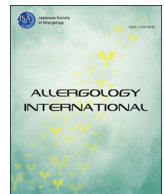




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Original article

Peripheral bronchial obstruction evaluation in patients with asthma by lung sound analysis and impulse oscillometry

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Abbreviations:

LSA, lung sound analysis; FeNO, fractional exhaled nitric oxide; FEV_{1.0}, forced expiratory volume in one second; FVC, forced vital capacity; and, maximal expiratory flow at 50% and 25%; E/I LF, the expiration-to-inspiration sound power ratio in a low-frequency range

ABSTRACT

Background: Computer-aided lung sound analysis (LSA) has been reported to be useful for evaluating airway inflammation and obstruction in asthma patients. We investigated the relation between LSA and impulse oscillometry with the evaluation of peripheral airway obstruction.

Methods: A total of 49 inhaled corticosteroid-naïve bronchial asthma patients underwent LSA, spirometry, impulse oscillometry, and airway hyperresponsiveness testing. The data were analyzed to assess correlations between the expiration: inspiration lung sound power ratio (dB) at low frequencies between 100 and 195 Hz (E/I LF) and various parameters.

Results: E/I LF and X5 were identified as independent factors that affect $\dot{V}_{50\% \text{ predicted}}$. E/I LF showed a positive correlation with R5 ($r = 0.34$, $p = 0.017$), R20 ($r = 0.34$, $p = 0.018$), reactance area (AX, $r = 0.40$, $p = 0.005$), and resonant frequency of reactance (Fres, $r = 0.32$, $p = 0.024$). A negative correlation was found between E/I LF and X5 ($r = -0.47$, $p = 0.0006$). E/I LF showed a negative correlation with FEV₁/FVC(%), FEV_{1\% \text{ predicted}}, $\dot{V}_{50\% \text{ predicted}}$, and $\dot{V}_{25\% \text{ predicted}}$ ($r = -0.41$, $p = 0.003$; $r = -0.44$, $p = 0.002$; $r = -0.49$, $p = 0.0004$; and $r = -0.30$, $p = 0.024$, respectively). E/I LF was negatively correlated with log PC₂₀ ($r = -0.30$, $p = 0.024$). Log PC₂₀, X5, and past smoking were identified as independent factors that affected E/I LF level.}

Conclusions: E/I LF as with X5 can be an indicator of central and peripheral airway obstruction in bronchial asthma patients.

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Introduction

In asthma patients, lung sounds have typically been used to assess the degree of airway narrowing, where rhonchi and wheezes are important adventitious sounds.^{1–3} However, it is often difficult to distinguish slight abnormalities in lung sounds in asthmatic patients when they are not having exacerbations and when no rhonchi or wheezes are audible. Several studies have attempted to overcome such difficulties by utilizing computer-aided lung sound analysis (LSA).^{4,5} In auscultation, vesicular breath sounds generally originate from areas far from the large airways, such as the base of

the lungs. Vesicular breath sounds are primarily inspiratory sounds that have a soft quality. In contrast, bronchial breath sounds have a harsher quality in areas closer to the large airways. When we listen to bronchial breath sounds in the peripheral lung area, they are abnormal and suggest stiff lungs or narrowing airways.⁶ We previously reported that the expiration-to-inspiration sound power ratio in a low-frequency range, between 100 and 195 Hz (E/I LF), increased in bronchial asthma patients with airway inflammation and obstruction.⁷

Recently, impulse oscillometry (IOS) has been increasingly used as a noninvasive method to assess airway resistance and reactance.^{8,9} IOS is effort independent and quantifies the obstruction degrees in the central and peripheral airways.¹⁰ Though the evaluation of IOS is still controversial, the reactance at 5 Hz (X5) is suggested as an index of the peripheral airway obstruction.⁹

We performed analyses to assess correlations between E/I LF or flow-volume curves, especially with $\dot{V}_{50}$ as peripheral airway

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obstruction index, and assessed whether E/I LF can be used to evaluate airway obstruction. We also investigated potential factors affecting E/I LF levels.

