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ORIGINAL ARTICLE

IMPAIRED PULMONARY FUNCTION IN THE UNIVERSITY STUDENTS WHO HAD ASTHMA IN CHILDHOOD

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Abstract **Background:** Bronchial asthma in children often resolves as they grow. In persons with resolved asthma, spirometry measurements such as FEV1 and FEV1/FVC show almost normal values. The forced oscillation technique (FOT) is a new index of pulmonary function, and seems to be useful in detecting small changes that are not seen on spirometry. This study aimed to compare spirometry, exhaled nitric oxide fraction (FeNO), and FOT between the subjects with resolved asthma and normal subjects.

Methods: We recruited 484 subjects from our university (mean age, 18.5; male, 257). A questionnaire about past history including bronchial asthma and other allergic diseases, spirometry, FeNO measurement, and FOT were completed by 119 resolved asthma patients and 365 normal subjects.

Results: FEV1/FVC was significantly lower and FeNO was higher in resolved asthma patients than in controls. There were significant differences between resolved asthma patients and controls in X5, Fres, and ALX as reactance parameters. There were, however, no differences in the resistance parameters such as R5, R20.

Conclusions: There is a group of patients whose childhood asthma has resolved with respiratory impairment. Further study will be required to determine whether spirometry, FeNO, and FOT are useful in making an early diagnosis of asthma relapse.

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Key words: asthma; exhaled nitric oxide; forced oscillation technique; spirometry.

原　著

小児喘息が寛解した大学生における肺機能異常

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抄録　小児喘息の多くは寛解することも多いが，成人になり再発する症例もある．弘前大学の学生484名(喘息寛解者群119名、健常者群365名)を対象に，スパイロメトリー，呼気一酸化窒素濃度(FeNO)測定，オシレーション法による呼吸インピーダンス測定(FOT)を行い，喘息既往者と健常者の肺機能に差があるかどうかを検討した．

一秒率は喘息寛解者群でわずかであるが有意に低かった．FeNOは喘息寛解者群で有意に高く，度数分布をみると二峰性のピークを示した．FOTでは，喘息寛解者群でX5，Fres，ALXなどの呼吸リアクタンス成分が有意に高かったが，R5，R20などの呼吸抵抗成分は両群間で差を認めなかった．

本研究によって，喘息寛解者ではスパイロメトリーによるわずかな閉塞障害，FeNOの上昇，呼吸リアクタンスの異常を認めることが明らかになった．これらの異常が将来の喘息再燃と関係があるかどうか，フォローが必要である．

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1. Introduction

The number of patients with bronchial asthma, especially childhood asthma, is increasing. Childhood bronchial asthma often resolves as children grow[1]. However, it is unknown whether pulmonary function returns to normal levels and whether airway inflammation remains. Furthermore, some patients with resolved childhood asthma have a relapse after the age of 20 years[2]. A longitudinal study reported that about 35% of patients with resolved childhood asthma relapse by 21 or 26 years of age[3].

There are few studies investigating the pulmonary function in patients with resolved childhood asthma. Recently, the measurement of the exhaled nitric oxide fraction (FeNO) has been widely used as a non-invasive examination[4]. FeNO levels are significantly higher in patients with asthma than in healthy subjects[5-7], and it is considered to be an index of airway hypersensitivity and airway inflammation[8]. Furthermore, the forced oscillation technique (FOT) was developed as a new method to measure respiratory impedance[9, 10]. The FOT is able to measure the respiratory impedance during respiratory cycles continuously and conveniently without requiring respiratory effort by the patient. In mild asthma patients, the results of spirometry such as FEV1 and FEV1/FVC are almost normal[3, 11]. The FOT may detect small changes that cannot be seen on spirometry[12]. Although the FOT is not a replacement for spirometry, it is useful to assess airway obstruction.

