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; FEV1.0, 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

A B S T R A C T

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

Methods: A total of 49 inhaled corticosteroid-naive 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 V50, 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(%), FEV1 predicted, V50 predicted, and V25 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.8,9,10 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 V50 as peripheral airway
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. 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. The sound recording was performed in a quiet room, but not in a soundproof booth, in the outpatient department.
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). We described the low-frequency (100–195 Hz) expiration: inspiration ratio at the sound pressure value with E/I LF.

Measurement of flow-volume curves

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and maximal expiratory flow at 50% and 25% (V50 and V25) 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., Wurzburg, 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.8,13–15 Briefly, the patient first inhaled a control of physiological saline through a nebulizer (PARI BOY 038, PARI GmbH, Germany). The operating air volume 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). We described the low-frequency (100–195 Hz) expiration: inspiration ratio at the sound pressure value with E/I LF.

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

The E/I LF levels in asthma patients with FEV1_{predicted} ≥ 80% were not significantly different from those in healthy volunteers. However, patients with FEV1_{predicted} < 80% showed significantly higher E/I LF levels than healthy volunteers and patients with FEV1_{predicted} ≥ 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 FEV1_{predicted} < 80% as positive for airway narrowing, the area under the curve (AUC) was 0.789, with a sensitivity of 0.76 and a specificity of 0.56 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 0.86 at a cut-off value of 0.42 (Fig. 3b).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of the subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Bronchial asthma (n = 49)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>(minimum–maximum)</td>
<td>(minimum–maximum)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>43 ± 13 (20–65)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.2 ± 2.9 (16.6–30.5)</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/38</td>
</tr>
<tr>
<td>Duration (year)</td>
<td>6.1 ± 9.6</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non/experience</td>
</tr>
<tr>
<td>current</td>
<td></td>
</tr>
<tr>
<td>Atopic/non-atopic</td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>77.9 ± 9.1</td>
</tr>
<tr>
<td>FEV1_{predicted} (%)</td>
<td>95.5 ± 16.6</td>
</tr>
<tr>
<td>V50_{predicted} (%)</td>
<td>71.3 ± 27.1</td>
</tr>
<tr>
<td>V25_{predicted} (%)</td>
<td>53.6 ± 27.0</td>
</tr>
<tr>
<td>IgE (IU/ml)</td>
<td>258 ± 312</td>
</tr>
<tr>
<td>PC20</td>
<td>1484 ± 1471</td>
</tr>
</tbody>
</table>

*p < 0.05, ***p < 0.001.
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 FEV1/FVC ($r = -0.41, p = 0.003$), FEV1,%predicted ($r = -0.44, p = 0.002$), V50,%predicted ($r = -0.49, p = 0.0004$), and V25,%predicted ($r = -0.30, p = 0.024$).

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 $V_{50}\%$predicted with the indices

$V_{50}\%$predicted 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 $V_{50}$ respectively without confounding each other. X5, known as a parameter of...
peripheral capacitive reactance, 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, but IOS is generally used as a respiratory function indicator, independent of spirometry, primarily for the evaluation of peripheral airways. IOS measurements, in addition to spirometric determinations of %V25 and %V50, provide valuable information for the assessment of airway obstruction.

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.

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Table 2

Multiple regression analysis to explain the $V_{50}$-predicted with the indices.

<table>
<thead>
<tr>
<th>Factor</th>
<th>n-k</th>
<th>SST F</th>
<th>p (Prob &gt; F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1</td>
<td>0.047</td>
<td>2.098</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>0.0005</td>
<td>0.021</td>
</tr>
<tr>
<td>BMI</td>
<td>1</td>
<td>0.008</td>
<td>0.343</td>
</tr>
<tr>
<td>Atopic/non-atopic</td>
<td>1</td>
<td>0.0075</td>
<td>0.331</td>
</tr>
<tr>
<td>Smoking amount</td>
<td>Non(&lt;10)=10 pack/y</td>
<td>2</td>
<td>0.192</td>
</tr>
<tr>
<td>X5 ($kPa/(L/s))$</td>
<td>1</td>
<td>0.148</td>
<td>6.541</td>
</tr>
<tr>
<td>R3 ($kPa/(L/s))$</td>
<td>1</td>
<td>0.004</td>
<td>0.173</td>
</tr>
<tr>
<td>$PC_{20}$</td>
<td>1</td>
<td>0.189</td>
<td>8.348</td>
</tr>
</tbody>
</table>

The significance of bold expresses $p < 0.05$.

$V_{50}$, will not only enable further differentiation of peripheral airway lesions but also serve as an index in monitoring the therapeutic course.5,17,18

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 intensity of lung sounds while breathing at a constant flow and 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 $V_{50}$ 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. VN participated in the data analysis. RK assisted in the data interpretation. TI coordinated the recruitment of patients.

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