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A breath sound analysis in children with cough variant asthma

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FVC, forced vital capacity; FEV₁, forced expiratory flow and volume in 1 s; FEV₂₅₋₇₅, mean forced expiratory flow between 25% and 75% of the FVC; V₅₀, maximal expiratory flow at 50% vital capacity; V₂₅, maximal expiratory flow at 25% vital capacity; FOT, forced oscillation technique; Rrs, respiratory resistance; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, resistance difference between 5 Hz and 20 Hz; X5, reactance at 5 Hz; HFp, highest frequency of the mV² power spectrum; HFz, highest frequency of the dB power spectrum; F₅₀, frequency limiting 50% of the power spectrum; F₉₉, frequency limiting 99% of the power spectrum; Slope, roll-off from 600 to 1200 Hz; P_T, total power area of 100 Hz to the highest frequency of the power spectrum; P₃, total power of the third area of the power spectrum; P₄, total power of the fourth area of the power spectrum; AUC, area under the curve; RPF₅₀, ratio of power and frequency at 50% of the highest frequency of the dB power spectrum; RPF₇₅, ratio of power and frequency at 75% of the highest frequency of the dB power spectrum

ABSTRACT

Background: Cough variant asthma (CVA) is characterized by a chronic cough and bronchial hyper-responsiveness without confirmation of wheezing. Using a breath sound analyzer, we evaluate the characteristics of breath sound in children with CVA.

Methods: Nine children with CVA (median age, 7.0 years) participated. The existence of breath sounds was confirmed by sound spectrogram. Breath sound parameters, the frequency limiting 50% and 99% of the power spectrum (F₅₀ and F₉₉), the roll-off from 600 to 1200 Hz (Slope) and spectrum curve indices, the ratio of the third and fourth area to the total area of the power spectrum (P₃/P_T and P₄/P_T) and the ratio of power and frequency at 50% and 75% of the highest frequency of the power spectrum (RPF₅₀ and RPF₇₅) were calculated before and after β₂ agonist inhalation. A spirogram and/or forced oscillation technique were performed in all subjects.

Results: On a sound spectrogram, wheezing was confirmed in seven of nine patients. All wheezing on the image was polyphonic, and they almost disappeared after β₂ agonist inhalation. An analysis of the breath sound spectrum showed that P_T, P₃/P_T, P₄/P_T, RPF₅₀ and RPF₇₅ were significantly increased after β₂ agonist inhalation.

Conclusions: Children with CVA showed a high rate of inaudible wheezing that disappeared after β₂ agonist inhalation. Changes in the spectrum curve indices also indicated the bronchial reversibility. These results may suggest the characteristics of CVA in children.

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Introduction

Clinically, the existence of airway narrowing can be confirmed by the presence of wheezing derived from the respiratory tract with auscultation. Pediatricians can estimate infantile asthma with the improvement of wheezing due to β_2 agonist inhalation. However, the auscultation technique is associated with some limitations,¹ as it naturally depends on an individual's hearing ability, the technique itself, and the cooperation of the patient. Although the existence and/or a history of wheezing are frequently discussed in associating with the diagnosis of childhood respiratory diseases, the role of such factors is unclear because no objective measurement of wheezing has yet been clinically utilized.

CVA is thought to be a phenotype of asthma and a common cause of chronic cough.² CVA is mainly diagnosed by an isolated chronic cough relieved by β_2 agonist inhalation and showing positive bronchial hyperresponsiveness (BHR).³ Usually, CVA patients have no history of wheezing. Hyperresponsiveness of cough receptors has been evaluated using chemical irritant inhalation challenges,^{4,5} and the relationship between cough hypersensitivity syndrome and CVA has been reported.⁶ BHR may induce specific or non-specific bronchoconstriction resulting in prolonged dry cough, whereas CVA patients hardly demonstrate audible wheezing.

Recently, the utility of breath sound analyses for assessing airway constriction has been studied.⁷ It has been reported that breath sounds are sensitive to airway changes and are a safe and simple to assess airway changes.⁸ Recent developments in signal processing methods have improved the possibility of extracting physiologically and clinically relevant information from respiratory sounds.^{9,10} Using a commercially available breath sound analyzer, we established a clinical method for detecting changes in the breath sounds in cases of airway narrowing in children^{11,12} and have reported a case of childhood CVA showing an inaudible wheeze-like shaped noises that was improved by β_2 agonist inhalation.¹³

In this report, using such a technique, we evaluated whether or not inaudible noises is present in children diagnosed with CVA and the lung sound spectrum changes after β_2 agonist inhalation.

