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Clinical Application of High-pitched Breath Sound in Children with Asthma

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Objective: Breath sound parameters have been suggested to be a new biomarker of airway conditions in asthmatic patients. We investigated new breath sound parameters to determine their utility for evaluating asthmatic children.
Methods: Fifty-seven children (mean age, 9.0 years, 6–16 years) were included in the present study. The new breath sound parameters, the area under the curve (AUC) > 1,000 Hz (A_{1000} [dBm · Hz]) and the ratio of the A_{1000} to the total AUC at 100 Hz to the highest frequency of the dBm power spectrum (A_T) (A_{1000}/A_T [%]) were measured before and after β_2 agonist inhalation. Spirography and the forced oscillation technique were also used to evaluate all subjects.
Results: The value of A_{1000} was negatively correlated with the FEV_1 ($p = 0.028$). The increase in the ΔFEV_1 was correlated with the decrease in the ΔA_{1000} ($p = 0.001$) and the $\Delta A_{1000}/A_T$ ($p = 0.036$).
Conclusions: The A_{1000} indicates the airway condition, and the ΔA_{1000} and the $\Delta A_{1000}/A_T$ well describe the dilatation of the airways. These parameters are useful for the assessment of bronchial reversibility in asthmatic children.

Key words: asthma, breath sound analysis, β_2 agonist, children, bronchial reversibility

INTRODUCTION

Evaluating bronchial hyperresponsiveness (BHR) is important for the diagnosis and treatment of asthma. In the pediatric field, the response to bronchodilators has been used to examine bronchial reversibility because of its safety with regard to assessment [1, 2]. However, most preschool children are not able to perform the required physiological maneuvers [3]. Even the measurement of respiratory resistance with forced oscillation technique (FOT), which requires using a mouthpiece, cannot be done in small children [1, 4].

It has been reported that breath sounds are sensitive to airway changes. A breath sound analysis is therefore expected to be a safe and simple method that can be applied in the clinical assessment of airway changes [5]. Recent developments in signal processing methods have improved the possibility of extracting physiologically and clinically relevant information from breath sounds [6–8]. In infants, the breath sound spectrum can be measured and clear changes in the sound parameters are observed when airway narrowing is present [9].

However, one issue with this new method is that the spectrum curve indices, the A_3/A_T (the ratio of the third area to the total area), B_4/A_T (the ratio of the fourth area to the total area), RPF_{75} (the ratio of power at F_{75} to the frequency value [F_{99}–F_{75}]) and RPF_{50} values (the ratio of power at F_{50} to the frequency value [F_{99}–F_{50}]), are calculated based on the ratio [7, 9, 10]. Although these breath sound parameters, which are mostly unaffected by the airflow rate, are reliable for assessments in small children unable to produce continuous stable breathing, these parameters are less sensitive than standard lung function tests, which can indicate direct airway changes [7, 9]. Fortunately, many preschool children can produce continuous stable breathing during respiratory examinations, even if they cannot satisfactorily perform deep breathing for lung function test according to an instruction by an examiner.

In the present report, given that high-pitched wheezing is a criterion for diagnosing asthma exacerbation, we focused on the change in the high-pitched breath sound before and after β_2 agonist inhalation using a breath sound analyzer. The aim of the present study was to examine whether or not more direct breath sound parameters related to high-pitched breath sounds are clinically useful for evaluating bronchial changes in asthmatic children.

PATIENTS AND METHODS

Study subjects

Pediatric outpatients who were more than six years of age, treated at the Tokai University Hospital from January 1, 2012, to March 31, 2014, and who agreed to participate were included in this study. The inclusion criteria were as follows: one or more positive specific

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IgE value (> 0.7 UA/ml) of major six antigens (house dust 1, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Japanese cedar, cat and egg white), recurrent wheezing and BHR, which was confirmed by methacholine inhalation challenge and/or bronchial reversibility [11, 12]. In all cases, atopic-type asthma was diagnosed by a physician.

