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Wheeze sound characteristics are associated with nighttime sleep disturbances in younger children

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ABSTRACT

Background: Wheezing is a typical symptom of respiratory conditions. Few objective methods are available for predicting sleep disturbance in young children with wheezing.
Objective: We investigated whether wheezing characteristics, detected by lung-sound analysis, were associated with risk of sleep disturbance.
Methods: We recorded the lung sounds of 66 young children (4–59 months) every morning, for the entire duration of a wheezing episode. On lung-sound analysis, wheezing was displayed as horizontal bars of intensity with corresponding sharp peaks of power. The sharp peak of power was defined as a wheeze band. Wheezing characteristics (e.g., number, frequency, duration, and frequency of maximum intensity of wheeze bands) were analyzed using lung-sound analysis. Patients were divided into 3 groups based on sleep disturbance on the first night after wheezing was recorded: mild group (no sleep disturbance and disappearance of wheezing within 2 days), moderate group (no sleep disturbance but disappearance of wheezing after 3 or more days), and severe group (sleep disturbance and disappearance of wheezing after 3 or more days). Wheezing characteristics on the first morning were compared among the 3 groups based on sleep disturbance on the first night.
Results: The highest frequency, the frequency of maximum intensity, and the number of wheeze bands per 30 seconds were significantly higher in the severe group than in the mild group ($p < 0.005$, $p < 0.005$, $p < 0.001$, respectively). The number of wheeze bands per 30 seconds was a predictor of nighttime sleep disturbance, with a cutoff value of 11.1. The sensitivity, specificity, and positive- and negative-predictive values were 100%, 65%, 32%, and 100% ($p < 0.001$), respectively, with an area under the curve of 0.86 ± 0.05.
Conclusions: The number of wheeze bands per 30 seconds on lung-sound analysis was a useful indicator of risk of prolonged exacerbation.

Keywords: Lung-sound analysis; Young children; Wheeze; Sleep disturbance; Exacerbation

INTRODUCTION

Wheezing is a typical symptom of respiratory conditions in individuals of all ages. Wheezing can be easily auscultated with only a stethoscope and is recognized as an important auscultatory finding when assessing respiratory conditions [1-3]. Wheezing that occurs repeatedly many

Conflict of Interest
Chizu Habukawa received a research grant from the Omron Health Care Corporation. Naoto Ohgami, Naoki Matsumoto, Kenji Hashino, Kei Asai, and Tetsuya Sato are employees of Omron Healthcare Co., Ltd.

Author Contributions
Conceptualization: CH, NO, NM, KH, KA, TS and KM. Data curation: CH and KM. Formal analysis: CH, NO, NM, KH, KA, TS and KM. Funding acquisition: NO, NM, KH, KA, and TS. Methodology: CH, NO, NM, KH, KA, TS and KM. Project administration: CH, NO, NM, KH, KA, TS and KM. Visualization: CH, NO, NM, KH, KA, TS and KM. Writing - original draft: CH, NO, NM, KH, KA, TS and KM. Writing - review & editing: CH, NO, NM, KH, KA, TS and KM.

times over a prolonged period is an important factor in the diagnosis of bronchial asthma. Some young children with repeated wheezing do not exhibit asthma [4, 5]. Asthma in young children must be carefully diagnosed; however, before the patient's respiratory condition worsens, the wheezing itself must be treated and managed [4].

Nighttime sleep disturbance is an important indicator for assessing respiratory conditions. Nighttime awakening should be evaluated when monitoring clinical control of wheezing in infants and young children [4, 6]. Factors that can predict nighttime sleep disturbance are useful not only for physicians but also for caregivers and parents. Some studies have evaluated the severity of airway obstruction by assessing the particular characteristics of wheezing [1, 2, 4, 6]. Few methods are available for predicting nighttime sleep disturbance at home after a medical examination in young children, and the assessment of wheezing by auscultation is recognized as an important method. However, the characteristics of wheezing have not yet been sufficiently analyzed to establish their association with clinical manifestations. Wheezing characteristics are still typically clinically classified, subjectively, by using a stethoscope.

Additionally, due to recent advances in computer technology, methods for mathematically and clinically evaluating biological sounds are progressing rapidly in science and engineering fields [7]. These methods have also been introduced in the medical field, and rapid progress has been observed in their use as noninvasive examination methods [8, 9].

