RESPNB-2017-1.R1

Respiratory Physiology & Neurobiology

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

Satoru Ito[1,*], Akemi Uchida[2], Yoshitaka Isobe[1], and Yoshinori Hasegawa[1]

[1]Department of Respiratory Medicine, [2]Clinical Laboratory, Nagoya University School of Medicine, Nagoya 466-8550, Japan

***Correspondence and proofs:** Satoru Ito, MD, PhD

Department of Respiratory Medicine, Nagoya University School of Medicine

65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

itori@med.nagoya-u.ac.jp

Tel: +81-52-744-2167 Fax: +81-52-744-2176

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 β_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.

Keywords (within 6): airway, airway smooth muscle, forced oscillation technique, impedance, bronchodilator, procaterol

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 β_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 β_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.

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 to 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 5Hz (R5), Xrs at 5Hz (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).

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 to 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 β_2 agonists, and short-acting β_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). Figure 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 (Figure 1A). Only one patient (1.7%) met the criteria of significant bronchoreversibility, an increase in FEV_1 of both ≥ 12% and ≥ 200 mL.

3.2. Frequency-dependence and within-breath analysis of respiratory impedance

The Rrs and Xrs results during a whole breath, inspiratory phase, and expiratory phase, at a given frequency before procaterol treatment of 60 patients are shown in Figure 2. The Rrs values during a whole breath, inspiratory phase, and expiratory phase, were significantly frequency-dependent ($p < 0.001$) and gradually decreased as a function of frequency (Figure 2A). Rrs values were significantly higher during the expiratory phase than during the inspiratory phase ($p < 0.001$) at all frequencies (Figure 2A). The Xrs values during a whole breath, inspiration, and expiration were significantly increased as a function of frequency ($p < 0.001$) (Figure 2B). Expiratory Xrs values were significantly lower (more negative) than inspiratory Xrs ($p < 0.001$) except at 32 and 36 Hz (Figure 2B).

3.3. Respiratory impedance after procaterol inhalation

The Rrs and Xrs results during a whole breath, inspiratory phase, and expiratory phase, at a given frequency after procaterol treatment of 60 patients are shown in Figure 3. Similar to the findings before procaterol inhalation, the Rrs values during a whole breath, inspiratory phase, and expiratory phase were significantly frequency-dependent ($p < 0.001$) and gradually decreased as a function of frequency (Figure 3A). Rrs values were significantly higher during the expiratory phase than during the inspiratory phase

($p < 0.001$) (Figure 3A). The Xrs values during a whole breath, inspiration, and expiration were significantly increased as a function of frequency (Figure 3B). Expiratory Xrs values were significantly lower (more negative) than inspiratory Xrs ($p < 0.001$) except at 36 Hz (Figure 3B).

3.4. Comparison of impedance before and after procaterol inhalation

Next, we compared the Zrs results during a whole breath at a given frequency before and after procaterol inhalation (Figure 4). There was a small but significant difference in R4 between the groups ($p < 0.05$) (Figure 4A). There was a significant interaction in the Rrs curves between group (either before or after procaterol) and frequency by two-way repeated-measure ANOVA ($p = 0.003$). Xrs became significantly higher (less negative) after procaterol treatment ($p = 0.004$) (Figure 4B). There was a significant interaction in the Xrs curves between group and frequency by two-way repeated-measure ANOVA ($p = 0.004$). There was no significant difference between inspiratory and expiratory phases in Zrs ($Rrs_{Insp-Exp}$ and $Xrs_{Insp-Exp}$) before and after procaterol administration (Figure 4C and D). Dellaca et al. reported that differences between inspiratory and expiratory phases of Xrs at low frequencies are increased by the expiratory flow limitation in COPD (Dellaca et al., 2004). Thus, the distributions of $Xrs_{Insp-Exp}$ at the lowest frequency (4 Hz; $X4_{Insp-Exp}$) before and after procaterol inhalation are shown in Figure 5.