All drugs were withdrawn for 12 hours before the test. None of the subjects had respiratory symptoms on the day of testing. Written informed consent was obtained from all of the children or their legal guardians and the study protocol was approved by the institutional review board of Tokai University Hospital (No. 11R-158, approval date; December 21, 2011). This investigation confirms with the principles outlined in the Declaration of Helsinki [13].

Study protocol

The assessments were performed before and 15 minutes after β_2 agonist inhalation. All subjects inhaled a β_2 agonist solution (procaterol 30 μg and saline 2.0 ml) [14]. The assessments were performed before and 15 minute after β_2 agonist inhalation.

As a general rule, each subject was requested to take tidal breaths when the breath sounds were collected. It was confirmed that the breath sound samples included no wheezing, rales or outside noises based on auscultation by a physician and the breath sound analyzer image. After the sound analysis, the patients' pulmonary function was tested using spirometry and the FOT.

Pulmonary function tests

The pulmonary function of the participants was determined via spirometry using a calibrated computerized spirometer (Chestgraph HI-105: Chest Co., Tokyo, Japan). The resting baseline was selected using the best-of-three resting results based on the highest sum of the forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). The results are shown as the percent predicted value, which were calculated using the prediction equations for Japanese children.

The FOT parameters were determined using an FOT system (Master- Screen-Impulse Oscillometry System: Jaeger Co., Wurzburg, Germany) according to the manufacturer's instructions [3]. The measurements were made in the standing position with a nose-clip on. During the measurements, the cheeks were supported by the hands of the investigators (for younger children) or by the children themselves. The pneumotachograph was calibrated each day prior to performing the measurements using a 3-L syringe, and the validity of the calibration was tested every time against a reference impedance of 0.2 kPa (L/s), which was supplied by the manufacturer [3]. Real-time recordings of the mouth pressure and flow signals pulsed through the 5- to 20-Hz spectrum were superimposed over tracings of the tidal breathing and displayed on a computer screen. Measurements of respiratory resistance (Rrs) at 5 and 20 Hz and their difference (R5, R20, and R5-R20) and respiratory impedance at 5 Hz (X5) were recorded.

Breath sound analyses

A breath sound analysis was performed for all participants, as described previously [7, 10]. As briefly described, breath sounds were recorded for ≥ 10 seconds in a silent room using a handheld microphone. The microphone was placed on the right upper anterior chest at the second inter-costal space along the mid-clavicular line. A sound analysis of the inspiration phase was performed using an LSA-2000 sound spectrometer (Kenz Medico Co., Saitama, Japan).

The sampling frequency was 10,240 Hz and the spectra were obtained using a Hanning window. The sounds were displayed as a spectrograph (Fig. 1a). To evaluate the dBm-based spectrum images, we decided to set the 0 point of the Y axis (dBm) based on the mean of the background noise (at > 2500 Hz) of all of the subjects. In this report, the 0 point for the calculation of the dBm-based area under the curve (AUC) was considered to be -90 dBm of the original dBm recorded by the sound spectrometer [7, 10]. The point of the maximum frequency (Hz) in the shape (Fig. 1a, arrowhead) during inspiration was used for the sound spectrum analysis. This sound spectrum (Y axis: dBm, X axis: Hz) is shown in Fig. 1b.

The new breath sound parameters of the AUC at > 1,000 Hz (A_{1000} [dBm・Hz]) and the ratio of A_{1000} to total AUC at 100 Hz to the highest frequency of the dBm power spectrum (A_T), (A_{1000}/A_T [%]) were measured before and after β_2 agonist inhalation (Fig. 2a). The ΔA_{1000} and the $\Delta A_{1000}/A_T$ were the changes in the values before and after β_2 agonist inhalation.

For comparison, the frequency limiting 99% of the power spectrum (F_{99} [Hz]) was measured in accordance with the methods of previous reports [10, 15-17] (Fig. 2b). The spectrum curve indices, the A_3/A_T, B_4/A_T, RPF_{75} and RPF_{50} values, were also calculated (Fig. 2b, 2c) [7, 10]. A five-point moving average was used as a smoothing technique.

