Changes in the Breath Sound Spectrum with Bronchodilator Inhalation in Asthmatic Children with Long-term Management

Tomohiko IMAMURA[*1], Mayumi ENSEKI[*1], Hiroyuki FURUYA[*2], Fumio NIIMURA[*1] and Hiroyuki MOCHIZUKI[*1]

[*1]*Department of Pediatrics, Tokai University School of Medicine*
[*2]*Department of Basic Clinical Science and Public Health, Tokai University School of Medicine*

(Received December 11, 2019; Accepted January 24, 2020)

Objective: Using a commercially available breath sound analyzer, the airway reversibility in asthmatic children during healthy periods was investigated.
Methods: Fifty samples of 34 children with asthma (median age, 11 years; range, 6–16 years) who visited our hospital and whose lung function was normal were included. The breath sound parameters, the frequency limiting 99% of the power spectrum (F_{99}) and spectrum curve indices, the total area under the curve of the dBm data (A_3/A_T and B_4/A_T) and the ratio of power and frequency at 50% and 75% of the highest frequency of the power spectrum (RPF_{75} and RPF_{50}) were evaluated before and after β_2 agonist inhalation.
Results: The values of spectrum curve indices were significantly increased after β_2 agonist inhalation. The changes in these parameters were more marked than the changes in the FOT parameters. The changes in A_3/A_T and B_4/A_T were significantly related to two FOT parameters: R5-R20 and X5.
Conclusions: Our study suggested that significant changes in breath sound parameters were present in asthmatic children during the period of good control. A breath sound analysis may be useful for assessing the airway condition of asthmatic children during long-term management.

Key words: asthma, acute exacerbation, breath sound, children, sound spectrum

INTRODUCTION

Keeping asthma well-controlled state by long-term management is recommended for the prevention of aggravation and protraction of asthma [1, 2]. A stable and good lung function is a criterion of a well-controlled state of asthma [3, 4]. Bronchial hyperresponsiveness or bronchial hyperreversibility has been measured to understand the control state of asthma. However, the evaluation of asthma control in children under five years of age, who are not able to perform a standard lung function test, is suggested to be difficult [1].

Breath sounds are reportedly sensitive to bronchial dilatation and bronchial constriction, so a breath sound analysis is expected to be a safe and simple method that can be applied in the clinical assessment of bronchial dilatation and bronchial constriction [5]. Recent developments in computed signal processing methods have improved the breath sound analyses [6, 7]. One issue with these methods is that breath sounds are affected by the airflow rate and pulmonary function [8, 9]. When evaluating younger children, it is particularly difficult to obtain continuous stable breathing during respiratory examinations.

To resolve this problem, new breath sound parameters that are largely unaffected by the airflow rate have been defined [7, 10, 11]. In the pediatric field, coupled with the improvement of clinical procedures, the breath sound spectrum can be measured, and changes in breath sound parameters can be observed when airway narrowing is present even in infants and younger children [10].

We hypothesized that the breath sound analysis could detect unnoticeable airway constriction in children and that breath sound parameters might be useful for assessing airway reversibility in asthmatic children with long-term management. The aim of the present study was to examine the changes in breath sound parameters caused by β_2 agonist-induced bronchial dilatation during the healthy period in asthmatic children.

METHODS

Study subjects

Thirty-four pediatric outpatients (median age, 11 years; range, 6–16 years; male: female, n = 22: 12) who came to Tokai University Hospital on a regular visit and agreed to participate were included in this study from January 1, 2012 to March 31, 2018. By their self-report, their condition was well controlled with long-term asthma management. The patient data from January 1, 2012 to March 31, 2014, partially overlapped with those in a previous report [12]. The inclusion criteria were as follows: subjects who had one or more positive specific IgE value, mainly Dermatophagoides farinae, D. pteronyssinus and house dusts (> 0.7 UA/ml), more than 3 incidents of

Hiroyuki MOCHIZUKI, Department of Pediatrics, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-94-3426 E-mail: mochihi@tokai-u.jp

recurrent wheezing and bronchial hyperresponsiveness on methacholine inhalation challenge (threshold of methacholin: ≤ 7.0 units) or bronchial reversibility by β_2 agonist inhalation (increase in FEV_1: ≥ 12.0%). The exclusion criteria were as follows: ≤ 5 years old, acute respiratory infection or systemic steroid therapy within 7 days and recurrent asthma exacerbation within 3 months. In this study, we defined subjects with ≧ 80% FEV_1 (% predicted) as those with a normal lung function.

