Original Article

Prediction of Airway Inflammation in Patients with Asymptomatic Asthma by Using Lung Sound Analysis

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What is already known about this topic? The intensity and frequency of sounds in a lung sound analysis may be related to airway constriction. The possibility of airway inflammation prediction by lung sound analysis was suggested.

What does this article add to our knowledge? A lung sound analysis can evaluate the eosinophilic airway inflammation in persons with asthma even without symptoms.

How does this study impact current management guidelines? Asthma control may be able to be evaluated by this totally noninvasive new method to evaluate lung sounds, but further studies will be necessary to confirm this.

BACKGROUND: The intensity and frequency of sounds in a lung sound analysis (LSA) may be related to airway constriction; however, whether any factors of an LSA can predict airway eosinophilic inflammation in patients with asthma is unknown.
OBJECTIVE: To determine whether an LSA can predict airway eosinophilic inflammation in patients with asymptomatic asthma.
METHODS: The expiratory-inspiratory ratios of sound power in the low-frequency range (E-I LF) from 36 patients with asymptomatic asthma were compared with those of 14 healthy controls. The relations of E-I LF with airway eosinophilic inflammation were analyzed. The E-I LF cutoff value for predicting airway eosinophilic inflammation also was analyzed.
RESULTS: The mean ± SD E-I LF was higher in the patients with asthma and with increased sputum eosinophils than in those patients without increased sputum eosinophils (0.45 ± 0.24 vs 0.20 ± 0.12; $P < .001$) or in the healthy controls (0.25 ± 0.10; $P = .003$). A multiple regression analysis showed that the sputum eosinophil ratio and exhaled nitric oxide were independently correlated with E-I LF, $P = .0003$ and $P = .032$, respectively. For the prediction of increased sputum eosinophils and increased fractional exhaled nitric oxide levels, the E-I LF thresholds of 0.29 and 0.30 showed sensitivities of 0.80 and 0.74 and specificities of 0.83 and 0.77, respectively.
CONCLUSIONS: We showed that LSAs can safely predict airway inflammation of patients with asymptomatic asthma. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:727-32)

Key words: *Lung sound analysis; Airway inflammation; Bronchial asthma*

The persistent airway inflammation in bronchial asthma enhances airway hyperresponsiveness and causes airway narrowing. Wheezes and rhonchi are recognized as accessory sounds in bronchial asthma and may be used to estimate the levels of airway inflammation and/or airway constriction in a clinical setting.[1,2] Although the auscultation is fairly subjective, the objectivity of a computerized lung sound analysis (LSA) of the intensity and frequency of lung sounds has been reported.[3,4] The intensity or frequency of lung sounds increases with increasing airway constriction[5] and correlates with pulmonary function and airway hyperresponsiveness.[6-8] An LSA can be performed even for patients with asthma and without audible wheezing during auscultation. Each of the highest frequencies at inspiration or expiration is inversely correlated with airway obstruction.[9,10]

Notably, airway inflammation is an important factor in the diagnosis and/or evaluation of the effects of treatment of patients with asthma. The degree of airway inflammation is now assessed by performing a bronchial biopsy and a bronchial lavage with a fiberoptic bronchoscope, which are invasive; by inducing sputum by using a hypertonic saline solution inhalation, which is cumbersome or unstable to be obtained; and by analyzing exhaled breath condensate or measuring exhaled nitric oxide (FeNO), which are expensive.[11,12] If airway inflammation in bronchial asthma can be estimated by an LSA, which can be performed repeatedly and noninvasively, then this tool could be very useful for clinical use. However, this method has not yet been thoroughly evaluated.[13] If any of the factors measured in an LSA can detect the level of airway inflammation consistently, automatically, and easily, then such a tool will be useful for controlling asthma in the clinic. In this study, we investigated whether any of the elements of an LSA could predict airway

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Abbreviations used
Ach- Acetylcholine
E-I LF- Expiratory-inspiratory ratio of sound power in the low-frequency range
Exp LF- Sound power during expiration
FeNO- Exhaled nitric oxide
FVC- Forced vital capacity
Ins LF- Sound power during inspiration
LABA- Long-acting β-agonist
LAS- Lung sound analysis
NO- Nitric oxide
PC_{20}- Concentration of acetylcholine when the FEV_1 had decreased by >20%
SABA- Short-acting β-agonist
V_{25}- Maximal expiratory flow at 25%
V_{50}- Maximal expiratory flow at 50%

eosinophilic inflammation in patients with asymptomatic asthma who do not have audible wheezing on auscultation.

