

ORIGINAL ARTICLE

Treatment evaluation using lung sound analysis in asthmatic children

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ABSTRACT

Background and objective: Non-invasive assessment of treatment and prediction of attacks in asthmatic children do not yet exist. Lung sound analysis can non-invasively evaluate airway obstruction. We used a recently developed technology for analysing lung sounds using ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz) to evaluate response to inhaled corticosteroid (ICS) in asthmatic children.

Method: Seventy asthmatic children, including infants, underwent lung sound recording in the asymptomatic state prior to and 1, 2, 4, 6 and 8 weeks after ICS treatment, and asthma control was assessed at 10 weeks. The ic700 scores at 4, 6 and 8 weeks were compared with the presence of attack during the following 2 weeks. Subjects were divided into uncontrolled and well-controlled groups.

Results: The mean ic700 scores of all subjects significantly reduced after 8 weeks of treatment. The mean scores of the uncontrolled group were significantly higher than those of the well-controlled group at 4, 6 and 8 weeks after starting treatment. The ic700 cut-off value for predicting asthma attacks within 2 weeks following the evaluation was set at 0.0. After 6 weeks of treatment, the area under the curve was 0.92 ± 0.04 ; the sensitivity, specificity and positive and negative predictive values were 83%, 88% and 88% and 84%, respectively. Similar results were observed at 4 and 8 weeks.

Conclusion: The ic700 score is useful in assessing the effects of ICS treatment, predicting attack symptoms and identifying asymptomatic asthmatic children at a high risk for asthma attack.

Key words: 700 Hz, asthma, infant, inhaled corticosteroid, lung sound analysis.

SUMMARY AT A GLANCE

We developed a new technology for analysing lung sounds using the ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz). We assess the effects of inhaled corticosteroid (ICS) in childhood and infantile asthma in a non-invasive manner and predict an attack while avoiding the influence of individual differences of airflow.

Abbreviations: ACT, Asthma Control Test; AUC, area under the curve; C-ACT, Childhood ACT; eNO, exhaled nitric oxide; FEF₅₀, forced expiratory flow at 50% of vital capacity; FEF₇₅, forced expiratory flow at 25% of vital capacity; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ic700, index of the chest wall at 700 Hz, sound intensity at 700 Hz; ICS, inhaled corticosteroid; MMF, maximal mid-expiratory flow; PEF, peak expiratory flow; ROC, receiver operating characteristic.

INTRODUCTION

The treatment and management guidelines for asthma recommend inhaled corticosteroid (ICS) treatment as the first-line therapy for children, including infants, with persistent asthma.¹ Accurate and objective evaluation of the effects of ICS is important for the proper use of ICS. Daily monitoring using peak expiratory flow (PEF) is useful as it reflects asthmatic symptoms and correlates well with forced expiratory volume in 1 s (FEV₁) in adults and older children.² However, PEF monitoring and lung function tests are technically challenging in small children and infants.

Lung sound analysis is a non-invasive method that does not require the cooperation of infants. Recent developments in signal processing methods have improved the extraction of physiologically and clinically relevant information from lung sounds.^{3–5}

There is a clinical need for a useful index that can be used for long-term management of asthma from infancy to adolescence. Although lung sounds are useful, they are affected by body size and airflow.⁶ We recently reported a method for simplifying this measurement and the development of a new index that requires the measurement of lung sounds at one

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location on the chest surface, the ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz), which is the inspiratory lung sound power within the frequency band between 650 and 750 Hz relative to the band power predicted from the total power between 150 and 1550 Hz.⁷ The ic700 enables the evaluation of airflow limitation in asymptomatic asthmatic children with airway narrowing.⁷ In the present study, we evaluated the utility of the ic700 in evaluating ICS treatment in asthmatic children, including infants.