3.5. Correlations between impedance and pulmonary function test results

Next, correlations between parameters of the Zrs and pulmonary function test were examined. Because the largest improvement in Rrs and Xrs values after procaterol inhalation was obtained at the lowest frequency (4 Hz) (Figure 4), R4 and X4 were

selected for analysis. The baseline R4 and X4 values during a whole breath significantly correlated with spirometric parameters (Table 3). Similar results were found in post-bronchodilator values (Table S1). Correlations between changes in R4 and X4 and pulmonary function test parameters before and after procaterol administration were examined (Table 4). Relationships between changes in R4 during a whole breath and % change in FEV_1 (Figure 6A) and those between changes in X4 during a whole breath and % change in FEV_1 (Figure 6B), changes in FEV_1 (Figure 6C) and changes in IC (Figure 6D) are also shown.

Discussion

The main findings of the present study were that in patients with COPD: 1) mean values of spirometric parameters, VC,%VC, FVC, %FVC, and IC, were significantly improved after procaterol inhalation, but those of FEV_1, $\%FEV_1$, FEV_1/FVC, and FEF_{25-75} were not, 2) Xrs values were significantly improved after procaterol administration, 3) Rrs and Xrs values were significantly dependent on frequency and differed between expiratory and inspiratory phases both before and after procaterol inhalation, and 4) changes in X4 significantly correlated with changes in FVC and % change in FEV_1. To our knowledge, this is the first study to characterize the Zrs measured by FOT and relate it to pulmonary functions before and after procaterol administration in patients with COPD.

We examined the Zrs data at a given frequency, between 4 and 36 Hz, and found that both the Rrs and Xrs were significantly frequency-dependent before and after procaterol inhalation (Figures 2-4). The frequency dependence of Rrs reflects the inhomogeneity in gas flow in the respiratory system, specifically during

bronchoconstriction as well as in patients with COPD (van Noord et al., 1989; Pride, 1992; Lutchen et al., 1996). Procaterol treatment slightly but significantly lowered R4 values, and as a result, frequency-dependent curves in Rrs became gentler (less steep) (Figure 4A). Similar to our results, it was demonstrated that Rrs at low frequencies decreased but frequency dependence remained after salbutamol inhalation in COPD patients (da Costa et al., 2014). We previously demonstrated that Rrs did not depend on frequency between 4 and 36 Hz in healthy subjects (Sokai et al., 2016), consistent with previous findings in healthy subjects (Cauberghs and Van de Woestijne, 1992; Di Mango et al., 2006; Oostveen et al., 2013; da Costa et al., 2014). Thus, these results suggest that the airflow inhomogeneity is partially improved but still exists after bronchodilation in COPD.

Being more sensitive than FEV_1 for detection of a change in bronchial tone in the clinical setting, measurement of Zrs, specifically Rrs, has been applied to assess airway hyperresponsiveness as well as bronchodilator responses in asthma and COPD (Takishima et al., 1981; Oostveen et al., 2003; Borrill et al., 2005; Borrill et al., 2008; Oostveen et al., 2013; da Costa et al., 2014). Indeed, the average values of the Zrs parameters R4 and Xrs were significantly improved after procaterol inhalation without improvement in spirometric parameters for airway obstruction, such as FEV_1, $\%FEV_1$, FEV_1/FVC, PEF, and FEF_{25-75} (Table 2, Figure 4). Thus, our results support the idea that measurement of Zrs is a sensitive tool to assess bronchodilation in COPD. Another possible reason for the improvement of the Zrs in COPD is changes in lung volume (da Costa et al., 2014). It was demonstrated that COPD patients with hyperinflation show significant reductions in residual volume and total lung capacity after administration of a SABA despite little change in FEV_1 (Newton et al., 2002). In the present study,

procaterol administration slightly but significantly increased lung volume parameters, IC and VC (Table 2), demonstrating that the lung volume at functional residual capacity was reduced by procaterol. Moreover, changes in the lung volume (FVC) significantly correlated with those in X4 during a whole breath (Table 4, Figure 6C). It is generally known that Zrs values are affected by lung volume (van den Elshout et al., 1990; Hirai et al., 1999; Ito et al., 2007). Thus, it is considered that reduced lung volume together with bronchodilation affected the Zrs values after procaterol administration in our COPD patients.