In this study, breath sound samples were obtained two times; before and 15 minutes after β_2 agonist inhalation. Each personal breath sound parameter was analyzed conventionally, using a sample with a median value from three tidal breaths. These data were automatically calculated using a software program

BHR: bronchial hyperresponsiveness
BMI: body mass index
FVC: forced vital capacity
FEV_1: forced expiratory flow and volume in 1 second
FEF_{25-75}: mean forced expiratory flow between 25% and 75% of the FVC
$\dot{V}_{50}$: maximum expiratory flow at 50% vital capacity
$\dot{V}_{25}$: maximum expiratory flow at 50% vital capacity
FOT: forced oscillation technique
Rrs: respiratory resistance
R5: resistance at 5 Hz
R20: resistance at 20 Hz
R5-R20: difference in resistance between 5 Hz and 20 Hz
X5: reactance at 5 Hz
HFz: Highest frequency of dBm power spectrum
F_{99}: frequency limiting 99% of the power spectrum
AUC: area under the curve
A_T: total area under the curve of 100 Hz to the highest frequency of the dBm power spectrum
A_3: third area under the curve
B_4: forth area under the curve
RPF_{50}: ratio of power and frequency at 50% of the highest frequency of the dBm power spectrum
RPF_{75}: ratio of power and frequency at 75% of the highest frequency of the dBm power spectrum
A_{1000}: AUC > 1000 Hz
A_{1000}/A_T: Ratio of A_{1000} to A_T

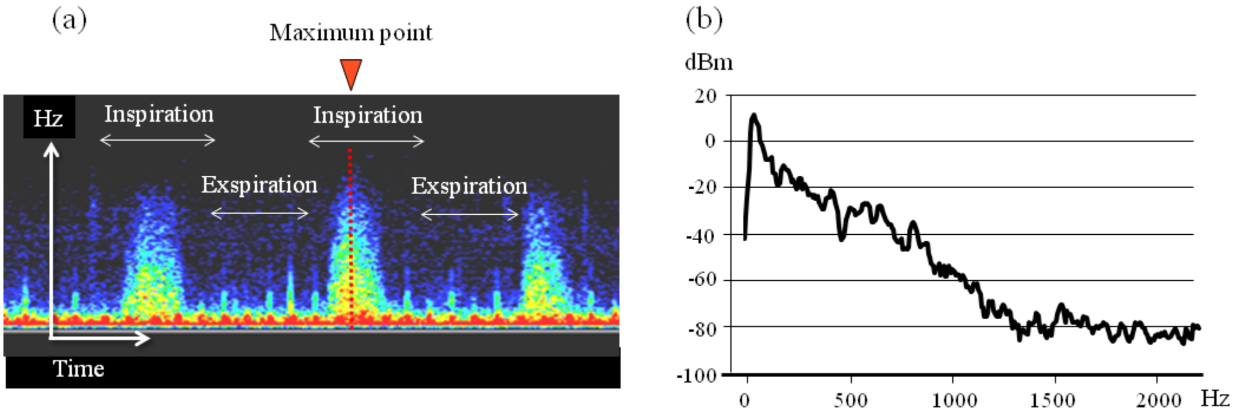
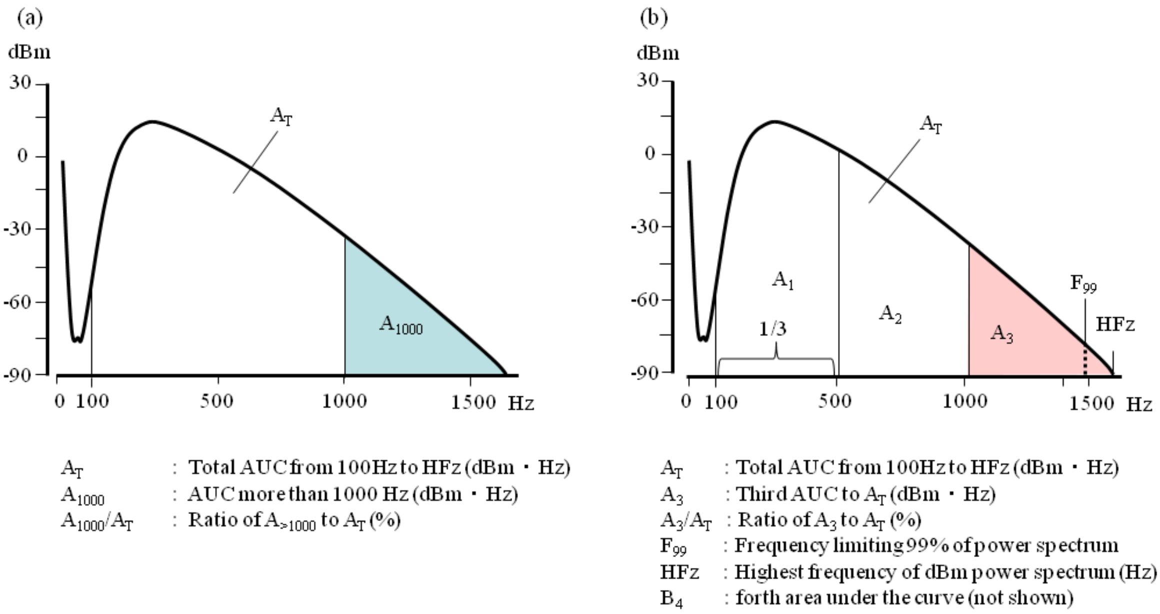