METHODS

Subjects and study design

Subject baseline characteristics are listed in Table 1. The age distribution of all participants was from 9 months to 15 years (age, numbers: from 9 months to 1 year, 2; from 1 to 2 years, 3; from 2 to 3 years, 8; from 3 to 4 years, 6; from 4 to 5 years, 7; from 5 to 6 years, 9; from 6 to 7 years, 10; from 7 to 8 years, 2; from 8 to 9 years, 7; from 9 to 10 years, 1; from 10 to 11 years, 4; from 11 to 12 years, 3; from 12 to 13 years, 4; from 13 to 14 years, 3; from 14 to 15 years, 1). All participants were outpatients of the Minami Wakayama Medical Center. The diagnosis of asthma was made according to the international guidelines.^{8,9} A total of 70 asthmatic children, who were never treated continuously with ICS and/or leukotriene receptor antagonists, were included in the present study.

All participants underwent lung sound recording for at least 20 s during an asymptomatic period before and 1, 2, 4, 6 and 8 weeks after the start of ICS treatment. Asymptomatic periods were defined as any period without any respiratory or systemic symptoms, including asthma attacks and respiratory tract infections. Lung sounds were evaluated to ensure the absence of wheezes and crackles using auscultation and lung sound analysis.

After recording, asthma control was assessed using Asthma Control Test (ACT) or Childhood ACT (C-ACT) scores.¹⁰ ACT was used for children ≥ 12 years, while the C-ACT was used for children < 12 years. For children < 4 years, physicians obtained information regarding symptoms from their parents.

At 10 weeks after ICS treatment, all patients were assessed for asthma control. A physician enquired about patient symptoms over the most recent 2 weeks at 4, 6, 8 and 10 weeks after therapy initiation. The

ic700 scores at 4, 6 and 8 weeks were compared with the presence of attack during the following 2 weeks; for example, the ic700 score at 4 weeks was compared with the presence of attack until before recording at 6 weeks from after recording at 4 weeks. The ic700 scores at 6 and 8 weeks were compared with the presence of attack within 2 weeks of recording. Accordingly, patients were divided into two groups: uncontrolled and well controlled. Patients with attack symptoms (i.e. coughing, wheezing and dyspnoea) requiring the administration of bronchodilators and/or oral corticosteroids until the subsequent lung sound recording were assigned to the uncontrolled group, whereas those without attack symptoms were assigned to the well-controlled group.

Participants over 6 years underwent spirometry (FUDAC-77; Fukuda Denshi, Saitama, Japan) and exhaled nitric oxide (eNO) evaluations. All tests were performed before and after 1, 2, 4, 6 and 8 weeks from the start of ICS treatment. Written informed consent was obtained from all subjects or their legal guardians, and the study protocol was approved by the ethics committee of the hospital.

Sound recording and signal processing

Lung sounds were recorded in the upper right anterior chest region at the second intercostal space in the mid-clavicular line using a sound sensor (MA-300; Fukuda Denshi, Tokyo, Japan) fixed with tape (H260; Nihon Kohden, Tokyo, Japan) on the chest wall. Lung sounds were recorded in a quiet room for at least 20 s during quiet breathing. Prior to sound analysis, all recordings were carefully listened to, and sound spectrograms were reviewed to exclude noise, such as friction and environmental noise.

Lung sounds were resampled at 6 kHz, and a 512-point fast Fourier transformation (FFT) was performed with 75% overlap into adjacent segments using a Hanning data window. Values of the index, which is explained in the following section, were calculated for all inspiratory breath sounds. Median values were calculated.

Index of the chest wall at 700 Hz

To avoid the effects of airflow on lung sounds, a wide-band power of breath sounds between 150 and 1550 Hz was used instead of directly measuring the airflow. The predicted value of sub-band power used for ic700 was determined by regression analysis using the wide-band power in normal subjects.⁷ The frequency band of the sub-band power was between 650 and 750 Hz. The difference in lung sound power was calculated by subtracting the predicted value from the measured sub-band power of the lung sounds. The difference in the sub-band power (which has a central frequency of 700 Hz) was defined as ic700. The level of sub-band power calculated with the prediction equation derived from the normal subjects was set as 0 dB of ic700. The sub-band power of asthmatic subjects who are not well controlled is usually greater than predicted. Accordingly, the ic700 in these children is over 0 dB.