In this study, spirometry, the FOT, and FeNO were measured in the childhood asthma patients in whom asthma had resolved, and their data were compared with those in normal subjects.

2. Methods

2.1. Subjects

This study was approved by the Institutional Review Board of Hirosaki University Graduate School of Medicine and the Health Administration Center of Hirosaki University (2012-244, January 29, 2013). Hirosaki University students were asked to fill out a questionnaire and to undertake exhaled nitric oxide measurements, respiratory impedance measurements, and spirometry, in that order. The study was performed from 2010 to 2013, and a notice asking for participation to this study was posted. A total of 519 students intended to take part in this study and were informed of the study. All 519 students consented to participate in the study and signed the consent form. Subjects were excluded from the study if they had current asthmatic symptoms, acute viral infections, a smoking history, or a history of pneumothorax or thoracic surgery.

2.2. Questionnaire

An original questionnaire was used in this study. The questionnaire included a history of bronchial asthma, atopic dermatitis, allergic rhinitis, any asthma-like symptoms such as wheezing, shortness of breath, cough, and chest discomfort within a year, and other past medical history. Their medical histories obtained from the questionnaires were compared with the

Abbreviations

FeNO, exhaled nitric oxide fraction; FOT, forced oscillation technique; VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow; MMF, maximal midexpiratory flow; MEF50, maximal expiratory flow at 50%; MEF75, maximal expiratory flow at 75%; Rrs, resistance; Xrs, reactance; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, the difference between R5 and R20; X5, reactance at 5 Hz; Fres, resonant frequency; ALX, low-frequency reactance area; ppb, parts per billion.

health condition questionnaires filled out by the students' parents upon university admission, and it was confirmed that the subjects were never smokers and not on any antiasthmatic medications.

2.3. The fraction of exhaled nitric oxide (FeNO)

FeNO values were measured by an offline method[4]. Breath samples were obtained using an offline kit (GE Analytical Instruments, Boulder, Colorado, USA) to measure FeNO under the same conditions as with online measurement. In this device, the expiratory flow rate is adjusted to 50 mL/s when subjects exhale at 5 cmH_2O oral pressure after inhaling deeply. A disposable paper mouthpiece and a viral and bacterial filter were connected to a plastic mouthpiece adaptor with a pressure gauge, followed by a plastic T-tube with a resistance valve and a bag reservoir for collecting samples. A 1.5-L Mylar bag (GE Analytical Instruments) was used for the reservoir bag. During expiration, the subjects were asked to maintain a constant mouth pressure (5 cmH_2O) by watching a pressure gauge. Air exhaled in the first 5 seconds was discarded, and the air exhaled between 5 and 10 seconds was collected in the Mylar bag. The samples obtained in bags were stored at room temperature, and FeNO was measured on the same day using a chemiluminescence analyzer (NOA 280 GE Analytical Instruments).

2.4. Respiratory impedance

Respiratory impedance was measured with the FOT using a device measuring impulse oscillometry (MostGraph-01; Chest, Tokyo, Japan)[9, 10]. Impulse oscillometry signals generated by a loudspeaker at intervals of 0.25 seconds were applied to the respiratory system during normal breathing. The mouth pressure and flow signals were measured and calculated to obtain resistance (Rrs) and reactance (Xrs) properties over an oscillatory frequency ranging from 4 to 35 Hz. During measurements, the subjects were asked to wear a nose clip while breathing normally through a mouthpiece, and they were instructed to close their lips tightly around the mouthpiece to avoid air leakage. Rrs at 5 and 20 Hz (R5 and R20, respectively) and the difference between R5 and R20 (R5-R20) were used as an indicator of the frequency dependence of Rrs. Xrs at 5 Hz (X5), which reflects the elastic and inertial properties of the lung, the resonant frequency (Fres) where Xrs crosses zero and the elastic and inertial forces are equal in magnitude and opposite, and the low-frequency reactance area (ALX), which is the integral of Xrs at 5 Hz to Fres, was also used. Each oscillatory index was expressed as the mean value during a respiratory cycle (whole breath), during the expiratory phase, and during the inspiratory phase.

