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Forced oscillation technique as a predictor of FEV1 improvement in asthma

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A B S T R A C T

The usefulness of the forced oscillation technique (FOT) for predicting the treatment outcomes in untreated asthmatic patients is unknown. We investigated whether FOT could predict an improvement in FEV1 following treatment. FOT, spirometry, and fractional exhaled nitric oxide were performed in 31 outpatients before and after undergoing a minimum of two months combination therapy of inhaled corticosteroids and long-acting β2-agonists. The patients were classified as responders or nonresponders to treatment based on the presence or absence of a 10% improvement in the FEV1. The responders to the treatment regimen exhibited lower FEV1, FEV1/FVC, FEF25-75%, and higher respiratory resistance at 5 Hz (R5), as well as a difference between R5 and R20 (R5–R20) at baseline compared to the nonresponders. In the multivariate logistic regression analyses, a change in FEV1 greater than 10% was independently predicted by the R5 (adjusted odds ratio: 15.9). The ROC curve analyses revealed that the area under the curve for R5 (0.731) was larger than that of the other parameters. Thus, R5 is a forced oscillatory parameter and predicts an improvement in FEV1 following treatment.

1. Introduction

The forced oscillation technique (FOT) is a noninvasive method used to measure respiratory system impedance, based on the spectral relationship between pressure and airflow during tidal breathing (Oostveen et al., 2003; Shirai and Kurosawa, 2016). The real part of impedance is called respiratory resistance (Rr), whereas the imaginary part is called respiratory reactance (Xr). Rr reflects the dissipative mechanical properties of the lung, such as airway resistance and respiratory tissue resistance. Moreover, Xr reflects the energy storage capacity, such as the elasticity and inertia of the lungs and air.

Recently, the clinical application of FOT has expanded throughout the world due to the spread of commercially available broadband frequency FOT devices. In addition to the use of mathematical or phantom models of lung mechanics (Tanimura et al., 2014; Al-Alwan et al., 2014), measured data has been interpreted based on correlations with known clinical parameters. Several investigators have reported the relevance of FOT to the indices of spirometry, as well as single-breath nitrogen washout or markers of eosinophilic airway inflammation in cross-sectional studies of asthma (Paredi et al., 2010; Mori et al., 2011; Matsumoto et al., 2011; Shirai et al., 2013). There are also clinical studies that have assessed the effect of inhaled corticosteroids (ICS) or ICS/long-acting β2-agonist (LABA) combinations using the FOT parameters in patients with asthma (Nakaji et al., 2013; Hozawa et al., 2014).

Since the correlations between the forced oscillatory parameters and spirometric indices in asthma are modest, the complementary use of both tests may provide useful information regarding the lung (e.g., the bronchial reversibility test) (Shirai and Kurosawa, 2016). Another promising use of the FOT is its ability to predict the effect of treatment for untreated patients; however, this has yet to be investigated in the literature. The purpose of this retro-

Abbreviations: AIC, Akaike's information criteria; ALX, low-frequency reactance area; Δ, differences between inspiratory and expiratory phases; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in one second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists; ROC, receiver operator characteristic; Rr, respiratory resistance; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; R5-R20, the difference between R5 and R20; X5, respiratory reactance at 5 Hz; Xr, respiratory reactance.

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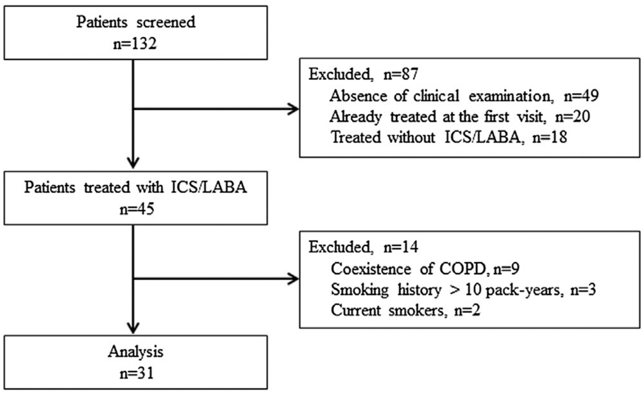

Fig. 1. The flow of the subjects. Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β2-agonists.

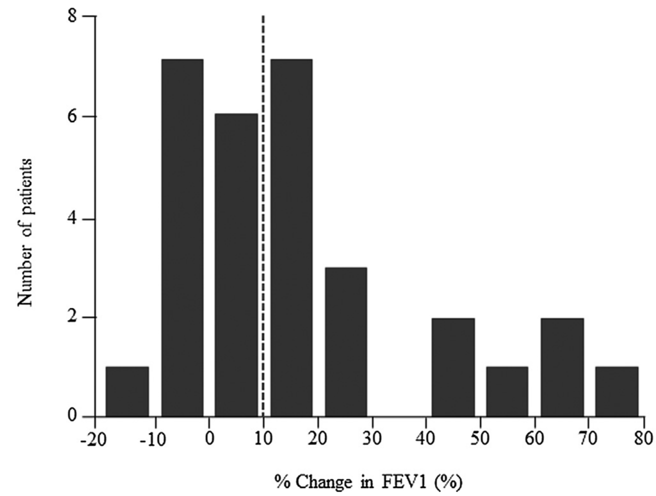

Fig. 2. Frequency distribution of the percent change in FEV1 following ICS/LABA combination treatment. Abbreviations: FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists.

spective study was to investigate whether FOT could predict FEV1 improvement in untreated asthmatic patients following a course of treatment with ICS/LABA combination therapy. We also compared the prediction capability of an improvement in FEV1 with that of fractional exhaled nitric oxide (FeNO).