It was confirmed that all subjects had no respiratory symptoms and no wheeze or no crackles were found by a physician's auscultation during breath sound sampling. All drugs were withdrawn overnight before the test.

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, No. 14R-133, approval date: October 23, 2014, and No. 17R-161, approval date: October 18, 2017).

Study protocol

The assessments were performed before and 15 minutes after β_2 agonist inhalation. During the breath sound analysis, each subject was requested to take tidal breaths. After the sound analysis, the patients' pulmonary function was evaluated using spirometry and the forced oscillation technique (FOT) [15].

Pulmonary function tests

The pulmonary function of the participants was determined via spirometry (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 FVC and FEV_1. The results are shown as the percent predicted value of Japanese children.

The FOT parameters were determined using an FOT system (Master-Screen-Impulse Oscillometry System; Jaeger Co, Wurzburg, Germany) [15]. The measurements were made in the standing position with a nose-clip on. Real-time recordings of mouth pressure and flow signals pulsed through the 5-20-Hz spectrum were superimposed over tracings of the tidal breathing. Measurements of the 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.

β_2 agonist inhalation

All subjects inhaled β_2 agonist solution (procaterol 30 μg and saline 2.0 ml) [2]. The assessments were performed before and 15 minutes after β_2 agonist inhalation.

Breath sound analyses

A breath sound analysis was performed as described previously [7, 11]. Breath sounds were recorded for ≥ 10 seconds in a silent room using a handheld microphone. The microphone was placed at the second intercostal 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 sound-amplifying unit was found to be effective for analyzing sounds in the range of 100–2500 Hz. The recorded sounds were analyzed according to a fast Fourier transformation. The sampling frequency was 10,240 Hz, and the spectra were obtained using a Hanning window. The sounds were displayed as a spectrograph. The dBm values were plotted on the Y axis and the Hz values were plotted on the X axis. 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. The mean background noise in our silent room was −88.1 ± 5.0 dBm. Thus, in this report, the zero point of dB 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 spectrum [7, 11].

The point of the maximum frequency (Hz) in the shape during inspiration was used for the sound spectrum analysis. The A_T, A_3 and B_4 were conventionally calculated according to the dBm and Hz (1 arbitrary unit [dBm・Hz] on a spectrum image). A_T means total area under the curve of 100 Hz to the highest frequency of the dBm power spectrum, and A_3 and B_4 means the third area under the curve and the forth area under the curve (Fig. 1a) [16]. The spectrum curve indices (RPF_{75} and RPF_{50} values) were also calculated. RPF_{50} means the ratio of power and frequency at 50% of the highest frequency of the power spectrum, and RPF_{75} means the ratio of power and frequency at 75% of the highest frequency of the power spectrum (Fig. 1b) [16]. Previous reports suggested that the spectrum sound parameters, A_3/A_T, B_4/A_T, RPF_{75} and RPF_{50}, are increased with bronchial dilatation which induces a decrease of high-pitched lung sound [16].

A five-point moving average was used as a smoothing technique to determine the suitable dBm value for identifying some checkpoints in the slope of each sound spectrum. Aside from this, the parameters of the total power of the power spectrum (P_T)(log[mV^2]) and the frequency limiting 99% of the power spectrum (F_{99}) were measured in accordance with the methods of previous reports.

In this study, breath sound samples were obtained 2 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 in-house-developed calculation software program [7, 10, 11].

Statistical analyses

The statistical analyses were conducted using the SPSS software program (IBM SPSS Statistics, Version 22 for Windows; IBM Corp., Armonk, N.Y., USA). The paired parameters were compared using Wilcoxon's signed-rank test. Correlations between individual breath sound parameters and other measurements were determined using Spearman's correlation test.

