)	39 (36)	17 (20)	10 (77)	12 (100)	<0.001
Current medication, n (%)	21 (19)	19 (23)	1 (8)	1 (8)	0.266
Seasonal medication, n (%)	8 (7)	7 (8)	1 (8)	0 (0)	0.32
Short acting beta-agonist, ^a n (%)	24 (22)	9 (11)	4 (31)	11 (92)	<0.001
Parental asthma, n (%)	41 (38)	31 (36)	3 (23)	7 (58)	0.19
Baseline R5 (kPa/l/s), median (range)	0.82 (0.52–1.84)	0.82 (0.52–1.84)	0.92 (0.72–1.66)	0.78 (0.54–1.02)	0.048
Baseline R5 z-score, median	0.16 (–3.0–5.53)	0.18 (–3.0–5.53)	0.41 (–1.14–3.64)	–0.63 (–2.47–0.62)	0.028^b
Baseline R20 (kPa/l/s), median (range)	0.62 (0.44–1.05)	0.63 (0.44–1.05)	0.67 (0.55–0.89)	0.59 (0.46–0.81)	0.182
Baseline R5–R20 (kPa/l/s), median (range)	0.19 (0.04–0.89)	0.19 (0.04–0.86)	0.25 (0.12–0.89)	0.18 (0.05–0.30)	0.064
Baseline X5 (kPa/l/s), median (range)	–0.23 (–0.82–0.42)	–0.23 (–0.82–0.42)	–0.23 (–0.52–0.21)	–0.20 (–0.3–0.25)	0.221
Baseline X10 (kPa/l/s), median (range)	–0.12 (–0.61–0.0)	–0.12 (–0.59–0.01)	–0.14 (–0.61–0.05)	–0.12 (–0.18–0.0)	0.151

^a During the past 2 months.^b Comparisons carried out by two sample test (Mann–Whitney) produced the following results: non EIB vs. moderate EIB, $p = 0.23$; non EIB vs. severe EIB, $p = 0.32$ and moderate EIB vs. severe EIB, $p = 0.004$.

three groups: 84 negative EIB children (R5 increase of less than 40%), 13 moderate EIB children (R5 increase from 40 to 80%) and 12 severe EIB children (R5 increase over 80%). Children in the severe EIB group were more atopic ($p < 0.001$) than children with moderate EIB or no EIB. The majority of children in the severe EIB group (92%) had used short-acting beta-agonist (SABA) during the past two months, compared with 31% in moderate EIB group and 11% in EIB negative group ($p < 0.001$).

3.1. Methacholine challenge

The children with moderate EIB (median PD40R5 500 μg) or severe (850 μg) EIB were more reactive to Mch than children with no EIB (2350 μg , $p = 0.01$). Seventy-four (68%) of the 109 children responded to mch by increasing their R5 40% or more.

3.2. IOS parameters before the methacholine challenge

The baseline oscillometric parameters are presented in Table 1. The median baseline R5 z-score was higher in the moderate EIB group (0.41 SD) than in children with no EIB (0.18 SD) or severe EIB (–0.63 SD, $p = 0.028$ by Kruskal–Wallis test). R5–20, R20, X5 and X10 did not differ significantly between the groups.

3.3. IOS parameters after the methacholine challenge

The IOS parameters were measured after the last dose of Mch. The challenge was continued until a 40% increase in R5 was observed or the maximum dose of Mch had been administered. Table 2 shows that after the Mch challenge, the median R5–20 increase was significantly higher in children with severe exercise induced bronchoconstriction, with a median 2.61 fold increase, than the 1.48 increase for children with moderate exercise induced

bronchoconstriction and 1.74 for children with a negative exercise test result ($p = 0.036$ by the Kruskal–Wallis test).

The R5–20 changes in the severe and moderate EIB groups, compared to the EIB negative group are shown in Fig. 1. The difference between the severe EIB group and the EIB negative group was statistically significant in a pairwise comparison ($p = 0.019$), but there were no differences in changes in R5, R20, X5 or X10 between the groups. Furthermore, the change in R5–20 and the use of SABA did not correlate.