Methods

Subjects

The analysis set consisted of 49 mild and moderate persistent bronchial asthma patients who visited our department since January 1st, 2012 to December 31st, 2014. Bronchial asthma was diagnosed according to the Global Initiative for Asthma Guidelines.¹¹ All subjects had positive airway hyperresponsiveness to inhaled acetylcholine and needed to have a history of wheezing and/or dyspnea. At the initial visit, 80% of the subjects showed positive reversibility (reversible with at least 12% and 200 ml improvements in FEV₁ after bronchodilator therapy), whereas the remaining 20% exhibited negative reversibility with normal respiratory function at the visit and were diagnosed with bronchial asthma based on airway hyperresponsiveness and medical history.

At the time of enrollment, the study patients were not receiving treatment with inhaled or systemic corticosteroids. The use of anti-asthma drugs, including bronchodilators, was discontinued for at least 24 h prior to the examination. Subjects with a history of chronic obstructive pulmonary disease (COPD) or any cardiovascular diseases, as well as those with a current viral or bacterial infection, were excluded from the study. The healthy volunteer subjects ($n = 32$) had no respiratory symptoms, had no overt illnesses, and exhibited no abnormalities in their lung function tests and chest radiographies. The ethics committee of Fukuoka National Hospital approved the study protocol (protocol No. 20-12), and all participants received verbal and written information about the study before providing their informed consent.

Measurement of LSA

Lung sounds were recorded for ≥ 30 s over the base of the left lung using a hand-held microphone according to the procedure described in a previous study.⁷ The sound recording was performed in a quiet room, but not in a soundproof booth, in the outpatient

