Respiratory Medicine 111 (2016) 16–20

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Aberrant small airways function relates to asthma severity in young children

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ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form
11 December 2015
Accepted 17 December 2015
Available online 19 December 2015

Keywords:
Pediatric asthma
Small airways
Airway hyperresponsiveness
Impulse oscillometry
Methacholine challenge
Exercise test

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 (ΔR5) after exercise, indicating either no EIB (ΔR5 $<$ 40%, n = 84), moderate EIB (ΔR5 40–80%, n = 13) and severe EIB (ΔR5 $>$ 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.

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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http://dx.doi.org/10.1016/j.rmed.2015.12.006

[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 ($PD_{40}R5$) 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 aeroallergens (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 $\geq$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 Kruskall–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, III).

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