Original Article

Lung Sound Analysis and Airway Inflammation in Bronchial Asthma

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What is already known about this topic? Lung sound analysis (LSA) was suggested as a new marker for airway inflammation in bronchial asthma.

What does this article add to our knowledge? LSA can be used to assess airway inflammation and obstruction in bronchial asthma. Furthermore, LSA can detect both central and peripheral airway inflammation.

How does this study impact current management guidelines? LSA is a noninvasive method for evaluating airway inflammation that could be useful for identifying and treating airway inflammation in asthmatic patients.

BACKGROUND: Our previous study on lung sound analysis (LSA) revealed that the expiration-to-inspiration sound power ratio in a low-frequency range (E/I LF) was increased in patients with bronchial asthma, even when they have no wheezes. OBJECTIVE: We also monitored the expiration-to-inspiration sound power ratio in a mid-frequency range (E/I MF) and the mid- to low-frequency sound power ratio for inspiration and expiration (ie, I MF/LF and E MF/LF, respectively) using a new software program to examine which parameter is most suitable as an index of airway inflammation in patients with asthma. METHODS: A study was conducted in 31 patients with mild-to-moderate bronchial asthma to examine potential correlations of LSA parameters (E/I LF, E/I MF, I MF/LF, and E MF/LF) with spirogram parameters, airway hyperresponsiveness (PC_{20}), fractional exhaled nitric oxide (NO), and sputum eosinophils. RESULTS: E/I LF was significantly correlated with airway narrowing (forced expiratory volume in 1 second [$FEV_{1.0}$]/forced vital capacity [FVC]%: r = −0.50, maximal expiratory flow at 50% [V_{50}],%pred: r = −0.50) and peripheral airway inflammation (alveolar NO: r = 0.36, eosinophils in peripheral sputum: r = 0.41). E/I MF was significantly correlated with airway narrowing ($FEV_{1.0}$/FVC%: r = −0.46, V_{50},%pred: r = −0.49), airway inflammation (bronchial NO: r = 0.43, alveolar NO: r = 0.47, eosinophils in peripheral sputum: r = 0.50), and airway hyperresponsiveness ($logPC_{20}$: r = −0.49). E MF/LF was significantly correlated with airway inflammation (NO: r = 0.36, eosinophils in sputum: r = 0.40) and airway hyperresponsiveness ($logPC_{20}$: r = −0.40). I MF/LF was not significantly correlated with any parameters. CONCLUSIONS: Among the 4 LSA parameters investigated, E/I MF demonstrated the highest correlation with airway inflammation, and also with bronchial hyperresponsiveness. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

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

Bronchial asthma is a chronic inflammatory disease characterized by airway infiltration of inflammatory cells, including eosinophils, mast cells, macrophages, neutrophils, and lymphocytes, as well as airway narrowing and increased airway hyperresponsiveness. The examination of airway inflammation is important for the diagnosis and treatment of bronchial asthma. Airway inflammation is assessed by various methods, including bronchofiberscopy, differential cell counts, and inflammatory cytokine assays in bronchoalveolar lavage and induced sputum, inflammatory cytokine assay in exhaled breath condensate, and fractional exhaled nitric oxide (FeNO). FeNO measurement with a varying expiratory flow rate has enabled bronchial and alveolar NO levels to be distinguished.[1-3] In addition, induced sputum can be distinguished as having a central or peripheral origin.[4-6]

We previously conducted a study on lung sound analysis (LSA) in patients with bronchial asthma with no rumbles or wheezes that showed that the expiration-to-inspiration sound power ratio in a low-frequency range (E/I LF), between 100 and 195 Hz, was increased along with airway inflammation.[7] LSA has advantages of being simple, noninvasive, and repeatable.[7] Our previous study used LSA analysis software, and it was incapable of analyzing data in cases when friction noise was introduced and

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Abbreviations used
E/I LF- The expiration-to-inspiration sound power ratio in a low-frequency range
E/I MF- The expiration-to-inspiration sound power ratio in a mid-frequency range
E LF- The expiration sound power in a low-frequency range
E LF/MF- The expiration sound power ratio in a low-frequency range to that in a mid-frequency range
E MF- The expiration sound power in a mid-frequency range
FVC- Forced vital capacity
$FEV_{1.0}$- Forced expiratory volume in 1 second
FeNO- Fractional exhaled nitric oxide
I LF- The inspiration sound power in a low-frequency range
I LF/MF- The inspiration sound power ratio in a low-frequency range to that in a mid-frequency range
I MF- The inspiration sound power in a mid-frequency range
LSA- Lung sound analysis
V_{50} and V_{25}- Maximal expiratory flow at 50% and 25%