Fig. 1 The analysis of a sound spectrograph
(a) The vertical axis shows the frequency in Hz and the horizontal axis shows time. (b) A five-point moving average was used for smoothing to determine the suitable values of dBm values.



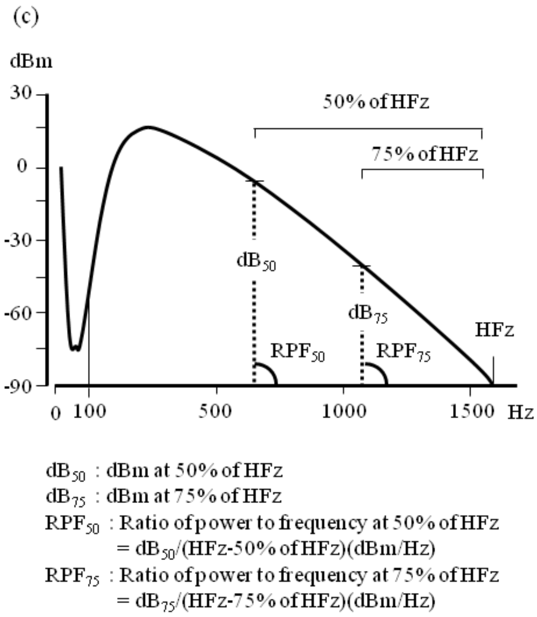


Fig. 2 The sound spectrum parameters
(a) A_T (dBm · Hz): the total AUC from 100Hz to HFz, A_{1000} (dBm · Hz): AUC > 1000 Hz (dBm · Hz), A_{1000}/A_T: ratio of A_{1000} to A_T (%).
(b) A_3: third AUC to A_T (dBm · Hz), A_3/A_T: ratio of A_3 to A_T (%), F_{99}; frequency limiting 99% of power spectrum, HFz: highest frequency of dBm power spectrum (Hz).
(c) dB_{50} (dBm): dBm at 50% of HFz, dB_{75} (dBm): dBm at 75% of HFz, RPF_{50} (dBm/Hz): the ratio of power to frequency at 50% of HFz = dB_{50}/(HFz-50% of HFz), RPF_{75} (dBm/Hz): the ratio of power to frequency at 75% of HFz = dB_{75}/(HFz-75% of HFz).

