

ORIGINAL ARTICLE

Relationship between bronchial hyperresponsiveness and lung function in children age 5 and 6 with and without asthma

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ABSTRACT

Background and objective: It is unknown whether wheezy children have bronchial hyperresponsiveness (BHR) or which lung function parameters are correlated with BHR in children. We evaluated the relationship between BHR parameters and the lung functions by minimizing the effects of age and height in asthmatic, non-asthmatic wheezers and healthy children.

Methods: The subjects comprised of 154 children aged 5 and 6 years (78 males, 76 females), who were divided into three groups: asthmatics, non-asthmatic wheezers and healthy controls. Spirometry and a methacholine inhalation challenge by the oscillation method were performed.

Results: The age of the study cohort was 5.9 ± 0.2 years (mean $\pm$ standard deviation), and the height was 114.4 ± 5.3 cm. No significant differences in height, weight, body mass index or lung function were observed in the three groups. The minimal dose of methacholine to start bronchoconstriction, a parameter of bronchial sensitivity, was lower in asthmatics and non-asthmatic wheezers than that in controls. The speed of bronchoconstriction in response to methacholine, a parameter of bronchial reactivity, was strongly correlated with baseline respiratory resistance (Rrs cont) in all three groups.

Conclusions: Our data suggest that it not possible to distinguish preschool children with asthma from non-asthmatic wheezers based on their bronchial sensitivity and that the baseline Rrs has a strong effect on the bronchial reactivity in children.

Key words: asthma, lung function, methacholine inhalation challenge, preschool children, respiratory resistance.

SUMMARY AT A GLANCE

We investigated the relationship between bronchial hyperresponsiveness and lung function in asthmatic, non-asthmatic wheezer and healthy children while minimizing the effects of age and height. No significant differences between asthmatics and non-asthmatic wheezers in bronchial sensitivity were observed. Bronchial reactivity was strongly correlated with the baseline respiratory resistance.

Abbreviations: BHR, bronchial hyperresponsiveness; Dmin, minimum dose of methacholine causing bronchoconstriction; Sm, speed of bronchoconstriction in response to methacholine.

INTRODUCTION

In adults and children, asthma symptoms are associated with bronchial hyperresponsiveness (BHR).¹ BHR is commonly measured by the response to bronchoconstrictors and is characterized by a decrease in forced expiratory volume in 1 s or an increase in airway resistance.² The degree of BHR may be more closely related to the severity of asthma than other lung function parameters.³

Although BHR is a key feature to make a precise diagnosis of asthma, many problems are associated with the use of BHR in children. These include whether preschool wheezers who have not been diagnosed with asthma by physicians have definite BHR and which lung function parameters are associated with the BHR parameters of bronchial sensitivity and bronchial reactivity in this age group. One problem that has prevented the investigation of these issues is that the evaluation of the bronchodilator and/or bronchoconstrictor response in younger children is difficult.⁴ Standard methods of BHR measurement using the forced expiratory volume in 1 s require repeated testing to ensure maximum inspiration and expiration,⁵ which requires good cooperation from the study participants.

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Previous observations suggested that the relationship between the asthma severity and BHR in children is different from that in adolescents.⁶ It has been speculated that airway smooth muscle reactivity in younger children to bronchoconstrictors is more variable than in adults because of their smaller lung size and the immaturity of airway smooth muscle.⁷ The lung function, which has a large effect on BHR measurements, is remarkably confounded by age and height in children.⁸ Despite the large number of previous studies on the BHR in children, the utility of BHR in preschool wheezers and the correlation between lung function parameters and BHR parameters are still unclear.

Because age and height have a large effect on the lung function in children, we limited these factors in the participants in the present study. We measured BHR in asthmatics, non-asthmatic wheezers and healthy controls by a continuous oscillation method, which is recommended for measuring the BHR in younger children.^{9–11} We also evaluated the relationship between the BHR parameters and the lung function in each group.

METHODS

Subjects

From 2003 to 2010, we performed a health check-up using questionnaires and lung functions in 154 preschool children aged 5 and 6 years in Gunma prefecture, Japan.