RESULTS

The lung function and breath sound analyses

A total of 50 samples obtained on different examination days over 5 years were obtained from 34

Table 1 The results of the breath sound analysis

	β_2 stimulant inhalation		
	Before	After	*P*-value**
FVC (%pred)	83.6* (80.8, 89.1)	85.4 (81.2, 88.7)	0.375
FEV_1 (%pred)	92.1 (89.0, 96.0)	93.6 (89.2, 97.6)	**0.002**
FEF_{25-75} (%pred)	110.5 (96.1, 126.8)	116.4 (101.3, 136.5)	**<0.001**
V'_{50} (%pred)	102.5 (85.8, 116.3)	110.0 (90.5, 128.5)	**<0.001**
V'_{25} (%pred)	108.0 (91.2, 120.6)	116.8 (102.9, 135.3)	**<0.001**
R20 [kPa/(L/s)]	0.37 (0.29, 0.41)	0.33 (0.26, 0.39)	**0.013**
R5 [kPa/(L/s)]	0.48 (0.32, 0.56)	0.40 (0.30, 0.54)	**0.003**
R5-R20 [kPa/(L/s)]	0.10 (0.05, 0.15)	0.09 (0.04, 0.14)	0.081
X5 [kPa/(L/s)]	−0.14 (−0.19, −0.09)	−0.14 (−0.17, −0.09)	0.079
A_T (dBm・Hz)	8854 (7586, 9739)	8983 (7207, 9739)	0.891
F_{99} (Hz)	1792 (1636, 1940)	1343 (1130, 1789)	**<0.001**
A_3/A_T (%)	12.1 (11.2, 13.7)	13.3 (12.1, 13.8)	**0.029**
B_4/A_T (%)	7.2 (6.6, 8.1)	8.1 (7.0, 8.6)	**0.011**
RPF_{75} (dBm/Hz)	6.3 (5.1, 7.4)	7.1 (6.0, 8.1)	**0.049**
RPF_{50} (dBm/Hz)	6.6 (6.0, 7.5)	7.1 (6.6, 7.7)	0.062

*; Median (First quartile, Third quartile), **; Wilcoxon signed-rank test.

subjects (median age, 11 years old; range, 6–16 years old, boys: girls = 33:17, median onset age, 5 years old; range, 2–6 years old, duration of asthma, 7 years; range, 5–8.5 years, severity: mild in 45, moderate in 5) (2 samples from 6 subjects and 3 samples from 5 subjects). All asthmatic patients were on controller therapy prior to admission (leukotriene receptor antagonist, n = 7, inhaled steroid, n = 1, inhaled steroid and leukotriene receptor antagonist, n = 23, inhaled steroid and long-acting beta adrenoceptor antagonist and leukotriene receptor antagonist, n = 19).

None of the subjects had wheeze or other respiratory symptoms and were declared to be in a good condition at the time. Chest auscultation by pediatric pulmonology specialists found no adventitious sounds. All subjects underwent spirometry, FOT and breath sound analyses. The median values of FVC and FEV_1 were 83.6% and 92.1%, respectively (Table 1).

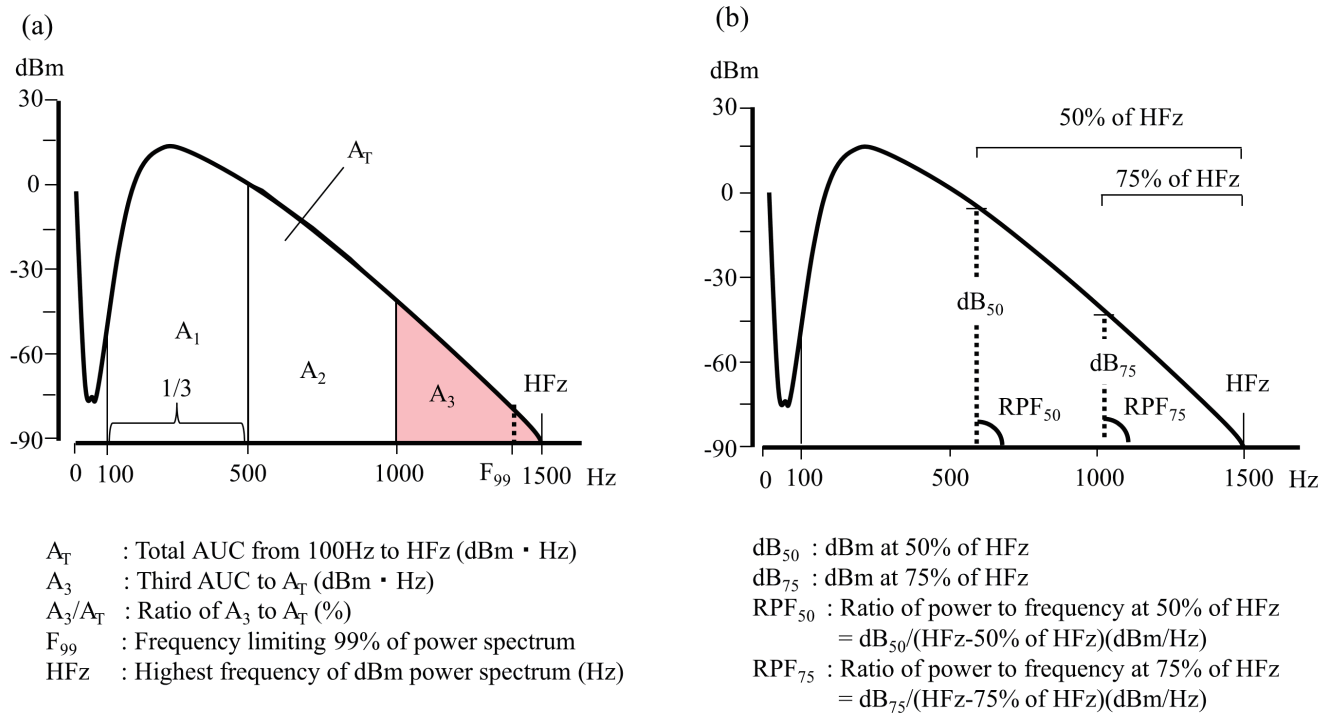
Differences in the lung function and breath sound analysis results before and after β_2 agonist inhalation