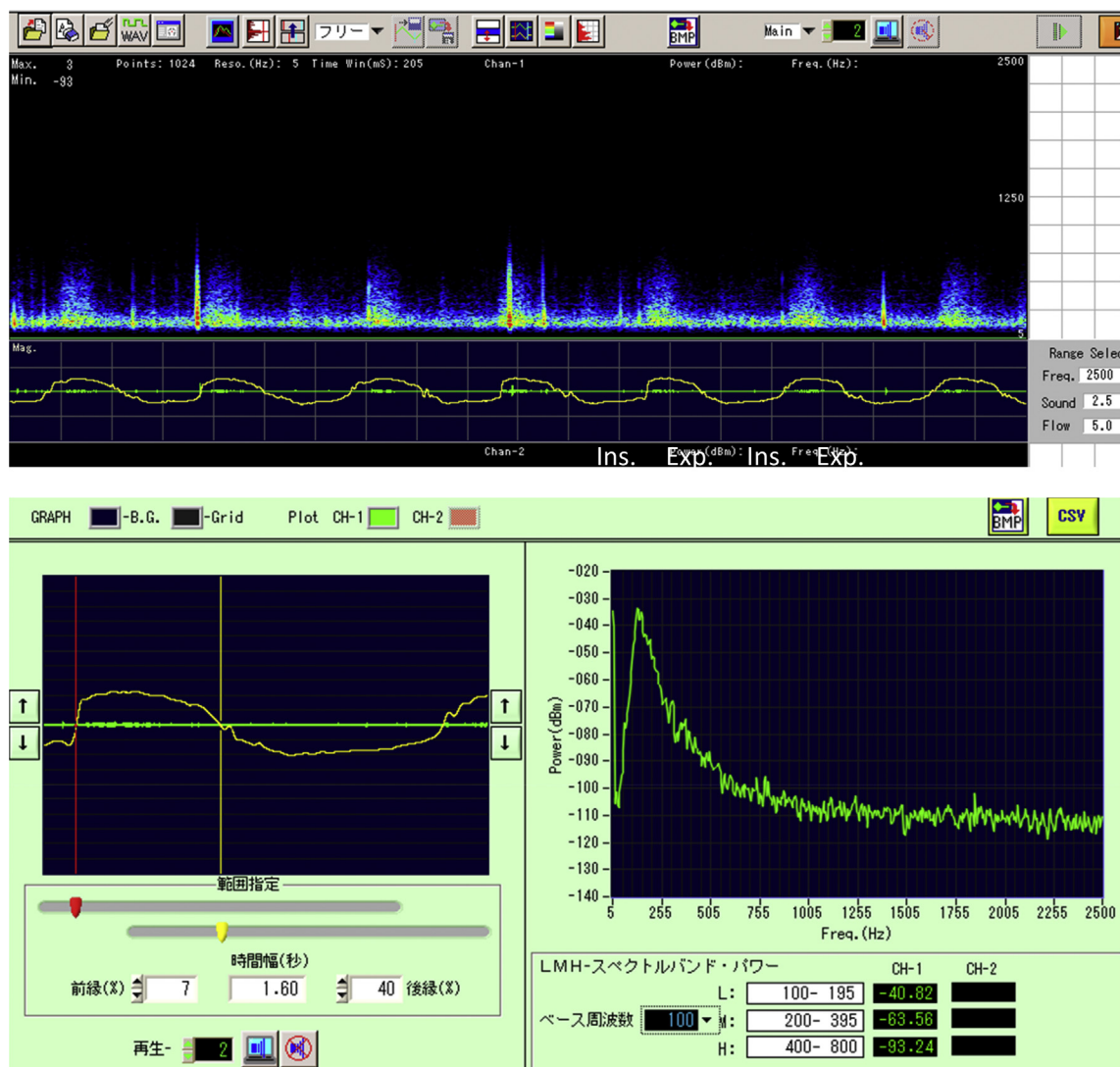


Fig. 1. Sound spectrogram display of lung sounds in a patient. **Upper figure.** The recorded sounds were analyzed using fast Fourier analysis, and the results are displayed as a spectrogram with the frequencies in Hz on the vertical axis and time on the horizontal axis. The sound intensity (dBm) is illustrated with color and brightness. **Lower figure.** A selected portion of the range of an inspiratory or expiratory position. We calculated the average power (dB) of low frequencies from 100 to 195 Hz.

department. The patients took a deep breath through a disposable mouthpiece to synchronize their breath cycles while the breath sounds were recorded. The recording system consisted of an electro-stethoscope containing a wide-range audio sensor attached to the inside of a diaphragm (Bio-Sound Sensor BSS-01; Kenz Medico, Saitama, Japan), a signal processing system, and a personal computer. The sensor had a band-pass filter range of 40–2500 Hz and good sound-collecting ability for the 40–2000 Hz range. The recorded sound was analyzed using a sound spectrometer (LSA-2008; Kenz Medico, Saitama, Japan).

The recorded sound was analyzed by fast Fourier analysis and displayed as a spectrograph, with the frequency in Hz on the vertical axis and time on the horizontal axis. The sound intensity (dBm) is shown as color and brightness (Fig. 1); dBm was used to express the power of the sound in this study and is an abbreviation for the power ratio in decibels (dB) of the measured power referenced to 0.001 volts (V).⁷ We described the low-frequency (100–195 Hz) expiration: inspiration ratio at the sound pressure value with E/I LF.⁷

Measurement of flow-volume curves

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and maximal expiratory flow at 50% and 25% ($\dot{V}_{50}$ and $\dot{V}_{25}$) were measured with a spirometer (Chest graph HI-701, Chest M.I., Tokyo, Japan). The results are expressed as a percentage of predicted values based on relevant reference standards.¹¹

Measurement of IOS

The MasterScreen device (Erich Jaeger Co., Wurtzburg, Germany) consists of a loudspeaker used as a pulse generator to send the pressure impulses to the respiratory system. The system was calibrated through a single volume of air (3 L) at different flow rates and with a reference resistance device (0.2 kPa/(L/s)). The patients used nose clips and a disposable mouthpiece (Fit mouthpiece, Chest, Japan), and they supported their cheeks with their hands to decrease the shunt compliance. In this study, mean respiratory resistance values were calculated over a measurement period of 30 s in the frequency range of 5–35 Hz. The impedance (Z) represents a complex airway resistance, which includes two components, namely, the real resistance (R) and the imaginary reactance (X), which were also determined.^{8,12}

Measurement of airway hyperresponsiveness

Airway hyperresponsiveness was tested by the standard method using acetylcholine, according to the procedure described in a previous study.^{7,13–15} Briefly, the patient first inhaled a control of physiological saline through a nebulizer (PARI BOY 038, PARI GmbH, Germany). The operating airflow rate was 5 L/min. They then inhaled increasing concentrations of diluted acetylcholine solutions, from 0.039 to 20 mg/mL, in 2-fold increments. The FEV₁ was measured after every 2 min of inhalation, and the acetylcholine concentration at which the FEV₁ decreased by 20% was recorded as PC₂₀, which was used as a marker of airway hyperresponsiveness. Subjects with a PC₂₀ of less than 8000 mcg/ml were considered to have airway hyperresponsiveness.