The parents of each child completed a respiratory questionnaire from the American Thoracic Society/Division of Lung Disease in Japanese.¹² The questionnaire was published by the Japanese Ministry of the Environment. The Ministry of the Environment obtained the permission to use the American Thoracic Society/Division of Lung Disease questionnaire, and developed a revised Japanese version by taking into consideration the circumstances in Japan.

If children had experienced three or more episodes of wheezing in their life and had been diagnosed with asthma by a physician, the child was determined to be asthmatic. All asthmatics were diagnosed with atopic asthma based on their reaction to common environmental allergens administered via the skin and/or the results of radioallergosorbent tests. All were well controlled. All drugs were withdrawn for at least 12 h prior to testing.

If children had experienced two or fewer episodes of wheezing in their life and had not been diagnosed with asthma by a physician, the child was determined to be a non-asthmatic wheezer.¹³ None of the wheezers regularly used inhaled steroids, inhaled long-acting beta agonists or leukotriene antagonists. The main difference between asthmatics and non-asthmatic wheezers was their frequency of wheezing and whether they had physician-diagnosed asthma. The control subjects consisted of healthy children without wheezing episodes.

All of the subjects were free from respiratory symptoms and respiratory infections for at least 4 weeks and had normal auscultation, oxygen saturation

>95% and no respiratory symptoms in everyday life and exercise. There were no differences between the three groups with regard to allergic rhinitis. Approval for the study was obtained from the Gunma University Hospital Ethics Committee, and informed parental consent for each child was obtained before the study.

Height and weight were recorded. Between 13:30 and 16:00 h, lung function, airway resistance and BHR parameters were measured at Gunma University Hospital. Spirometry was performed prior to the evaluation of respiratory resistance (Rrs) and methacholine inhalation.

Pulmonary function tests

Spirometry was obtained with a calibrated computerized pneumotachograph spirometer (Jaeger Master-scope PC, Hoechberg, Germany). Spirometry was performed by two or more paediatricians who were experts in paediatric allergy and respirology. The maximum expiratory flow volume curve was checked in all participants.¹⁴ Standard measurements of pulmonary function were performed, including the forced vital capacity, forced expiratory volume in 1 s, forced expiratory flow at 50% of the vital capacity and forced expiratory flow at 25% of the vital capacity per height. The procedure for all pulmonary function tests involved the following pattern: (i) three normal tidal volume breaths; (ii) inhalation to total lung capacity; (iii) forced maximal exhalation; and (iv) a final maximal inhalation. Only one manoeuvre was performed at each post-challenge time point to minimize subject fatigue and guard against the effects of deep inhalation. However, if any measurement was found to be technically unacceptable, the manoeuvre was repeated immediately.

Methacholine inhalation challenge

Methacholine inhalation challenge followed the procedure described by Takishima *et al.*¹⁵ Briefly, methacholine (Daiichi Kagaku Yakuhin, Tokyo, Japan) was serially diluted twofold on the day of the test with saline to provide a series of 10 strengths from 25 mg/mL to approximately 49 µg/mL. Saline and the methacholine solution were administered via an Astograph (Chest Co, Tokyo, Japan), which included 12 identical nebulizers connected to a main tube and an air compressor shifted from one nebulizer to the next at 1-min intervals. A constant-amplitude pressure generator connected to the mouthpiece produced pressure conforming to sine waves of a constant amplitude using a 'loudspeaker box' system. Constant-bias flow was introduced between the nebulizer and the flow meter to minimize dead space. The airflow at the mouth was measured with a pneumotachometer and a differential pressure transducer. It was also used to measure the mouth pressure relative to the ambient pressure. Saline was set up in the first nebulizer as a control. The 12th nebulizer contained salbutamol hemisulfate (1.7 mg/mL in saline to be administered for 2 min).