Table 1 Patients' characteristics

	Total (n = 70)	Over 6 years (n = 35)	Under 6 years (n = 35)
Gender M/F	41/29	20/15	21/14
Age (years)	6.4 $\pm$ 3.8	9.5 $\pm$ 3.0	3.5 $\pm$ 1.4
Height (cm)	114.7 $\pm$ 23.6	133.6 $\pm$ 16.0	95.9 $\pm$ 12.0
Weight (kg)	23.3 $\pm$ 11.6	31.6 $\pm$ 10.6	15.0 $\pm$ 3.7
ic700	1.8 $\pm$ 1.0	1.8 $\pm$ 1.0	1.9 $\pm$ 1.1

ic700, index of the chest wall at 700 Hz; sound intensity at 700 Hz.

Spirometry

Spirometry was performed after recording breath sounds. Spirometric parameters included forced vital capacity (FVC), FEV_{1.0}, maximal mid-expiratory flow (MMF), PEF, forced expiratory flow at 50% of vital capacity (FEF₅₀) and forced expiratory flow at 25% of vital capacity (FEF₇₅). These parameters are expressed as a percentage of normal predicted values.

Exhaled nitric oxide

Online measurement of eNO was performed according to the European Respiratory Society/American Thoracic Society recommendations^{11,12} using a chemiluminescence analyser (Model 280i, Nitric Oxide Analyser; Sievers, Boulder, CO, USA).

Statistical analysis

The ic700 values, spirometric parameters, eNO values, ACT scores and C-ACT scores were presented as a mean $\pm$ SD. Comparisons of ic700 values, spirometric parameters, eNO values, ACT scores and C-ACT scores between periods of treatment were carried out using the t-test. Comparisons of ic700 values between the uncontrolled group and well-controlled group were performed using the t-test. Sensitivity (true-positive rate), specificity (true-negative rate) and positive/negative predictive values (probability of an asthma attack according to the ic700 score cut-off value) were

calculated. The receiver operating characteristic (ROC) curve described the relationship between the sensitivity and specificity of different cut-off values; ic700 as predictors of attack symptoms. The area under the curve (AUC) for all possible cut-off values of ic700 was also calculated. *P*-values < 0.05 were considered significant.

RESULTS

eNO, ACT, C-ACT and spirometry during ICS treatment

Table 2 shows the changes of spirometric parameters, eNO and ACT or C-ACT scores at 8 weeks after treatment. All the parameters except for %FVC improved significantly after treatment.

The ic700 in children over 6 years following 8-week ICS treatment

Figure 1 shows that the ic700 scores of children over the age of 6 improved significantly after treatment for 8 weeks (*P* < 0.001). The ic700 scores were 1.7 $\pm$ 1.0 dB before treatment, 0.6 $\pm$ 1.8 at 1 week after treatment, 0.2 $\pm$ 2.2 dB at 2 weeks after treatment, -0.5 $\pm$ 1.9 dB at 4 weeks after treatment, 0.0 $\pm$ 1.9 dB at 6 weeks after treatment and 0.2 $\pm$ 2.3 dB at 8 weeks after treatment.