In this study, we collaborated with science and engineering researchers to investigate whether wheezing characteristics, detected by lung-sound analysis, could be used to determine the risk of nighttime sleep disturbance in young children, including infants.

We aimed to evaluate the association between the characteristics of wheezing and nighttime sleep disturbance and its role in the prediction and assessment of respiratory conditions in younger children, including infants.

MATERIALS AND METHODS

Subjects and study design

All participants were outpatients at the Minami Wakayama Medical Center. Written informed consent was obtained from parents or legal guardians of all subjects, and the study protocol was approved by the ethics committee of the hospital (approval number: 2016-22(2)).

The study population comprised 66 pediatric outpatients (median age, 17 months; range, 4–59 months; male: female ratio, 38:28) who were brought to the hospital for the treatment of recurrent wheezing, cough, and dyspnea. A pediatrician specializing in childhood respiratory and allergic diseases excluded other chronic wheezing conditions: chronic sinusitis, laryngomalacia, whooping cough, immunodeficiency, cardiac or neonatal pulmonary problems, infantile lung diseases, and gastroesophageal reflux disease.

Information regarding exacerbation symptoms, including wheezing, cough, heavy breathing, reduced activity, shortness of breath, and sleep disturbance, was obtained from the parents or legal guardians.

On the first morning before treatment, lung sounds were recorded for at least 30 seconds in the upper right anterior chest region at the second intercostal space and in the midclavicular line on the chest wall. All patients were examined for evaluation of heart rate, oxygen saturation, and respiratory rate. Each patient had audible wheezes during tidal breathing, as observed on auscultation by 2 trained physicians and a nurse, independently (blinded to each other's results). All patients were treated in accordance with international guidelines [10].

On the second morning, the parents or legal guardians provided information regarding exacerbation symptoms, including sleep disturbance during the night after the first day of lung-sound recording. The characteristics of wheezing on the first morning, as assessed by lung-sound analysis, were compared with the information regarding nighttime sleep disturbance on the first night as obtained from the parents or legal guardians. Thereafter, lung sounds were recorded for each patient on each day until wheezing disappeared.

Each day, the recorded lung sounds (with or without wheezes) were confirmed with independent auscultation by the 2 physicians and a nurse. The lung sounds recorded independently by the 2 physicians and a nurse were not only in agreement with each other but also accorded with the auscultation findings in each case; hence, the results in each case were confirmed.

Accordingly, the patients were divided into 3 groups—mild, moderate, and severe wheezing—according to the nighttime sleep disturbance on the first night. Patients who did not exhibit nighttime sleep disturbance and whose wheezing disappeared within 2 days were assigned to the mild group. Patients who did not exhibit nighttime sleep disturbance but whose wheezing persisted for 3 or more days were assigned to the moderate group. Patients who exhibited nighttime sleep disturbance and persistence of the wheeze for 3 or more days were assigned to the severe group. Physical signs, including heart rate, oxygen saturation, and respiratory rate, on the first morning when lung sounds were recorded, were compared among the 3 groups. Wheezing characteristics on the first morning before treatment were compared among the 3 groups with respect to nighttime sleep disturbance on the first night, as described below.

Sound recording and sound analysis

Fig. 1 shows a block diagram of lung-sound recording. The sound recording system comprised a handy-type assembled microphone unit (Omron Healthcare Corp., Kyoto, Japan) and a pulse-code modulation recorder (Sony Corp., Tokyo, Japan). Two microphones (ST Microelectronics, Kyoto, Japan) were set in the microphone unit; one collected ambient sounds around the device, while the other collected lung sounds from the right side of the chest. Lung sounds were resampled at a rate of 44.1 kHz/16-bit quantization bit rate; 4,096-point Fast Fourier transformation was performed using Adobe Audition.

Fig. 2 presents a sample of the spectrogram and spectrum of the wheezing sounds. Prior to the sound analysis, all recordings were carefully evaluated by the engineering researchers and two trained physicians. The recorded lung sounds were reviewed to discriminate wheezing and other sounds, such as noises generated due to friction between the microphone and the skin. We detected wheezing on the sound spectrograms as defined by the computerized respiratory sound analysis (CORSA) guidelines [11].