Subjects were challenged during quiet breathing in a seated position, with a nose clip attached and air-

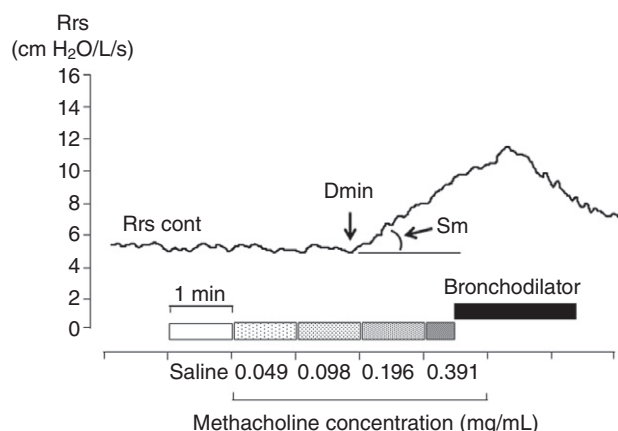


Figure 1 The dose-response curve of respiratory resistance (Rrs) in methacholine inhalation challenge using the oscillation method. Rrs increased with inhalation of incremental amounts of methacholine. When Rrs reached about twice the baseline value, inhalation of methacholine was stopped, and bronchodilator was administered. The calculated parameters were: control value of Rrs (Rrs cont), minimum dose of methacholine causing bronchoconstriction (Dmin) and speed of bronchoconstriction in response to methacholine (Sm).

filled balloons pressing against both cheeks. Methacholine administration was stopped when the Rrs reached double the baseline value. Salbutamol solution was then administered. The Rrs was measured continuously until it stabilized¹¹ (Fig. 1).

The minimum dose of methacholine causing bronchoconstriction (Dmin), which is the cumulative methacholine dose at the inflection point of the Rrs trace, represents the bronchial sensitivity. One Dmin unit was considered to be equal to 1 min of inhaling 1.0 mg/mL aerosolized methacholine solution during tidal breathing. The linear rate of the increase in the Rrs indicates the speed of bronchoconstriction in response to methacholine (Sm) and represents the bronchial reactivity.¹⁶ The Dmin and Sm were measured at the same time in one provocation test. Routine auscultation was performed before and during the methacholine challenges to document wheezing.

Data analysis

The statistical analyses and data presentation were performed with the SPSS computer software package (version 11.0; SPSS, Inc., Chicago, IL, USA). The comparison of each parameter among the three groups was performed with an analysis of variance. Correlations among BHR parameters and lung functions were made by using Pearson's correlation. The effects of confounding variables were removed by a multivariate logistic regression analysis. Data are expressed as the means $\pm$ standard deviation. *P*-values <0.05 were considered to be significant.

RESULTS

The mean and standard deviation of the age, height, weight and body mass index were 5.9 ± 0.2 years,

114.4 ± 5.3 cm, 21.3 ± 3.6 kg and 16.2 ± 2.1 kg/m², respectively. No significant differences in the age, height, weight, body mass index (Table 1), gender or allergic diseases, such as allergic rhinitis, was observed in the three groups. No significant differences in the spirometric parameters were detected in the three groups (Table 1).

No significant differences between the three groups in the baseline value of Rrs (Rrs cont) (Fig. 2) was detected. The Dmin values in asthmatics and non-asthmatic wheezers were lower than those in controls ($P = 0.001$, $P = 0.022$, respectively). The difference between asthmatics and non-asthmatic wheezers (Fig. 3) was not statistically significant. No differences of the Sm were observed in the three groups (Fig. 4). No significant differences between the odds ratios of each group after adjusting for confounding variables including age, height, gender and the allergic diseases of the children were observed.

The Dmin was significantly correlated with the forced expiratory flow at 25% of the vital capacity per height in controls ($P = 0.039$, Table 2). The Sm was significantly correlated with the Rrs cont in each group of; asthmatics, non-asthmatic wheezers and controls ($P = 0.001$, $P = 0.021$, $P = 0.001$, respectively, Table 2), despite the lack of differences in other lung function parameters.

DISCUSSION

BHR plays a central role in the pathophysiology of asthma.^{17,18} It has been suggested that the evaluation of BHR is especially important because objective BHR results help provide an accurate diagnosis, thus resulting in appropriate asthma treatment for each individual.¹⁹ However, the measurement of BHR in younger children is difficult.