Table 2 Changes in eNO, ACT, C-ACT and spirometry during ICS treatment and differences between the uncontrolled and well-controlled groups at 4, 6 and 8 weeks after the start of ICS treatment

	0 week	1 week	2 weeks	4 weeks	6 weeks	8 weeks
%FVC	86.6 $\pm$ 10.8	91.8 $\pm$ 9.4	91.8 $\pm$ 7.9	91.2 $\pm$ 8.6	91.1 $\pm$ 8.6	93.0 $\pm$ 9.0
%FEV _{1.0}	79.4 $\pm$ 12.9	89.4 $\pm$ 8.9*	89.5 $\pm$ 8.7*	88.0 $\pm$ 8.3*	86.6 $\pm$ 9.3	90.5 $\pm$ 9.6***
%FEV ₁	82.3 $\pm$ 8.2	87.8 $\pm$ 5.1*	87.7 $\pm$ 4.4*	86.8 $\pm$ 3.1***	85.6 $\pm$ 6.2*	87.1 $\pm$ 4.8**
%MMF	66.0 $\pm$ 22.4	88.0 $\pm$ 18.4*	89.0 $\pm$ 17.9*	83.9 $\pm$ 14.1**	81.2 $\pm$ 18.2*	88.2 $\pm$ 20.8****
%PEF	82.8 $\pm$ 17.3	98.8 $\pm$ 17.4*	105.6 $\pm$ 19.6**	101.5 $\pm$ 16.1****	104.4 $\pm$ 82.1*	106.0 $\pm$ 19.5****
%FEF ₅₀	69.7 $\pm$ 21.7	90.7 $\pm$ 18.2	90.8 $\pm$ 17.9****	85.9 $\pm$ 14.6*	83.5 $\pm$ 18.7*	88.2 $\pm$ 19.7***
%FEF ₇₅	63.0 $\pm$ 28.8	84.6 $\pm$ 23.5	81.8 $\pm$ 22.5*	77.3 $\pm$ 17.4*	74.3 $\pm$ 23.5*	83.5 $\pm$ 26.8***
eNO (ppm)	52.8 $\pm$ 52.1	25.6 $\pm$ 20.0	25.6 $\pm$ 13.1*	22.6 $\pm$ 12.7***	22.8 $\pm$ 16.3***	20.3 $\pm$ 10.2*
ACT	22.0 $\pm$ 3.0	22.0 $\pm$ 1.6	23.3 $\pm$ 1.7*	24.3 $\pm$ 1.4	24.1 $\pm$ 1.4	24.0 $\pm$ 1.3
C-ACT	21.2 $\pm$ 3.8	24.2 $\pm$ 2.7	24.8 $\pm$ 2.4**	24.8 $\pm$ 3.5**	24.7 $\pm$ 3.5**	25.5 $\pm$ 1.5**
	4 weeks Well controlled	Uncontrolled	6 weeks Well controlled	Uncontrolled	8 weeks Well controlled	Uncontrolled
%FVC	93.3 $\pm$ 9.8	90.1 $\pm$ 9.2	88.3 $\pm$ 8.4	96.8 $\pm$ 8.3	93.5 $\pm$ 10.6	91.6 $\pm$ 6.7
%FEV _{1.0}	91.6 $\pm$ 9.9	86.5 $\pm$ 8.9	85.3 $\pm$ 8.8	90.0 $\pm$ 12.0	91.7 $\pm$ 9.9	87.6 $\pm$ 10.5
%FEV ₁	88.2 $\pm$ 2.5	86.6 $\pm$ 2.9	86.4 $\pm$ 4.2	83.6 $\pm$ 9.8	87.9 $\pm$ 4.8	85.4 $\pm$ 5.5
%MMF	84.1 $\pm$ 14.5	82.3 $\pm$ 14.6	83.5 $\pm$ 16.0	80.1 $\pm$ 26.6	91.4 $\pm$ 21.5	80.5 $\pm$ 21.6
%PEF	113.4 $\pm$ 7.2	92.6 $\pm$ 13.4***	112.7 $\pm$ 18.6	98.9 $\pm$ 15.2	112.5 $\pm$ 18.6	90.5 $\pm$ 15.1*
%FEF ₅₀	87.2 $\pm$ 13.7	84.4 $\pm$ 15.6	86.2 $\pm$ 15.4	83.9 $\pm$ 27.7	92.0 $\pm$ 20.0	79.0 $\pm$ 19.9
%FEF ₇₅	80.5 $\pm$ 24.4	75.0 $\pm$ 16.1	72.1 $\pm$ 22.0	75.4 $\pm$ 32.0	84.6 $\pm$ 22.0	80.7 $\pm$ 22.0
eNO (ppm)	25.8 $\pm$ 14.2	14.4 $\pm$ 8.8	20.2 $\pm$ 15.8	21.1 $\pm$ 14.6	20.1 $\pm$ 10.3	21.0 $\pm$ 12.5
ACT	25.0 $\pm$ 0.0	24.2 $\pm$ 1.6	24.7 $\pm$ 0.6	22.5 $\pm$ 2.1	25.0 $\pm$ 0.0	23.3 $\pm$ 1.6
C-ACT	24.0 $\pm$ 1.4	24.6 $\pm$ 4.9	25.4 $\pm$ 1.1	25.4 $\pm$ 2.4	25.0 $\pm$ 1.0	25.7 $\pm$ 1.7