The within-breath behavior of the Zrs results showed that Rrs and Xrs during the expiratory phase were significantly different from those during the inspiratory phase both before and after procaterol inhalation (Figures 1 and 2). It has been reported that Rrs is higher during the expiratory phase, but there was no significant difference in Xrs between the expiratory and inspiratory phases in healthy subjects (Kanda et al., 2010; Sokai et al., 2016). Dellaca et al. analyzed individual respiratory cycles and reported that a difference in Xrs between inspiratory and expiratory phases at low frequencies is useful for detecting expiratory flow limitation in patients with COPD (Dellaca et al., 2004). They proposed a difference of 2.8 $cmH_2O/L/s$ Xrs at 5 Hz as an optimal threshold value of for expiratory flow limitation (Dellaca et al., 2004). In contrast to their analysis, we calculated the average of 5 to 6 respiratory cycles during the Zrs measurements for $Xrs_{Insp-Exp}$ analysis as reported by our and other groups (Kanda et al., 2010; Paredi et al., 2010; Mori et al., 2013; Mikamo et al., 2014; Sokai et al., 2016). There was no significant difference in $Xrs_{Insp-Exp}$ before and after procaterol treatment (Figure 4D). The distributions of $X4_{Insp-Exp}$ values at baseline were similar to those after procaterol inhalation (Figure 5). Values of $Xrs_{Insp-Exp}$ were above 2.8 $cmH_2O/L/s$ in four

(6.7%) cases at baseline and five (8.3%) cases after procaterol inhalation (Figure 5), indicating that several COPD patients had a severe expiratory flow limitation that was not improved by procaterol. However, the Zrs data vary between different FOT devices used for the measurements and normative reference values have not been established (Oostveen et al., 2013; Shirai and Kurosawa, 2016).

In our cohort, responses to procaterol varied among patients (Figure 1). Changes in X4 during a whole breath significantly correlated with those in spirometric parameters, but those in R4 did not (Table 4, Figure 6C). Kolsum et al. examined the relationship of the Zrs and spirometric results in a one-year follow-up study of COPD patients and found that changes in Xrs at 5 Hz correlated with % changes in FEV_1, but those in Rrs at 5 Hz did not (Kolsum et al., 2009). These results indicate that Xrs measurements are useful to evaluate time-to-time or year-to-year changes in the respiratory mechanics of the same individual with COPD.

This study has several limitations. The data were retrospectively collected from COPD patients without the data from healthy control subjects. Only one fixed dose (20 μg) of procaterol was applied. Bronchodilator responses in FEV_1 of the present study were much lower than those of a larger cohort of COPD (Tashkin et al., 2008). Unlike those of our cohort, the near-maximal post-bronchodilator responses were examined by inhalations of both the anti-cholinergic drug ipratropium (80 μg via a metered-dose inhaler) and salbutamol (400 μg via a metered-dose inhaler) in the study by Tashkin et al. (Tashkin et al., 2008). Borrills et al. reported that salbutamol (20–800 μg) improved Rrs and FEV_1 in a dose-dependent manner (Borrill et al., 2005). Prospective studies with a larger number of subjects including dose-dependent effects of procaterol are necessary to characterize the respiratory impedance of COPD in more detail. Moreover,

future studies are necessary to establish the methodology and reference values for Zrs measurements.

In summary, changes in the respiratory mechanics together with pulmonary functions after procaterol inhalation were characterized in patients with COPD. Significant frequency-dependence was found in the Rrs parameters, and the Zrs-specific Xrs parameters were sensitive to changes in bronchial tone and lung volume. Because Zrs measurements are little invasive, FOT combined with spirometry may be beneficial to evaluate alterations in respiratory functions after administration of bronchodilators and anti-inflammatory drugs in COPD patients.

Acknowledgements

The authors thank Ms. Katherine Ono for providing language help. We also thank Ms. Marika Endo (CHEST M.I.) for technical advice. This study was supported by a grant from the Aichi Health Promotion Foundation in 2016.

Figure Legends

Figure 1

The distributions of absolute improvement **(A)** and percent change **(B)** in forced expiratory volume in one second (FEV_1) and absolute improvement in inspiratory capacity (IC) **(C)** after inhalation of 20 μg procaterol.