4. Discussion

This study relates to asthma severity. Despite similar degrees of

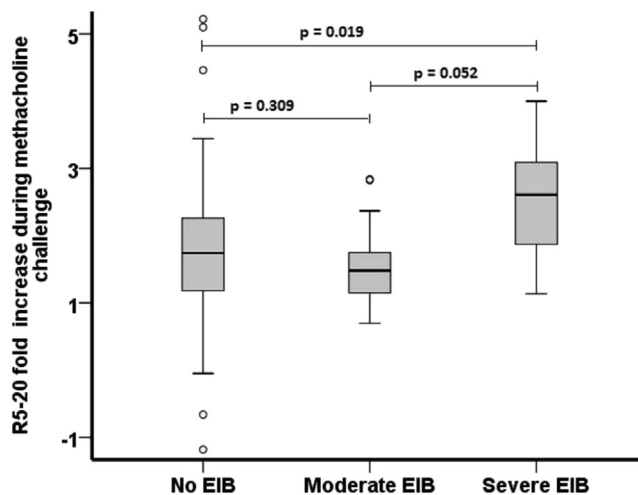


Fig. 1. R5–R20 change (fold increase) after methacholine challenge in children with no EIB, moderate EIB and severe EIB.

Table 2

Change in oscillometry parameters after the methacholine challenge.

	All (109)	ET negative (84)	ET 40–80% (13)	ET > 80% (12)	P-value
R5 (fold increase), median (range)	0.52 (–0.13–1.09)	0.50 (–0.13–0.90)	0.49 (0.28–0.94)	0.46 (0.35–1.09)	0.88
R5–20 (fold increase), median (range)	1.74 (–4.52–11.5)	1.74 (–4.52–11.5)	1.48 (0.70–2.84)	2.61 (1.13–4.00)	0.036^a
R20 (fold increase), median (range)	0.12 (–0.22–0.58)	0.12 (–0.22–0.47)	0.12 (–0.14–0.28)	0.12 (–0.10–0.58)	0.79
X5 (fold increase), median (range)	0.96 (–4.58–3.91)	1.05 (–4.58–3.91)	0.67 (–3.48–2.62)	0.79 (–2.80–2.82)	0.58
X10 (fold increase), median (range)	2.13 (–0.50–20.0)	2.17 (–0.50–20.0)	2.07 (0.38–3.71)	2.25 (0.92–5.60)	0.34

^a The pairwise comparisons using the Mann–Whitney test showed the following results: non EIB vs. moderate EIB, $p = 0.309$; non EIB vs. severe EIB, $p = 0.019$ and moderate EIB vs. severe EIB, $p = 0.052$ (shown in Fig. 1).

bronchial obstruction, expressed as a similar change in R5, some children with obstructive symptoms showed more enhanced signs of small airways involvement, expressed by frequency dependence of resistance (R5–20). This pattern was associated with more severe EIB in an exercise test. They also experienced more symptoms, which was indicated by more frequent use of short acting beta-agonist over the previous two months. These findings suggest that small airways obstruction is associated with severe asthma, even in young children. To our knowledge, this is the first study to use IOS parameters to determine small airways function during induced bronchoconstriction in young children.

The severity of asthma has traditionally been classified based on clinical features, such as the level of symptoms and lung function assessment before the treatment [20]. Asthma control refers to controlling the disease manifestations and various validated scoring systems for measuring the level of asthma control have been introduced [20]. These scoring instruments have included determining the need for rescue medication. In our study, the children with severe EIB used more reliever treatment than children with no EIB or moderate EIB. This supports the assumption that these children had more severe underlying disease than the other two groups. Assessing the severity of asthma based on lung function in young children is challenging. Free running is a natural way of inducing asthmatic symptoms in children and EIB is highly specific for paediatric asthma [21]. Airway inflammation and EIB are related [5] and the severity of EIB correlates with eosinophilic inflammation in bronchial mucosa [22,23]. Increase in mucosal osmolarity, induced as a consequence of evaporative water loss, is thought to result in release of bronchoconstrictive mediators from a variety of cells, including mast cells, but also thermal conditions, airway cooling and reactive hyperemia may contribute to the response in EIB [5,6]. Exercise tests, combined with IOS, are also available for assessing respiratory symptoms in preschool children who are not capable of performing spirometry [18]. Changes in respiratory resistance during the exercise test have been shown to correlate with spirometry results (the forced expiratory volume in one second) in school aged children [24] and adults [25]. An increase of 35–40% in R5 has been considered as an abnormal response to bronchial challenge tests [19,26]. We considered an increase of R5 of 40% or more after free running as an indication of significant EIB. The children were categorized arbitrarily according to the magnitude of their response in an exercise test analogously to common guidelines of EIB [6]. An R5 increase from 40 to 80% was considered as moderate EIB and an R5 increase over 80% was considered severe EIB.