overlapped with breath sounds at auscultation. In this study, we analyzed lung sounds using the new analysis software. Easy LSA software (Easy-LSA, Fukuoka National Hospital, Fukuoka, Japan) allows for the correction of background noise and exclusion of a small portion of data that are affected by friction noise from the analysis. We examined the expiration and inspiration sound powers (dB) and the ratios of individual measurements (ie, E/I LF, E/I MF, I MF/LF, and E MF/LF), not only in the low-frequency range, between 100 and 200 Hz, but also in the mid-frequency range, between 200 and 400 Hz, which had previously been difficult to analyze because of the greater influence of noise. We hypothesized that the lung sound power analysis in the mid-frequency can improve the prediction of the airway inflammation over that in the low frequency. We assessed whether the new LSA index is a better predictor of peripheral airway eosinophilic inflammation based on peripheral sputum eosinophil number.

METHODS

Subjects and study design

We examined 31 patients who newly visited our hospital from November 2011 to November 2014 and were diagnosed with mild-to-moderate persistent asthma and 22 healthy control subjects. LSA, blood examination, pulmonary function tests, FeNO measurement, acetylcholine (Ach) bronchial provocation test, and induced sputum analysis were performed.[8,9] To evaluate the usefulness of the LSA, we carefully selected patients without auscultatory wheeze and also without decreased lung function. All patients included in this study fulfilled the Global Initiative for Asthma criteria.[10] All included patients had a history of asthmatic symptoms, including recurrent cough, wheezing, or dyspnea, and had positive airway hyperresponsiveness, that is, PC_{20} for Ach < 8 mg/mL. Airway reversibility was confirmed in 80% of the patients in whom bronchial asthma was diagnosed based on medical history and positive PC_{20} results. All subjects had no smoking history and had a forced expiratory volume in 1 second/forced vital capacity (FEV1.0/FVC) ratio after bronchodilator inhalation of greater than 70%. Chest X ray and high-resolution computed tomography revealed no findings indicative of emphysema, chronic obstructive pulmonary disease, or other organic lesions in any patients. All patients demonstrated normal diffusion capacity. No patients had previously used inhaled or oral corticosteroids. Antiasthma drugs, including bronchodilators, were discontinued for at least 24 hours before this examination. Wheezing was not heard on auscultation in any patient. After the examination had been performed, appropriate treatment, including inhaled corticosteroids, was provided to all patients.

The ethics committee of Fukuoka National Hospital approved the study protocol (protocol no.: 20-12), and all participants received verbal and written study information before providing their informed consent.

Lung sound analysis

Lung sounds were recorded for 30 seconds or more using a totally noninvasive hand-held microphone over the left lung base, where we could most clearly recognize the alveolar respiratory sound. The recording system consisted of an electro-stethoscope containing a wide-range audio sensor adhered 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 in the 40-2000 Hz range. The recorded sound was analyzed using a sound spectrometer (Easy-LSA).

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. Thus, dBm is an absolute unit that is used when measuring absolute power. On the display, the vertical axis indicates the cycles in kilohertz, and the horizontal axis indicates the time in seconds. The intensity (dBm) of the sound is shown as color and brightness. The recording system was calibrated with a reference sound pressure (1 kHz; 94 dB [0 dB $=$ 20 μPa]).

We defined low frequencies (LF) as frequencies of 100-200 Hz and middle frequencies (MF) as frequencies of 200-400 Hz and determined inspiration sound power, expiration sound power, inspiration-to-expiration sound power ratio in the low-frequency and mid-frequency ranges (E/I LF and E/I MF, respectively), and the MF/LF sound power ratio for inspiration and expiration (I MF/LF and E MF/LF, respectively). E/I LF, E/I MF, I MF/LF, and E MF/LF data were converted into logarithmic values (dBm).[7]

The sound recording was performed in a quiet room, but not in a soundproof booth, in the outpatient department. The patients breathed freely during the breath sound recording.

Measurement of flow-volume curves

The FVC, FEV1, and maximal expiratory flow at 50% and 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 based on relevant reference standards.[11]

Measurement of FeNO concentration

Following the guidelines published by the American Thoracic Society, FeNO was measured using the single-breath online method and a fast response (0.02 seconds) chemiluminescence analyzer (Sievers Nitric Oxide Analyzer NOA 280i, GE Analytical Instruments, Boulder, Colo).[9] All of the measurements were performed using a mouth pressure of 16 cm H_2O, which corresponds to expiratory flows of 50, 100, 150, and 200 mL/s. Alveolar and central airway contributions to FeNO were calculated using the slope intercept model and the NO measurements at 50-200 mL/s.[1,2] By referring to these reports, we measured FeNO parameters, that is,