Methods

Study subjects

The study participants who agreed to participate in this study included a total of 9 pediatric outpatients (median age, 7.0 years; range, 4–13 years; male: female, 4: 5) who visited for the treatment of chronic cough at the Tokai University Hospital and Yamato Municipal Hospital from April 1, 2012 to March 31, 2017 for the treatment of chronic cough (Table 1).

CVA is diagnosed based on the following criteria: cough lasting >8 weeks without wheezing that is relieved by β_2 agonist inhalation, and positive BHR as measured by a methacholine inhalation test or β_2 agonist inhalation test.^{11,14} Five of 9 subjects underwent BHR measurement by methacholine inhalation test and all of them showed positive BHR ($D_{min} < 7.0$ units).^{15,16} Four of 9 subjects underwent BHR measurement by bronchial reversibility with β_2 agonist inhalation and all of them showed positive bronchial reversibility (increase of FEV₁ >12% and/or decrease of R5 >20%).

Pediatrician specializing in childhood respiratory and allergic diseases excluded other chronic cough diseases¹⁷; chronic sinusitis, bronchiectasis, whooping cough, immunodeficiency, cardiac or neonatal pulmonary problems, infantile chronic lung diseases and gastroesophageal reflux disease, and ultimately diagnosed CVA.

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; Dec 21, 2011).

Study protocol

The lung sound analyses were performed before and 15 min after the β_2 agonist inhalation.^{11,12} Each subject was requested to take tidal breaths when the breath sounds were collected. It was confirmed that the breath sound samples included no audible wheeze, crackles or outside noises based on the findings of the physician's auscultation. After the sound analysis, the patients' pulmonary function was tested using spirometry and/or the forced oscillation technique (FOT).

Table 1
The profile of the patients.

No.	Age (Years)	Sex	Height (cm)	Weight (kg)	BMI (%)	IgE (IU/ml)	Allergen (Score)	Effective Medicines	Inaudible noises
1	7	f	123.1	25.4	16.8	<3	no	FP, Mon	(1) 1300 Hz, −68.0 dB, 194 ms (2) 770 Hz, −45.3 dB, 752 ms
2	13	m	168.6	57.5	20.2	1988	Df (1), HD (1) Cedar (6)	FP, Mon	(1) 1110 Hz, −95.4 dB, 738 ms (2) 790 Hz, −56.0 dB, 690 ms
3	8	f	128.5	24.9	15.1	40	no	FP, Mon	(1) 1060 Hz, −71.7 dB, 716 ms (2) 710 Hz, −60.8 dB, 505 ms
4	11	m	139.9	35.0	17.9	145	Df (6), HD (6) Cedar (3)	FP, Mon	(1) 1060 Hz, −86.6 dB, 353 ms (2) 660 Hz, −73.7 dB, 980 ms
5	8	f	132.3	33.1	18.9	201	Df (3), HD (2) Cat(2)Cedar (5)	FP, Mon	(1) 1060 Hz, −63.1 dB, 664 ms (2) 850 Hz, −61.7 dB, 1062 ms (3) 690 Hz, −49.7 dB, 545 ms
6	6	m	115.6	24.9	18.6	24	Cedar (1)	FP, Mon	(1) 1010 Hz, −47.1 dB, 1195 ms (2) 820 Hz, −26.9 dB, 1460 ms (3) 390 Hz, −39.3 dB, 1230 ms
7	5	f	104.4	16.4	15.0	415	Df (2), HD (2) Cedar (1)	FP, Mon	No
8	4	f	100.9	17.3	17.0	42	Rag (3)	Bud, Mon	No
9	6	m	111.4	18.0	14.5	193	Df (3), HD (2) Dog (3), Cedar (3)	CIC, Mon	(1) 1130 Hz, −133.9 dB, 280 ms (2) 760 Hz, −104.5 dB, 340 ms (3) 390 Hz, −95.8 dB, 579 ms

Df, *Dermatophagoides farinae*; HD, house dust; Cedar, Japanese cedar pollen; Rag, ragweed pollen; FP, fluticasone; Mon, montelukast; Bud, Budesonide; CIC, cyclosonide.

All subjects inhaled β_2 agonist solution (procaterol 10–30 μg and saline 2.0 ml).¹⁸ The assessments were performed before and 15 min after β_2 agonist inhalation.