Table 1 The results of the data analysis

	Before β_2 inhalation	After β_2 inhalation	P value
FVC (%pred)	79.4 (11.2)*	81.4 (10.7)	0.076
FEV_1 (%pred)	91.0 (7.5)	93.1 (5.2)	**< 0.001**
FEF_{25-75} (%pred)	89.4 (20.7)	99.7 (20.1)	**< 0.001**
$\dot{V}_{50}$ (%pred)	86.7 (21.7)	97.0 (23.2)	**< 0.001**
$\dot{V}_{25}$ (%pred)	91.5 (28.4)	98.6 (30.4)	0.065
R20 [kPa/(L/s)]	0.45 (0.12)	0.39 (0.10)	**< 0.001**
R5 [kPa/(L/s)]	0.64 (0.21)	0.52 (0.17)	**< 0.001**
R5-R20 [kPa/(L/s)]	0.20 (0.11)	0.15 (0.10)	**< 0.001**
X5 (Hz) [kPa/(L/s)]	-0.20 (0.09)	-0.20 (0.07)	0.976
F_{99} (Hz)	931.6 (268.0)	970.1 (201.3)	0.255
A_3/A_T (%)	12.1 (1.7)	13.6 (1.5)	**< 0.001**
B_4/A_T (%)	7.16 (1.3)	8.12 (1.2)	**< 0.001**
RPF_{75} (dBm/Hz)	6.00 (1.7)	7.47 (1.8)	**< 0.001**
RPF_{50} (dBm/Hz)	5.80 (1.3)	7.00 (1.4)	**< 0.001**
A_{1000} (dBm・Hz)	1635.5 (946.6)	1566.7 (776.3)	0.591
A_{1000}/A_T(%)	20.1 (7.5)	19.6 (6.1)	0.585

(n = 57, paired t-test, *; Mean(SD))

developed in-house [7, 9, 10].

Statistical analyses

The statistical analyses were conducted using the SPSS software program (IBM SPSS Statistics, Version 22 for Windows: Chicago, IL). The parameters, before and after β_2 agonist inhalation, were compared using the paired *t*-test. Correlations between individual breath sound parameters and other measurements were determined using Pearson's correlation coefficient. The data are expressed as the mean ± standard deviation (SD).

RESULTS

The lung function and breath sound analyses

All 61 pediatric outpatients (age, 9.2 ± 2.8 years, 6–16 years, male: female, 39: 22) participated in this study. All subjects successfully underwent spirometry. The spirometric data, FVC and FEV_1, were within the normal range for children, and a chest auscultation by specialists in pediatric pulmonology found no abnormalities. In each of the 61 subjects, the breath sound spectrum parameters were also successfully calculated. None of the breath sound images showed wheezing, rales or distinct outside noises. The shape of the sound spectrum showed good similarity in the same patients.

However, 4 of 61 subjects (6.6%) showed no breath sounds of > 1,000 Hz in the sound spectrum. Thus, these 4 subjects were omitted, and 57 subjects (age, 9.0 ± 2.8 years, 6–16 years, male: female ratio, 35: 22) ultimately participated this study. The new spectrum curve indices, A_{1000} and A_{1000}/A_T, were not correlated by age, height, weight and body mass index (BMI) by Pearson's correlation coefficient.

Differences in the lung function before and after β_2 agonist inhalation

With the exception of FVC and V'_{25}, all of the spirometric parameters showed a statistical increase after β_2 agonist inhalation (Table 1). With the exception of X5, all of the FOT parameters showed a statistical decrease after β_2 agonist inhalation (Table 1).

Differences in the breath sound parameters before and after β_2 agonist inhalation

With the exception of F_{99}, all of previous spectrum curve indices showed a statistical difference after β_2 agonist inhalation (Table 1). The new spectrum curve indices, A_{1000} and A_{1000}/A_T, did not show a statistical difference after β_2 agonist inhalation (Table 1).

Relationship between the lung function parameters and the breath sound parameters before β_2 agonist inhalation

The previous spectrum curve indices, RPF_{75} and RPF_{50} were negatively correlated with the value of R5 (p = 0.044 and p = 0.039, respectively). The A_{1000} was negatively correlated with the FEV_1 (p = 0.028). No correlations were observed among the other lung function parameters.

Relationship between the changes in the lung function parameters and the changes in the breath sound parameters before and after β_2 agonist inhalation

The increase in the ΔFVC was correlated with the increase in the ΔA_{1000} (p = 0.044), and the increase in the ΔFEV_1 was remarkably correlated with the decrease in the ΔA_{1000} (p = 0.001) and the $\Delta A_{1000}/A_T$ (p = 0.036) (Table 2). The $\Delta A_3/A_T$ and ΔRPF_{75} were negatively correlated with the ΔFEV_1 (p = 0.028 and p = 0.028, respectively) (Table 2). No correlations were observed among the other lung function parameters.

