Changes in the breath sound spectrum during methacholine inhalation in children with asthma

HIDEYUKI TABATA,1 MAYUMI ENSEKI,1 MARIKO NUKAGA,1 KOTA HIRAI,1 SHINICHI MATSUDA,1 HIROYUKI FURUYA,2 MASAHIKO KATO1 AND HIROYUKI MOCHIZUKI1

1Department of Pediatrics, Tokai University School of Medicine, Isehara; 2Department of Basic Clinical Science and Public Health, Tokai University School of Medicine, Isehara, Japan

ABSTRACT

Background and objective: An effort-independent breath sound analysis is expected to be a safe and simple method for clinical assessment of changes in airway function. The effects of bronchoconstriction and bronchodilation on novel breath sound parameters in asthmatic children were investigated.

Methods: The study population included 49 children with atopic asthma (male = 33; mean age: 10.2 years). We evaluated breath sound parameters of the highest frequency of the power spectrum (HFp), frequency limiting 50% and 99% of the power spectrum (F50 and F99) and roll-off from 600 Hz to the HFp (Slope). We also assessed new parameters obtained using the ratios of sound spectrum parameters (spectrum curve indices), such as the ratio of the third and fourth power area to the total power area (P3/PT and P4/PT), the ratio of the third and fourth areas to the total area under the curve (A3/A4 and B3/B4) and the ratio of power and frequency at 75% of HFp and 50% of HFp (RPF75 and RPF50). This was measured before and after methacholine inhalation challenge and after β2 agonist inhalation.

Results: The parameters, F50 and F99, showed no changes after methacholine inhalation. Conversely, the A3/A4 (12.5–10.0%, P < 0.001), B3/B4 (7.6–5.5%, P < 0.001), RPF75 (6.7–4.0 dBm/Hz, P < 0.001) and RPF50 (5.8–4.3 dBm/Hz, P < 0.001) were significantly decreased. These values returned to the original level after β2 agonist inhalation.

Conclusion: Spectrum curve indices indicate bronchoconstriction and bronchodilation. These parameters may play a role in the assessment of airway narrowing in asthmatic children.

Key words: asthma, breath sound analysis, bronchoconstriction, children, sound spectrum.

SUMMARY AT A GLANCE

We evaluated the breath sound parameters before methacholine inhalation challenge, after methacholine inhalation challenge and after β2 agonist inhalation in 49 children with atopic asthma. Spectrum curve indices indicate bronchoconstriction and bronchodilation. These parameters may play a role in the assessment of airway narrowing in asthmatic children.

INTRODUCTION

As an objective method to evaluate asthmatic patients, challenges of inhaled bronchoconstrictors are widely used.1,2 Unfortunately, most infants and preschool children are not able to voluntarily perform the physiologic manoeuvres. Commercial devices which use the forced oscillation technique have become available.1,3 However, this method cannot be used to evaluate infants, as they are unable to use a mouthpiece. These problems in the accuracy of the measurements of pulmonary function in infants and younger children have meant that the diagnosis of childhood asthma remains a challenge for all physicians.

On the other hand, breath sounds are sensitive to airway changes. An effort-independent breath sound analysis is expected to be a safe and simple method for clinical assessment of airway changes.4 Recent
developments in signal processing methods have improved the possibility of extracting physiologically and clinically relevant information from respiratory sounds. Even in the absence of adventitious sounds, breath sounds may show changes when disorders of the respiratory system are present.

However, breath sounds are strongly affected by pulmonary function. In particular, the airflow rate has a strong effect on the sound spectrum. Pulmonary function has a major effect on the airflow during breathing, and age and body size remarkably affect the pulmonary function of children. In consideration of this problem, we have defined new respiratory sound parameters which are mostly unaffected by the airflow rate. The aim of the present study was to study the changes of breath sound parameters caused by bronchoconstriction and bronchodilation using methacholine inhalation challenge, and to evaluate the possibility of breath sound analysis in asthmatic children.

