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# Responsiveness to bronchodilator procaterol in COPD as assessed by forced oscillation technique

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ABSTRACT

The aim of this retrospective study was to assess responses to a bronchodilator by forced oscillation technique (FOT) and to relate the results of respiratory impedance (Zrs) to spirometric parameters in patients with chronic obstructive pulmonary disease (COPD). Zrs was measured as a function of frequency from 4 to 36 Hz before and after inhalation of procaterol, a short-acting $\beta_2$-agonist (n = 60). Respiratory resistance (Rrs) and reactance (Xrs) were significantly frequency-dependent, and inspiratory and expiratory phases were different both before and after procaterol inhalation. The Rrs at 4 Hz and Xrs at 4–20 Hz during a whole breath were significantly improved after procaterol inhalation. The response to procaterol inhalation varied among patients, and changes in Xrs at 4 Hz significantly correlated with% change in forced expiratory volume in one second and changes in forced vital capacity. Taken together, Zrs, and specifically Xrs parameters, are sensitive to acute physiological responses to a bronchodilator in COPD.


## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully normalized after inhalation of a bronchodilator (GOLD-2016, 2016). Short-acting $\beta_2$-agonists (SABAs) are the drug of choice for rescue from acute bronchoconstriction in patients with both asthma and chronic obstructive pulmonary disease (COPD) (Billington et al., 2013). Procaterol is one of the SABAs and has high efficacy for $\beta_2$-adrenergic receptors (Kume et al., 2015). In Japan, procaterol is widely used not only as a rescue medication for the treatment of asthma and COPD but also to examine bronchoreversibility by spirometry (Asano et al., 2010). The degree of acute improvement of pulmonary functions after bronchodilator inhalation varies among COPD patients (Tashkin et al., 2008; Han et al., 2010). Thus, bronchodilator responsiveness is a potential phenotypic characteristic of COPD (Dellaca et al., 2009; Albert et al., 2012).

Forced oscillation technique (FOT) is a method to assess respiratory mechanics from input impedance measurements (Dubois et al., 1956; Grimby et al., 1968; Michaelson et al., 1975). Measurement of respiratory system impedance (Zrs), respiratory resistance (Rrs), and reactance (Xrs), has been used to assess respiratory functions of pulmonary diseases, specifically COPD (Dellaca et al., 2004; Ito et al., 2005; Mishima, 2009; Kanda et al., 2010; Paredi et al., 2010; Ohishi et al., 2011; Hasegawa et al., 2015; Akita et al., 2016; Shirai and Kurosawa, 2016). FOT enables measurement of both inspiratory and expiratory parameters during tidal breathing (Cauberghs and Van De Woestijne, 1992; Peslin et al., 1992; Dellaca et al., 2004; Kanda et al., 2010; Paredi et al., 2010; Fujii et al., 2015; Sokai et al., 2016). Spirometry is a standard method to diagnose COPD and evaluate severity and response to medications of this disease (GOLD-2016, 2016). It is expected that FOT will be able to identify respiratory abnormalities and bronchodilator responses in patients with COPD that are not detectable by spirometric examinations (Borrill et al., 2005; Da Costa et al., 2014). However, the effects of a bronchodilator have not yet been fully evaluated by this technique in patients with COPD. Moreover, it is not known how procaterol acutely affects respiratory mechanics in patients with COPD.

The purpose of this retrospective study was to investigate short-term responses to the bronchodilator procaterol as assessed by FOT and spirometry in patients with COPD. In addition, frequency-dependent and within-breath behaviors of Zrs before and after procaterol administration were evaluated.

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## 2. Methods

### 2.1. Subjects

The records of patients who met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for COPD (GOLD-2016, 2016) and attended the outpatient clinic of the Department of Respiratory Medicine, Nagoya University Hospital, between April 2011 and March 2016 were retrospectively reviewed. Cases complicated by lung or mediastinal tumors were excluded from the analysis. Sixty patients who underwent the bronchodilator reversibility test with Zrs measurements and pulmonary function tests for clinical evaluation were enrolled in this study. This retrospective study was approved by the local ethics committee of Nagoya University Hospital (approval No. 44). No patient identifiers were included. The informed consent requirement to participate and publish was waived for this retrospective analysis.

### 2.2. Respiratory impedance measurements

Impedance data was collected by FOT using a commercially available machine (MostGraph-01; Chest M.I., Tokyo, Japan) that generates a broad-band waveform at frequencies from 4 to 36 Hz in 4-Hz steps as described previously (Uchida et al., 2013; Sokai et al., 2016). Briefly, impulse oscillatory signals generated by a loudspeaker at intervals of 0.25 s were applied to the respiratory system during tidal breathing at rest. The Zrs was calculated using the system computer algorithms. The Zrs was recorded for approximately 20 s (5–6 respiratory cycles) while the patients firmly supported their cheeks with their palms and with their nose clipped in the sitting position with the neck in a comfortable neutral posture. Upper airway artifacts resulting from glottal changes, air leaks, and cheek support techniques during measurements significantly affect the impedance results (Peslin et al., 1985; Uchida et al., 2013; Bikov et al., 2015). Therefore, such upper airway artifacts were carefully eliminated. Three to five technically acceptable measurements were performed as recommended in the guidelines (Oostveen et al., 2003). At our institution, FOT has been clinically applied to patients with respiratory diseases such as asthma and COPD since April 2010.