P* < 0.05; *P* < 0.005; ****P* < 0.01; *****P* < 0.001.

ACT, Asthma Control Test; C-ACT, Childhood ACT; eNO, exhaled nitric oxide; FEF₅₀, forced expiratory flow at 50% of vital capacity; FEF₇₅, forced expiratory flow at 25% of vital capacity; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; MMF, maximal mid-expiratory flow; PEF, peak expiratory flow.

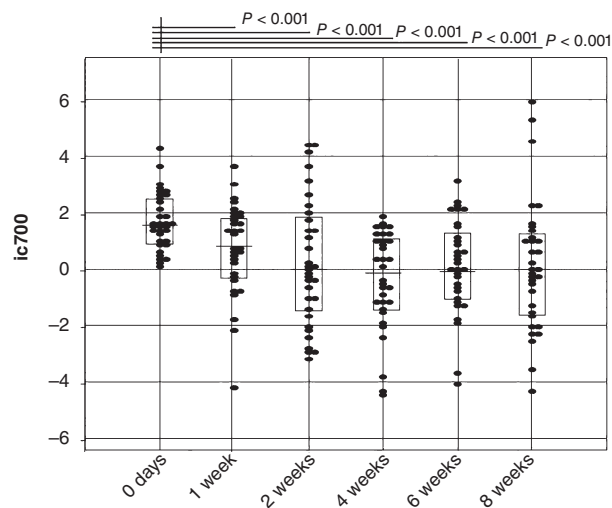


Figure 1 Changes in the ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz) scores of children over 6 years following inhaled corticosteroid (ICS) treatment for 8 weeks.

The ic700 in children under 6 years following 8-week ICS treatment

Figure 2 shows that the ic700 scores of children under the age of 6 improved significantly after treatment for 8 weeks ($P < 0.001$). The ic700 scores were 1.9 ± 1.1 dB before treatment, 0.1 ± 2.1 at 1 week after treatment, -0.4 ± 2.1 dB at 2 weeks after treatment, -0.5 ± 1.9 dB at 4 weeks after treatment, -0.4 ± 2.2 dB at 6 weeks after treatment and -0.5 ± 1.9 dB at 8 weeks after treatment.

eNO, ACT, C-ACT and spirometry in uncontrolled and well-controlled children after 4-, 6- and 8-week ICS treatment

Table 2 shows that there were no significant differences in eNO levels, ACT scores or C-ACT scores between the