Wheezing indices

On lung-sound analysis, wheezing was displayed as horizontal bars of intensity with corresponding sharp peaks of power. The sharp peak of power was defined as a wheeze band

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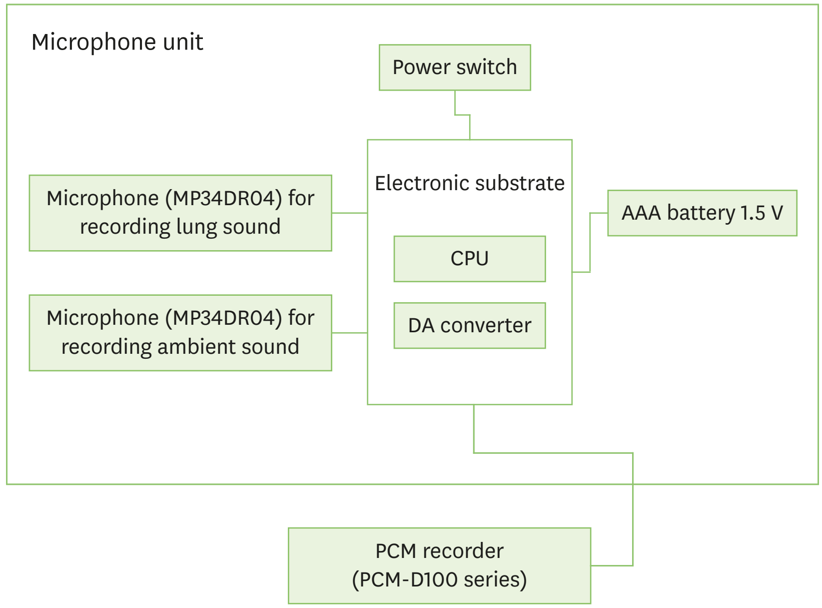

Fig. 1. Block diagram presenting sound recording. CPU, central processing Unit; DA, digital to analog; PCM, pulse-code modulation recorder.

[12-14] (**Fig. 2**). Wheezing was analyzed both during inspiratory and expiratory periods in each recorded file; the indices are explained below.

Respiratory cycle

The number of cycles during which sounds of inspiration and expiration could be discerned, per 30 seconds, were counted (**Fig. 2A**, left).

