Respiratory Physiology & Neurobiology 239 (2017) 41–45

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

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

The relationship between respiratory system impedance and lung function in asthmatics: A prospective observational study

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form 27 January 2017
Accepted 31 January 2017
Available online 8 February 2017

Keywords:
Airway disease
Asthma
Forced oscillation technique
Lung function test
Respiratory system resistance
Respiratory system reactance

ABSTRACT

Introduction: The aim was to elucidate the relationship between the annual changes in respiratory system impedance, measured by FOT, and lung function tests in patients with asthma.
Methods: Between March 2011 and March 2012, asthma outpatients who attended Kobe City Medical Center West Hospital were recruited. Lung function tests, FOT were conducted every 6 months until March 2016. The relationships between annual parameter changes were evaluated.
Results and conclusion: Sixty-four patients were completed this study. The median follow-up period was 55 months. At enrollment, although resistance showed no relationship with forced expiratory volume in one second (%FEV_1), the reactance was moderately correlated with X5 ($r = 0.524$, $r^2 = 0.275$, <0.001), Fres ($r = -0.498$, $r^2 = 0.248$, <0.001) and ALX ($r = -0.416$, $r^2 = 0.173$, $p = < 0.001$). By contrast, the annual resistance change at 5 Hz (R5) was highly and significantly associated with%FEV_1 change ($r = -0.564$, $r^2 = 0.318$, $p < 0.001$). Longitudinal changes in airway resistance and reactance measured by FOT might be useful for the assessment of lung function in patients with asthma.

1. Introduction

The forced oscillation technique (FOT) is a noninvasive method for measuring lung mechanics (Oostveen et al., 2003). Forced oscillations are applied to the airway opening from the mouth, producing respiratory system impedance that manifests because of the relationship between the resultant pressure and airflow. Actual impedance is termed respiratory system resistance (Rrs), whereas estimated impedance is called respiratory system reactance (Xrs), which reflects the elastic and inertial properties of the lung. Recently, the usefulness of FOT in the evaluation and management of obstructive lung diseases, including asthma and chronic obstructive lung diseases (COPD) has been reported (Paredi et al., 2010; Kanda et al., 2010; Yamaguchi et al., 2009; Mori et al., 2011). A few cross-sectional studies have demonstrated the relationships between FOT parameters and lung function tests (Mori et al., 2011; Shirai et al., 2013). However, to our knowledge, a longitudinal assessment of FOT and lung function tests in patients with asthma has not been conducted. Therefore, in the present study, we explored the relationships between the annual changes in FOT parameters and lung function tests.

2. Methods

2.1. Patients and materials

This study is a prospective observational study. Between March 2011 and March 2012, outpatients with a diagnosis of asthma who attended Kobe City Medical Center West Hospital (a 358-bed community teaching hospital, Kobe, Japan) were recruited. All asthma patients fulfilled the inclusion criteria: 1) having a history of episodic dyspnea and wheezing and a history of the presence of significant airflow reversibility; 2) being administered inhaled corticosteroids or a combination of inhaled corticosteroids with other medications including long-acting β2-agonists, leukotriene receptor antagonists, or sustained release theophylline, for at least 6 months.; 3) no exacerbations requiring systemic corticosteroid in the previous 3 months; 4) without a > 10 pack-year smoking history; 5) without other lung diseases nor uncontrolled comorbidities such as severe cardiovascular diseases and malignant disorders. The periodic assessment was postponed when patients were pre-

Abbreviations: ACT, asthma control test; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FeNO, fractional exhaled nitric oxide; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; X5, respiratory system reactance at 5 Hz.

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http://dx.doi.org/10.1016/j.resp.2017.01.016
1569-9048/

Table 1
Baseline patient characteristics.

	N = 64
Observation period (month)	55 [50–60]
Age (years)	63 [45–72.75]
Sex (male/female)	25/39
Body mass index (kg/m^2)	24.1 [20.7–28.6]
Asthma in childhood	59 (92.2%)
Atopic dermatitis	27 (42.2%)
Allergic rhinitis	43 (67.2%)
Sinusitis	14 (21.9%)
Asthma Control Test	22.5 [20.3–25]
Neutrophils (/μL), (%)	3756 [3243–5164], 61.4 [53.4–68.3]
Eosinophils (/μL), (%)	275[188–453], 4.1[2.6–6.5]
IgE (IU/mL)	317 [77–353]
FeNO (p.p.b.)	25 [17–35]
The number of times of measurement (range)	9–11
Smoking status (current/ex/never)	0/8/56

Values are the median [25%–75%].
IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide.

scribed prednisolone treatment for asthma exacerbations in the three months before the each follow-up visit.

Patient baseline characteristics (age, sex, body mass index, atopic state, type of asthma onset) were obtained at enrollment. Lung function tests, FOT, blood tests (neutrophils, eosinophils, and immunoglobulin E), measurement of fractional exhaled nitric oxide (FeNO), and the asthma control test (Nathan et al., 2004) were performed every 6 months until March 2016. The same equipment and standardized methods were used for all examinations.