Fig. 1 shows the sound spectrograms and sound spectra of a patient with a normal lung function before (Fig. 2a) and after β_2 agonist inhalation (Fig. 2b). The high-pitched sound areas of the sound spectrum were decreased after β_2 agonist inhalation (Fig. 2b).

In the subjects with good control, all of the spirogram parameters except for the FVC were increased and the FOT parameters of R20 and R5 were decreased after β_2 agonist inhalation (Table 1). In addition, the breath sound parameter of F_{99} was decreased and the spectrum curve indices of A_3/A_T, B_4/A_T and RPF_{75} were increased after β_2 agonist inhalation in these patients.

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

In the sound spectrum curve index data, the $\Delta A_3/A_T$ and $\Delta B_4/A_T$ values were significantly correlated with the ΔR5-R20 value ($p = 0.015$ and $p = 0.001$, respectively) and the $\Delta B_4/A_T$ values were significantly correlated with the ΔR5 value ($p = 0.026$) and the ΔX5 value ($p = 0.016$ and $p = 0.024$, respectively) before and after β_2 agonist inhalation (Table 2). However, no correlations were observed between spirogram parameters and the spectrum curve indices.



A_T : Total AUC from 100Hz to HFz (dBm・Hz)
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)

dB_{50} : dBm at 50% of HFz
dB_{75} : dBm at 75% of HFz
RPF_{50} : Ratio of power to frequency at 50% of HFz
= dB_{50}/(HFz-50% of HFz)(dBm/Hz)
RPF_{75} : Ratio of power to frequency at 75% of HFz
= dB_{75}/(HFz-75% of HFz)(dBm/Hz)

Fig. 1 The sound spectrum parameters
(a) A_T (dBm・Hz): the total AUC from 100Hz to HFz, 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), (b) 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).