Finding an accurate and simple measurement technique to assess small airways function has been difficult. Functional features of small airways dysfunction are peripheral ventilation heterogeneity, air trapping and premature airway closure [27]. Forced expiratory volume in one second by spirometry mainly reflects large airways, and forced expiratory flow at 25% and 75% of forced capacity, which is considered a marker of small airways, has poor reproducibility [28]. High resolution computed tomography to visualize regional air-trapping in distal airways, bronchoscopic techniques and helium-oxygen breathing test are invasive and technically complex [1]. Less invasive, but still potentially sensitive, methods to measure small airways are multiple-breath nitrogen wash-out and forced oscillation techniques, with the latter also being useful in young children [2,18].

IOS enables us to measure frequency characteristics of respiratory mechanics [10]. Due to redistribution of flows, effective resistance and compliance have been shown to decrease with increasing frequency in the lungs with heterogenous time constants in the peripheral airways [10]. This phenomenon has been experimentally demonstrated in adult patients with obstructive

lung disease, but mostly at frequencies below 5 Hz [29]. It has also been suggested that the frequency dependence of resistance above 5 Hz reflects artefactual upper airway shunting, particularly in children with high respiratory impedance [30]. However, the association of increased R5–20 responses and severity of asthma in the present study cannot be explained solely by artefactual mechanism. It suggests that, even in young children, R5–20 reflects clinically relevant small airways dysfunction.

Widespread ventilation heterogeneities with airway closure or near closure are also accompanied by changes in elastic properties of the respiratory system [11]. As a result, the oscillometric parameters X5 (reactance at 5 Hz) and AX (reactance area) have been used to reflect small airways function [8,13]. Downie et al. [2] studied oscillometric parameters after Mch provocation of mild to moderate adult asthmatics and found that changes in reactance (X5) were indicative of airway closure and peripheral ventilation heterogeneities assessed with the multiple washout technique. In our series of young children, we could not assess any association between reactance parameters and the severity of EIB. This may be because it is difficult to measure impedance at low frequencies in young children, due to artefacts caused by higher harmonics of the fundamental breathing frequency [31]. Recent reports by Shi et al. showed that measures of small airway parameters carried out using IOS, such as the frequency dependence R5–20 and reactance area AX, were better at predicting loss of asthma control in children than spirometric indices [8,12]. An Italian study found an association between small airways dysfunction (by IOS R5, R20 and X5) and the magnitude of the hyperresponsiveness to **mch** in adults and school-aged children [32].

We chose to evaluate small airways dysfunction during Mch provocation, because similar studies in adult asthmatics have shown associations between signs of airway closure during induced bronchoconstriction and the severity of asthma [3,4]. The present results suggest a similar association, even in young children with obstructive symptoms. The pattern of induced bronchoconstriction also seems to be a more sensitive marker of small airways dysfunction than baseline lung function changes, since the latter failed to predict the severity of EIB in our series. Our results agree with the findings of Mansur et al., who reported an association between the small airways obstruction, measured by IOS, during a Mch challenge and dyspnea perception in adult asthmatics [33]. Boudewijn et al. also showed less distal obstruction (R5–20 and X5) during the Mch challenge in adult patients with asymptomatic airway hyperresponsiveness (AHR) than in asthmatics and patients with symptomatic AHR [9].

All small airway tests have shortcomings, and the influence of large airways cannot be excluded in most measurements [1]. Therefore the results of this study are indicative rather than conclusive, and no gold standard for small airways assessment exists [1]. The exact role of the small airways in asthma, especially in pediatric asthma, still needs to be explained. Nevertheless, an increasing number of published studies support the contribution of small airways dysfunction to the clinical expression on asthma and our findings support this hypothesis.

In conclusion, we describe a pattern of increase in frequency dependence of resistance (R5–20), measured by IOS, during the Mch challenge which is most pronounced in children with severe EIB. Children with severe EIB also used more short-acting beta-agonists than children with moderate or no EIB. The result suggests that small airways dysfunction is involved in early childhood asthma.

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