Statistical analysis

By using a boxplot, we examined potential differences in E/I/LF values between the three groups: “healthy volunteers”, “positive airway obstruction”, and “negative airway obstruction”. To test the significance of the difference between the pairs of groups, we used

the Steel–Dwass test. The correlation between E/I LF and each parameter tested was analyzed by Pearson's correlation test. These data analyses were performed with StatMate IV (ATMS, Tokyo, Japan). Ordinary least squares procedures were used in the multiple regression analysis. A receiver operating characteristic (ROC) analysis was performed for E/I LF by defining subjects with airway narrowing as positive. The regression and ROC analyses were performed with JMP (SAS Institute, Cary, North Carolina, USA). P values below 0.05 were regarded as statistically significant.

Results

Demographic and clinical characteristics of the subjects

The demographic and clinical characteristics of the asthmatic patients and healthy volunteers are summarized in Table 1. The flow-volume measurements were significantly lower in the asthma patients, but the BMI, age, M/F ratio, and Smoking status were not different.

Comparison of E/I LF values between bronchial asthma patients and healthy volunteers

The E/I LF levels in asthma patients with FEV_{1,%}predicted $\geq$ 80% were not significantly different from those in healthy volunteers. However, patients with FEV_{1,%}predicted < 80% showed significantly higher E/I LF levels than healthy volunteers and patients with FEV_{1,%}predicted $\geq$ 80% ($p = 0.01$ and $p = 0.04$, respectively, Fig. 2a). Similarly, no significant difference was observed in E/I LF levels between healthy volunteers and asthma patients with IOS X5 > -0.15 kPa/(L/s). However, patients with X5 ≤ -0.15 kPa/(L/s) showed significantly higher E/I LF levels than both healthy volunteers and patients with X5 > -0.15 kPa/(L/s) ($p = 0.0005$ and $p = 0.04$, respectively) (Fig. 2b).

ROC analysis

When ROC analysis was performed with E/I LF data by defining asthma patients with FEV_{1,%}predicted < 80% as positive for airway narrowing, the area under the curve (AUC) was 0.789, with a sensitivity of 0.86 and a specificity of 0.76 at a cut-off value of 0.42 (Fig. 3a). Similarly, when ROC analysis was performed with E/I LF data by defining patients with X5 ≤ -0.15 kPa/(L/s) as positive for airway narrowing, the AUC was 0.758, with a sensitivity of 0.67 and a specificity of 0.75 at a cut-off value of 0.42 (Fig. 3b).

Table 1
Demographic and clinical characteristics of the subjects.

	Bronchial asthma (n = 49)	Healthy volunteers (n = 32)
	Mean $\pm$ SD (minimum–maximum)	Mean $\pm$ SD (minimum–maximum)
Age (year)	43 $\pm$ 13 (20–65)	41 $\pm$ 14 (21–66)
BMI	22.2 $\pm$ 2.9 (16.6–30.5)	22.6 $\pm$ 3.9 (17.0–22.9)
Male/female	11/38	13/19
Duration (year)	6.1 $\pm$ 9.6	–
Smoking		
Non/experience/ current	24/13/12	16/7/9
Atopic/non-atopic	20/28	–
FEV ₁ /FVC (%)	77.9 $\pm$ 9.1	84.2 $\pm$ 6.8***
FEV _{1,%} predicted (%)	95.5 $\pm$ 16.6	102.0 $\pm$ 11.4*
$\dot{V}_{50,%}$ predicted (%)	71.3 $\pm$ 27.1	90.1 $\pm$ 18.5***
$\dot{V}_{25,%}$ predicted (%)	53.6 $\pm$ 27.0	79.5 $\pm$ 23.7***
IgE (IU/ml)	258 $\pm$ 312	–
PC ₂₀	1484 $\pm$ 1471	–

* $p < 0.05$, *** $p < 0.001$.