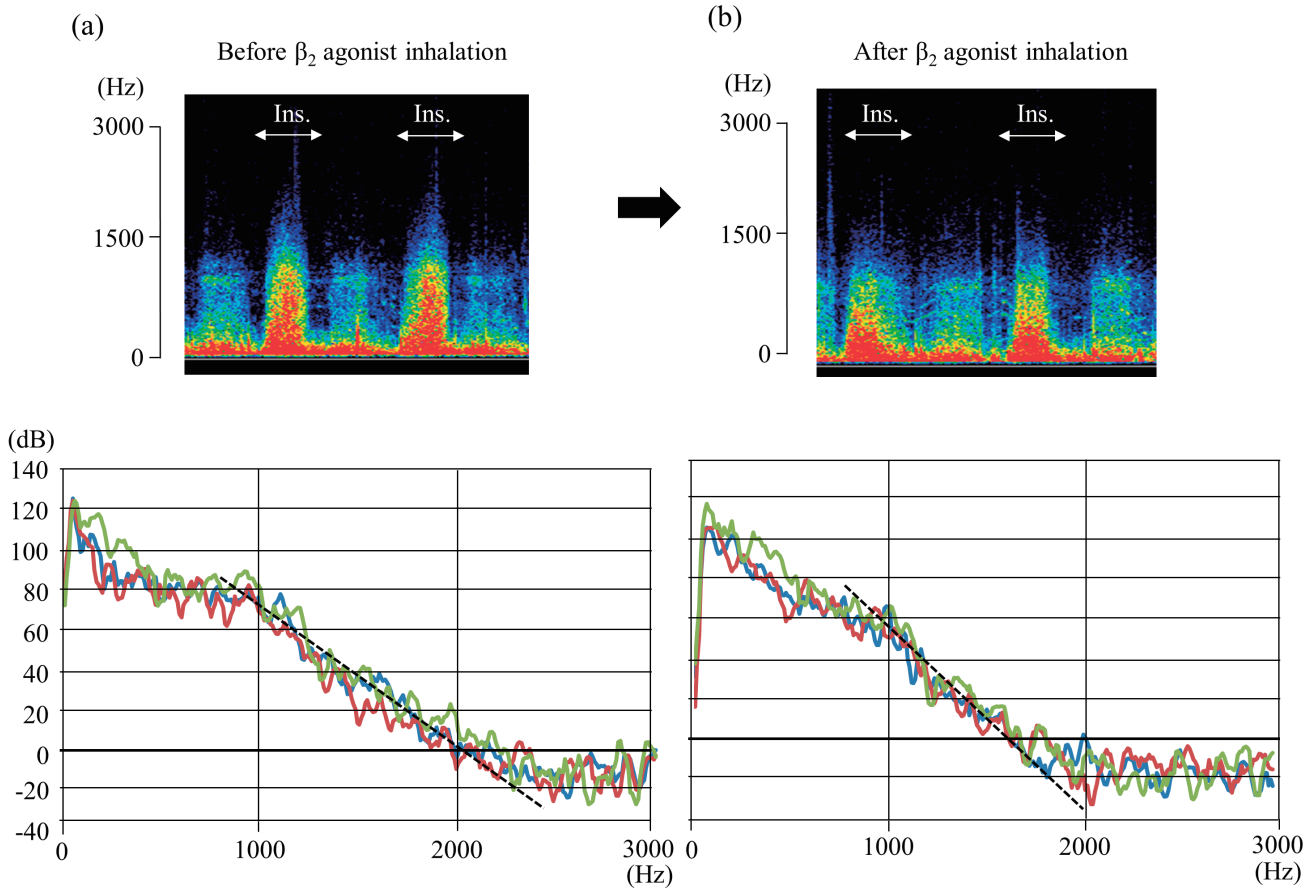


Fig. 2 Changes in sound spectrograms and sound spectra before and after β_2 agonist inhalation
Sound spectrograms and sound spectra of an asthmatic children with a normal lung function before (a) and after β_2 agonist inhalation (b).

Table 2 The relationship between the changes of sound spectrum parameters and other pameters

		ΔFVC (%pred)	ΔFEV_1 (%pred)	ΔFEF_{25-75} (%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 [ka/(L/s)]
$\Delta A_3/A_T$	CC*	0.049	0.099	0.194	0.125	0.175	0.126	−0.081	−0.260	−0.259
	P	0.651	0.363	0.072	0.250	0.106	0.246	0.457	**0.015**	**0.016**
$\Delta B_4/A_T$	CC	0.017	0.058	0.172	0.129	0.177	0.006	−0.238	−0.339	−0.242
	P	0.879	0.591	0.110	0.234	0.100	0.957	**0.026**	**0.001**	**0.024**
ΔRPF_{75}	CC	0.117	0.105	0.177	0.188	0.164	0.123	0.050	−0.050	0.077
	P	0.279	0.332	0.100	0.082	0.128	0.255	0.645	0.644	0.479
ΔRPF_{50}	CC	0.053	0.029	0.095	0.132	0.037	0.167	0.069	−0.008	−0.046
	P	0.624	0.791	0.382	0.222	0.734	0.121	0.523	0.941	0.674

*; Spearman's correlation test.

DISCUSSION

The relationship between the breath sound parameters and lung function test results has been demonstrated. According to previous studies, the breath sound parameters change during methacholine and histamine provocation challenges [11, 17], and a relationship is thought to exist between changes in the breath sound parameters and airway narrowing in asthmatic patients [18, 19].