2. Methods

2.1. Subjects

We retrospectively collected the clinical data of outpatients who had performed FOT, pulmonary function tests, and FeNO measurements before and after a minimum of two months of ICS/LABA therapy at the Shizuoka General Hospital between July 2010 and June 2014. All patients satisfied the definition of asthma as outlined by the Global Initiative for Asthma, including: a heterogeneous disease, typically characterized by chronic airway inflammation with a history of respiratory symptoms (e.g., wheeze, shortness of breath, chest tightness, and cough) that vary over time and in intensity, together with a variable expiratory airflow limitation (Global, 2015, 2016). The inhaler technique and adherence of each patient were checked by the doctors, nurses, or pharmacists involved during the treatment period. Short-acting β2 agonists were not used for more than 12 h before these tests in every case. The patients were excluded from the study if they were current smokers, had a smoking history of >10 pack-years, or had quit smoking within one year before the study and had COPD. The diagnosis of COPD was based on the presence of a post-bronchodilator FEV1/FVC < 0.7 (GOLD 2016) and the exclusion of other diseases with a persistent airflow limitation. The study was approved by the Institutional Review Board of Shizuoka General Hospital (SGHIRB #2015063).

2.2. Asthma control test

The Asthma Control Test (Japanese version, supplied by GlaxoSmithKline Japan) questionnaire consists of five items used to assess the impact of asthma on everyday functioning at school or work, shortness of breath, nocturnal asthma symptoms, the use of rescue medication, and the patient's self-rating of asthma control during the previous four weeks (Nathan et al., 2004).

2.3. Measurement of respiratory impedance and spirometry

On the same day, the measurement of respiratory impedance and spirometry were performed in that order. To avoid any influence of forced breathing, spirometry was performed after the FOT. Respiratory impedance was measured via broadband frequency FOT using a commercially available device (MostGraph-01; Chest M.I. Co. Ltd., Tokyo, Japan) and met the standard recommendations (Oostveen et al., 2003). Impulse oscillatory signals generated by a loudspeaker at intervals of 0.25 s were applied to the respiratory system through the mouthpiece during tidal breathing at rest. The mouth pressure and flow signals were measured and calculated to obtain the Rr and Xr properties against the oscillatory frequencies ranging from 4 to 36 (4, 8, 12, 16, 20, 24, 28, 32, and 36) Hz. While taking the measurements, the subjects firmly supported their cheeks to reduce upper airway shunting while sitting with their neck in a comfortable neutral posture. The measurements began automatically after two consecutive stable respirations; for this instrument, two consecutive and consistent respiratory signals that measure a coherence of 0.7 or higher were required for the initiation of the measurements. In addition, the operator evaluated the 3D graphical measurement of Rr in real time during the examination. If the operator observed an apparent irregularity in the signal images, the subject was re-examined until a successful examination was achieved (Abe et al., 2016). In this study, we used Rr at 5 Hz (R5) and 20 Hz (R20), and the difference between R5 and R20 (R5-R20) was used as an indicator of the frequency dependence of Rr. We also used: 1) Xr at 5 Hz (X5), which reflects the elastic and inertial properties of the lung; 2) resonant frequency (Fres) where Xr crosses zero; 3) the elastic and inertial forces are equal in magnitude and opposite; and 4) a low-frequency reactance area (ALX), which is the integral of Xr at 5 Hz to the Fres. The R5 and X5 values were calculated via spline interpolation, a numerical analysis in the mathematical field. Based on the Rr and Xr values at nine oscillation frequency points (from 4 to 36 Hz); the spline curve was obtained automatically by the device's built-in computer (MostGraph-01). Oscillatory indices were expressed as the mean values during a respiratory cycle (whole-breath), inspiratory and expiratory phases, as well as the differences between the inspiratory and expiratory phases (Δ). The changes in airflow determined the inspiratory and expiratory phases.

Spirometry was performed using computerized equipment (model CHESTAC-8800; Chest M.I. Co., Ltd., Tokyo, Japan) according to the recommendations (Miller et al., 2005). Briefly, after checking the spirometer calibration, well-trained examiners performed the technique on the subject while instructing the correct posture, position of the mouthpiece, rapid inhalation, and exhalation with maximal force. Individual spirograms were acceptable if they were free from artifacts, had good starts, and exhibited satisfactory exhalation. The technique was repeated until three