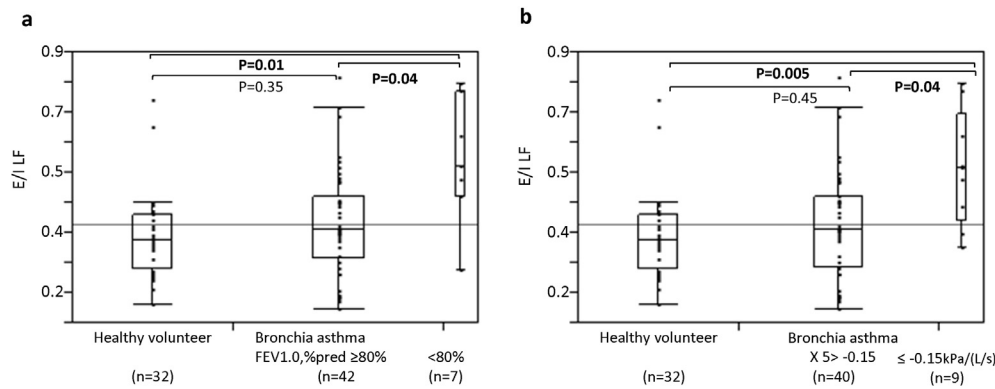


Fig. 2. Comparison of E/I LF values between bronchial asthma patients and healthy volunteers. **a.** Patients with $FEV_{1,\%pred} < 80\%$ showed significantly higher E/I LF levels than healthy volunteers and patients with $FEV_{1,\%pred} \geq 80\%$. **b.** Patients with $X5 \leq -0.15$ kPa/(L/s) exhibited significantly higher E/I LF levels than healthy volunteers or patients with $X5 > -0.15$ kPa/(L/s).

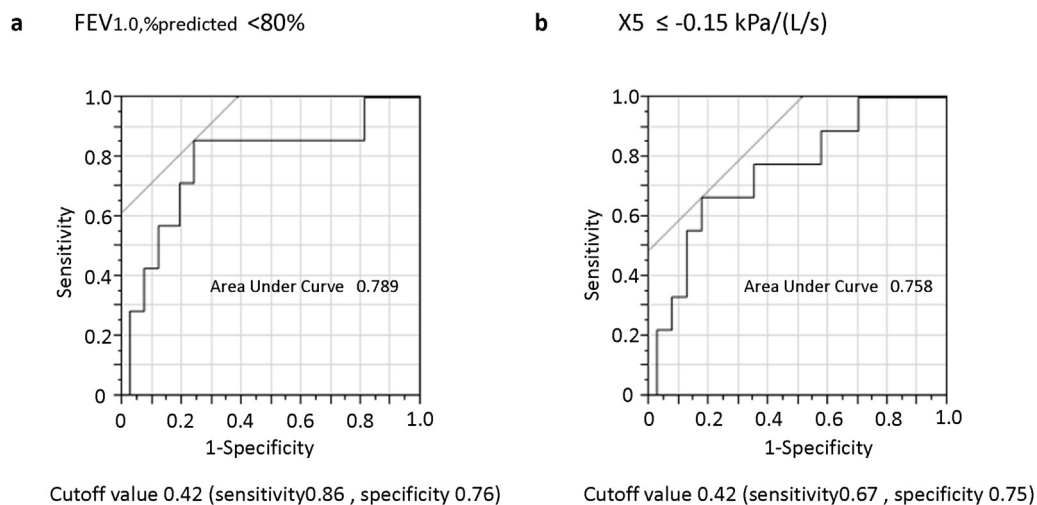


Fig. 3. Receiver operating characteristic (ROC) analysis. **a.** When ROC analysis was performed by defining asthma patients with $FEV_{1,\%pred} < 80\%$ as positive for airway narrowing, the area under the curve was 0.789, with a sensitivity of 0.86 and a specificity of 0.76 at a cut-off value of 0.42. **b.** When ROC analysis was performed by defining asthma patients with $X5 \leq -0.15$ kPa/(L/s) as positive for airway narrowing, the area under the curve was 0.758, with a sensitivity of 0.67 and a specificity of 0.75 at a cut-off value of 0.42.