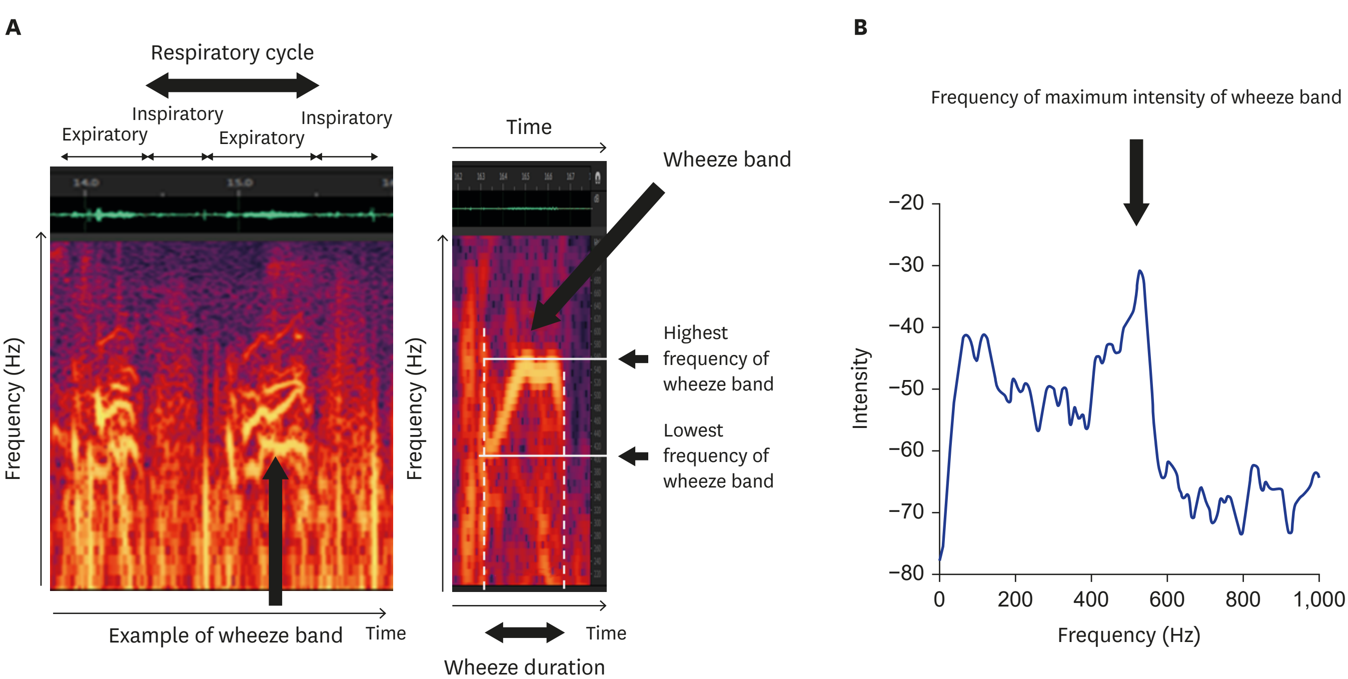

Fig. 2. Wheezing indices. (A) Spectrogram. (B) Fast Fourier transformation spectrum.

Highest frequency of wheeze bands

The highest frequency that could be recognized in the spectrogram (**Fig. 2A**, right) was recorded. Furthermore, the highest frequencies of all wheezes in each file were recorded and the average frequencies of all wheezes were calculated from the individual data.

Lowest frequency of wheeze bands

The lowest frequencies of all wheezes were calculated as described above (**Fig. 2A**, right).

Frequency of maximum intensity of wheeze bands

The frequency of maximum intensity of all wheezes was recorded [13, 14]. The average frequencies of the maximum intensity of wheeze bands were calculated for each recorded file (**Fig. 2B**).

Duration of wheeze bands

The duration of wheeze band was recorded, and the average duration of all wheeze bands in each file was calculated (**Fig. 2A**, right).

Number of wheeze bands per 30 seconds

The number of wheeze bands per 30 seconds in each file was counted.

Statistical analyses

The wheezing indices and patient characteristics are presented as mean ± standard deviation. The patient characteristics and wheezing indices among the 3 groups were evaluated with the Kruskal-Wallis test. The number of wheeze bands of the mild group and that of the severe group were compared using the unpaired *t*-test. Sensitivity (true-positive rate), specificity (true-negative rate), and positive/negative-predictive values (probability of exacerbation symptoms according to the wheezing index cutoff value) were calculated. The receiver operating characteristic (ROC) curve describes the relationship between the sensitivity and specificity of different cutoff values (wheezing index) as predictors of exacerbation symptoms. The areas under the curve (AUCs) for all possible cutoff values of number of wheeze bands were also calculated. A p value of <0.05 was considered statistically significant.

RESULTS

Differences in patient characteristics among the 3 groups

Table 1 lists the patient characteristics and respiratory statuses of the 3 groups. The respiratory status of the severe group was significantly worse than that of the mild group.

Comparison of respiratory cycle scores among the 3 groups

No significant differences were observed in respiratory cycle scores among the 3 groups. The respiratory cycle score of the mild group was 44.4 ± 14.4 per 30 seconds, that of the moderate group was 43.5 ± 12.5 per 30 seconds, and that of the severe group was 55.2 ± 13.7 per 30 seconds.

Comparison of highest frequency of wheeze bands among the 3 groups

Fig. 3 depicts significant differences that were observed in terms of the highest frequency of wheeze bands among the 3 groups ($p < 0.005$). The highest frequency of wheeze bands was significantly greater in the severe group than in the mild group. The highest frequency of wheeze bands in the mild group was 466.0 ± 147.3 Hz, that in the moderate group was 663.5 ± 179.5 Hz, and that in the severe group was 738.3 ± 190.4 Hz.

