ARTICLE IN PRESS

RESPIRATORY INVESTIGATION ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Changes in the breath sound spectrum with bronchodilation in children with asthma

Mariko Nukaga[a], Hideyuki Tabata[a], Mayumi Enseki[a], Kota Hirai[a], Hiroyuki Furuya[b], Masahiko Kato[a], Hiroyuki Mochizuki[a,*]

[a]Department of Pediatrics, Tokai University School of Medicine, Japan
[b]Department of Basic Clinical Science and Public Health, Tokai University School of Medicine, Japan

ARTICLE INFO

Article history:
Received 29 November 2017
Received in revised form
4 April 2018
Accepted 18 May 2018

Keywords:
Asthma
Breath sound analysis
β_2-agonist
Children
Bronchial reversibility

ABSTRACT

Background: Breath sound parameters have been suggested to be new biomarkers of airway function in patients with asthma.
Methods: We investigated the effect of bronchodilation on breath sound parameters in sixty-four children (mean age, 8.9 years; range, 6–16 years) using a breath sound analyzer. The breath sound parameters included frequency limiting 50% and 99% of the power spectrum (F_{50} and F_{99}), roll-off from 600–1200 Hz (slope), and spectrum curve indices such as the ratios of the third and fourth power area to the total area of the power spectrum (P_3/P_T and P_4/P_T), total area under the curve (A_3/A_T and B_4/A_T), and the ratio of power and frequency at 50% and 75% of the highest frequency of the power spectrum (RPF_{75} and RPF_{50}). Lung function was assessed using spirometry and the forced oscillation technique (FOT). All variables were assessed before and after inhalation of a β_2-agonist.
Results: The spectrum curve indices, A_3/A_T, B_4/A_T, RPF_{75}, and RPF_{50}, showed statistically significant increase following β_2-agonist inhalation. The increase in RPF_{50} was correlated with the decrease in the difference between resistance at 5 Hz and 20 Hz, R5-R20, measured by FOT. In the multiple regression analysis adjusted for the effect of ΔRPF_{75}, the changes in A_3/A_T and B_4/A_T were positively correlated with that in the

Abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25\text{-}75}$, mean forced expiratory flow between 25% and 75% of the FVC; V'_{50}, maximal expiratory flow at 50% of vital capacity; V'_{25}, maximal expiratory flow at 25% of vital capacity; FOT, forced oscillation technique; Rrs, respiratory resistance; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; R5-R20, difference between resistance at 5 Hz and 20 Hz; X5, respiratory reactance at 5 Hz; HFp, highest frequency of the mV^2 power spectrum; HFz, highest frequency of the dBm power spectrum; F_{50}, frequency limiting 50% of the power spectrum; F_{99}, frequency limiting 99% of the power spectrum; Slope, roll-off from 600 to 1200 Hz; P_T, total power area from 100 Hz to the highest frequency of the power spectrum; P_3, total power of the third area of the power spectrum; P_4, total power of the fourth area of the power spectrum; AUC, area under the curve; A_T, total area under the curve from 100 Hz to the highest frequency of the dBm power spectrum; A_3, third area under the curve; B_4, forth area under the curve; RPF_{50}, ratio of power and frequency at 50% of the highest frequency of the dBm power spectrum; RPF_{75}, ratio of power and frequency at 75% of the highest frequency of the dBm power spectrum

*Correspondence to: Department of Pediatrics, Tokai University School of Medicine, Shimokasuya 143, Isehara, Kanagawa 259-1193, Japan. Fax: +81 463 94 3426.
E-mail address: mochihi@tokai-u.jp (H. Mochizuki).

https://doi.org/10.1016/j.resinv.2018.05.004

Please cite this article as: Nukaga M, et al. Changes in the breath sound spectrum with bronchodilation in children with asthma. Respiratory Investigation (2018), https://doi.org/10.1016/j.resinv.2018.05.004

forced expiratory volume in one second.

Conclusions: The spectrum curve indices indicated bronchodilation, and may be useful for the assessment of bronchial reversibility in children with asthma.