Pulmonary function tests and FOT

The pulmonary function of all participants was determined via spirometry using a calibrated computerized spirometer (Chest-graph HI-105, Chest, Tokyo, Japan).¹¹ The resting baseline was selected using the best-of-three resting results based on the highest sum of the FVC and FEV₁. The results are shown as the percent predicted value, which was calculated using the prediction equations for Japanese children.

The FOT parameters were determined with an FOT system (Master- Screen-Impulse Oscillometry System: Jaeger, Wurzburg, Germany) using techniques recommended by the manufacturer.¹⁹ The measurements were made in the standing position with a nose-clip on. During the measurements, the cheeks were supported by the hands of investigators (for younger children) or by the children themselves. The pneumotachograph was calibrated each day prior to 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) supplied by the manufacturer. Real-time recordings of mouth pressure and flow signals pulsed through a 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. It was agreed that the value of R20 mainly demonstrated the central Rrs, and that the value of R5-R20, as the Rrs difference between 5 Hz and 20 Hz, demonstrated the peripheral airway.¹⁹

Breath sound analyses of wheezing

A breath sound analysis was performed for all participants, as described previously.^{11,20,21} 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). During the recording, trained examiners confirmed the outside noises and inside noises with or without using vocal cord.

In the sound spectrogram (time vs sound frequency), typical wheezing can be observed as a bright wave-type band from left to right, mainly in the high-pitched area of the expiratory phase.¹³ In this study, based on previous reports,^{13,21} three pediatrician specializing in childhood respiratory diseases evaluated the findings. We focused the wheeze-like inaudible noises as, (1) clear waves enhanced mainly during the expiratory phase in sound spectrogram, (2) with a length exceeding 250 ms, (3) that disappeared or were clearly diminished after β_2 agonist inhalation.²²

Breath sound analyses of the sound spectrum

The sound-amplifying unit was found to be effective for analyzing sounds in the range of 100–2500 Hz.¹¹ The recorded inspiratory 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 (Fig. 1a). We used dB in the Y axis and Hz in the X axis. To evaluate the dB-based spectrum images, we decided to set the 0 point of the Y axis (dB) based on the mean of the background

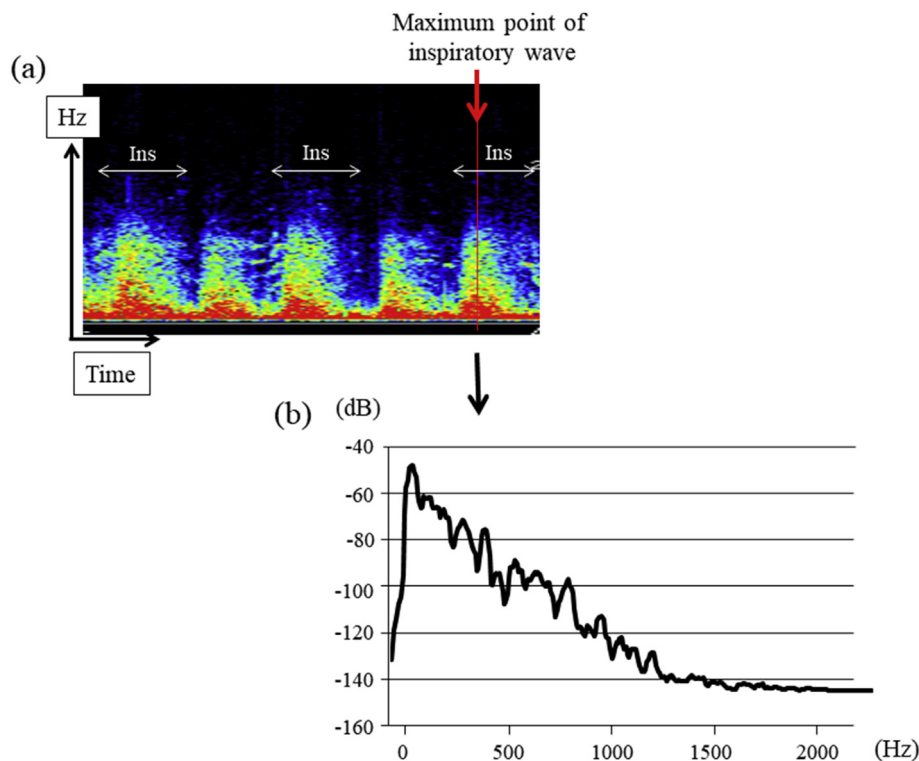


Fig. 1. An analysis of the sound spectrograph. The spectrograph was displayed after a Fourier analysis, with the vertical axis showing the frequency in Hz and the horizontal axis showing time. **(a)** The sound intensity of the breath sounds is indicated by the color. The red vertical line indicates the highest frequency of the inspiratory breath sounds. **(b)** A five-point moving average was used for smoothing to determine the suitable values of dB or mV^2 for determining some checkpoints in the slope for each sound spectrum. Ins, inspiration phase.