**METHODS**

**Study participants**

The study participants included a total of 49 paediatric outpatients (mean age: 10.2 ± 2.5 years; range: 5–16 years; male:female: 33: 16) who were treated at the Tokai University Hospital from 1 April 2012 to 31 March 2015 (Table 1). The inclusion criteria were as follows: one or more positive specific IgE value (>0.7 UA/mL), recurrent wheezing and bronchial hyperresponsiveness by methacholine inhalation challenge, and to evaluate the possibility of methacholine inhalation challenge, and the inclusion criteria were as follows: one or more positive specific IgE value (>0.7 UA/mL), recurrent wheezing and bronchial hyperresponsiveness by methacholine inhalation challenge. All of the participants had been diagnosed with atopic-type asthma by a physician.

Inhaled steroids and leukotriene receptor antagonists were withdrawn for 24 h, and β2 agonist inhalation was withdrawn for 12 h before the test. Written informed consent was obtained from all of the children and their legal guardians and the study protocol was approved by the institutional review board of Tokai University Hospital (No. 11R-158, approval date: 21 December 2011).

**Study protocol**

The assessments were performed before and just after the methacholine challenge, and 15 min after the β2 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, crackles and outside noises based on the findings of the physician's auscultation and the image of the breath sound analysis. After the sound analysis, the patients' pulmonary function was tested using spirometry.

**Pulmonary function testing**

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 flow and volume in 1 s (FEV1).

**Methacholine inhalation challenge**

The methacholine inhalation challenge was performed according to the method described by Takishima et al. Briefly, methacholine was diluted twofold with saline on the day of the test to provide a series of 10 strengths, from 25 mg/mL to approximately 49 μg/mL. During the methacholine inhalation test, the respiratory resistance (Rrs) was continuously measured using an Astograph (Chest Co.). Methacholine administration was stopped when the Rrs reached twice the baseline value (Fig. 1). The minimum cumulative dose of methacholine to cause bronchial constriction (Dmin (minimal dose of methacholine)), represents the bronchial sensitivity. One Dmin unit was considered to be equal to the inhalation of 1.0 mg/mL of aerosolized methacholine solution for 1 min (Fig. 1). The speed of bronchoconstriction in response to methacholine (St), which represents the bronchial sensitivity, was also calculated.

**Breath sound analysis**

A breath sound analysis was performed for all participants, as described previously. Breath sounds were recorded using a handheld microphone for ≥10 s in a silent room. The microphone was placed on the right upper anterior chest 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 analysing sounds in the range of 100–2500 Hz. The recorded sounds were analysed according to a fast Fourier transformation. The sampling frequency was 10 240 Hz and the spectra were obtained using a Hamming window. The sounds were displayed as a

| Patient | Number | Age (years) | Sex (male:female) | FVC (% predicted) | FEV1 (% predicted) | Rrs.cont (cm H2O/L/s) | Dmin (unit) | St (cm H2O/Ls/min) |
|---------|--------|-------------|-------------------|-------------------|-------------------|-----------------------|--------------|-------------------|
| Atopic asthma | 49 | 10.2 ± 2.5¹ | 33:16 | 83.1 ± 10.9 | 86.1 ± 9.8 | 7.36 ± 3.84 | 1.03 ± 3.33 | 2.06 ± 2.30 |

¹Mean ± SD.

Dmin, minimal dose of methacholine; FEV1, forced expiratory flow and volume in 1 s; FVC, forced vital capacity; Rrs.cont, Rrs control value; St, speed of bronchoconstriction to methacholine.
spectrograph (Fig. 2A). We used dBm in the Y-axis and Hz in the X-axis. As an evaluation on the dBm-based spectrum images, we decided to set the zero point of the Y-axis (dBm) based on the mean of the background noise from 2500 to 3000 Hz for the data of all of the subjects. The mean background noise in our silent room was $-88.1\pm 5.0$ dBm. Therefore, for the calculation of the dBm-based area under the curve (AUC), the zero point in this study was considered to be $-90$ dBm of the original dBm recorded by the sound spectrometer.13

The point of the maximum frequency (Hz) in the shape (arrowhead) during inspiration was used for the sound spectrum analysis (Fig. 2A, B). This sound

Figure 1 The breath sound analysis during the methacholine inhalation challenge. The dose–response curve for the Rrs during the methacholine inhalation challenge using the oscillation method. The Rrs increased with the inhalation of incremental amounts of methacholine. When the Rrs reached exactly twice the baseline value, the administration of methacholine was stopped and a bronchodilator was administered. Three parameters, the Rrs.cont, the Dmin and the St, were calculated. The breath sound samples were obtained three times: before methacholine inhalation and just after methacholine inhalation when the Rrs was increased to twice the baseline Rrs value and 15 min after $\beta_2$ agonist inhalation. Dmin, minimal dose of methacholine; Rrs, respiratory resistance; Rrs.cont, Rrs control value; St, speed of bronchoconstriction to methacholine.