Figure 2

Frequency dependences of respiratory resistance (Rrs) and reactance (Xrs) at 4–36 Hz, during a whole breath, inspiratory phase and expiratory phase, at baseline were examined. The Rrs **(A)** and Xrs **(B)** are shown (n=60). Values during inspiratory and expiratory phases are means ± SD ($cmH_2O/L/s$). Averages of Rrs and Xrs during a whole breath are also shown (dashed lines). *Significant difference ($p < 0.05$) between inspiratory and expiratory phases by two-way repeated measure ANOVA, followed by Tukey's test for post hoc analysis.

Figure 3

Frequency dependences of Rrs **(A)** and Xrs **(B)** after inhalation of procaterol are shown (n=60). Values during inspiratory and expiratory phases are means ± SD ($cmH_2O/L/s$). Averages of Rrs and Xrs during a whole breath are also shown (dashed lines). *Significant difference ($p < 0.05$) between inspiratory and expiratory phases by two-way repeated measure ANOVA, followed by Tukey's test for post hoc analysis.

Figure 4

Rrs **(A)** and Xrs **(B)** during a whole breath before (baseline) and after procaterol administration (post-procaterol) are compared (n=60). Differences between inspiratory and expiratory phases in Rrs ($Rrs_{Insp-Exp}$) **(C)** and Xrs ($Xrs_{Insp-Exp}$) **(D)** calculated as mean inspiratory values minus mean expiratory values are also compared. Values are means ± SD ($cmH_2O/L/s$). *Significant difference ($p < 0.05$) between baseline and post-procaterol values by two-way repeated measure ANOVA, followed by Tukey's test for post hoc analysis.

Figure 5

The distributions of differences between inspiratory and expiratory phases in Xrs at 4 Hz ($X4_{Insp-Exp}$) before **(A)** and after **(B)** procaterol inhalation are shown (n=60).

Figure 6

Correlations between changes in pulmonary function test results and respiratory impedance before and after procaterol inhalation. A correlation between % change in FEV_1 and change in Rrs at 4 Hz (R4) during a whole breath **(A)**, and correlations between % change in FEV_1 **(B)**, change in forced vital capacity (FVC) **(C)**, and change in IC **(D)** and those in Xrs at 4 Hz (X4) during a whole breath are shown.

References

Akita T, Shirai T, Mori K, Shimoda Y, Suzuki T, Hayashi I, Noguchi R, Mochizuki E, Sakurai S, Saigusa M, Akamatsu T, Yamamoto A, Shishido Y, Morita S, Asada K, Suda T (2016) Association of the forced oscillation technique with negative expiratory pressure in COPD. Respir Physiol Neurobiol 220:62-68.

Albert P, Agusti A, Edwards L, Tal-Singer R, Yates J, Bakke P, Celli BR, Coxson HO, Crim C, Lomas DA, Macnee W, Miller B, Rennard S, Silverman EK, Vestbo J, Wouters E, Calverley P (2012) Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. Thorax 67:701-708.

Asano K, Yamada-Yamasawa W, Kudoh H, Matsuzaki T, Nakajima T, Hakuno H, Hiraoka R, Fukunaga K, Oguma T, Sayama K, Yamaguchi K, Nagabukuro A, Harada Y, Ishizaka A (2010) Association between beta-adrenoceptor gene polymorphisms and relative response to beta 2-agonists and anticholinergic drugs in Japanese asthmatic patients. Respirology 15:849-854.

Bikov A, Pride NB, Goldman MD, Hull JH, Horvath I, Barnes PJ, Usmani OS, Paredi P (2015) Glottal aperture and buccal airflow leaks critically affect forced oscillometry measurements. Chest 148:731-738.

Billington CK, Ojo OO, Penn RB, Ito S (2013) cAMP regulation of airway smooth muscle function. Pulm Pharmacol Ther 26:112-120.

Borrill ZL, Houghton CM, Tal-Singer R, Vessey SR, Faiferman I, Langley SJ, Singh D (2008) The use of plethysmography and oscillometry to compare long-acting bronchodilators in patients with COPD. Br J Clin Pharmacol 65:244-252.

Borrill ZL, Houghton CM, Woodcock AA, Vestbo J, Singh D (2005) Measuring bronchodilation in COPD clinical trials. Br J Clin Pharmacol 59:379-384.

Cauberghs M, Van De Woestijne KP (1992) Changes of respiratory input impedance during breathing in humans. J Appl Physiol 73:2355-2362.