The study was approved by the Institutional Review Board of the Kobe City Medical Center West Hospital (reference number 14-024) and oral informed consent was obtained from all patients before the study.

2.2. Measurements

2.2.1. Lung function tests

After inhaled bronchodilator use (400 μg of salbutamol), spirometry was performed using the Chestac–65 V (Chest MI, Inc., Tokyo, Japan). The predicted pulmonary function test values and%FEV_1 were calculated based on the Japanese Respiratory Society guidelines (Kubota et al., 2014). In this article, FEV_1 is defined as postbronchodilator FEV_1.

2.2.2. Forced oscillation system

After inhaled bronchodilator use (400 μg of salbutamol), respiratory impedance was measured with a commercially available FOT device (MostGraph-01, Chest MI, Inc. Tokyo, Japan). During the measurements, subjects were placed in the seated position, wore a nose clip, and breathed at tidal volume through a mouthpiece. In addition, they supported their cheeks to reduce upper airway shunting. A noise signal was applied to the airway, and the respiratory system impedance was automatically calculated using the MostGraph-01 software (version 1.31, Chest MI, Inc.). Recordings were performed for 60 s after steady breathing was confirmed. The mean Rrs at 5 Hz (R5), mean Rrs at 20 Hz (R20), their difference (R5–R20), Xrs at 5 Hz (X5), resonant frequency (Fres) and integrated low-frequency reactance area (ALX). were calculated after manually excluding artifacts (whole-breath analysis). The differences between the mean Rrs, Xrs, and Fres in the expiratory phase and those in the inspiratory phase were also examined (expressed as Delta). Whole-breath analysis and within-breath analysis were performed automatically by the software. The average levels of at least 3 acceptable measurements were used.

2.2.3. Fractional exhaled nitric oxide

FeNO levels were measured using a nitric oxide monitor (NIOX MINO®, Aerocrine, Sweden) according to the 2005 American Thoracic Society/European Respiratory Society guidelines (American Thoracic Society; European Respiratory Society, 2005). The subjects were asked about current medications or food intake that could interfere with the FeNO measurement results. In addition, they were instructed to avoid smoking, exercise, and ingestion of food, water, or caffeine at least 1 h before testing.

While seated, subjects exhaled fully then inhaled for 2–3 s to total lung capacity through an NIOX filter, then exhaled with an upper airway pressure of 5–20 cm H_2O. FeNO measurements were taken from a 3-s stable plateau of the exhaled NO concentration. The lowest detection limit of the NIOX MINO® is 5 parts per billion (ppb), and values <5 ppb were considered as 2.5 ppb. The average values of at least 2 acceptable measurements were used.

2.3. Statistical analyses

All statistical analyses were performed using JMP 9 software (SAS Institute, Cary, NC, USA). Categorical data were summarized as counts, and quantitative data were summarized as the median. The changes of FEV_1, %FEV_1 and respiratory system impedance during the observation period were evaluated using the Wilcoxon rank-sum test. Annual parameter changes were calculated by subtracting the values obtained at the last follow-up from the baseline values, divided by the number of follow-up years. Spearman's rank correlation tests were performed to investigate any associations between 2 variables. Z-score was used to standardize the value. Statistical significance was defined as $p < 0.05$.

3. Results

Seventy patients were enrolled in this study and the final study population comprised of 64 patients. Six patients were excluded for the following reasons; death from sepsis (2 patients), house-moving (2 patients) and loss of follow-up (2 patients). The mean

Table 2
Longitudinal changes in the forced oscillation technique parameters and forced expiratory volume in 1 s.

	First assessment	Last assessment	p Value
R5 (cmH2O/L/s)	3.568 [2.495–4.461]	3.720* [3.148–4.723]	0.0324
R20 (cmH2O/L/s)	2.745 [2.143–3.12]	2.895* [2.285–3.37]	0.0207
R5-R20 (cmH2O/L/s)	0.720 [0.05–1.4]	0.745 [−0.188–1.875]	0.4827
X5 (cmH2O/L/s)	−0.820 [−1.608–−0.25]	−1.040* [−2.368– −0.348]	0.0130
Fres (Hz)	11.39 [6.759–13.559]	12.25* [8.79–17.085]	<0.0001
ALX	5.015 [1.633–10.803]	5.315* [2.115–11.385]	<0.0001
FEV_1 (L)	1.955 [1.355–2.67]	1.930* [1.273–2.625]	0.0100
%FEV_1 (%)	69.9 [56.8–84.5]	67.7 [54.6–81.8]	0.0589

Values are the median [25%–75%]. *P < 0.05.
FEV_1, forced expiratory volume in 1 s; R5 and R20, respiratory system resistance at 5 Hz and 20 Hz, respectively; X5, respiratory system reactance at 5 Hz; Fres, resonant frequency; ALX, integrated low-frequency reactance area.