2.5. Pulmonary function tests

Spirometry was performed using a pulmonary function testing system (HI-801 Chest). The test was performed in accordance with the findings of the ATS/ERS Taskforce 2005[13].

2.6. Statistical analysis

Statistical analysis was performed using JMP 10 software (SAS Institute Inc., Cary, North Carolina, USA). Quantitative data were summarized as means ± SEM. Differences in means between two groups were analyzed using Welch's *t*-test and considered significant at $p<0.05$. All tests were two-sided.

3. Results

A total of 519 students gave a consent to participate to this study. None of them were either current or previous smokers, but 35 were excluded from the study because of asthmatic symptoms (n=23), current viral infections (n=7), and a history of chest diseases such as pneumothorax (n=5). On the basis of the questionnaire, the remaining 484 subjects were divided into two groups: those with resolved

Table 1 Subjects' characteristics

Subjects	Group N	Group A	P value
n	365	119	
age (years)	18.5 ± 0.1	18.5 ± 0.1	0.98
gender (male / female)	187 / 178	70 / 49	0.17
height (cm)	165.2 ± 0.5	165.7 ± 0.8	0.56
body weight (kg)	58.7 ± 0.6	61.1 ± 1.0	0.05
BMI (kg/m^2)	21.4 ± 0.2	22.1 ± 0.3	0.04
history of atopic dermatitis	80 (21.9%)	46 (38.7%)	<0.01
history of allergic rhinitis	200 (54.8%)	78 (65.5%)	0.04
Pulmonary functions			
VC (L)	4.07 ± 0.05	4.06 ± 0.08	0.87
VC (% predicted)	107.1 ± 0.7	104.0 ± 1.2	0.03
FVC (L)	3.96 ± 0.05	3.98 ± 0.08	0.82
FVC (% predicted)	104.3 ± 0.7	102.5 ± 1.2	0.18
FEV1 (L)	3.61 ± 0.04	3.55 ± 0.07	0.51
FEV1 (% predicted)	95.3 ± 0.7	92.3 ± 1.2	0.01
FEV1/FVC (%)	91.5 ± 0.3	89.6 ± 0.6	<0.01
PEF (L/s)	7.10 ± 0.21	6.82 ± 0.37	0.37
PEF (% predicted)	78.8 ± 1.0	76.6 ± 1.8	0.30
MMF (L/s)	4.60 ± 0.06	4.31 ± 0.11	0.02
MMF (% predicted)	119.9 ± 1.7	110.9 ± 2.9	<0.01
MEF50 (L/s)	5.08 ± 0.07	4.83 ± 0.13	0.09
MEF50 (% predicted)	90.6 ± 1.1	85.0 ± 1.9	<0.01
MEF75 (L/s)	2.81 ± 0.05	2.53 ± 0.08	<0.01
MEF75 (% predicted)	83.8 ± 1.2	74.5 ± 2.1	<0.01
FeNO (ppb)	45.5 ± 1.3	51.5 ± 2.2	0.04

Values represent mean ± SEM.
BMI, body mass index; VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PEF, peak expiratory flow; MMF, maximal midexpiratory flow; MEF50, maximal expiratory flow at 50%; MEF75, maximal expiratory flow at 75%; ppb, parts per billion.

childhood asthma (Group A; n=119), and those with no history of asthma (Group N; n=365).