Da Costa GM, Faria AC, Di Mango AM, Lopes AJ, Lopes De Melo P (2014) Respiratory impedance and response to salbutamol in healthy individuals and patients with COPD. Respiration 88:101-111.

Dellaca RL, Pompilio PP, Walker PP, Duffy N, Pedotti A, Calverley PM (2009) Effect of bronchodilation on expiratory flow limitation and resting lung mechanics in COPD. Eur Respir J 33:1329-1337.

Dellaca RL, Santus P, Aliverti A, Stevenson N, Centanni S, Macklem PT, Pedotti A, Calverley PM (2004) Detection of expiratory flow limitation in COPD using the forced oscillation technique. Eur Respir J 23:232-240.

Di Mango AM, Lopes AJ, Jansen JM, Melo PL (2006) Changes in respiratory mechanics with increasing degrees of airway obstruction in COPD: detection by forced oscillation technique. Respir Med 100:399-410.

Dubois AB, Brody AW, Lewis DH, Burgess BF, Jr. (1956) Oscillation mechanics of lungs and chest in man. J Appl Physiol 8:587-594.

Fujii M, Shirai T, Mori K, Mikamo M, Shishido Y, Akita T, Morita S, Asada K, Suda T (2015) Inspiratory resonant frequency of forced oscillation technique as a predictor of the composite physiologic index in interstitial lung disease. Respir Physiol Neurobiol 207:22-27.

Gold-2016 (2016) Global Initiative for Chronic Obstructive Lung Disease 2016. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Workshop Report. Bethesda: National Heart,

Lung and Blood Institute; 2001 [Updated 2015]. Available from: http://www.goldcopd.com. [homepage on the Internet] Accessed January 31, 2016.

Goldman MD, Saadeh C, Ross D (2005) Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol 148:179-194.

Grimby G, Takishima T, Graham W, Macklem P, Mead J (1968) Frequency dependence of flow resistance in patients with obstructive lung disease. J Clin Invest 47:1455-1465.

Han MK, Wise R, Mumford J, Sciurba F, Criner GJ, Curtis JL, Murray S, Sternberg A, Weinman G, Kazerooni E, Fishman AP, Make B, Hoffman EA, Mosenifar Z, Martinez FJ (2010) Prevalence and clinical correlates of bronchoreversibility in severe emphysema. Eur Respir J 35:1048-1056.

Hasegawa K, Sato S, Tanimura K, Fuseya Y, Uemasu K, Sato A, Hirai T, Mishima M, Muro S (2015) Emphysema and airway disease affect within-breath changes in respiratory resistance in COPD patients. Respirology 20:775-781.

Hirai T, Mckeown KA, Gomes RF, Bates JH (1999) Effects of lung volume on lung and chest wall mechanics in rats. J Appl Physiol (1985) 86:16-21.

Ito S, Ingenito EP, Brewer KK, Black LD, Parameswaran H, Lutchen KR, Suki B (2005) Mechanics, nonlinearity, and failure strength of lung tissue in a mouse model of emphysema: possible role of collagen remodeling. J Appl Physiol (1985) 98:503-511.

Ito S, Lutchen KR, Suki B (2007) Effects of heterogeneities on the partitioning of airway and tissue properties in normal mice. J Appl Physiol 102:859-869.

Japanese-Respiratory-Society (2004) Guidelines of respiratory function tests-spirometry, flow-volume curve, diffusion capacity of the lung. Nihon Kokyuki Gakkai Zasshi 42:1-56.

Kanda S, Fujimoto K, Komatsu Y, Yasuo M, Hanaoka M, Kubo K (2010) Evaluation of respiratory impedance in asthma and COPD by an impulse oscillation system. Intern Med 49:23-30.

Kolsum U, Borrill Z, Roy K, Starkey C, Vestbo J, Houghton C, Singh D (2009) Impulse oscillometry in COPD: identification of measurements related to airway obstruction, airway conductance and lung volumes. Respir Med 103:136-143.

Kume H, Fukunaga K, Oguma T (2015) Research and development of bronchodilators for asthma and COPD with a focus on G protein/KCa channel linkage and beta2-adrenergic intrinsic efficacy. Pharmacol Ther 156:75-89.