We previously described a technique for evaluating the BHR involving continuous monitoring of the Rrs.¹⁰ This method is simple and painless, so that it can be used in children, and yields effort-independent, highly reproducible results.¹¹ Age-related changes in the BHR have been reported to occur in both asthmatic patients and normal controls throughout childhood.¹¹ We have evaluated subjects in a narrow age range to minimize the effects of age and height.²⁰

One key finding of the present study is that in children age 5–6 years, no significant differences were observed between asthmatics and non-asthmatic wheezers in terms of the Dmin. We had speculated that it might be possible to distinguish children with asthma from non-asthmatic wheezers by their absolute BHR level because Dmin has been considered to be closely related to the severity of asthma.^{21,22} However, we did not find a significant difference in our present study. Other reports have also reported that wheezers display BHR.²³ In our study population, asthmatics and non-asthmatic wheezers had a history of wheezing. The main difference was their frequency of wheezing. The majority of the non-asthmatic wheezers in the present study had a degree of BHR (94% of non-asthmatic wheezers). Badier *et al.* also reported that the BHR of asthmatic preschool

Table 1 The profiles of the study subjects

Subject	No.	Age (years)	Height (m)	Weight (kg)	BMI (kg/m ²)	FVC(L)	FEV ₁ (L/s)	V'50 (L/s)	V'25/HT (L/s)
Total	154	5.9 ± 0.2	114.4 ± 5.2	21.3 ± 3.6	16.2 ± 2.1	1.24 ± 0.4	1.16 ± 0.3	1.70 ± 0.6	0.86 ± 0.3
Asthmatics	64	6.0 ± 0.2	115.1 ± 5.1	21.3 ± 3.7	16.0 ± 2.3	1.28 ± 0.5	1.16 ± 0.3	1.62 ± 0.5	0.91 ± 0.3
Wheezers	37	6.0 ± 0.0	114.5 ± 5.8	21.0 ± 2.9	16.0 ± 1.7	1.25 ± 0.4	1.15 ± 0.3	1.57 ± 0.6	0.95 ± 0.4
Controls	53	5.9 ± 0.3	113.5 ± 5.0	21.5 ± 3.9	16.6 ± 2.1	1.18 ± 0.2	1.15 ± 0.3	1.88 ± 0.6	1.10 ± 0.3

All data are expressed as the means ± SD.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation; V'25/HT, forced expiratory flow at 25% of vital capacity per height; V'50, forced expiratory flow at 50% of vital capacity.

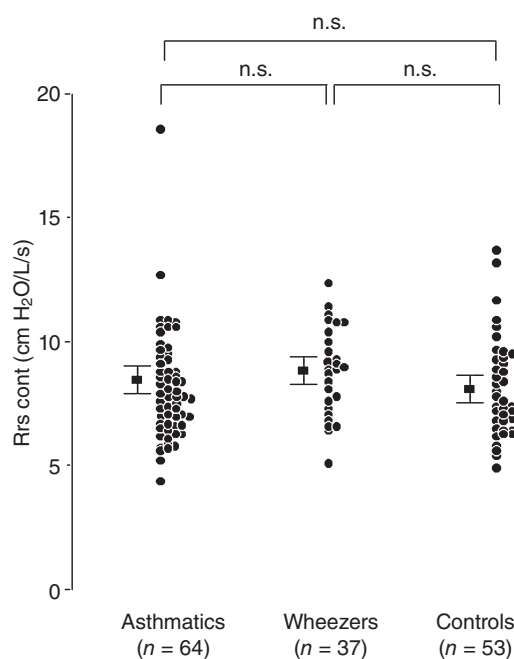


Figure 2 A comparison of respiratory resistance (Rrs cont) between asthmatics, non-asthmatic wheezers and controls. Squares show the means. Error bars show 95% confidence intervals of the means. n.s., not significant.