Correlation between E/I LF and IOS

E/I LF yielded a statistically significant positive correlation with R5 ($r = 0.34$, $p = 0.017$) and R20 ($r = 0.34$, $p = 0.018$) (Fig. 4a, b). E/I LF also showed a significant positive correlation with AX ($r = 0.40$, $p = 0.005$) and Fres ($r = 0.32$, $p = 0.024$) (Fig. 4e, f). A negative correlation was found between E/I LF and X5 ($r = -0.47$, $p = 0.0006$) (Fig. 4d). However, no correlation was observed with R5–R20 (Fig. 4c).

Correlation between E/I LF and flow-volume curves (Fig. 5a–d)

E/I LF showed a negative correlation with FEV_1/FVC ($r = -0.41$, $p = 0.003$), $FEV_{1,\%pred}$ ($r = -0.44$, $p = 0.002$), $\dot{V}_{50,\%pred}$ ($r = -0.49$, $p = 0.0004$), and $\dot{V}_{25,\%pred}$ ($r = -0.30$, $p = 0.024$).

Correlation between E/I LF and log PC₂₀ (Fig. 5e)

E/I LF was negatively correlated with log PC₂₀ ($r = -0.30$, $p = 0.024$).

Multiple regression analysis to explain the $\dot{V}_{50,\%pred}$ with the indices

$\dot{V}_{50,\%pred}$ was explained by E/I LF ($p = 0.018$) and by X5 ($p = 0.048$) independently by stepwise method.

Multiple regression analysis of E/I LF (Table 2)

In the multiple regression analysis, log PC₂₀ ($p = 0.048$), X5 ($p = 0.021$), and the smoking history ($p = 0.020$) were identified as factors affecting E/I LF level independently.

Discussion

In this study, the E/I LF values were higher in bronchial asthma patients with airway obstruction than healthy volunteers or asthmatic patients with mild or no airway narrowing. In addition, E/I LF showed a significant correlation with R5, R20, X5, AX, Fres, and flow volume. In these factors, E/I LF and X5 explained $\dot{V}_{50}$ respectively without confounding each other. X5, known as a parameter of