Lutchen KR, Greenstein JL, Suki B (1996) How inhomogeneities and airway walls affect frequency dependence and separation of airway and tissue properties. J Appl Physiol 80:1696-1707.

Michaelson ED, Grassman ED, Peters WR (1975) Pulmonary mechanics by spectral analysis of forced random noise. J Clin Invest 56:1210-1230.

Mikamo M, Shirai T, Mori K, Shishido Y, Akita T, Morita S, Asada K, Fujii M, Suda T (2014) Predictors of expiratory flow limitation measured by forced oscillation technique in COPD. BMC Pulm Med 14:23.

Mishima M (2009) Physiological differences and similarities in asthma and COPD--based on respiratory function testing. Allergol Int 58:333-340.

Mori K, Shirai T, Mikamo M, Shishido Y, Akita T, Morita S, Asada K, Fujii M, Hozumi H, Suda T, Chida K (2013) Respiratory mechanics measured by forced oscillation technique in combined pulmonary fibrosis and emphysema. Respir

Physiol Neurobiol 185:235-240.
Newton MF, O'donnell DE, Forkert L (2002) Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 121:1042-1050.
Ohishi J, Kurosawa H, Ogawa H, Irokawa T, Hida W, Kohzuki M (2011) Application of impulse oscillometry for within-breath analysis in patients with chronic obstructive pulmonary disease: pilot study. BMJ Open 1:e000184.
Oostveen E, Boda K, Van Der Grinten CP, James AL, Young S, Nieland H, Hantos Z (2013) Respiratory impedance in healthy subjects: baseline values and bronchodilator response. Eur Respir J 42:1513-1523.
Oostveen E, Macleod D, Lorino H, Farre R, Hantos Z, Desager K, Marchal F (2003) The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 22:1026-1041.
Paredi P, Goldman M, Alamen A, Ausin P, Usmani OS, Pride NB, Barnes PJ (2010) Comparison of inspiratory and expiratory resistance and reactance in patients with asthma and chronic obstructive pulmonary disease. Thorax 65:263-267.
Peslin R, Duvivier C, Gallina C, Cervantes P (1985) Upper airway artifact in respiratory impedance measurements. Am Rev Respir Dis 132:712-714.
Peslin R, Ying Y, Gallina C, Duvivier C (1992) Within-breath variations of forced oscillation resistance in healthy subjects. Eur Respir J 5:86-92.
Pride NB (1992) Forced oscillation techniques for measuring mechanical properties of the respiratory system. Thorax 47:317-320.
Shirai T, Kurosawa H (2016) Clinical application of the forced oscillation technique. Intern Med 55:559-566.
Shirai T, Mori K, Mikamo M, Shishido Y, Akita T, Morita S, Asada K, Fujii M, Suda T, Chida K (2013) Respiratory mechanics and peripheral airway inflammation and dysfunction in asthma. Clin Exp Allergy 43:521-526.
Sokai R, Ito S, Iwano S, Uchida A, Aso H, Kondo M, Ishiguro N, Kojima T, Hasegawa Y (2016) Respiratory mechanics measured by forced oscillation technique in rheumatoid arthritis-related pulmonary abnormalities: frequency-dependence, heterogeneity and effects of smoking. Springerplus 5:335.
Takishima T, Hida W, Sasaki H, Suzuki S, Sasaki T (1981) Direct-writing recorder of the dose-response curves of the airway to methacholine. Clinical application. Chest 80:600-606.
Tashkin DP, Celli B, Decramer M, Liu D, Burkhart D, Cassino C, Kesten S (2008) Bronchodilator responsiveness in patients with COPD. Eur Respir J 31:742-750.
Uchida A, Ito S, Suki B, Matsubara H, Hasegawa Y (2013) Influence of cheek support on respiratory impedance measured by forced oscillation technique. Springerplus 2:342.
Van Den Elshout FJ, Van De Woestijne KP, Folgering HT (1990) Variations of respiratory impedance with lung volume in bronchial hyperreactivity. Chest 98:358-364.
Van Noord JA, Clement J, Cauberghs M, Mertens I, Van De Woestijne KP, Demedts M (1989) Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. Eur Respir J 2:846-852.