DISCUSSION

For the better diagnosis and treatment of children with asthma, a non-invasive and reliable method for detecting bronchoconstriction is required. Auscultation is useful for detecting bronchoconstriction during asth-

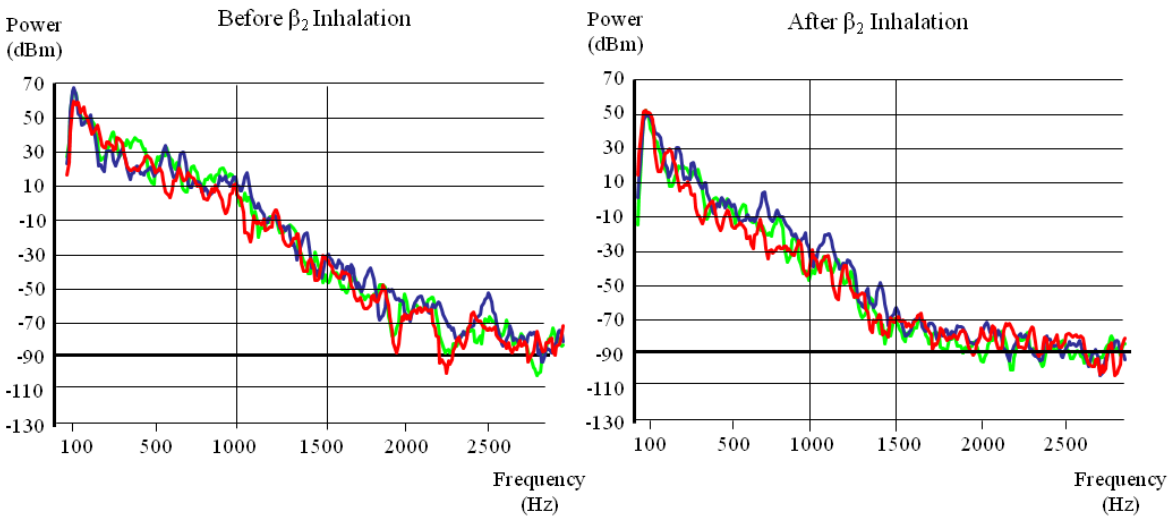


Fig. 3 Changes in the sound spectrum before and after β_2 agonist inhalation
After β_2 agonist inhalation, the sound spectrum of the high-pitched area (>1,000 Hz) was decreased.

Table 2 The relationship between changes in lung function data and breath sound parameters

		ΔFVC (%pred)	ΔFEV_1 (%pred)	$\Delta FEF_{25\text{-}75}$ (%pred)	$\Delta \dot{V}_{50}$ (%pred)	$\Delta \dot{V}_{25}$ (%pred)	ΔR20 [kPa/(L/s)]	ΔR5 [kPa/(L/s)]	ΔR5-R20 [kPa/(L/s)]	ΔX5 [kPa/(L/s)]
ΔF_{99}	CC	0.059	-0.230	0.016	0.044	0.043	-0.029	-0.131	-0.042	0.020
	P	0.681	0.085	0.909	0.759	0.765	0.836	0.350	0.765	0.886
$\Delta A_3/A_T$	CC	-0.138	-0.292	-0.167	-0.196	-0.093	0.203	0.022	-0.119	0.194
	P	0.335	**0.028**	0.242	0.168	0.514	0.146	0.878	0.401	0.163
$\Delta B_4/A_T$	CC	-0.183	-0.080	-0.024	-0.034	-0.012	0.107	0.073	0.066	0.108
	P	0.200	0.556	0.866	0.815	0.933	0.445	0.603	0.644	0.443
ΔRPF_{75}	CC	-0.161	-0.291	-0.180	-0.198	-0.159	0.103	-0.038	-0.187	0.167
	P	0.261	**0.028**	0.207	0.164	0.265	0.463	0.786	0.184	0.231
ΔRPF_{50}	CC	-0.179	-0.008	-0.101	-0.089	-0.105	0.044	0.042	0.-65	-0.114
	P	0.210	0.956	0.482	0.535	0.462	0.756	0.766	0.646	0.415
ΔA_{1000}	CC	0.286	-0.421	-0.032	0.036	-0.068	0.067	-0.001	-0.042	-0.083
	P	**0.044**	**0.001**	0.823	0.805	0.639	0.639	0.993	0.768	0.557
$\Delta A_{1000}/A_T$	CC	0.154	-0.283	0.145	0.170	0.072	0.104	0.017	-0.027	-0.091
	P	0.292	**0.036**	0.321	0.244	0.623	0.469	0.907	0.855	0.525