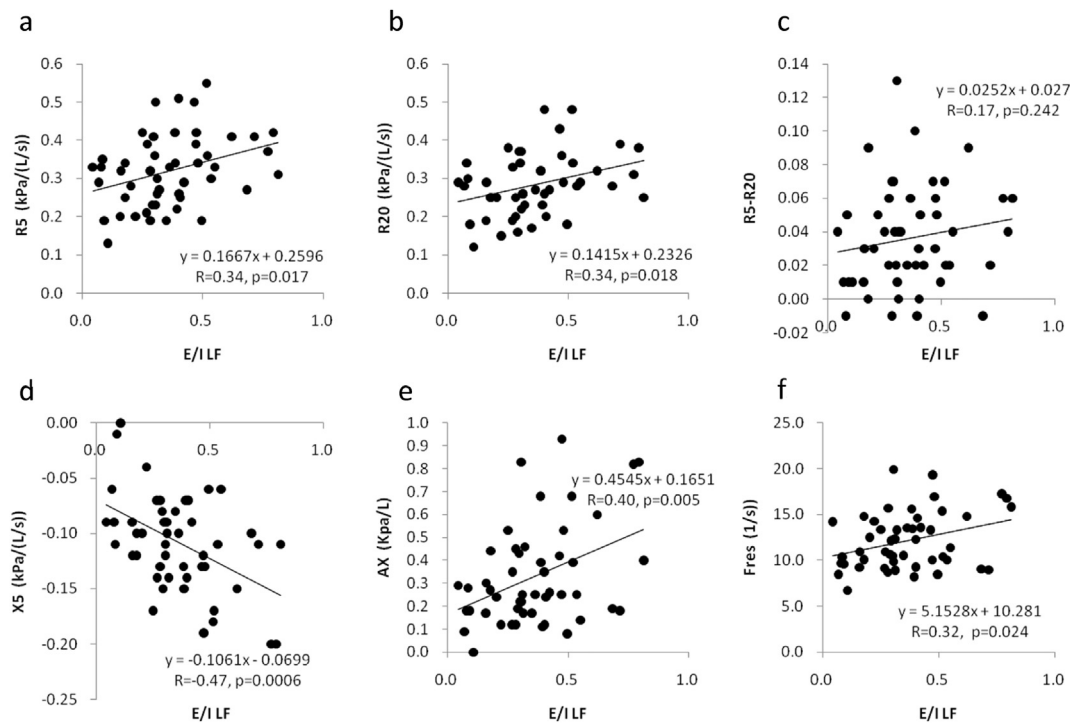


Fig. 4. Correlation between E/I LF and IOS factors. E/I LF showed a statistically significant positive correlation with R5, R20, AX, and Fres (a, b, e, f), but did not with R5-R20 (c). E/I LF showed a statistically significant negative correlation with X5 (d).

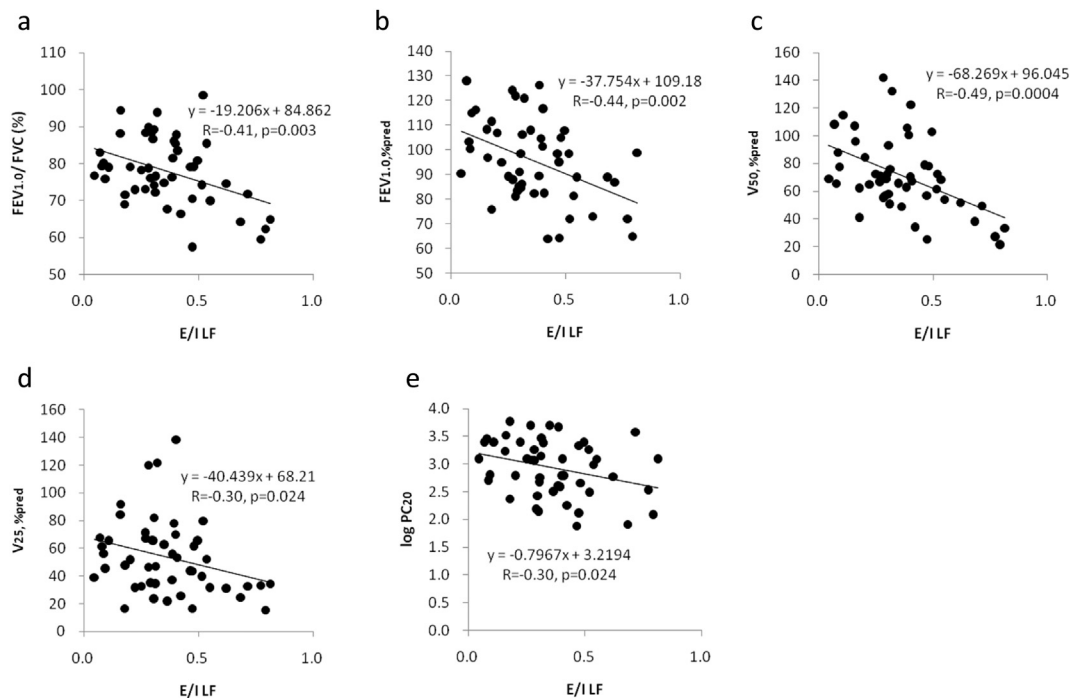


Fig. 5. Correlation of E/I LF with respiratory function and log PC₂₀. E/I LF showed a statistically significant negative correlation with FEV₁/FVC, FEV₁,%predicted, V₅₀,%predicted, V₂₅,%predicted, and log PC₂₀.

peripheral capacitive reactance,^{8,9} log PC₂₀, known as a parameter of bronchial hyperresponsiveness, and smoking history were independent factors to explain the E/I LF. Based on the ROC analysis to predict FEV₁, an E/I LF of 0.42 is a cut-off value suggesting airway narrowing.

A correlation between R5 measured by IOS, and FEV₁ has been reported in bronchial asthma patients,¹⁶ but IOS is generally used as a respiratory function indicator, independent of spirometry, primarily for the evaluation of peripheral airways.¹⁷ IOS measurements, in addition to spirometric determinations of % V₂₅ and %

Table 2
Multiple regression analysis to explain the $\dot{V}_{50\%}$ predicted with the indices.