The characteristics of the subjects, pulmonary function results, and FeNO are shown in Table 1. Significant differences were noted in history of atopic dermatitis and history of allergic rhinitis between Group A and Group N. There were no significant differences in VC, FVC, FVC (% pred.), and FEV1 between them. However, VC (% pred.), FEV1 (% pred.), MMF, MEF75, and MEF75 (% pred.) were all significantly lower in Group A than in Group N. Frequency distributions of VC and FEV/FVC are shown in Figure 1. VC was within normal limits in 98.1% (358/365) of Group N subjects and 96.6% (115/119) of Group A subjects. Similarly, FEV1/FVC was within normal limits in 99.5% (363/365) of Group N subjects and 99.2% (118/119) of

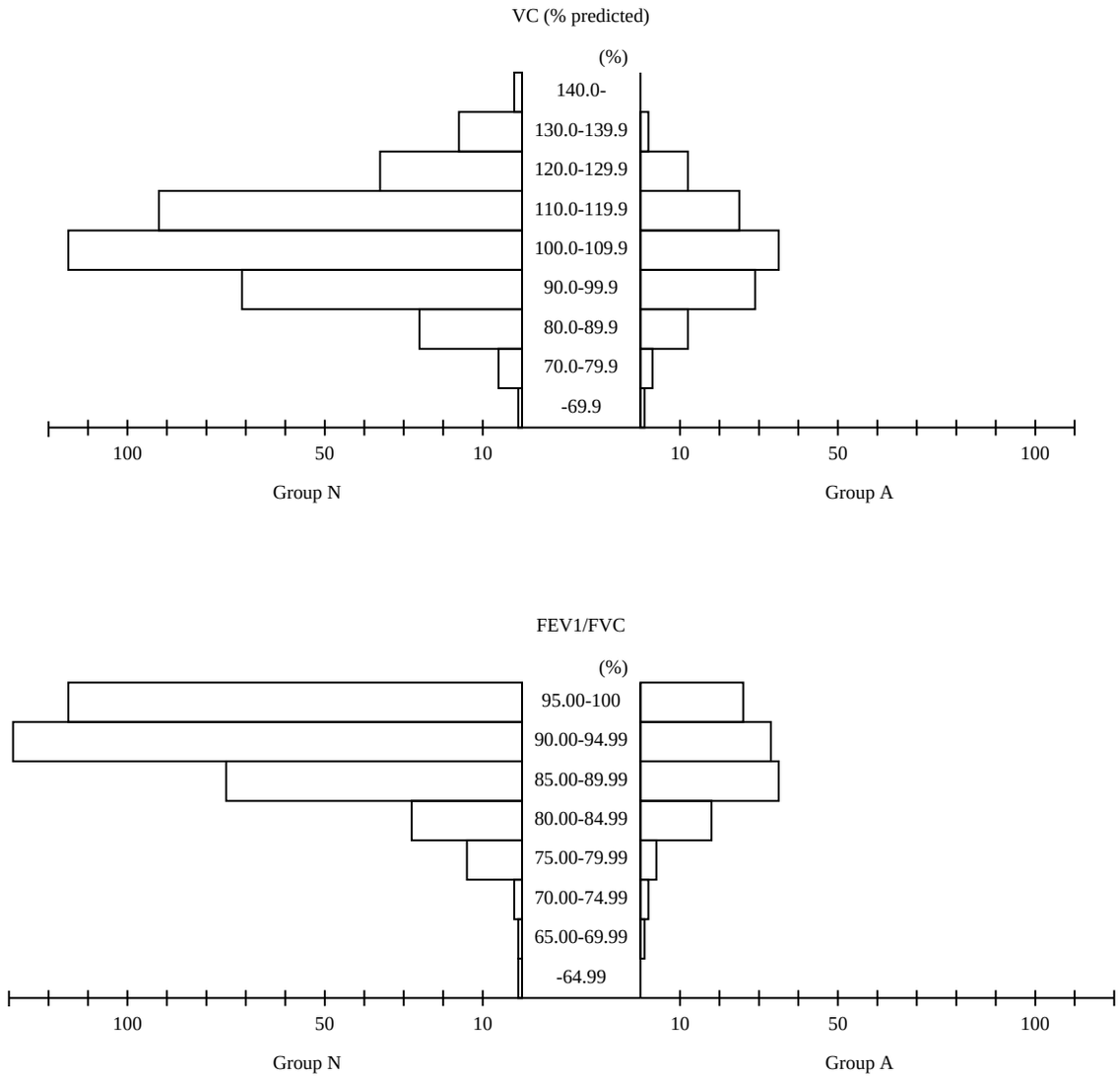

Figure 1 Frequency distributions of spirometry results. Group N: subjects without a history of asthma. Group A: subjects with resolved childhood asthma. Although there are no significant differences in the % predicted value of VC, FEV1/FVC is significantly lower in Group A.

Group A subjects. Although differences of FEV1/FVC between Groups N and A were small, there were significant differences between the two groups.

FeNO was significantly higher in Group A than in Group N (51.5 ± 2.2 ppb vs. 45.5 ± 1.3 ppb; p=0.04). The frequency distribution of FeNO is shown in Figure 2. Although most subjects showed FeNO levels under 40 ppb, some showed FeNO levels over 70 ppb. In Group A, the frequency distribution showed two peaks (under 40 ppb and about 70 ppb).

The results of respiratory impedance measurements are shown in Table 2. In the whole breathing cycle, although there were no significant differences in R5, R20, and R5-R20 between the two groups, reactance parameters (X5, Fres, and ALX) were significantly higher in Group A than in Group N. Similarly, X5, Fres, and ALX were significantly higher in Group A than in Group N in the expiratory and the inspiratory phases. In addition, R5-R20