Table 2

The results of the data analysis (n = 9).

	Before β_2 inhalation	After β_2 inhalation	P value
FVC (%pred) [†]	82.9 (52.9, 100.6) [‡]	85.7 (73.6, 104.1)	0.036
FEV ₁ (%pred)	88.0 (57.2, 102.2)	88.5 (80.5, 113.2)	0.012
FEF _{25–75} (%pred)	98.1 (53.1, 100.9)	113.1 (63.7, 110.0)	0.012
V(·) ₅₀ (%pred)	100.2 (49.4, 142.2)	112.7 (61.0, 166.7)	0.025
V(·) ₂₅ (%pred)	92.2 (42.9, 128.9)	108.0 (43.5, 167.1)	0.093
R20 [§]	0.44 (0.27, 0.66)	0.43 (0.22, 0.65)	0.345
R5	0.62 (0.25, 1.74)	0.60 (0.22, 1.05)	0.030
R5–R20		0.20 (0.02, 1.08)	0.15 (0.047)
X5	–0.20 (–0.37, –0.07)	–0.19 (–0.32, –0.08)	0.149
RPF ₇₅	4.2 (3.1, 3.4)	7.3 (6.7, 8.2)	0.024
RPF ₅₀	6.0 (2.3, 8.1)	6.9 (4.7, 9.2)	0.011
Slope	23.4 (14.8, 31.5)	28.5 (19.7, 29.2)	0.057
P _T	725 (480, 970)	769 (634, 801)	0.049
F ₅₀	140 (110, 170)	160 (120, 190)	0.061
F ₉₉	950 (380, 1310)	1080 (620, 1290)	0.021
P ₃ /P _T	49.8 (8.8, 76.6)	55.2 (11.9, 89.8)	0.021
P ₄ /P _T	38.4 (3.7, 60.9)	43.0 (2.8, 72.1)	0.015

[†] Eight of nine subjects were able to undergo the spirogram.[‡] Median (range).[§] Eight of nine subjects were able to undergo the FOT. Bold letters of p value represent numbers with significant difference.

noise from 2500 to 3000 Hz for the data of all of the subjects. The mean background noise in our silent room was -148.1 ± 5.0 dB. Therefore, to calculate the dB-based area under the curve (AUC), the 0 point in this report was considered to be -170 dB of the original dB recorded by the sound spectrometer.¹¹

The point of the maximum frequency (Hz) in the shape (arrowhead) during inspiration was used for the sound spectrum analysis (Fig. 1a). This sound spectrum (Y axis; dB, X axis; Hz) is shown in Figure 1b. The data were automatically calculated using a custom software program.^{11,20,21} The parameters of the total power of the power spectrum (P_T) (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, -dB/octave) and the frequency limiting 50% and 75% of the power spectrum (F₅₀ and F₉₉) were measured in accordance with the methods of previous reports.^{23,24} The Slope indicates the roll-off of the middle

spectrum curve (-dB/octave).²⁵ The spectrum curve indices, the P₃/P_T, P₄/P_T, RPF₇₅ and RPF₅₀ values, were also calculated.^{11,21} A five-point moving average was used as a smoothing technique to determine the suitable dB value for identifying some checkpoints in the slope of each sound spectrum.

In this study, breath sound samples were obtained twice; before β_2 agonist inhalation and 15 min after β_2 agonist inhalation.¹¹ Each personal breath sound parameter was analyzed conventionally using a sample with a median value from three tidal breaths.

Statistical analyses

The statistical analyses were conducted using the SPSS software program (IBM SPSS Statistics, Version 22 for Windows, IBM, Chicago, IL). The parameters before and after β_2 agonist inhalation were compared using a Wilcoxon signed-rank test. The level of statistical significance was set at $p < 0.05$. The data are expressed as the median and range.

Results

The lung function before and after β_2 agonist inhalation

Eight of nine subjects underwent spirometry. There were significant increases in the spirometric parameters (FVC, FEV₁, FEF_{25–75} and V(·)₅₀) before and after β_2 agonist inhalation (Table 2). Eight of nine subjects underwent the FOT. There were significant decreases in the FOT parameters (R5 and R5–R20) before and after β_2 agonist inhalation (Table 2).