(n = 57, CC; correlation coefficient)

ma exacerbation. Practically, however, a breath sound analysis using sound analyzer is more objective, and an association between changes in the breath sounds and airway obstruction has been recognized [11].

The potential application of a breath sound analysis to test the pulmonary function has been demonstrated [12]. According to previous studies, some breath sound parameters change during histamine and methacholine inhalation challenges [18, 19], and a strong relationship exists between increased changes in the values of breath sound parameters and airway narrowing in asthmatic patients [20, 21].

As breath sound analyses are limited by the fact that the common breath sound parameters are strongly affected by the maximum airflow of a patient's breath [22, 23], such analyses are difficult to perform in young children who cannot breathe as instructed by the examiner. We recently evaluated a reliable breath sound analysis method using the parameters calculated based on the ratio [7, 10]. The benefits of the new spectrum curve indices, A_3/A_T, B_4/A_T, RPF_{50} and RPF_{75}, as simple and reliable biomarkers of the respiratory function in infants [9], children with asthma [10] and cough variant asthma [24] have been reported.

Unfortunately, such spectrum curve indices are believed to be less sensitive than the directly measured parameters of the lung function like FEV_1 [7, 9]. In the present report, we focused on narrowed-airway-induced wheezing, and developed new sound parameters that can directly quantify the presence of high-pitched breath sounds. A_{1000} in particular may directly show breath sound changes. All of pediatric patients in this study were able to breathe with calm and same-level breaths. We believe that many preschool children can produce stable breathing during respiratory examinations without strict cooperation.

The A_{1000} was negatively correlated with the value of FEV_1. The FEV_1 is the most commonly used parameter of spirometry for assessing large airway constriction during the exacerbation of asthma [25]. Patients with lower values of FEV_1 tended to show higher A_{1000}. This result also indicates that slight airway narrowing existed during attack-free periods in some participating asthmatics. Since there are no parameters for infants and preschool children that are significantly correlated with FEV_1, A_{1000} is a sensitive parameter for evaluating inaudible bronchoconstriction.

As inferred from the previous results, the RPF_{75} and RPF_{50} were negatively correlated with the value of R5, resistance at 5 Hz. R5 is said to indicate the total airway resistance in the FOT method [3]. The increase in the RPF_{75} and RPF_{50} showed the airway dilatation with β_2 agonist inhalation [7, 9].

Of note, before and after β_2 agonist inhalation, the ΔFEV_1 was negatively correlated with the ΔA_{1000} ($p = 0.001$) and the $\Delta A_{1000}/A_T$ ($p = 0.036$). This clear result is convincing, given the above results, and shows that the ΔA_{1000} is superior to other parameters for indicating the changes in large airways. In addition, the A_3/A_T and B_4/A_T are the ratio of the high frequency areas (A_3 and B_4) to the total area (A_T) in the sound spectrum [7]. When bronchial dilatation by β_2 agonist inhalation is induced with the regression of the prolonged high-pitched area in the sound spectrum [9], the values of A_3/A_T and B_4/A_T are increased [7]. In contrast, the A_{1000} is an absolute value of the sound spectrum. After bronchial dilatation, the A_{1000} and A_{1000}/A_T decrease, resulting in a reduction in the high-pitched area of the sound spectrum.