Figure 1

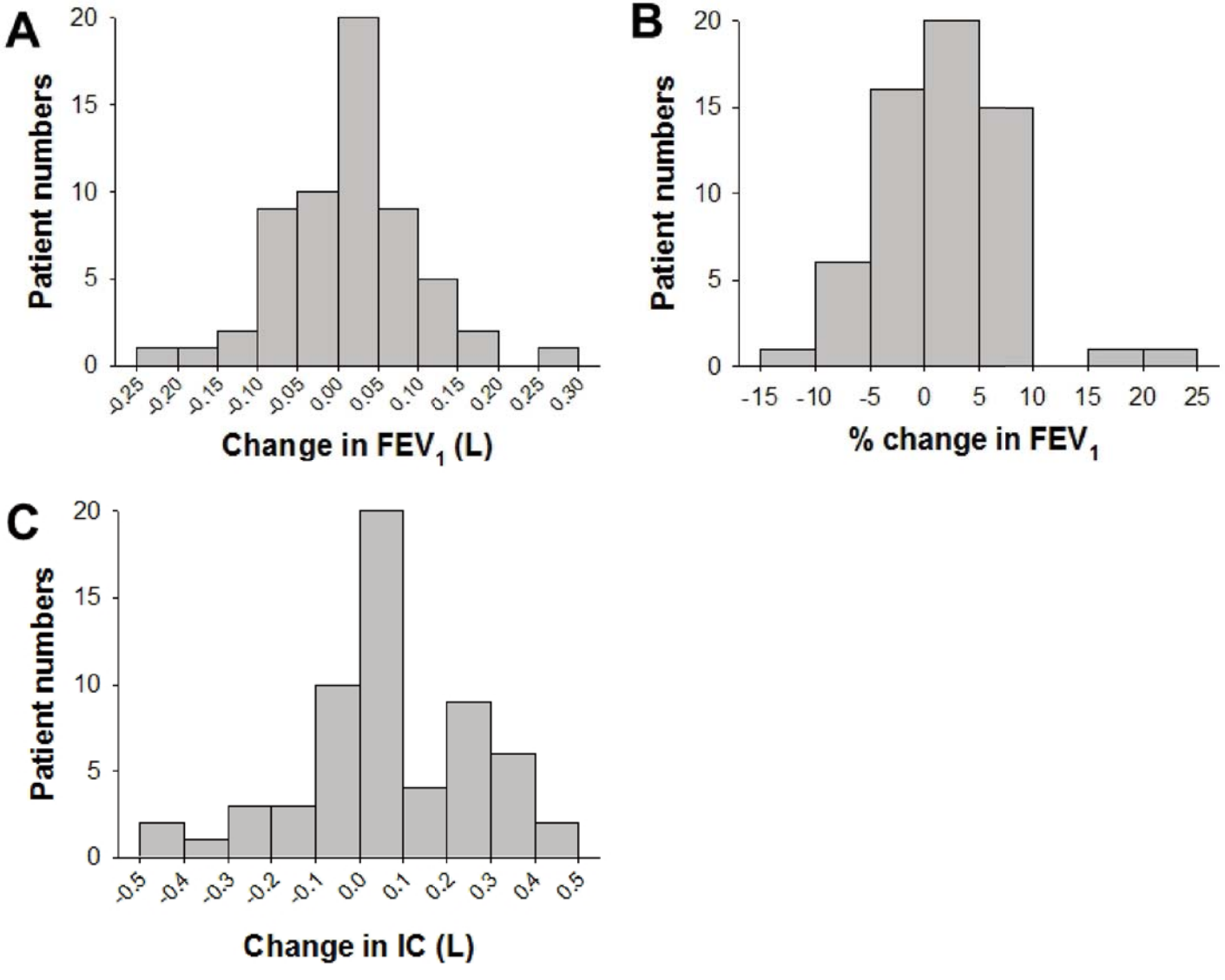
A
Patient numbers
20
15
10
5
0
-0.25
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
0.25
0.30
Change in FEV1 (L)
B
Patient numbers
20
15
10
5
0
-15
-10
-5
0
5
10
15
20
25
% change in FEV1
C
Patient numbers
20
15
10
5
0
-0.5
-0.4
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
Change in IC (L)