Factor	n-k	SST	F	p (Prob > F)
Sex	1	0.047	2.098	0.16
Age	1	0.0005	0.021	0.89
BMI	1	0.008	0.343	0.56
Atopic/non-atopic	1	0.0075	0.331	0.57
Smoking amount				
Non/<10/>10 pack/y	2	0.192	4.237	0.022
X5 (kPa/(L/s))	1	0.148	6.541	0.015
R5 (kPa/(L/s))	1	0.004	0.173	0.68
PC ₂₀	1	0.189	8.348	0.006

The significance of bold expresses $p < 0.05$.

$\dot{V}_{50\%}$ will not only enable further differentiation of peripheral airway lesions but also serve as an index in monitoring the therapeutic course.^{9,17,18}

In asthmatic patients, the frequency and strength of lung sounds are modified due to fluctuations in respiratory flow and airway damage caused by inflammation.^{19,20} In broncho-provocation tests, acute airway narrowing causes an increase in the frequency and intensity of lung sounds while breathing at a constant flow rate.^{21–25} Habukawa *et al.* analyzed the strength ratio of high- and low-frequency-range sounds at two points of the bronchi and the chest wall.²⁶ As a result, they reported that LSA was useful for evaluating the impact of medications on bronchial asthma control. Our previously proposed LSA, which uses E/I LF as an index of inflammation and obstruction in asthmatic patients, is useful, simple, and noninvasive.⁷

The IOS system is expensive and space-consuming, making it impractical for use in general practice. In contrast, the recording of lung sounds is an affordable and space-saving option. We know that it is still not clear whether LSA could be better marker than spirometry. The evaluations of the changes of various asthma-related indices caused by the specific treatment may be useful study theme in the future. Previous reports stressed the utility of LSA mainly in children, who unable to perform reliable spirometry, however, we expect that it is useful for elder patients also. When sound analysis equipment will be affordable in general practice, it could be a sophisticated substitute for stethoscope. This report may be of some value as basic data for the future. Even asthma is not severe, airway obstruction may be uneven. In this study, the LSA was carried out by recording from just one area (the base of the left lung). In our preliminary unpublished data, there was no differences between the recording place is one area and multiple area for the purpose so far. In this study, R5-R20, which is supposed to be an indicator of the small airway obstruction, did not related with E/I LF. The resistance at expiration could be meaningful for evaluation of the small airways,⁷ but the both of R5 and R20 values were in average of the respiratory cycle. We are setting another study for this issue.

In bronchial asthma patients, persistent airway inflammation induces hyperresponsiveness and damage and triggers subsequent structural changes (remodeling) of the airways, resulting in irreversible airflow restriction. Eosinophilic allergic airway inflammation is considered to be the main cause of most asthmatic cases, while neutrophilic inflammation may play a role in some asthmatic patients.^{27,28} Aging, smoking, obesity, and the presence of COPD and chronic respiratory illnesses are known to affect airway narrowing in bronchial asthma. Our multiple regression analysis identified increased airway hyperresponsiveness, peripheral airway lesions (seen as a decreased X5), and past smoking as factors associated with an increase in E/I LF values. In bronchial asthma patients, E/I LF seems to be increased by greater levels of airway hyperresponsiveness and obstruction because of inflammation, as well as by the peripheral airway obstruction seen with excessive

smoking. Because the lung sound is also caused by the air turbulence, which may be affected by the airway wall deformations, for example, the airway inflammatory roughness, remodeling bulge.

We know that the IOS evaluation is still controversial, therefore, it is quite difficult to say E/I LF can show the airway obstruction definitively only by the significant relationship with X5. However, E/I LF and X5 related with $\dot{V}_{50\%}$ independently, that might suggest that both could be good indices of peripheral airway obstruction. The pathological differences between them should be clarified in further studies. In conclusion, E/I LF can be an indicator of relatively peripheral airway obstruction in bronchial asthma patients.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

TS designed the study and wrote the manuscript. YO, HM supported the writing of the manuscript and the data analysis. YN participated in the data analysis. RK assisted in the data interpretation. TI coordinated the recruitment of patients.

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