We may reasonably presume that, as the ΔA_{1000} and the $\Delta A_{1000}/A_T$ increase, so should the improvement of airway constriction. In contrast, the $\Delta A_3/A_T$ and ΔRPF_{75} were slightly negatively correlated with the ΔFEV_1. These results show the utility of A_{1000} and A_{1000}/A_T for detecting large airway narrowing more clearly than the A_3/A_T and the RPF_{75} which were reported to be potentially useful for indicating the small airway condition [7, 9]. We next plan to examine the utility of standard values of A_{1000} and A_{1000}/A_T for the detecting silent asthma.

The ΔFVC value was only weakly correlated with the ΔA_{1000} value. We suspect that the larger inspiration volume induced by airway enlargement may increase the FVC. Because all asthmatic patients were asked to perform tidal breathing during the test, it is possible to say that the total inspired breath sounds and their power likely decreased with the disappearance of any turbulence after the airway narrowing was improved [7]. However, the total inspired breath sounds and their power may have been increased by the bronchial dilatation-induced larger respiration. Given the above, we speculate that the ΔA_{1000} value might increase with the ΔFVC after β_2 agonist inhalation.

As a limitation of this study, the new parameters, A_{1000} and A_{1000}/A_T, can only be used for the patients who are able to take calm, same-level breaths during the test. In this report, we did not examine whether A_{1000} is superior to A_3/A_T or other previous breath sound parameters; we only evaluated the utility of A_{1000} in analyses of children who cannot perform the standard lung function tests.

Furthermore, the values of A_{1000} and A_{1000}/A_T did not significantly increase after β_2 agonist inhalation. Although a decreasing trend was noted, we speculate that a significant difference was not observed due to changes in the respiratory airflow. Improvements in the airway constriction after β_2 agonist inhalation may induce large respiration, which induces high-pitched breath sounds. We can also infer this from the fact that no significant changes were observed in F_{99}, almost the highest frequency on the spectrum, after β_2 agonist inhalation (Table 1). We believe this is a disadvantage of the breath sound parameters that has been used thus far [22, 23], and we feel that the absolute value of A_{1000} should be used with care. However, ΔA_{1000} and $\Delta A_{1000}/A_T$ value showed a good relationship with the ΔFEV_1 values. Due to these excellent characteristics, we particularly recommend that the ΔA_{1000} value be used to evaluate the bronchial reversibility using β_2 agonist inhalation.

The question remains as to why the breath sound parameters obtained during tidal breathing that might reflect the caliber of the small airways were significantly correlated with the parameters of spirometry obtained during forced expiration that reflect mostly the caliber of the large airways. β_2 agonist inhalation has been suggested to induce bronchial dilatation in both large and small airways [26]. However, we cannot directly suggest which part of the airway caused the observed breath sounds. Whether or not the high-pitched sounds are generated in the peripheral airways remains unclear, although a previous study in an animal model suggested which parts of the airway might be involved in the breath sound production [27].

Considering the characteristics of sound production, when the air flow of breath increases, not only the low-pitched sound area but also the high-pitched sound area increase [7] despite the difference in the caliber size. We speculate that both large and small airway constriction induces high-pitched sounds and that A_{1000} represents tidal breathing while FEV_1 represents forced expiration, both of which can describe airway constriction well.

Consequently, the main finding of the present study is that the high-pitched breath sound parameters, A_{1000} and A_{1000}/A_T, reflect the airway changes in asthmatic children. Although spirometry is the gold standard method of assessing the lung function [3], the present findings suggest that our clinical approach provides certain information about bronchial reversibility. This technique is safe and simple to perform during tidal breathing without patients' strict cooperation. We believe that many preschool children who cannot complete lung function test may repeatedly perform these physiological maneuvers [10]. Based on the findings of this study, we are planning to assess the significance of the differences in the changes of β_2 agonist-induced breath sound between asthmatic and normal preschool children.

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DISCLOSURE

The authors declare no conflicts of interest in association with the present study.

AUTHORSHIP CONTRIBUTION

H.M. and H.T. designed the study. Y.K., M.N., H.T., M.E. and K.H. collected the data. Y.K. calculated all of data. M.K. analyzed the data. The final manuscript was read and approved by all of the authors.

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