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

Before β_2 agonist inhalation, chest auscultation by a pediatric respirologist revealed no abnormalities in any patients. The breath sound images showed inaudible noises in seven of nine patients (Fig. 2a–d).

Waves of inaudible noises were shown in the middle and high frequency area (390–1500 Hz) of the sound spectrum, and the sound power of wheeze was -133.9 to -26.9 dB (Table 1). These

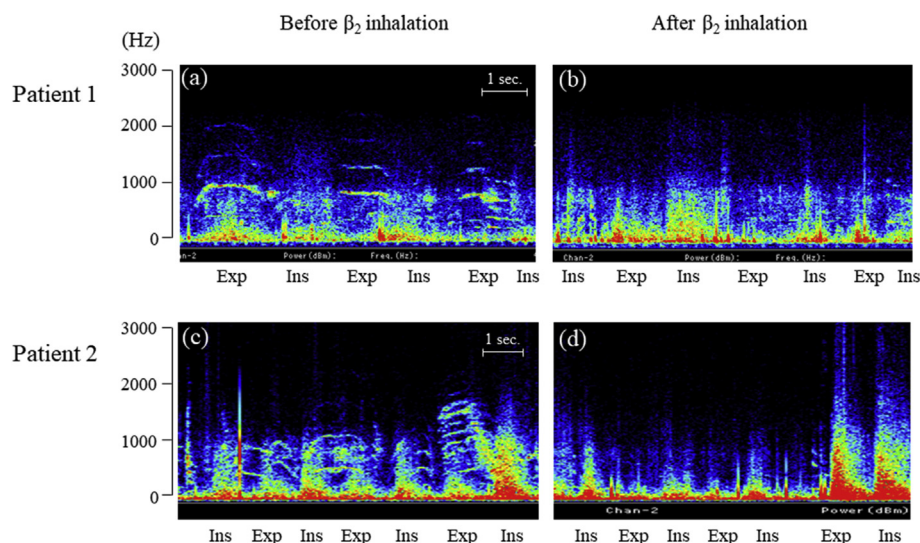


Fig. 2. Changes in the sound image before and after β_2 agonist inhalation. Before β_2 agonist inhalation, the breath sound images showed clear wheeze-like shape noises in seven of nine patients. Waves of noises were shown in the middle and high frequency area (390–1500 Hz) of the sound spectrum during expiration in Patient #1 and #2 (Table 2a, c). These waves of noises almost disappeared after β_2 agonist inhalation (Table 2b, d). Ins, inspiration phase; Exp, expiration phase.

waves of noises in seven patients almost disappeared after β_2 agonist inhalation.

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

In each of the nine subjects, the parameters of the breath sound spectrum were successfully calculated (Table 2). The shape of the sound spectrum showed good similarity in the same patients. An analysis of the data revealed that the median values of the common parameters, F_{50} and Slope, did not significantly change, whereas the spectrum curve indices, P_T , P_3/P_T , P_4/P_T , RPF_{50} and RPF_{75} , significantly increased after β_2 agonist inhalation (Table 2).

Discussion

CVA is a representative chronic cough entity in adults and children. Some reports have suggested the presence of soundless bronchoconstriction in CVA patients, i.e. the airway of CVA patients is located superior to point of sound creation²⁶ or very slow or fine bronchoconstriction of CVA patients does not produce audible wheezing.¹⁷ However, few studies have explored the mechanisms underlying the inaudible noises in CVA despite of persistent cough. The development of asthma with a certain probability in CVA²⁷ further complicates this issue.

In the present study, we tried two different approaches to evaluate the breath sound specificity in children with CVA. First, using a breath sound spectrogram,^{13,28} breath sounds were objectively analyzed. With this approach, when patients had a prolonged cough, clear inaudible noises were detected with a high rate. Although no wheezing was detected at the testing in two of children, inaudible sounds might have been able to detect on another occasion. Thus, inaudible noises in CVA children may occur at a higher rate than the data of this study.

The analysis of breath sounds is useful not only for making assessments based on sound images, but also for measuring noises objectively with power, Hz and duration.¹³ Considering the inaudible breath noises in CVA patients, the Hz of all noises placed in the audible range, and was same level as previous data.^{22,29,30} The inaudible noises may have been inaudible because of the low power of the sounds. Unfortunately, previous reports failed to clarify the power of breath sounds in their definitions of wheezing. We also lack data on the boundaries for classifying audible and inaudible wheezing. We believe that it is necessary to consider the distinction between audible and inaudible noises in a larger number of patients. We should make careful note that, since dB is a relative value, the dB values used in this study were incomparable with those used in the auditory test.