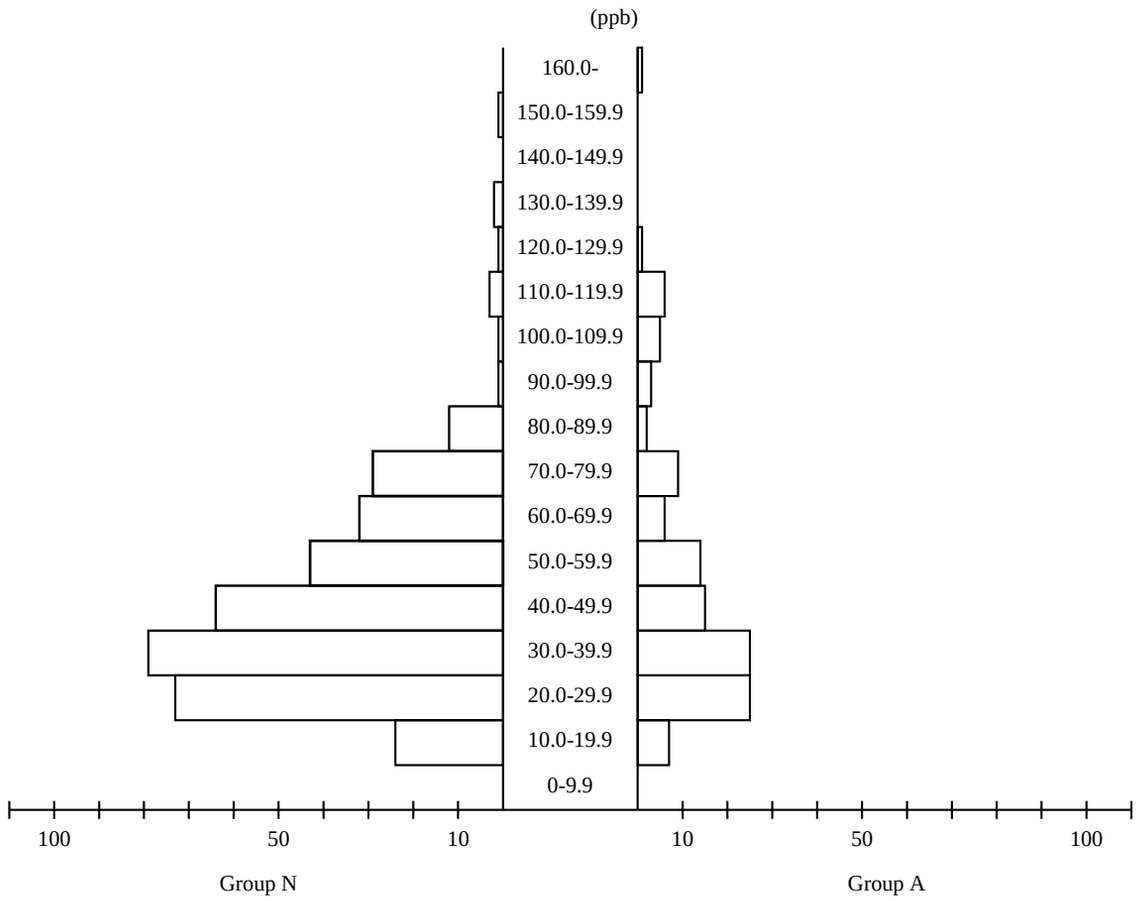

Figure 2 Frequency distribution of FeNO levels. Group N: subjects without a history of asthma. Group A: subjects with resolved childhood asthma. Although most subjects in both groups show FeNO levels under 40 ppb, Group A subjects show a frequency distribution of two peaks at under 40 ppb and about 70 ppb. ppb = parts per billion.

was significantly higher in Group A only in the inspiratory phase. The frequency distributions of R5 and Fres are shown in Figure 3. For R5, an Rrs parameter, the frequency distribution was similar between the two groups. In contrast, Fres was higher in Group A than in Group N, which had a peak at 7.00 to 7.99 Hz.

4. Discussion

Spontaneous resolution of childhood asthma is relatively common, especially during adolescence. In this study, spirometry, the FOT, and FeNO measurements were performed in our university students who had resolved bronchial asthma, and the results were compared with those of normal subjects at our university. We found that on spirometry, VC (% pred.), FEV1 (% pred.), FEV1/FVC, MMF, MMF (% pred.), MEF50 (% pred.), MEF75, and MEF75 (% pred.) were significantly lower, FeNO was significantly higher, and on the FOT, reactance parameters such as X5, Fres, and ALX were higher in resolved asthma subjects than in normal subjects.