We previously investigated the potential of a breath sound analysis as a simple and non-invasive lung function test for a biomarker of childhood asthma [7, 11]. As breath sound analyses are limited by the fact that the common breath sound parameters are markedly affected by the maximum airflow of breath or other growth-related factors [8, 9], we evaluated a reliable breath sound analysis method and demonstrated its usefulness in the assessment of bronchial constriction in children [7, 11].

One interesting finding of the present study is that, in the well-controlled asthmatic children with normal lung function, the spectrum curve indices of A_3/A_T, B_4/A_T and RPF_{75} were significantly increased after β_2 agonist inhalation. It has been suggested that when bronchial dilatation is introduced, the main change that occurs is in the high-pitched part of the sound spectrum [7, 20, 21]. The direct high-pitched sound spectrum parameter F_{99} was also significantly decreased after β_2 agonist inhalation. Our results indicated that the high-pitched part of the breath sound of inspiration in the asthmatic children with a reduced lung function was reduced by β_2 agonist inhalation. In addition, the spirogram values in the asthmatic children with a normal lung function were significantly changed after β_2 agonist inhalation. These data suggest that asthmatic children who are considered to be in good health based on self-reported information may actually have an airway narrowing.

However, in these subjects, no such high-pitched sounds were detected by normal auscultation. The changes in breath sound parameters that we noted in this study were change in the breath sound spectrum that differed from the clinical wheeze detected by auscultation or a sound spectrogram [22, 23]. Since the degree of bronchoconstriction and the effect of β_2 agonist inhalation in the asthmatic children with a normal lung function were smaller than in those with an exacerbation of asthma, the breath sound parameters were considered useful for assessing the airway condition in the long-term management of children with asthma. Breath sound analyses are sensitive, and future studies should explore how to capitalize on this sensitivity for clinical use in younger children and elderly patients who cannot undergo spirography.

Although the changes in the breath sound parameters were not well correlated with those in the spirogram parameters, the changes in the breath sound parameters were significantly correlated with those in FOT parameters. The differences between the results of the spirometry and FOT have been reported [24, 25]. During a breath sound analysis and FOT, patients are required to practice tidal breathing. However, during spirogram testing, patients are required to perform maximal inspiration and expiration. We therefore believe that spirogram results should be considered to evaluate a different respiratory physiology from a breath sound analysis and FOT [12]. Maximal inspiration and expiration may induce large structural changes in the small airways in children, as such small airways are soft and easily deformed. Such clear changes induced by maximal inspiration and expiration are one advantage of spirograms, differentiating from breath sound analyses and FOT.

We believe that examining whether or not the breath sounds of asthmatics are normal is significant for physicians, even in the absence of symptoms of acute exacerbation of asthma. When an improvement in the breath sound parameter is seen after β_2 agonist inhalation, the level of asthma control must be reviewed. Furthermore, in the present results, the correlation between the changes in the FOT and the changes in the breath sound parameters was shown to be important for developing a new lung function test for infants and younger children. The FOT is a reliable technique for children [26]. However, in our study, we lacked sufficient data on infants and younger children, in whom the evaluation of bronchial hyperresponsiveness and bronchial reversibility is difficult [2]. We therefore plan to evaluate the airway condition based on the changes in breath sound parameters after β_2 agonist inhalation for infants [27, 28] and younger children with asthma in a future study.

In this report, the value of AT, which is the total area under the curve [7, 10], did not decrease after β_2 agonist inhalation. Because all asthmatic patients attempted to perform tidal breathing during the test, it is possible to say whether or not the airway nar-

rowing was improved and the total power of inspired breath sounds decreased with the disappearance of turbulence [7]. However, the total power of inspired breath sounds may be naturally increased by bronchial dilatation-induced increases in respiration. Based on these results, we assume that the A_T values were not markedly changed after β_2 agonist inhalation.

As one limitation associated with this study, we lacked any age-specific standard values for the breath sound parameters, and were thus unable to calculate the percent of predicted values of breath sound parameters, as with spirogram parameters [29]. Significant differences in the breath sound parameters were not very clear between the two groups that were clearly differentiated by FEV_1 value, possibly because the breath sound parameters were not represented as the percent of predicted values. Although our breath sound parameters were not markedly affected by changes in individual expiratory flow rates [7], aging may have some effects on the formation of breath sounds in children. We therefore next intended to collect large data on breath sounds in normal infants and children to determine standard values.