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Table 1. Patient characteristics

Charcteristic	Mild group (n = 42)	Moderate group (n = 17)	Severe group (n = 7)	*p* value
Sex, male:female	23:19	11:06	4:03	NS
Age (mo)	18 ± 14	18 ± 13	9 ± 6	NS
Height (cm)	82.8 ± 11.9	81.8 ± 11.3	77.0 ± 12.1	NS
Weight (kg)	14.3 ± 16.4	12.0 ± 3.5	10.8 ± 3.6	NS
SaO_2 (%)	99.2 ± 1.3	98.1 ± 1.7	96.4 ± 1.0	<0.001
Heart rate (beats/min)	122.5 ± 18.5	128.5 ± 17.8	121.3 ± 14.2	<0.001
Respiratory rate (counts/min)	88.8 ± 28.8	87.0 ± 25.0	110.4 ± 27.4	NS
Sleep disturbance on the previous night	2/42	6/17	7/7	<0.001
Sleep disturbance on the first night	0/42	3/17	7/7	<0.001
No. of days after which wheezes disappeared	1.9 ± 0.9	3.5 ± 1.1	5.1 ± 0.9	<0.001

Values are presented as number or mean ± standard deviation.
SaO_2, oxygen saturation; NS, not significant.

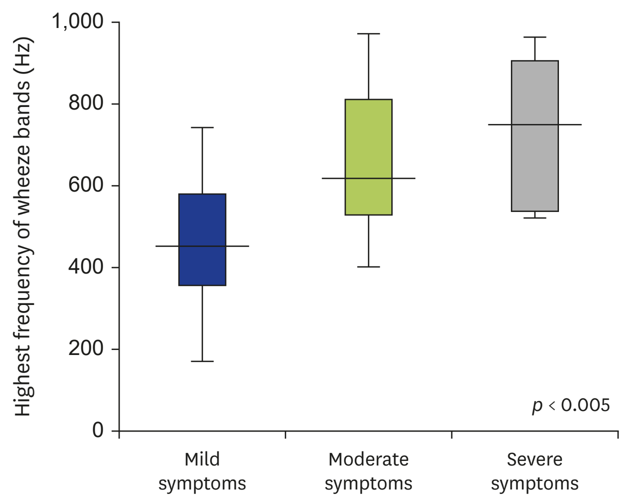

Fig. 3. Comparison of highest frequency of wheeze bands among the 3 groups

Comparison of lowest frequency of wheeze bands among the 3 groups

No significant differences were observed in the lowest frequency of wheeze bands among the 3 groups. The lowest frequency of wheeze bands in the mild group was 246.1 ± 90.5 Hz, that in the moderate group was 290.0 ± 110.9 Hz, and that in the severe group was 262.0 ± 66.0 Hz.

Comparison of frequency of maximum intensity wheeze bands among the 3 groups

Fig. 4 depicts significant differences observed in the frequency of wheeze bands among the 3 groups ($p < 0.005$). The frequency of wheeze bands was significantly higher in the severe group than in the mild group. The frequency of wheeze bands in the mild group was 340.9 ± 108.9 Hz, that in the moderate group was 443.9 ± 138.9 Hz, and that in the severe group was 509.5 ± 156.2 Hz.

Comparison of wheeze duration among the 3 groups

No significant differences were observed in wheeze duration among the 3 groups. The wheeze duration in the mild group was 285.7 ± 135.7 ms, that in the moderate group was 340.6 ± 108.1 ms, and that in the severe group was 378.9 ± 174.3 ms.

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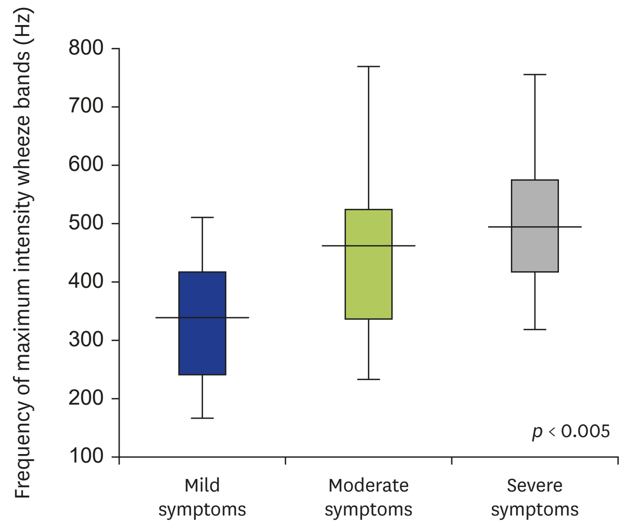

Fig. 4. Comparison of frequency of maximum intensity wheeze bands among the 3 groups

Comparison of number of wheeze bands per 30 seconds among the 3 groups

Fig. 5 reveals significant differences in the number of wheeze bands per 30 seconds among the 3 groups ($p < 0.001$). The number of wheeze bands per 30 seconds in the mild group was 8.3 ± 7.1, in the moderate group was 14.3 ± 8.6, and in the severe group was 17.7 ± 5.7.