Figure 2 Analysis of sound spectrograph. The spectrograph was displayed after a Fourier analysis, with the vertical axis showing the frequency in Hz and the horizontal axis showing time. (A) The sound intensity of the breath sounds is indicated by the colour. The red vertical line indicates the highest frequency of the inspiratory breath sounds. (B) The horizontal axis shows the frequency in Hz and the vertical axis shows the power in dBm at the point of red vertical line in (A). (C) A five-point moving average was used for smoothing to determine the suitable values of dBm for determining some checkpoints in the Slope for each sound spectrum.

© 2017 The Authors
Respirology published by John Wiley & Sons Australia, Ltd on behalf of Asian Pacific Society of Respirology

Respirology (2018) 23, 168–175
Breath sound changes in childhood asthma

spectrum (Y-axis; dBm, X-axis; Hz) is shown in Figure 2C. Data were automatically calculated using a custom software programme. The parameters of the total power of the power spectrum (P3) (log[mV²]), the total power of the third area (P3) (log[mV²]), the total power of the fourth area (P4) (log[mV²]), the roll-off of middle spectrum curve (Slope, dBm/octave) and the frequency limiting 50% and 99% of the power spectrum (F50 and F99) were measured in accordance with the methods of previous reports (Figure 3a, 3b). The Slope indicates the roll-off of the middle spectrum curve (−dBm/octave). The total AUC of 100 Hz to the HFP (A5), the third AUC (A3) and the fourth AUC (A4) were conventionally calculated by dBm and Hz (one arbitrary unit (dBm-Hz) on a spectrum image). The spectrum curve indices, the ratio of the third power area to the total power area (P3/P4), the ratio of the fourth power area to the total power area (P4/P3), the ratio of third area to total AUC (A3/AT), the ratio of fourth area to the total AUC (A4/AT), ratio of power and frequency at 75% of the HFP (RPF75) and ratio of power and frequency at 50% of the HFP (RPF50) values, were also calculated (Fig. 3C, D). 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.

In the present study, breath sound samples were obtained three times; before methacholine inhalation, just after methacholine inhalation when the Rrs value increased to twice the baseline Rrs value and 15 min after β2 agonist inhalation (Fig. 1). Each personal breath sound parameter was analysed conventionally, using a sample with a median value from three tidal breaths.

Statistical analysis

The statistical analyses were conducted using the SPSS software programme (IBM SPSS Statistics, Version 22 for Windows, IBM SPSS Statistics, Chicago, USA). The parameters, before methacholine inhalation, just after methacholine inhalation and after β2 agonist inhalation were compared using the paired t-test. Data are expressed as the mean ± SD. A Bonferroni correction was used to test multiple comparison, and the level of statistical significance was set at P = 0.016 (0.05/3=0.016).

RESULTS

Lung function and the breath sound analysis

All of the 49 subjects underwent spirometry. In the data of spirometric parameters, the % predicted FVC was 83.1 ± 10.9% (mean ± SD) and % predicted FEV1 was 86.1 ± 9.8% (Table 1). Chest auscultation by a paediatric respirologist revealed no abnormalities. In each of the 49 subjects, the parameters of the breath sound spectrum were successfully calculated. None of the breath sound images showed wheezing, crackles or distinct outside noises. The shape of the sound spectrum showed good similarity in the same patients.

Differences in the breath sound parameters before and just after methacholine inhalation

In 49 subjects, the Rrs control value (Rrs.cont) was 7.36 ± 3.84 cm H2O/L/s (mean ± SD), the Dmin was 1.03 ± 3.33 units (3.03 ± 0.66 log (milliunits)), and the St was 2.06 ± 2.30 cm H2O/L/s/min (Table 1). According to these data, all of the patients had appreciable bronchial hyperresponsiveness. After methacholine inhalation, some patients showed an increase in the middle and high frequency area (600–2000 Hz) of the sound spectrum, and some patients showed an increase in the high frequency area (1000–2000 Hz) of the sound spectrum (Fig. 4).