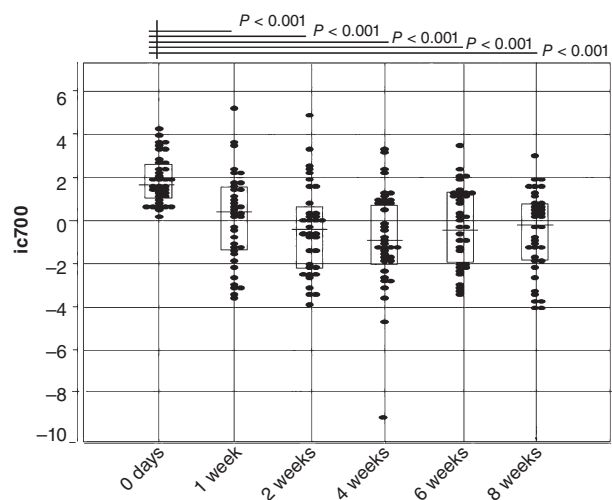


Figure 2 Changes in the ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz) score of children under 6 years following inhaled corticosteroid (ICS) treatment for 8 weeks.

groups at 4, 6 and 8 weeks after the start of therapy. In the well-controlled group, %PEF was significantly higher than that in the uncontrolled group at 4 and 8 weeks after the start of therapy ($P < 0.01$ and 0.05 , respectively).

The ic700 between uncontrolled group and well-controlled children after 4-, 6- and 8-week ICS treatment

Table 3 shows the differences in the ic700 between the uncontrolled group and well-controlled group at 4, 6 and 8 weeks after the start of ICS treatment (all $P < 0.001$).

ROC curve analysis

There was a better predictive ic700 cut-off value (0.0) for attack symptoms within 2 weeks in all children at 4 weeks after the start of therapy; the sensitivity, specificity and positive and negative predictive values were 94%, 77% and 60% and 98% ($P < 0.001$), respectively, with an AUC of 0.90 ± 0.04 .

The arrow shows that there was a better predictive ic700 cut-off value (0.0) for attack symptoms within 2 weeks in all children at 6 weeks after the start of therapy; the sensitivity, specificity and positive and negative predictive values were 83%, 89% and 88% and 83% ($P < 0.001$), respectively, with an AUC of 0.92 ± 0.04 (Fig. 3).

There was a better predictive ic700 cut-off value (0.0) for attack symptoms within 2 weeks in all children at 8 weeks after the start of therapy; the sensitivity, specificity and positive and negative predictive values were 84%, 82% and 79% and 86% ($P < 0.001$), respectively, with an AUC of 0.86 ± 0.04 .

DISCUSSION

Several problems remain for long-term asthma management in small children, including infants. There is a clear need for a new non-invasive method with which to evaluate the effects of ICS treatment and to predict attack in the long-term management of asthmatic small children. The findings of our present study demonstrate that the index of lung sound analysis, the ic700, has utility in assessing the effects of ICS treatment and to predict asthma attack within the following 2 weeks in asthmatic children, including infants. The ic700

Table 3 Difference in the ic700 score between well-controlled and uncontrolled groups

	4 weeks $P < 0.001$	6 weeks $P < 0.001$	8 weeks $P < 0.001$
Uncontrolled (n)	19	35	31
ic700	1.2 ± 0.9	1.1 ± 1.2	1.2 ± 1.9
Well-controlled (n)	51	35	39
ic700	-1.0 ± 1.7	-1.5 ± 1.9	-1.2 ± 1.5

ic700, index of the chest wall at 700 Hz; sound intensity at 700 Hz.