A number of studies have reported the lung function of subjects with asthma in remission. Some reports concluded that asthma causes irreversible airflow obstruction[14-16]. Other showed almost normal FEV1 values[3, 17]. The results vary with the subjects' age and the definition of remission. The present study

Table 2 Respiratory impedance results

	Group N (n=365)	Group A (n=119)	P value
Whole breath			
R5 ($cmH_2O/L/s$)	3.10 ± 0.07	3.16 ± 0.12	0.56
R20 ($cmH_2O/L/s$)	2.36 ± 0.05	2.34 ± 0.08	0.79
R5-R20 ($cmH_2O/L/s$)	0.75 ± 0.03	0.83 ± 0.05	0.16
X5 ($cmH_2O/L/s$)	−0.30 ± 0.03	−0.49 ± 0.05	<0.01
Fres (Hz)	6.74 ± 0.13	7.79 ± 0.23	<0.01
ALX ($cmH_2O/L/s*Hz$)	1.65 ± 0.15	2.36 ± 0.26	0.02
Expiratory phase			
R5 ($cmH_2O/L/s$)	3.36 ± 0.08	3.34 ± 0.14	0.86
R20 ($cmH_2O/L/s$)	2.47 ± 0.05	2.43 ± 0.10	0.59
R5-R20 ($cmH_2O/L/s$)	0.89 ± 0.03	0.91 ± 0.06	0.68
X5 ($cmH_2O/L/s$)	−0.40 ± 0.04	−0.59 ± 0.06	<0.01
Fres (Hz)	7.18 ± 0.16	8.23 ± 0.27	<0.01
ALX ($cmH_2O/L/s*Hz$)	2.08 ± 0.18	2.90 ± 0.32	0.04
Inspiratory phase			
R5 ($cmH_2O/L/s$)	2.84 ± 0.06	2.99 ± 0.10	0.15
R20 ($cmH_2O/L/s$)	2.23 ± 0.04	2.25 ± 0.07	0.72
R5-R20 ($cmH_2O/L/s$)	0.61 ± 0.03	0.74 ± 0.05	0.02
X5 ($cmH_2O/L/s$)	−0.19 ± 0.03	−0.40 ± 0.05	<0.01
Fres (Hz)	6.28 ± 0.12	7.32 ± 0.22	<0.01
ALX ($cmH_2O/L/s*Hz$)	1.22 ± 0.13	1.82 ± 0.23	0.02