An analysis of the data revealed that the median values of the common parameters, F50 and F99, did not increase, whereas the spectrum curve indices, A3/AT, B4/AT, RPF50 and RPF75, significantly decreased after methacholine inhalation (Table 2). The Slope did not show a significant change.

Differences in the breath sound parameters just after methacholine inhalation and after β2 agonist inhalation

In two patients, the common parameters and spectrum curve indices after β2 agonist inhalation returned to almost same value as before methacholine inhalation (Fig. 4). An analysis of the data revealed that the median values of the common parameters, F50 and F99, did not increase after β2 agonist inhalation. In the same way, the Slope and the spectrum curve indices, P3/P4, P4/P3, A3/AT, B4/AT, RPF50 and RPF75 significantly increased after β2 agonist inhalation (Table 2).

DISCUSSION

Breath sound parameters change during histamine and methacholine inhalation challenges with a strong relationship between changes of sound parameters and narrowing of the airway. Breath sound analysis may have potential as a novel method of non-invasive pulmonary function testing to detect airway obstruction in young children. Importantly, breath sounds are significantly affected by the maximum airflow rate of the breaths. Commonly, large breaths induce high-power and high-pitched sounds. Stature or lung size has an influence on the frequency and power of breath sounds and the patient’s age and body size have significant effects on the sound spectrum. New breath sound parameters which are not affected by the airflow rate will be of considerable clinical utility.

In recent reports, we demonstrated the reliability of our breath sound analysis method and its possible application to the assessment of bronchial constriction in children. It is noteworthy that the spectrum curve indices of the simple method, A3/AT, B4/AT, RPF50 and RPF75, had only a minor impact from airflow rate. It is feasible that a breath sound analysis method will enable the diagnosis of young asthmatic children by evaluating the breath sound changes during tidal breathing in a period of just 30 s.

Using this technique, we assessed the changes in spectrum curve indices during a methacholine
Significant increases were not observed in F50 and F99 values, while the P3/AT, A3/AT, B4/AT, RPF50 and RPF75 values were significantly decreased by bronchoconstriction, which occurred in response to the inhalation of methacholine, at the point that the Rrs reached exactly twice the baseline value. The F99, P5 and A7 showed the tendency of an increasing trend due to the methacholine-induced narrowing of the airway. Because all patients intended to perform tidal breathing during test, it is possible to say that the total inspired breath sound increased after bronchoconstriction. It is possible that methacholine-induced bronchoconstriction decreased the total inspiratory power and frequency range at 50% and 75% of the HFp.

Figure 3 The common sound spectrum parameters. (A) F99, F50, and P5. (B) A7 (dBm-Hz), A3 (dBm-Hz), A3/AT (%), HFp (Hz) and A7. P5 was calculated by same method as A3. (C) B4 (dBm-Hz) and B4/AT (%). P4 was calculated by same method as B4. (D) dB50, dB75, RPF50 = dB50/(HFp - 50% of HFp) (dBm/Hz) and RPF75 = dB75/(HFp - 75% of HFp) (dBm/Hz). A3, the third AUC; A3/AT, the ratio of third area to the total AUC; A7, total AUC of 100 Hz to the HFp; A7, area under the curve; B4, the fourth AUC; B4/AT, the ratio of fourth area to the total AUC; dB50, dBm at 50% of HFp; dB75, dBm at 75% of HFp; F50, frequency limiting 50% of the power spectrum; F99, frequency limiting 99% of the power spectrum; HFp, highest frequency of the power spectrum; P5, total power of the third area of the power spectrum; P4, total power of the fourth area of the power spectrum; P7, total power area of 100 Hz to the HFp; RPF50, ratio of power and frequency at 50% of the HFp; RPF75, ratio of power and frequency at 75% of the HFp; Slope, roll-off from 600 to 1200 Hz.
induced bronchoconstriction induces rough and large respiration and some high-pitch respiratory noises. These changes may induce increases in the F99, PT and AT values. Conversely, the P3/PT, A3/AT, B4/AT, RPF75 and RPF50 values were decreased by bronchoconstriction. The P3/PT, A3/AT and B4/AT values are the ratio of the higher frequency areas (P3, A3 and B4) to the total area (PT and AT) of the sound spectrum. B4/AT may be more sensitive to increases in the high-pitched sound areas. It has been suggested that when bronchial constriction is introduced, the main change that occurs is in the high-pitched area of the sound spectrum.24,27,33 The right corner of our spectrum triangle was prolonged with or without an increase in the maximum sound power of the sound spectrum. Thus, the decrease in the P3/PT, A3/AT and B4/AT values after methacholine inhalation resulted in a prolonged right side of the triangle with a small change in area. The Slope, RPF75 and RPF50 indicate the right-sided angle of the sound spectrum. For the same reason, the right corner of the spectrum triangle becomes flattened by bronchial constriction.