Another limitation was that we were unable to directly suggest which part of the airway caused the high-pitched breath sounds. Whether or not the high-pitched sounds are generated in the peripheral airways remains unclear [16]. A previous report in animal model suggested a part of the airway that may be involved in the lung sound production [30]. Further examinations are expected to identify the part of the airway that is associated with these changes in breath sounds.

Consequently, the main finding of the present study is that the breath sound parameters were significantly changed by β_2 agonist inhalation in children with asthma who were in a good condition. Although spirometry is the gold standard for assessing the lung function [15], a breath sound analysis is safe and simple to perform during tidal breathing [7, 10]. The results of the present study suggest that the spectrum curve indices were sufficiently sensitive to detect bronchial dilatation with the same level of FOT and that these parameters may be useful for assessing the airway condition in the long-term management of asthmatic children. Based on the results of this study, we will next test the significance of the differences in the changes in β_2 agonist-induced breath sound parameters between infants and younger children.

ACKNOWLEDGMENTS

We thank Dr. Akifumi Suzuki of Suzuka University of Medical Science and Dr. Hiroshi Nakano of the National Hospital Organization Fukuoka Hospital for their valuable technical assistance.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DISCLOSURE

This study was supported by the Environmental Restoration and Conservation Agency of Japan in 2009–2018.

ABBREVIATIONS

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, **V'_{50}**: maximal expiratory flow at 50% vital capacity, **V'_{25}**: maximal 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, **F_{99}**: frequency limiting 99% of the power spectrum, **P_T**: total power area of 100 Hz to the highest frequency 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, **A_3/A_T**: the ratio of the third area under the curve to total area under the curve, **B_4**: forth area under the curve, **B_4/A_T**: the ratio of the fourth area under the curve to total 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

REFERENCES

1) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Available at https://ginasthma.org/wp-content/uploads/2019/06/GINA. [Accessed 27 December 2019].
2) Japanese Society of Pediatric Allergy and Clinical Immunology. Guidelines for the Treatment and Management of Pediatric Bronchial Asthma 2012 (Japanese). Tokyo: Kyowa Kikaku, 2011.
3) Ducharme FM, Davis GM. Measurement of respiratory resistance in the emergency department: feasibility in young children with acute asthma. *Chest*. 1997; **111**: 1519–25.
4) Bentur L, Beck R, Shinawi M, Naveh T, Gavriely N. Wheeze monitoring in children for assessment of nocturnal asthma and response to therapy. *Eur Respir J*. 2003; **21**: 621–6.
5) Bentur L, Beck R, Berkowits D, Hasanin J, Berger I, Elias N, *et al*. Adenosine bronchial provocation with computerized wheeze detection in young infants with prolonged cough. *Chest*. 2004; **126**: 1060–5.
6) Oweis RJ, Abdulhay EW, Khayal A, Awad A. An alternative respiratory sounds classification system utilizing artificial neural networks. *Biomed J*. 2015; **38**: 153–61.
7) Tabata H, Hirayama M, Enseki M, Nukaga M, Hirai K, Furuya H, *et al*. A novel method for detecting airway narrowing using breath sound spectrum analysis in children. *Respir Invest*, 2016; **54**: 20–8.
8) Anderson K, Aitken S, Carter R, MacLeod JE, Moran F. Variation of breath sound and airway caliber induced by histamine challenge. *Am Rev Respir Dis*. 1990; **141**: 1147–50.
9) Shykoff BE, Ploysongsang Y, Chang HK. Airflow and normal lung sounds. *Am Rev Respir Dis*. 1988; **137**: 872–6.
10) Enseki M, Nukaga M, Tabata H, Hirai K, Matsuda S, Mochizuki H. A clinical method for detecting bronchial reversibility using a breath sound spectrum analysis in infants. *Respir Invest*, 2017; **55**: 219–28.
11) Tabata H, Enseki M, Nukaga M, Hirai K, Matsuda S, Furuya H, *et al*. Changes in the breath sound spectrum during methacholine inhalation in children with asthma, *Respirology* 2018; **23**: 168–75.
12) Nukaga M, Tabata H, Enseki M, Hirai K, Furuya H, Kato M, *et al*. Changes in the breath sound spectrum with bronchodilation in children with asthma. *Respir Investig*. 2018; **56**: 392–8.
13) Mochizuki H, Shigeta M, Tokuyama K, Morikawa A. Difference in airway reactivity in children with atopic vs nonatopic asthma. *Chest*. 1999; **116**: 619–24.
14) Nishimura H, Mochizuki H, Tokuyama K, Morikawa A.

