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The application of impulse oscillation system for the evaluation of treatment effects in patients with COPD

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ABSTRACT

There are only a few reports of the use of impulse oscillation system (IOS) for the evaluation of COPD treatment. In this study, we applied IOS and spirometry to evaluate the effectiveness of fluticasone propionate and salmeterol (SFC) combined with tiotropium (TIO) in COPD patients. Following a 4-week run-in period with TIO (18 μg once daily) treatment, COPD patients were randomized to SFC (250/50 μg twice daily; SFC + TIO group, $n = 25$), or TIO alone (TIO group, $n = 31$). Pulmonary functions were recorded by IOS and spirometry before and after the study period. The SFC + TIO group showed significant improvements in inspiratory resistance at 5 Hz and resonant frequency, as well as in FVC and FEV_1, after the 12-week treatment ($p < 0.05$). Since there were no significant correlations between improvements in IOS measurements and FVC or FEV_1, IOS may provide a physiological point of view that is different from spirometry and seemed to be applicable as an additional assessment tool targeting COPD patients.

1. Introduction

Spirometric measurements, especially forced expired volume in 1 s (FEV_1), are the gold standard in the diagnosis, assessment of severity, and monitoring treatment effects for chronic obstructive pulmonary disease (COPD). Although spirometry is non-invasive, easy to perform, and used worldwide, patient effort and cooperation are essential to record an appropriate measurement. For elderly COPD patients, cognitively impaired individuals, or patients with severe airway obstruction, difficulties with adequate validity and reproducibility have been reported during spirometry (Sherman et al., 1993; Janssens et al., 2001). Furthermore, repeated forced manoeuvers may induce bronchoconstriction (Burns and Gibson, 2002) in COPD patients with airway hypersensitivity. Therefore, the introduction of an effort-independent and reliable physiological assessment tool is required for COPD evaluation.

Dubois et al. (1956) described the measurements of impedance on the respiratory system using imposed forced oscillations at the mouth. This technique is a non-invasive method with which to measure respiratory mechanics (Oostveen et al., 2003). The impulse oscillometry system (IOS) (MasterScreen^{TM} IOS, CareFusion, San Diego, CA, USA) is a commercially available device for assessing pulmonary resistance and reactance by applying forced oscillations at various frequencies (Frantz et al., 2012). IOS is used during tidal breathing, requires no forced expiration maneuver, and is applied

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for the assessment of COPD, asthma, and obstructive sleep apnea syndrome (Borrill et al., 2008; Cao et al., 2009; Kubota et al., 2009; Abe et al., 2011; Matsumoto et al., 2011; Mineshita et al., 2014). However, there are only a few reports on the use of IOS for the evaluation of COPD treatment (Kubota et al., 2009; Abe et al. 2011; Crim et al., 2011; Mineshita et al., 2014).

Kubota et al. (2009) compared the inspiratory and expiratory IOS parameters in 15 COPD patients and 23 healthy subjects. Thereafter, the COPD patients were treated with TIO and their pulmonary function was re-evaluated. They concluded that the expiratory IOS parameters varied more than the inspiratory parameters, particularly in COPD patients—possibly because of flow-limitation during expiration. Thus, they concluded that the evaluation of IOS parameters may be more accurate during inspiration in COPD patients. However, comparison of IOS parameters during inspiration with those during expiration is reported to be important for the evaluation of flow-limitation in COPD patients at rest (Dellaca et al., 2007), and some symptoms of COPD patients, such as dyspnea due to a decrease in inspiratory capacity during exercise, is related to flow-limitation during expiration. The introduction of these IOS parameters to the physiological analysis in COPD patients may provide valuable insights.

Recently, Hanania et al. (2012) and Jung et al. (2012) demonstrated that triple combination therapy with tiotropium (TIO), 250 μg fluticasone propionate and 50 μg salmeterol (SFC 250, twice daily), SFC + TIO, showed greater improvements in lung function when compared to TIO alone, without increasing the risk of adverse events. We hypothesized that the assessment using IOS parameters would be useful in detecting the physiological effects of SFC addition on TIO treatment in COPD patients.

The primary endpoint of this study was to investigate the applicability of IOS parameters in the evaluation of treatment in COPD patients by assessing the change in the inspiratory and expiratory IOS parameters after the treatment of SFC addition on TIO (SFC + TIO), compared to spirometry parameters. The secondary endpoint was to confirm the effectiveness of SFC + TIO compared with TIO alone in Japanese patients with moderate to severe COPD.