**Table 2** The results of the data analysis

|                          | Before methacholine | Just after methacholine | 15 min after β2 agonist inhalation | P-value     |
|--------------------------|---------------------|-------------------------|------------------------------------|-------------|
| PT (log (mV²))           | 149.6 ± 58.3        | 170.4 ± 87.5            | 146.3 ± 76.0                       | 0.137 vs 0.084 vs 0.779 |
| F50 (Hz)                 | 145.6 ± 30.9        | 144.1 ± 27.5            | 139.6 ± 32.8                       | 0.710 vs 0.335 vs 0.087 |
| F90 (Hz)                 | 722.3 ± 207.0       | 789.9 ± 294.3           | 754.0 ± 263.9                      | 0.078 vs 0.363 vs 0.403 |
| P3/PT (%)                | 56.8 ± 15.7         | 53.9 ± 13.5             | 59.3 ± 16.0                        | 0.031 vs 0.007 vs 0.215 |
| P4/PT (%)                | 44.7 ± 14.2         | 42.4 ± 12.3             | 46.9 ± 14.5                        | 0.050 vs 0.011 vs 0.212 |
| A3/AT (%)                | 12.5 ± 2.2          | 10.0 ± 2.1              | 12.5 ± 2.7                         | <0.001 vs <0.001 vs 0.925 |
| B4/AT (%)                | 7.6 ± 1.6           | 5.5 ± 1.6               | 7.4 ± 1.8                          | <0.001 vs <0.001 vs 0.502 |
| RPF75 (dBm/Hz)           | 6.7 ± 1.7           | 4.0 ± 1.4               | 6.6 ± 2.2                          | <0.001 vs <0.001 vs 0.793 |
| RPF50 (dBm/Hz)           | 5.8 ± 1.1           | 4.3 ± 1.3               | 6.0 ± 1.4                          | <0.001 vs <0.001 vs 0.345 |

①,② and ③ indicate time points of breath sound sampling as illustrated in Figure 1. Bold type indicates a significant difference. n = 49, t-test, mean ± SD.

A3/AT, the ratio of third area to the total AUC; A3, total AUC of 100 Hz to the HFp; AUC, area under the curve; B4/AT, the ratio of fourth area to the total AUC; F50, frequency limiting 50% of the power spectrum; F90, frequency limiting 90% of the power spectrum; HFp, highest frequency of the power spectrum; P3/PT, the ratio of the third power area to the total power area; P4/PT, the ratio of the fourth power area to the total power area; PT, total power area of 100 Hz to the HFp; RPF75, ratio of power and frequency at 75% of the HFp; RPF50, ratio of power and frequency at 50% of the HFp; Slope, roll-off from 600 to 1200 Hz.

Figure 4 Changes in the sound spectrum before and after methacholine inhalation. After methacholine inhalation, the power of the middle and high frequency area (600–2000 Hz) was widely increased in Patient #1 (A). The power of the high frequency area (1000–2000 Hz) was partially increased in Patient #2 (B). At 15 min after β2 agonist inhalation, the sound spectrum returned to the same position as before methacholine inhalation in both patients (----, before methacholine inhalation; ---, just after methacholine inhalation; -----, 15 min after β2 agonist inhalation).
constriction-induced high-pitched sounds, thus resulting in a significant decrease in the Slope, RPF_{2-5} and RPF_{50} values. The Slope did not significantly decrease after methacholine inhalation. We believe that the Slope was measured a mid range of sound spectrum in this report, so changes in very high-pitched sounds may not be well detected.