ROC curve analysis for the association of nighttime sleep disturbance with the number of wheeze bands per 30 seconds

The cutoff value for the number of wheeze bands per 30 seconds that could predict nighttime sleep disturbance on the second night was 11.1; the sensitivity, specificity, and positive- and negative-predictive values were 100%, 65%, 32%, and 100% ($p < 0.001$), respectively, with an AUC of 0.86 ± 0.05 (**Fig. 6**).

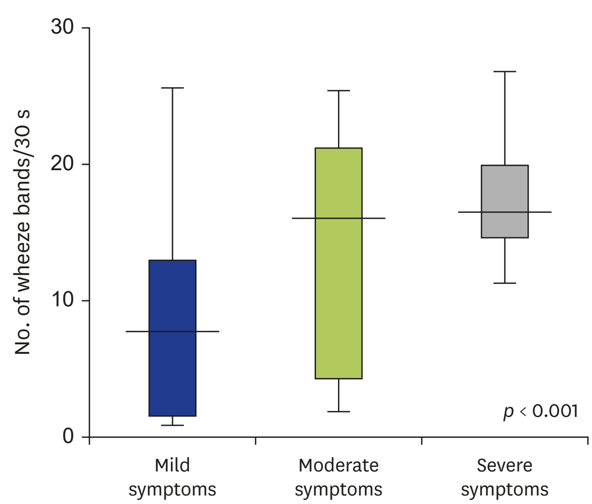

Fig. 5. Comparison of number of wheeze bands per 30 seconds among the 3 groups

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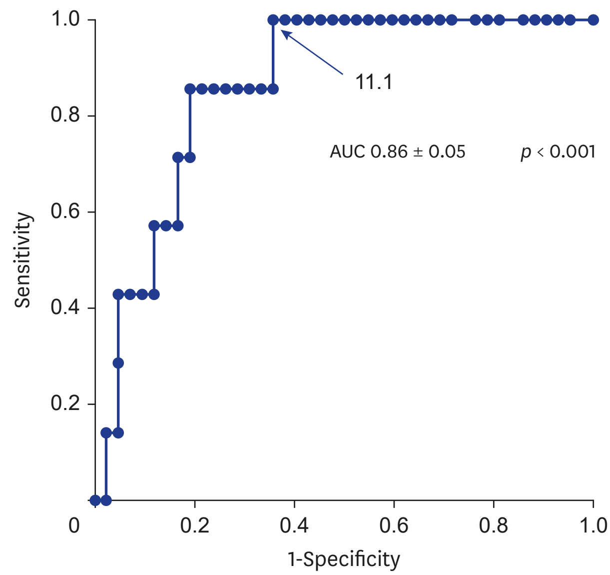

Fig. 6. Detection of nighttime sleep disturbance using the number of wheeze bands per 30 seconds.

DISCUSSION

It is important to noninvasively and objectively detect the risk of nighttime sleep disturbance or prolonged exacerbation of symptoms before treatment for managing wheezing in young children. Lung-sound analysis performed with tidal breathing before treatment in the morning shows many wheeze bands per 30 seconds in patients with severe respiratory disturbance at night. Notably, young children cannot perform lung function tests, such as peak expiratory flow measurements, in order to predict exacerbation of symptoms (e.g., wheezing, cough, heavy breathing, reduced activity, shortness of breath, and sleep disturbance), in accordance with international guidelines [10].

Wheezing is easily auscultated with only a stethoscope; however, this method is based on the subjective judgment of the treating physician. During auscultation, physicians cannot discern subtle differences among the components of wheezing. Lung-sound analysis is helpful in performing objective evaluation of wheezing characteristics. Understanding the differences in spontaneous wheezing characteristics before they occur may be beneficial for treatment and management decisions in small children, including infants, with wheezing.