### 2.3. Analysis of impedance results

The actual values of Rrs and Xrs at given frequencies between 4 and 36 Hz were analyzed (Sokai et al., 2016). Each impedance parameter was expressed as a mean value during a respiratory cycle, whole-breath, inspiration, and expiration. The difference between inspiratory and expiratory phases of Rrs ($Rrs_{Insp-Exp}$) and Xrs ($Xrs_{Insp-Exp}$) were calculated as mean inspiratory values minus mean expiratory values as described previously (Sokai et al., 2016). Rrs reflects the extent of airflow obstruction (Di Mango et al., 2006; Hasegawa et al., 2015). Under normal conditions, Xrs is determined by the elasticity of the respiratory system at the lowest frequency and the inertial properties at higher frequencies (Oostveen et al., 2003; Goldman et al., 2005). In patients with asthma and COPD, airflow limitation decreases Xrs levels (Dellaca et al., 2004; Da Costa et al., 2014; Mikamo et al., 2014). Other parameters such as Rrs at 5 Hz (R5), Xrs at 5 Hz (X5), resonant frequency, and the low-frequency reactance area (Goldman et al., 2005; Shirai et al., 2013), which are calculated from Rrs and Xrs curves, were not assessed.

### 2.4. Pulmonary function tests

After impedance measurements, spirometry was performed and lung volumes were determined using computerized equipment (Fudak77, Fukuda Sangyo, Tokyo, Japan). The following spirometric parameters, vital capacity (VC), inspiratory capacity (IC), forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$), peak expiratory flow (PEF), and the mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25-75}$), were measured. Data are also calculated as the % of predicted values (%VC, %FVC, %$FEV_1$, %PEF, and %$FEF_{25-75}$) according to the method of the Japanese Respiratory Society (Japanese Respiratory Society, 2004).

**Table 1**
Clinical characteristics of subjects.

| Subjects | |
|---|---|
| Age, years (range) | 69.1 ± 8.3 (37–86) |
| Sex, male/female | 55/5 |
| Height, cm | 162.5 ± 7.5 |
| Weight, kg | 60.5 ± 10.8 |
| Body mass index | 22.9 ± 3.3 |
| Current/ex-/never smoker | 26/33/1 |
| Supplemental oxygen | None |

Total number of subjects was 60. Values are mean ± SD otherwise indicated.

### 2.5. Assessment of reversibility in response to bronchodilator

After the baseline values of the Zrs and spirometry were obtained, 20 μg (two puffs) of procaterol hydrochloride (Otsuka Pharma. Co., Tokyo, Japan) was administered by a metered-dose inhaler (MDI) through a spacer (AeroChamber Plus; Trudell Medical International, London, Canada). Then, measurements of Zrs were repeated for 15–30 min thereafter, and spirometry was performed. At our institution, 20 μg of procaterol has been used for the bronchoreversibility test because this dose is recommended for clinical use in Japan. Patients were asked not to use inhaled bronchodilators, long-acting muscarinic antagonists, long-acting $\beta_2$ agonists, and short-acting $\beta_2$ agonists for more than 12 h.

### 2.6. Statistical analysis

Repeated-measure analysis of variance (ANOVA) followed by Tukey's *post hoc* test or a *t*-test was used to evaluate the statistical significance (SigmaPlot11.0; Systat Software Inc., San Jose, CA, USA). When data failed a normality test, ANOVA on ranks followed by Tukey's test or the Mann-Whitney test was used. $P < 0.05$ was considered statistically significant. Correlations between valuables were analyzed using the Spearman's rank or Pearson's correlation coefficient. Fisher's exact test was used to evaluate significance in group differences in various categories. Data are given as mean ± SD.

## 3. Results

### 3.1. Clinical characteristics and pulmonary function test results

The baseline characteristics of 60 COPD patients are shown in Table 1. Pulmonary function test results before and after administration of procaterol are compared in Table 2. Lung volume parameters, VC, %VC, IC, FVC, and %FVC, were significantly higher after procaterol inhalation than before procaterol treatment (baseline) (Table 2). In contrast, there was no significant improvement in parameters of airway obstruction, such as $FEV_1$, %$FEV_1$, $FEV_1$/FVC, PEF, and $FEF_{25-75}$ (Table 2). Fig. 1 shows the distributions of the absolute improvement and % change in $FEV_1$ and absolute improvement in IC after procaterol inhalation. Eight patients (13.3%) showed an increase in $FEV_1$ of >100 mL (Fig. 1A). Only one patient (1.7%) met the criteria of significant bronchoreversibility, an increase in $FEV_1$ of both ≥12% and ≥200 mL.