Relationship between bronchial hyperresponsiveness and development of asthma in children with chronic cough. *Pediatr Pulmonol*, 2001: **31**; 412–8.
15) Mochizuki H, Hirai K, Tabata H. Forced oscillation technique and childhood asthma. *Allergol Int*. 2012; **61**: 373–83.
16) Kondo Y, Nukaga M, Enseki M, Tabata H, Hirai K, Kato M, *et al*. Clinical application of high-pitched breath sound in children with asthma. *Tokai J Exp Clin Med*. 2018; **43**: 74–80.
17) Rietveld R, Dooijes EH, Rijssenbeek-Nouwens LH, *et al*. Characteristics of wheeze during histamine-induced airways obstruction in children with asthma. *Thorax*. 1995; **50**: 143–8.
18) Spence DP, Bentley S, Evans DH, Morgan MDL. Effect of methacholine induced bronchoconstriction on the spectral characteristics of breath sounds in asthma. *Thorax*. 1992; **47**: 680–3.
19) Beck R, Dickson U, Montgomery MD, Mitchell I. Histamine challenge in young children using computerized loung sounds analysis. *Chest*. 1992: **102**; 759–63.
20) Sovijärvi AR, Malmberg LP, Paajanen E, Piirila P, Kallio K, Katila T. Averaged and time-gated spectral analysis of respiratory sounds. Repeatability of spectral parameters in healthy men and in patients with fibrosing alveolitis. *Chest*. 1996; **109**: 1283–90.
21) Hidalgo HA, Wegmann MJ, Waring WW. Frequency spectra of normal breath sounds in childhood. *Chest*. 1991; **100**: 999–1002.
22) Imai E, Enseki M, Nukaga M, Tabata H, Hirai K, Kato M, *et al*. A lung sound analysis in a child thought to have cough variant asthma: A case report. *Allergol Int*. 2018; **67**: 150–2.
23) Enseki M, Nukaga M, Tadaki H, Tabata H, Hirai K, Kato M, *et al*. A breath sound analysis in children with cough variant asthma. *Allergol Int*. 2019; **68**: 33–8.
24) Song TW, Kim KW, Kim ES, Park JW, Sohn MH, Kim KE. Utility of impulse oscillometry in young children with asthma. *Pediatr Allergy Immunol*. 2008; **19**: 763–8.
25) Larsen GL, Morgan W, Heldt GP, Mauger DT, Boehmer SJ, Chinchilli VM, *et al*. Impulse oscillometry versus spirometry in a long-term study of controller therapy for pediatric asthma. *J Allergy Clin Immunol*. 2009; **123**: 861–7.
26) Duiverman EJ, Clément J, van de Woestijne KP, Neijens HJ, van den Bergh AC, Kerrebijn KF. Forced oscillation technique. Reference values for resistance and reactance over a frequency spectrum of 2–26 Hz in healthy children aged 2.3–12.5 years. *Bull Eur Physiopathol Respir*. 1985; **21**: 171–8.
27) Fischer HS, Puder LC, Wilitzki S, Usemann J, Bührer C, Godfrey S, *et al*. Relationship between computerized wheeze detection and lung function parameters in young infants. *Pediatr Pulmonol*. 2016; **51**: 402–10.
28) Shioya H, Tadaki H, Yamazaki F, Miyamoto M, Yoshihara S, Enseki M, *et al*. Characteristics of breath sound in infants with risk factors for asthma development. *Allergol Int*. 2019; **68**: 90–5.
29) Takase M, Sakata H, Shikada M, Tatara K, Fukusima T, Miyagawa T. Standard value of spirogram parameters in Japanese children (Japanese). *Jpn J Pediatr Pulmonol*, 2009; **19**: 164–76.
30) Habukawa C, Murakami K, Sugitani K, Ohtani T, Saputra GP, Kashiyama K, *et al*. Changes in lung sounds during asthma progression in a guinea pig model. *Allergol Int*. 2016; **65**: 425–31.