It is interesting that measured values returned to the original level after p_{2} agonist inhalation. These results clearly indicate that these sound spectrum changes are solely dependent on bronchoconstriction and bronchodilation. We previously suggested that the increase in the Rrs after the inhalation of methacholine and the subsequent decrease of the Rrs value after p_{2} agonist inhalation showed the same shape during the methacholine inhalation challenge, although the mechanism of bronchoconstriction and bronchodilation is not the same.12 This recovery is partially dependent on the specificity of methacholine-induced bronchoconstriction, which is artificial and originally transient. Furthermore, the fact that the inhaled methacholine and p_{2} agonist particles were of the same size and had the same deposition site may have resulted in the good recovery of the participants.

The changes in the sound spectrum that were discussed in this report were not affected by ‘wheezing’. In our sound spectrogram (time vs sound frequency), typical wheezing can be observed as a bright wave-type. In our sound spectrogram (time vs sound frequency),

Acknowledgement

This study was commissioned by the Environmental Restoration and Conservation Agency of Japan in fiscal years 2009–2016.

REFERENCES

1 Ducharme FM, Davis GM. Measurement of respiratory resistance in the emergency department: feasibility in young children with acute asthma. Chest 1997; 111: 1519–25.

2 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.

3 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.

4 Bentur L, Beck R, Berkowitz D, Hasain J, Berger I, Elias N, Gavriely N. Adenosine bronchial provocation with computerized wheeze detection in young infants with prolonged cough. Chest 2004; 126: 1060–5.

5 Oweis RJ, Abdulhay EW, Khayal A, Awad A. An alternative respiratory sounds classification system utilizing artificial neural networks. Biomed. J. 2015; 38: 153–61.

6 Pasterknap H, Powell RE, Sanchez I. Lung sound spectra at standardized airflow in normal infants, children, and adults. Am. J. Respir. Crit. Care Med. 1996; 154: 424–30.

7 Malmberg LP, Sorva R, Sovijärvi AR. Frequency distribution of breath sounds as an indicator of bronchoconstriction during histamine challenge test in asthmatic children. Pediatr. Pulmonol. 1994; 18: 170–7.

8 Shimoda T, Obase Y, Nagasaka Y, Kishikawa R, Mukae H, Iwanaga T. Peripheral bronchial obstruction evaluation in patients with asthma by lung sound analysis and impulse oscillography. Allergol. Int. 2017; 66: 132–8.

9 Anderson K, Atken S, Carter R, MacLeod JE, Moran F. Variation of breath sound and airflow caliber induced by histamine challenge. Am. Rev. Respir. Dis. 1990; 141: 1147–50.

10 Kraman SS, Wang PM. Airflow-generated sound in a hollow canine airway cast. Chest 1990; 97: 461–6.

11 Shykoff BE, Ploysongsang Y, Chang HK. Airflow and normal lung sounds. Am. Rev. Respir. Dis. 1988; 137: 872–6.

12 Mochizuki H, Shimizu T, Shigeta M, Arakawa H, Tokuyama K, Morikawa A. Effect of age, height, and prechallenge respiratory resistance on bronchial hyperresponsiveness in childhood asthma using the forced oscillation technique. Pediatr. Pulmonol. 1996; 22: 1–6.

13 Tabata H, Hirayama M, Enseki M, Nukaga M, Hirai K, Furuya H, Morikawa A. Effect of age, height, and prechallenge respiratory resistance on bronchial hyperresponsiveness in childhood asthma using the forced oscillation technique. Pediatr. Pulmonol. 1996; 22: 1–6.

14 Tabata H, Hirayama M, Enseki M, Nukaga M, Hirai K, Furuya H, Morikawa A. A novel method for detecting airway narrowing using breath sound spectrum analysis in children. Respir. Investig. 2016; 54: 20–8.

15 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. Investig. 2017; 55: 219–28.

16 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.