Second, the sound spectrum curve indices calculated by a breath sound spectrum were assessed before and after β_2 agonist inhalation. Recently, breath sound analyses have shown potential utility as a non-invasive and sensitive biomarker of the pulmonary function to detect asthma attacks in younger children.^{12,20} According to previous reports, sound parameters change after the inhalation of bronchoconstrictors and bronchodilators, and a good relationship exists between the changes in the sound parameters and airways.⁸ We have demonstrated the reliability of our simple method and its possible application to the assessment of bronchial constriction in children.^{11,21} It is noteworthy that the spectrum curve indices of our method receive only minor influence from the airflow rate.¹¹

In this study, significant increases after β_2 agonist inhalation were observed in the values of P_3/P_T , P_4/P_T , RPF_{75} and RPF_{50} , similar to the increase in the siprometric parameters (Table 2). The P_3/P_T and P_4/P_T are the ratios of the higher pitched power/area (P_3 and P_4) to the total power/area (P_T) of the sound spectrum. According to

previous reports, when bronchial dilatation is introduced, the decrease occurs in the high-pitched power/area of the sound spectrum.^{11,21} Thus, after β_2 agonist inhalation, a decrease in the higher pitched power/area resulted in an increase in the values of P_3/P_T and P_4/P_T . For this same reason, after β_2 agonist inhalation, bronchial dilatation induced an increase in the RPF_{75} and RPF_{50} values.¹² However, the Slope and F_{50} were not significantly increased by β_2 agonist inhalation. We believe that the Slope and F_{50} mainly measured the midrange of the sound spectrum, so changes in high-pitched sounds may not have been well detected.

Our results indicate that inaudible noises and reversible bronchoconstriction exists at a high rate in the children with CVA.¹³ We are concerned that the absence of wheezing and bronchial reversibility is not the basis of the pathology of the children with CVA. Future studies should explore why the sound power of the noises is so small, even with presence of the reversibility of airway walls, and whether or not this mechanism has a potent effect on chronic cough in CVA.

It has been speculated that the airways of CVA patients are rigid and not easily constricted, resulting in no wheezing.^{17,31} However, under the standard method of BHR measurement, the threshold of BHR indicates the occurrence of definite constriction associated with a more than 20% decrease in the FEV_1 . Therefore, we should pay close attention to previous reports noting that patients with CVA have a higher wheezing threshold than those with classic asthma, bearing in mind that this is not due to BHR.²⁶ The existence of airway remodeling or mechanisms that introduce rigidity of airway walls in CVA has been suggested.³² Of course, the airway-wall vibration is not simply decreased since the walls are hard. There may be an optimum level in hardness and conduction in individual airways that produces wheezing via airway narrowing.

Discussion continues regarding whether or not CVA is an independent disease.³³ We suspect that there are at least two phenotypes in CVA: patients who develop asthma and those who do not. We believe that the patients with highly rigid airways may not develop asthma who have highly reversible airway walls. With the establishment of phenotypes, appropriate treatment and patient guidance for CVA can be planned. Research on such establishment should therefore be promoted in a large-scale study, and breath sound analyses will be useful for the classification of phenotypes of children with CVA.

One limitation associated with our study was the small number of patients examined. In this study, we clearly defined the childhood CVA based on the BHR measurement and differential diagnoses. However, despite the small patient population with strict exclusion criteria,^{2,14} the significant results were obtained because typical children with CVA diagnosed using strict criteria were able to participate in this study.

The present findings suggest that this clinical approach provides certain information about the specific airway state in CVA.^{17,32} The children with CVA with persistent cough have inaudible respiratory noises and β_2 agonist-sensitive airway narrowing at a high rate. Given the previous findings of CVA,^{13,17} it is not surprising that there is a faint noises during prolonged coughing with a high probability. Furthermore, the definition of wheezing is still not clear. Breath sound analyses may aid in the clarification of wheezing itself.

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Conflict of interest

HM received honoraria from Taisho Toyama Pharmaceutical. The rest of the authors have no conflict of interest.

Authors' contributions

HM conceptualized the study, drafted the initial manuscript, and performed all analyses; ME, MN, HTab, KH, and HTad collected data and critically reviewed and revised the manuscript; MK commented on the analyses and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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