METHODS

Subjects and study design

From October 2004 to June 2011, we examined 36 patients, new to our hospital, diagnosed with mild persistent asthma and 14 healthy controls (Table I). An LSA, a blood examination, pulmonary function tests, an FeNO measurement, an acetylcholine (Ach) bronchial provocation test, and an induced sputum analysis were performed.[12,14] The following inclusion criteria were used: fulfillment of the Global Initiative for Asthma criteria[11]; a history of asthma symptoms, including recurrent cough, wheezing, or dyspnea, and had positive airway hyperresponsiveness (PC_{20}) (ie, PC_{20} for Ach <8 mg/mL) or positive bronchial reversibility (ie, 12% and 200 mL or more of FEV_1 increase); and no current treatment with inhaled or systemic corticosteroids. The use of antiasthma drugs, including bronchodilators, was discontinued for at least 24 hours before the examination. Patients were included if whole-lung auscultation failed to detect any evidence of wheezing. The subjects with a history of cigarette smoking, chronic obstructive pulmonary disease, any cardiovascular disease, or current viral or bacterial infection were excluded from this study.[15] The healthy controls had no respiratory symptoms and no overt illnesses, and exhibited no abnormalities in their lung function tests and chest radiographies. All of the healthy controls and the patients with asthma were younger than 60 years old, and their body mass index values ranged between 18.2 and 26.8 kg/m^2. The ethics committee of the Fukuoka National Hospital approved the study protocol (protocol 20-12); all of the participants received verbal and written study information before providing their informed consent.

LSA

Lung sounds were recorded for ≥30 seconds over the base of the left lung by using a hand-held microphone. The sound recording was performed in a quiet room, but not in a soundproof booth, in the outpatient department. The patients breathed freely through a disposable mouthpiece to synchronize their breath cycles while the breath sounds were recorded. The recording system consisted of an electrostethoscope that contained a wide-range audio sensor adhered inside a diaphragm (Bio-Sound Sensor BSS-01; Kenz Medico, Saitama, Japan), a signal processing system, and a personal computer (see Figure E1A in this article's Online Repository at www.jaci-inpractice.org). The sensor had a band-pass filter range of 40 to 2500 Hz and sound-collecting ability in the 40 to 2000 Hz range. The recorded sounds were analyzed by using a sound spectrometer (LSA-2008; Kenz Medico, Saitama, Japan). The recorded sounds were resampled to 10,000 Hz and analyzed by 1024-point fast Fourier transformation with 60% overlap into adjacent segments byusing a Hanning data window. The results are presented as a sound spectrograph with frequencies in Hz on the vertical axis and time on the horizontal axis (see Figure E1B and E1C in this article's Online Repository at www.jaci-inpractice.org). The sound intensity (dBm) was shown with color and brightness; dBm, which was used to express the power of the sound in this study, is an abbreviation for the ratio of the measured power in decibels (dB) in reference to 0.001 V. Thus, dBm was an absolute unit that was used when measuring the absolute power. We developed a new indicator because expiratory sound power correlated with sputum eosinophils positively, and inspiratory sound power correlated with sputum eosinophils inversely. The expiratory-inspiratory ratio of sound power (dB) in the low frequency range (E-I LF) is defined by the following formula:

E-I LF = $10^{\Lambda}([e - i]/20)$, in which "e" is the sound power during expiration and "i" is the sound power during inspiration.

TABLE I. Subject characteristics

	Healthy controls, mean ± SD (n = 14)	Patients with asthma, mean ± SD (n = 36)	*P* value
Age (y)	36.2 ± 13.3	41.1 ± 13.2	.25
Body mass index (kg/m^2)	22.1 ± 4.3	22.5 ± 2.1	.77
Men/women	1/13*	12/24*	.06
Atopic/nonatopic	—	22/14*	
Disease duration (y)	—	7.2 ± 10.4	—
FEV_1-FVC (%)	88.0 ± 6.7	74.5 ± 9.9	<.001
FEV_1 %predicted	102.1 ± 14.0	88.0 ± 16.9	.005
V_{50} %predicted	98.5 ± 16.2	62.7 ± 24.8	<.001
V_{25} %predicted	87.4 ± 24.9	44.7 ± 18.4	<.001
Log PC_{20} (mcg)	—	2.7 ± 0.6†	—
IgE (IU/mL)	74.8 ± 102.6	613.7 ± 1272.0	.020
FeNO (ppb)	16.9 ± 9.6	105.9 ± 100.8	<.001
Sputum macrophages (%)	65.4 ± 19.6	44.0 ± 20.1‡	.002
Sputum neutrophils (%)	27.0 ± 13.5	32.7 ± 20.0‡	.27
Sputum eosinophils (%)	0.2 ± 0.4	17.4 ± 22.3‡	<.001
E-I LF	0.25 ± 0.10	0.37 ± 0.25	.02

*No. subjects.
†n = 33.
‡n = 32.

Measurement of flow-volume curves

The forced vital capacity (FVC), the FEV_1, and the maximal expiratory flow at 50% (V_{50}) and maximal expiratory flow at 25% (V_{25}) were measured with a spirometer (Chest Graph HI-701; Chest M.I., Tokyo, Japan). The results are expressed as a percentage of the predicted values (FEV_1-FVC, FEV_1 %predicted, V_{50} %predicted, and V_{25} %predicted), based on the relevant reference standards.[15]

Measurement of FeNO concentration

By following the guidelines published by the American Thoracic Society, FeNO was measured by using the single-breath