2. Methods

2.1. Study design

This was a randomized, open-label, two-arm parallel study, conducted at 6 medical centers installed with MasterScreen™. One-arm was SFC + TIO (SFC inhalation therapy added to TIO inhalation), and the other arm was TIO alone to confirm the stability of the measurements and to exclude seasonal effects. The institutional review boards at the participating institutes have approved this study design, and all participants provided written informed consent. This study is registered with the University Hospital Medical Information Network (UMIN-CTR, number UMIN000004196).

After a 4-week run-in period in which TIO was administered, the 12-week study period began. The patients were randomized into two treatment groups: the TIO group (Spiriva® once daily delivered either by HandiHaler® or Respimat® [Boehringer Ingelheim Pharma, Ingelheim, Germany]) and the SFC + TIO group (Adoair® Diskus® in Japan, which is equivalent to Advair® in USA and Canada and to Seretide® in EU [GlaxoSmithKline, Brentford, UK], 250/50 μg/puff, 1 puff twice daily with TIO with the same inhalation device). The randomization was performed in a 1:1 ratio at a single randomization center. Treatment groups were stratified by the use of HandiHaler® or Respimat® to ensure the TIO effect was similar across groups. Neither the researchers nor the patients were aware of the treatment arms until after randomization.

2.2. Patients

The inclusion criteria were as follows: the ability to give informed consent; over 20 years old; a diagnosis of COPD according to ATS-ERS guidelines; a smoking history of more than 10 pack-years; a post-bronchodilator FEV_1 < 80% of predicted and a post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%; treatment with TIO; and respiratory symptoms such as cough, phlegm or dyspnea on exertion. The exclusion criteria were previous treatments with ICS and LABA and a history of asthma.

2.3. Outcome assessment and statistical analysis

Patients underwent post-dose spirometry at the start of the study and again at 12 weeks using the predicted values of FVC (predFVC) and FEV_1 (predFEV_1), derived from the Japanese Respiratory Society (JRS) guidelines (The Committee of Pulmonary Physiology, the Japanese Respiratory Society, 2004). The predicted value for the single-breath carbon monoxide diffusing capacity (DLco) was derived from Roca et al. (1990). The residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC) were measured using inert gas dilution method. For IOS, a nose clip was used and the patients were advised to cradle their cheeks with their hands in a seated position while the impulses were applied during tidal breathing. The average inspiratory and expiratory respiratory resistance (R) and reactance (X) were calculated at 5 Hz (R5, R5ins, R5exp, X5, X5ins and X5exp). The respiratory resistance at 20 Hz (R20) and resonant frequency (Fres) were also recorded. IOS was performed before spirometry during every visit. The IOS measurements were performed three times and the mean IOS measurement was used for analysis. Health-related QOL was assessed using the Japanese version of the St. George's Respiratory Questionnaire (SGRQ) version 2 (Jones et al., 1992) at the beginning and end of the study period.

The data are reported as mean ± standard error (SE). All analyses were performed using SPSS software (ver19; IBM, Armonk, NY, USA). All statistical tests of significance were two-sided, and p values of less than 0.05 were defined as significant. The data points of differences between baseline and at 12 weeks in pulmonary function tests (PFTs) as well as IOS who yielded a z-score, −3.0 or >3.0 were identified as outliers and were excluded from further analysis. The differences in PFTs were evaluated using Wilcoxon matched-pairs signed-ranks test, and the correlations between improvements in spirometry and the IOS data were evaluated with Spearman's rank correlation coefficient.

3. Results

The study participants were enrolled from June 2010 to March 2012. Of the 73 patients who were recruited, 67 satisfied the inclusion criteria. During the run-in and study period, 7 patients suffered from acute exacerbations (5 patients in SFC + TIO and 2 patients in TIO), 1 patient withdrew consent, and 2 patients were lost at follow-up. One patient was excluded from the analysis due to inadequate IOS data. Finally, 25 patients allocated to the SFC + TIO group and 31 patients of the TIO group completed the study (Fig. 1). From each group, HandiHaler® was prescribed to 11 patients, while the rest were prescribed Respimat®. With exception of mean age in the TIO group being slightly higher than that of the SFC + TIO group, all other characteristics between the two groups were similar (Table 1).

For spirometric assessments, both FVC and FEV_1 increased significantly at 12 weeks after SFC + TIO treatment when compared with the beginning of the study (Table 2). For IOS measurements, after 12 weeks compared with baseline of the SFC + TIO group, two measurements of R5 and R5exp were excluded as outliers, but