Values represent mean ± SEM.
R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, the difference between R5 and R20; X5, reactance at 5 Hz; Fres, resonant frequency; ALX, a low-frequency reactance area.

demonstrated that the young subjects with a mean age of 18.5 and resolved asthma showed not only peripheral airway obstruction but lower FEV1/FVC values, although the difference was small. In the frequency distribution of FEV1/FVC, the peak was lower in the resolved asthma patients. A study by Robin et al. suggested that a lower FEV1/FVC ratio at 18 years of age was a significant independent prognostic factor for relapse of asthma[3]. Therefore, the subjects with a lower FEV1/FVC value are considered to be in need of follow-up.

FeNO is an index of eosinophilic inflammation that is used to evaluate the airway inflammation of asthma[4]. In clinical remission of childhood asthma, after discontinuation of inhaled corticosteroids, an elevation of FeNO is a marker of asthma relapse[18]. Leon et al. reported that FeNO correlated with bronchial hyperresponsiveness measured by adenosine-5-monophosphate levels, and FeNO can be used as a non-invasive index of clinical relapse of asthma[19]. In the present study, elevated FeNO levels were found in resolved childhood asthma patients, suggesting that airway inflammation remains even in such subjects. Interestingly, in the frequency distribution, some of the resolved childhood asthma patients had high FeNO levels, suggesting that such subjects are at risk of the relapse in the future[18].