In the present study, lung-sound analysis was performed to compare wheezing characteristics, including respiratory cycle, frequency, duration, frequency of maximum intensity, and number of wheeze bands per 30 seconds in young children, including infants. The goal of this lung-sound analysis of wheezing characteristics was to detect the association of nighttime sleep disturbance with exacerbation of wheezing symptoms. We found that the number of wheeze bands per 30 seconds could reflect the risk of prolonged exacerbation of symptoms. Higher frequency of wheeze bands and an increased number of wheeze bands per 30 seconds were associated with nighttime sleep disturbance on the night after lung sounds were recorded.

Wheezing is a continuous adventitious lung sound, which is superimposed on breath sounds. According to the new definitions in the present CORSA guidelines, the maximal frequency of

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a wheeze is typically > 100 Hz and its duration is > 100 ms [12-15]. We confirmed that none of the wheezing index values were influenced by age, including that of infants.

Several studies have reported the association between wheezing characteristics and lung function. Baughman and Loudon [16] reported that wheezing was also associated with a peak in the signal, and that peak amplitude constituted a criterion for classifying the sound as a wheeze. Forgacs [3] divided wheezing, the best-known signs of airway obstruction, into 2 categories: monophonic and polyphonic. Wheezing is considered monophonic when only one pitch is heard, whereas they are considered polyphonic when multiple frequencies are simultaneously perceived. Polyphonic wheezing involves more severe bronchial constriction than monophonic wheezing [3, 17, 18]. In patients with polyphonic wheezing, we counted the total number of wheeze bands; thus, polyphonic wheezing may comprise many wheeze bands. The number of wheeze bands in patients with polyphonic wheezing was greater than that in patients with monophonic wheezing. Moreover, patients with more wheeze bands have a greater risk of exacerbation.

Shim and Williams [17] found a relationship between wheezing characteristics and the severity of airway obstruction. High-pitch, louder, and longer wheezing is associated with a lower peak expiratory flow rate. Loudness and high-pitch wheezing are associated with more severe obstruction. Wheezing characteristics are generally associated with the severity of airway obstruction [17]. Baughman and Loudon [16] reported a correlation between the proportion of respiratory cycles that involve wheezing and the degree of airway obstruction.

In this study, the severe group had a higher frequency of maximum intensity of wheeze bands; however, the duration of each wheeze was not predictive of symptoms in young children.

Baughman and Loudon [18] and Pasterkamp et al. [19] reported that a strong association was found between the degree of bronchial obstruction and the proportion of the respiratory cycle occupied by wheezing (tw/ttot); however, this association exhibited excessive variability and could not be used to predict the forced expiratory volume in 1 second based on the duration of wheezing. The degree of bronchospasm (abnormal contraction of muscles in the wall of the bronchi causing airway obstruction) is related to the frequency of wheezing sound signals, rather than the wheezing intensity [18].

In this study, the number of wheeze bands per respiratory cycle may correlate with tw/ttot; however, the number of wheeze bands per respiratory cycle exhibited excessive variability and we selected the number of wheeze bands per 30 seconds for highly accurate index.

Bentur et al. [8] reported utilization of overnight nocturnal monitoring for assessment of asthma activity in symptomatic school-aged children by a wheeze-detection device. Monitoring of wheezing is useful for asthma management; however, it is not possible to record wheezing overnight in young children, including infants. Recently, it was reported that infants' expiratory wheezes show high respiratory resistance [20].

Wheezing characteristics are presumably associated with lung function, but it is challenging for young children, especially infants, to undergo lung function tests, particularly during acute exacerbation. Thus far, there have been no reports about how the characteristics of wheezing can predict sleep disturbance during the night after physical examination, as a predictor of the risk of prolonged exacerbation in young children, including infants.

We successfully performed lung-sound analysis to reveal how the characteristics of wheezing relate to the risk of prolonged exacerbation. The indices of wheezing characteristics using lung-sound analysis may provide a high-sensitivity index to assess airway obstruction in younger children; this information can be obtained before treatment using a noninvasive method and over an assessment period of 30 seconds. This information may be useful for nighttime home management, both by physicians and by parents or legal guardians. This study has a limitation in that patients with severe airway obstruction did not demonstrate any audible lung sounds (known as “silent chest”).

In conclusion, lung-sound analysis can noninvasively detect wheezes in young children including infants. The number of wheeze bands per 30 seconds can be used to detect the risk of prolonged exacerbation in young children, including infants, despite the presence of mild exacerbation before treatment.

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