17 Takase M, Sakata H, Shikada M, Tatara K, Fukusima T, Miyagawa T. Standard value of spirometric parameters in Japanese children (Japanese). Jpn. J. Pediatr. Pulmonol. 2009; 19: 164–76.

18 Takishima T, Hida W, Sasaki H, Suzuki S, Sasaki T. Direct-writing recorder of the dose-response curves of the airway to methacholine. Clinical application. Chest 1981; 80: 600–6.

19 Habukawa C, Murakami K, Mochizuki H, Takami S, Muramatsu R, Tadaki H, Hagiwara S, Mizuno T, Arakawa H, Nagasaka Y. Changes in the highest frequency of breath sounds without wheezing during methacholine inhalation challenge in children. Respirology 2010; 15: 485–90.

20 Charbonneau G, Ademovic E, Cheetah BGM, Malmberg LP, Vanderschoot J, Sovijärvi ARA. Basic techniques for respiratory sound analysis. Eur. Respir. Rev. 2000; 10: 625–35.

© 2017 The Authors
Respirology published by John Wiley & Sons Australia, Ltd on behalf of Asian Pacific Society of Respirology

Respirology (2018) 23, 168–175
Breath sound changes in childhood asthma

20 Habukawa C, Nagasaka Y, Murakami K, Takemura T. High-pitched breath sounds indicate airflow limitation in asymptomatic asthmatic children. *Respirology* 2009; 14: 399–403.

21 Hidalgo HA, Wegmann MJ, Waring WW. Frequency spectra of normal breath sounds in childhood. *Chest* 1991; 100: 999–1002.

22 Wodicka GR, Shannon DC. Transfer function of sound transmission in subglottal human respiratory system at low frequencies. *J. Appl. Physiol.* (1985) 1990; 69: 2126–30.

23 Gavriely N, Palti Y, Alroy G, Grotberg JB. Measurement and theory of wheezing breath sounds. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* 1984; 57: 481–92.

24 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.

25 Beck R, Dickson U, Montgomery MD, Mitchell I. Histamine challenge in young children using computerized lung sounds analysis. *Chest* 1992; 102: 759–63.

26 Sovijärvi AR, Malmberg LP, Paajanen E, Piirilä 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.

27 Schreur HJ, Diamant Z, Vanderschoot J, Zwinderman AH, Dijkman JH, Sterk PJ. Lung sounds during allergen-induced asthmatic responses in patients with asthma. *Am. J. Respir. Crit. Care Med.* 1996; 153: 1474–80.

28 Ellington LE, Emmanouilidou D, Elhilali M, Gilman RH, Tielsh JM, Chavez MA, Martin-Concha J, Figueroa D, West J, Checkley W. Developing a reference of normal lung sounds in healthy Peruvian children. *Lung* 2014; 192: 765–73.

29 Oliveira A, Marques A. Respiratory sounds in healthy people: a systematic review. *Respir. Med.* 2014; 108: 550–70.

30 Meslier N, Charbonneau G, Racineux JL. Wheezes. *Eur. Respir. J.* 1995; 8: 1942–8.

31 Gross V, Dittmar A, Penzel T, Schuttler F, von Wichert P. The relationship between normal lung sounds, age, and gender. *Am. J. Respir. Crit. Care Med.* 2000; 162: 905–9.

32 Habukawa C, Murakami K, Horii N, Yamada M, Nagasaka Y. A new modality using breath sound analysis to evaluate the control level of asthma. *Allergol. Int.* 2013; 62: 29–35.

33 Takase M. Lung sounds in children. *Pediatr. Otolaryngol. Jpn.* 2006; 27: 64–70 (in Japanese).

34 Nagasaka Y. Lung sounds in bronchial asthma. *Allergol. Int.* 2012; 61: 353–63.

35 Fischer HS, Puder LC, Wilitzki S, Uschmann J, Bührer C, Godfrey S, Schmalsich G. Relationship between computerized wheeze detection and lung function parameters in young infants. *Pediatr. Pulmonol.* 2016; 51: 402–10.

36 Emmanouilidou D, McCollum ED, Park DE, Elhilali M. Adaptive noise suppression of pediatric lung auscultations with real applications to noisy clinical settings in developing countries. *IEEE Trans. Biomed. Eng.* 2015; 62: 2279–88.