1. Introduction

Early intervention is recommended for preventing aggravation and progression of asthma. However, the diagnosis of asthma in children $<$ 5 years of age is difficult [1,2]. In asthma, bronchial reversibility is evaluated based on airway response to bronchodilators [3,4]. However, infants and preschool children are unable to perform the forced respiratory maneuvers involved in spirometry [5]. Measurement of respiratory resistance with forced oscillation technique (FOT) does not require the forced expiratory maneuvers [3,6]; however, FOT cannot be used to evaluate lung function in infants, as they are unable to hold the mouthpiece required in the technique. Therefore, the diagnosis of childhood asthma remains a challenge for all physicians.

Previous studies report that breath sounds are sensitive to airway changes, and analysis of breath sounds is a safe and simple method that can be applied in the clinical assessment of airway function [7]. Moreover, recent developments in signal processing methods have improved the possibility of extracting clinically relevant information from breath sounds [8–10]. Breath sound spectrum can be easily measured in infants, and changes in breath sound parameters with airway narrowing have been reported in this patient population [11].

One of the limitations of breath sound analysis is that breath sounds are affected by airflow rate and pulmonary function [12,13]. When evaluating lung function in small children, it is particularly difficult to have continuous, stable breathing during respiratory examinations. To address this limitation, new breath sound parameters that are unaffected by airflow rate have been defined [9,11,14]. Because it is impossible to conduct lung function test in children ≤ 5 years of age, we first confirmed if the bronchial reversibility can be evaluated using a new lung sound analysis technique. The aim of the present study was to examine the changes in breath sound parameters following β_2-agonist-induced bronchodilation, and evaluate the reliability of breath sound analysis for evaluating bronchial reversibility in school children with asthma.

2. Patients and methods

2.1. Study subjects

Sixty-four well-controlled pediatric outpatients (age, 8.9 $\pm$ 2.8 years; range, 6–16 years; male:female, 38:26) who were treated at the Tokai University Hospital from January 1, 2012 to March 31, 2014, were included in the study (Table 1). The inclusion criteria included one or more of the following conditions: positive specific IgE value ($>$ 0.7 UA/ml), recurrent wheezing, and bronchial hyperresponsiveness (BHR) to methacholine inhalation challenge or bronchial reversibility [15, 16]. In all children, atopic-type asthma was diagnosed by a physician.

Children's asthma medications were withdrawn for 12 h before the study measurements. None of the subjects had respiratory symptoms on the day of testing. Written informed consent was obtained from all children or their legal guardians prior to the study, and the study protocol was approved by the institutional review board of Tokai University Hospital (No. 11R-158; approval date, Dec 21, 2011).

2.2. Study protocol

All assessments were performed before and 15 minutes after the inhalation of β_2-agonist. Each subject took normal tidal breaths. We confirmed that the breath sound samples included no wheezing, crackles, and background noises based on the auscultation and breath sound analyzer images. After the sound analysis, the patients' pulmonary function was assessed using spirometry and forced oscillation technique (FOT).

2.3. Pulmonary function tests and forced oscillation technique

Pulmonary function was assessed using spirometry (Chestgraph HI-105, Chest Co., Tokyo, Japan). The resting baseline lung function was selected using the best-of-three resting results based on the highest sum of the forced vital capacity (FACE) and forced expiratory volume in one second (FEV_1). The results are shown as the percent predicted value of Japanese children.

The FOT parameters were measured using the impulse oscillometry system (Master- Screen-Impulse Oscillometry System, Jaeger CO, Wurzburg, Germany) [5]. All measurements were made in the standing position with the patients' noses clipped. Real-time recordings of mouth pressure and flow signals pulsed through a 5–20-Hz spectrum were superimposed over tidal breathing. Respiratory resistance at 5 and 20 Hz and their difference (R5, R20, and R5-R20 respectively), and respiratory reactance at 5 Hz (X5) were evaluated.

2.4. β_2-agonist inhalation

All patients inhaled a β_2-agonist solution (procaterol 30 μg and saline 2.0 ml) [2]. All assessments were performed before and 15 minutes after the inhalation of β_2-agonist.

2.5. Breath sound analysis

Breath sound analysis was performed as described previously [9,14]. Breath sounds were recorded for ≥ 10 seconds in a silent room using a handheld microphone. The microphone

Please cite this article as: Nukaga M, et al. Changes in the breath sound spectrum with bronchodilation in children with asthma. Respiratory Investigation (2018), https://doi.org/10.1016/j.resinv.2018.05.004