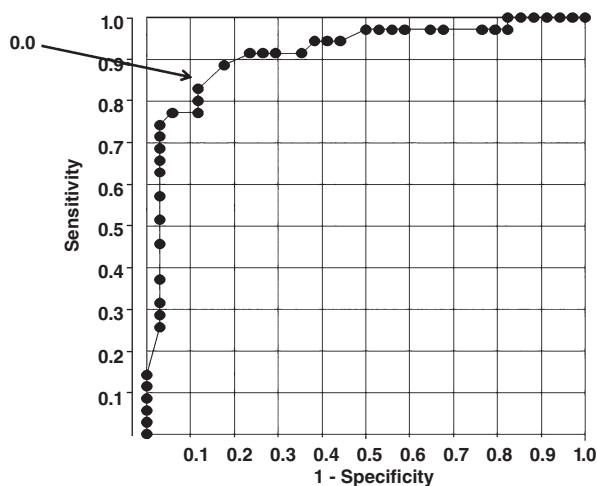


Figure 3 Receiver operating characteristic (ROC) curve analysis for the prediction of symptoms within 2 weeks using the ic700 (index of the chest wall at 700 Hz, sound intensity at 700 Hz) in all children at 6 weeks after the start of inhaled corticosteroid (ICS) treatment. The arrow shows the better predictive ic700 cut-off value (0.0) for symptoms within the following 2 weeks in all children (area under the curve (AUC) = 0.92 ± 0.04 , $P < 0.001$).

represents the change in intensity of inspiratory lung sounds in a rather asymptomatic state. A previous report concluded that the intensity and/or frequency of lung sounds under stable conditions without wheezing is related to the degree of airway obstruction.^{13–16} However, there are several problems which need to be solved before lung sound analysis can be applied routinely in the clinic.

First, why can the change in intensity of normal breath sounds detect the changes of asthmatic airways? Thickening of the airway wall indicates structural changes of the airway caused by chronic inflammation. Such inflammatory changes are assumed to increase the stiffness of the airway.¹⁷ A previous study used a chronic asthmatic guinea pig model to consider whether the change in intensity of the inspiratory lung sounds was associated with the changes in the airway wall. The intensity of inspiratory lung sounds was stronger according to the progression of asthma from onset than in a control model. Furthermore, changes in lung sound intensity from 500 to 1000 Hz have been shown to be well correlated with structural changes (hyperplasia) of the bronchial wall, although these changes were limited to peripheral airways in an asthmatic animal model.¹⁸ A further study by Malmberg *et al.* reported a significant difference in the frequencies of baseline lung sounds between healthy subjects and asthmatic patients.¹⁵ Schreur *et al.* further reported that, at similar levels of airway obstruction, changes in both the frequency and the intensity of lung sounds with airflow were more prominent in asthma patients than in healthy subjects.¹⁶ These studies reported characteristic lung sounds during acutely induced airway obstruction while airflow was standardized, indicating that the lung sounds in asthmatic patients do not simply reflect the degree of airway obstruction. These

studies of breath sounds in asthmatic conditions have demonstrated that breath sounds are affected by changes in generation or transmission.^{19,20} We reported in 2009 that the intensity of inspiratory lung sounds reflects airway obstruction in asymptomatic asthmatic children.^{5–7} When the intermediate-frequency components of lung sounds are transferred to the chest wall, the ic700 increases, implying that there is asthmatic airway dysfunction even when children are asymptomatic. We assume that the change in lung sounds with mild flow limitation is caused by airway wall thickening and mild airway narrowing in the small airways.

As for the next problem, non-paroxysmal lung sounds are affected by individual differences such as body size and airflow. We confirmed that the ic700 was not affected by individual differences when using only lung sound data.⁷ Next, which is the index that is the most appropriate for the management of asthmatic small children? In this study, most of PEF data were higher than 80% of the predicted values even before treatment. Shimoda *et al.* reported that the intensity of middle frequency range of lung sounds correlated to FEF₅₀ in adults.¹⁴ The ic700 associated with classification of asthma severity.⁷ The ic700 is, therefore, very useful for the management of small asthmatic children.

In conclusion, the ic700 allows the assessment of asthma control in children, including infants. The ic700 can be measured non-invasively by analysing breath sounds alone without measuring body size and airflow and does not require the use of a mouthpiece and/or nose-clip. We conclude that the ic700 represents a new and easy procedure for the non-invasive monitoring of childhood asthma.

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