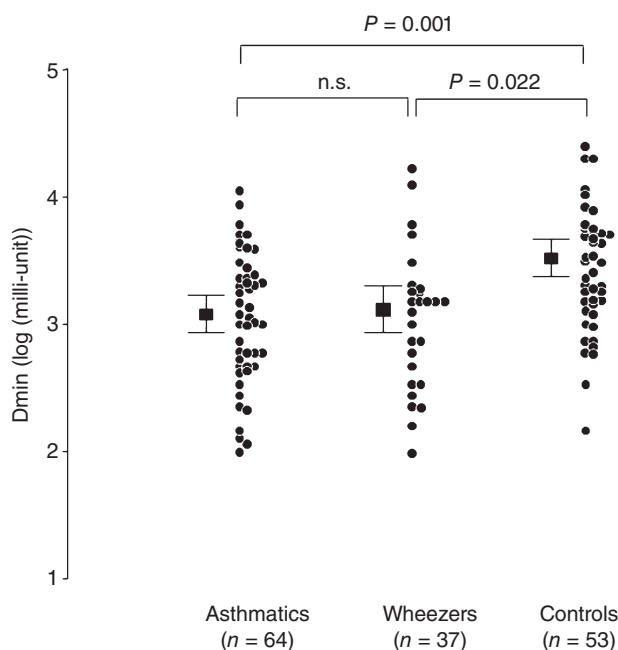


Figure 3 A comparison of the minimum methacholine dose to cause bronchoconstriction (Dmin) in asthmatics, non-asthmatic wheezers and controls. Squares show the means. Error bars show 95% confidence intervals of the means. n.s., not significant.

children was similar to that of wheezy bronchitis.²⁴ Our findings correlated with their results that wheezy bronchitis, as well as asthma, is associated with BHR.

Another reason why non-asthmatic wheezers showed BHR may be because contamination of phenotypes. Previous reports have suggested three or more phenotypes of preschool wheezers.^{23,25,26} Both the non-atopic wheezers, whose wheezing is associated with respiratory syncytial virus infection during the infantile period, and the immunoglobulin E-associated wheezers/asthmatics may have BHR. The pathophysiology of preschool wheezers may therefore be complex, and some of them likely have chronic airway inflammation and/or airway remodeling. It is possible that some asthmatic patients may have been included in the non-asthmatic wheezers group because we used only a questionnaire to diagnose the subjects.

Our second finding was that bronchial reactivity, as indicated by the Sm, was closely correlated with the Rrs cont in all groups, despite the lack of differences in the other lung function parameters. Bronchial reactivity is another important BHR parameter represented on the time-dependent slope of the bronchial reaction during an inhalation challenge.¹⁵ We have previously reported that the Sm is independent of the forced expiratory volume in 1 s and asthma severity, and that the Sm in children with non-atopic asthma is markedly higher compared with children with atopic asthma.^{11,27} The relationship between the Sm and age is clinically interesting,⁷ as it may be related to bronchial cartilage stiffening during childhood development, which is likely to lead to airway rigidity.²⁸ Also, airway smooth muscle development is related to activity of the vagal nerve, which may lead to more rapid constriction of the airways. In order to study

factors affecting bronchial reactivity in children, data need to be obtained from subjects of the same ages,²⁰ as in our present study.

In adults, bronchial reactivity correlates with the Rrs, and a high Rrs induces high bronchial reactivity.²⁹ However, Niimi *et al.* reported that the airway wall thickening induced by airway remodelling attenuates the bronchial reactivity in patients with asthma.³⁰ Although the precise relationship between airway

rigidity and aging in children is not clear, our previous report suggested that the bronchial reactivity reflects the total airway activity and depends on the airway muscle maturity in younger children and the airway wall rigidity in older children.⁷ Our present results suggest the possibility that airway disturbance may be present in preschool children with asthma and non-asthmatic wheezing and that the Rrs, which relates to airway rigidity and/or airway narrowing, has a major effect on the Sm. Further investigations about airway physiology are needed.