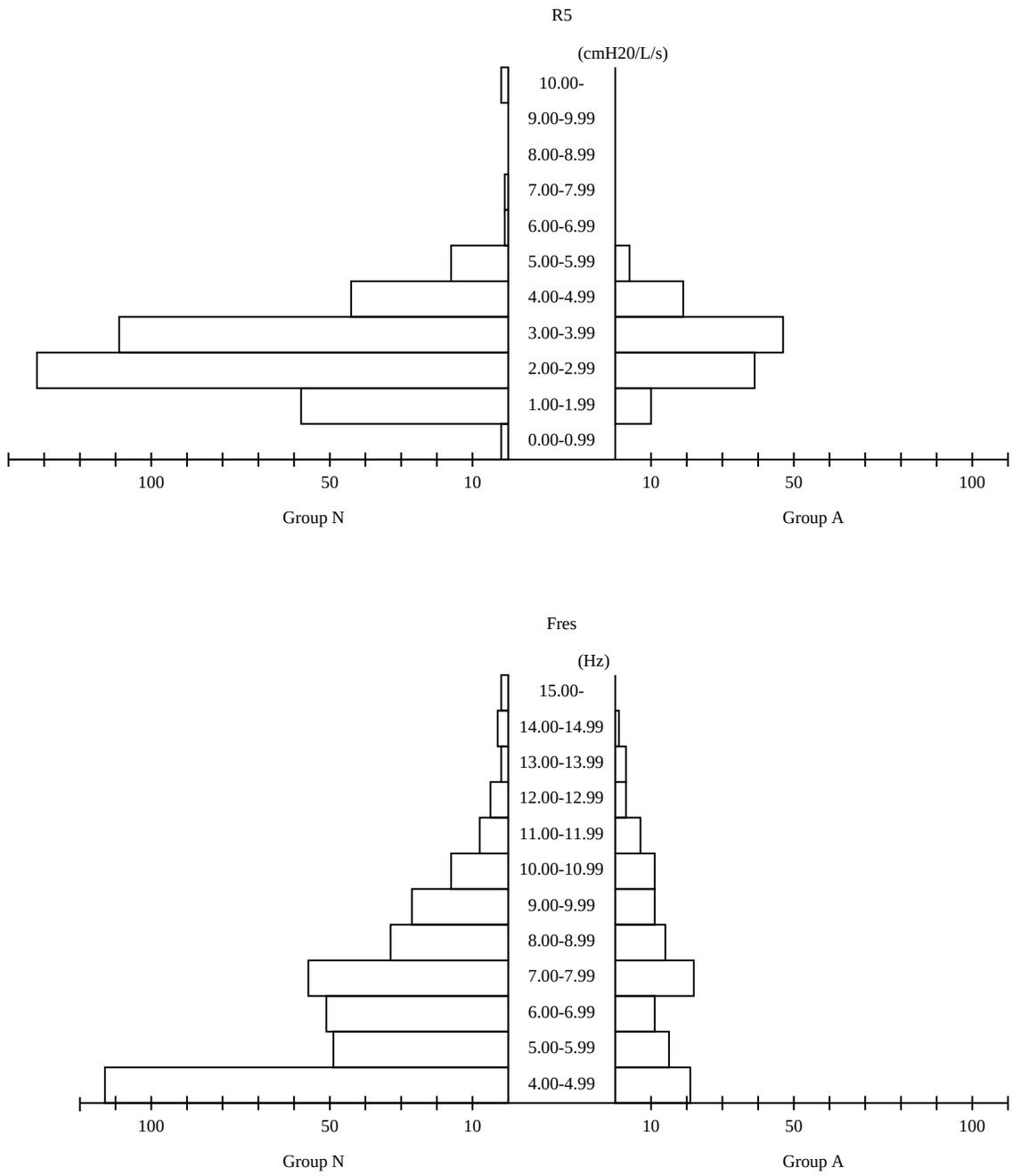

Figure 3 Frequency distributions of R5 and Fres levels. Group N: subjects without a history of asthma. Group A: subjects with resolved childhood asthma. There is no significant difference in R5, while Fres is higher in group A than in group N.

The FOT is a new method that allows measuring both respiratory resistance and respiratory reactance[9, 10], although there have been only few reports regarding it. To our best knowledge, this is the first study to report the FOT parameters in subjects with resolved childhood asthma. There were significant differences between subjects with resolved childhood asthma and normal subjects in X5, Fres, and ALX as Xrs parameters, but there were no differences in R5, R20, and R5-R20 as Rrs parameters. Xrs parameters are thought

to show lung elasticity and lung inertia and are more sensitive than Rrs parameters[20]. This may explain why differences were found in the Xrs parameters.

This study provides evidence that subjects with resolved childhood asthma have impaired pulmonary function, higher FeNO values, and abnormal respiratory reactance. Furthermore, the present study showed that there is a group of subjects with resolved childhood asthma who have respiratory impairment. Follow-up examinations may be necessary to determine whether these differences are related to asthma relapse[21, 22]. There are a great number of subjects with resolved asthma in a real world, and it is impossible to measure airway hyperresponsiveness as a predictor of asthma relapse in all such subjects. Non-invasive examinations, such as pulmonary function, FeNO measurements, and FOT can be useful in the detection of respiratory impairment in patients with resolved childhood asthma[23]. Further study will be required to determine whether spirometry, FeNO, and FOT are useful in making an early diagnosis of asthma relapse.

Conflict of interest

The authors have no potential conflicts of interest.

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