In this report, the Dmin significantly correlated with the forced expiratory flow at 25% of the vital capacity per height only in the controls. In asthmatic children, chronic 'silent' small airway inflammation significantly increased the small airway obstruction in lung function tests.³¹ In children, the presence of a small airway disturbance with or without allergic inflammation may induce a decrease in the forced expiratory flow at 25% of the vital capacity per height level, thus resulting in an increase in bronchial sensitivity. Although the relationship was not obvious in asthmatics and non-asthmatic wheezers in our present report, this finding may be partially dependent on the small range of the Dmin values in both asthmatics (2.10 ± 2.2 units) and non-asthmatic wheezers (2.56 ± 3.4 units) in comparison with the controls (4.56 ± 5.0 units).

In summary, bronchial sensitivity is unreliable to gauge asthma in preschool children, while the BHR is an important factor underlying the clinical aspects of childhood asthma. Furthermore, the bronchial reactivity in preschool children is strongly correlated with baseline Rrs. This introduces the possibility of effort-independent measurement of bronchial reactivity in younger children. Children age 5 and 6 are unique subjects, who are experiencing a wide spectrum of rapidly occurring physical and psychosocial changes.

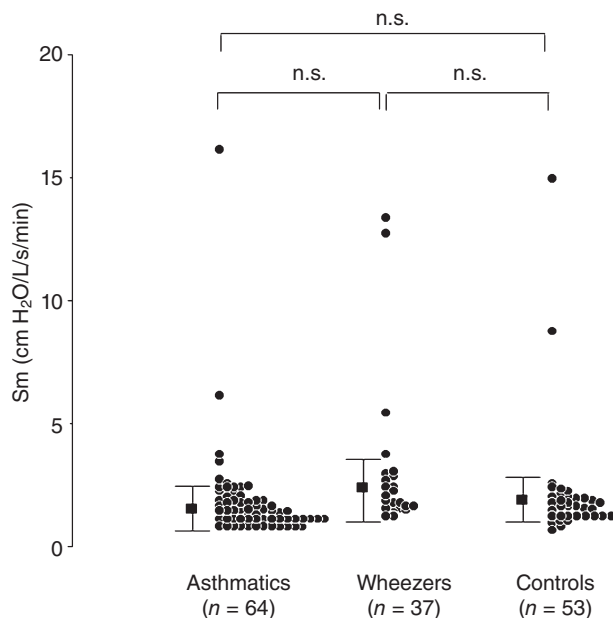


Figure 4 Comparison of speed of bronchoconstriction in response to methacholine (Sm) in asthmatics, non-asthmatic wheezers and controls. Squares show the means. Error bars show 95% confidence intervals of the means. n.s., not significant.

Table 2 The correlation coefficients and *P*-values for the Dmin, Sm and other parameters

Group		FVC	FEV ₁	V'50	V'25/HT	Rrs cont
Asthmatics (n = 64)						
Dmin	CC	-0.062	-0.082	-0.027	0.040	-0.023
	<i>P</i>	0.629	0.521	0.829	0.752	0.855
Sm	CC	0.044	0.022	0.135	0.031	0.609
	<i>P</i>	0.731	0.861	0.287	0.357	<0.001
Wheezers (n = 37)						
Dmin	CC	0.178	0.080	-0.046	-0.039	0.077
	<i>P</i>	0.291	0.638	0.786	0.817	0.652
Sm	CC	-0.103	0.172	-0.042	0.151	0.379
	<i>P</i>	0.544	0.309	0.803	0.374	0.021
Controls (n = 53)						
Dmin	CC	-0.010	-0.020	0.121	0.285	-0.112
	<i>P</i>	0.943	0.885	0.390	0.039	0.558
Sm	CC	-0.270	-0.022	0.038	0.105	0.558
	<i>P</i>	0.051	0.879	0.789	0.455	<0.001

Wheezers; non-asthmatic wheezers.

CC, correlation coefficient; Dmin, minimal dose of methacholine; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Rrs cont, baseline value of respiratory resistance; Sm, speed of bronchoconstriction in response to methacholine; V'50, forced expiratory flow at 50% of vital capacity; V'25/HT, forced expiratory flow at 25% of vital capacity per height.

More detailed studies on children are needed to identify clinically useful predictors of their airway outcomes.

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