Figure 2

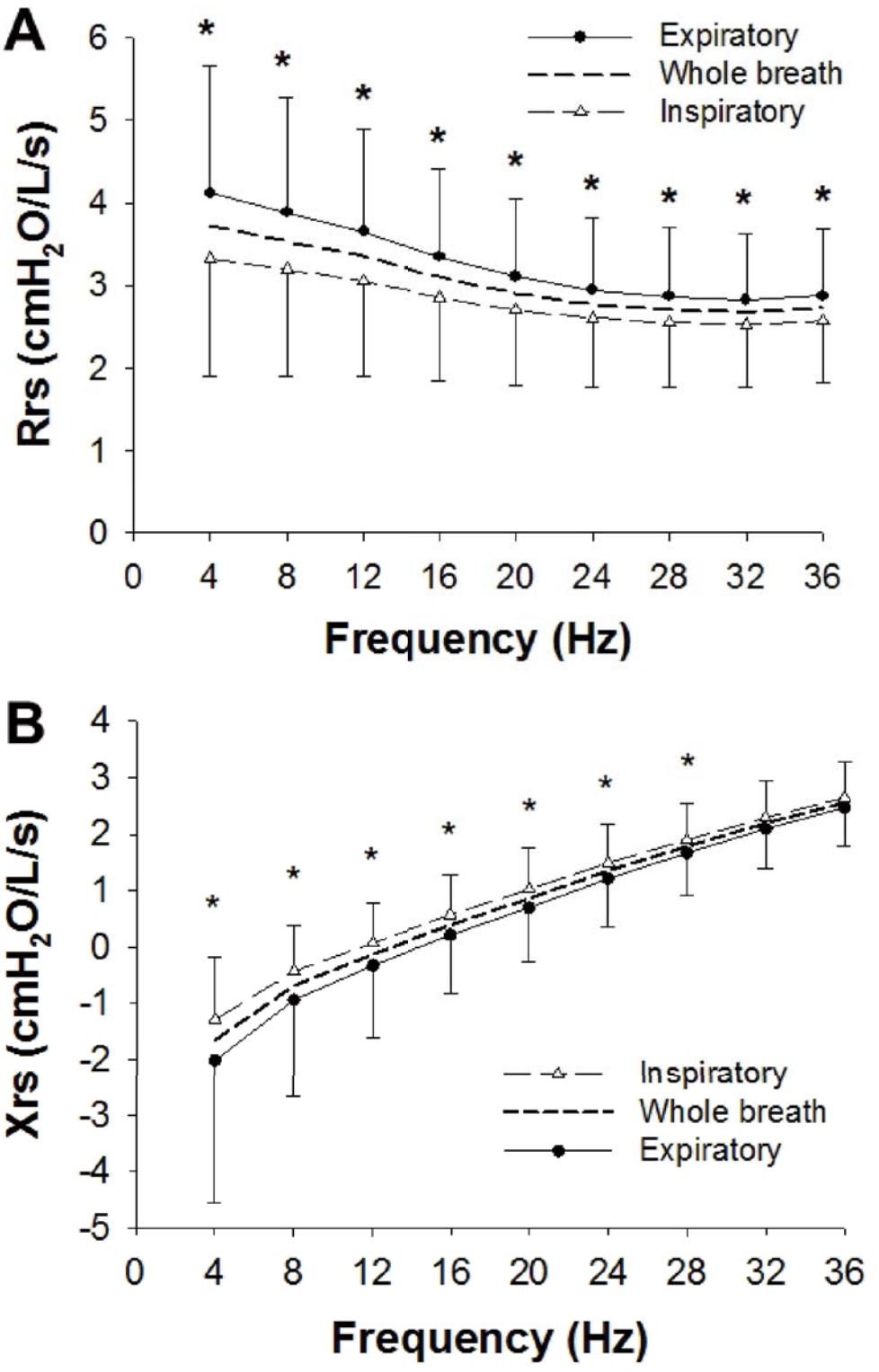
A
Rrs (cmH2O/L/s)
Expiratory
Whole breath
Inspiratory
Frequency (Hz)
B
Xrs (cmH2O/L/s)
Inspiratory
Whole breath
Expiratory
Frequency (Hz)

Figure 3

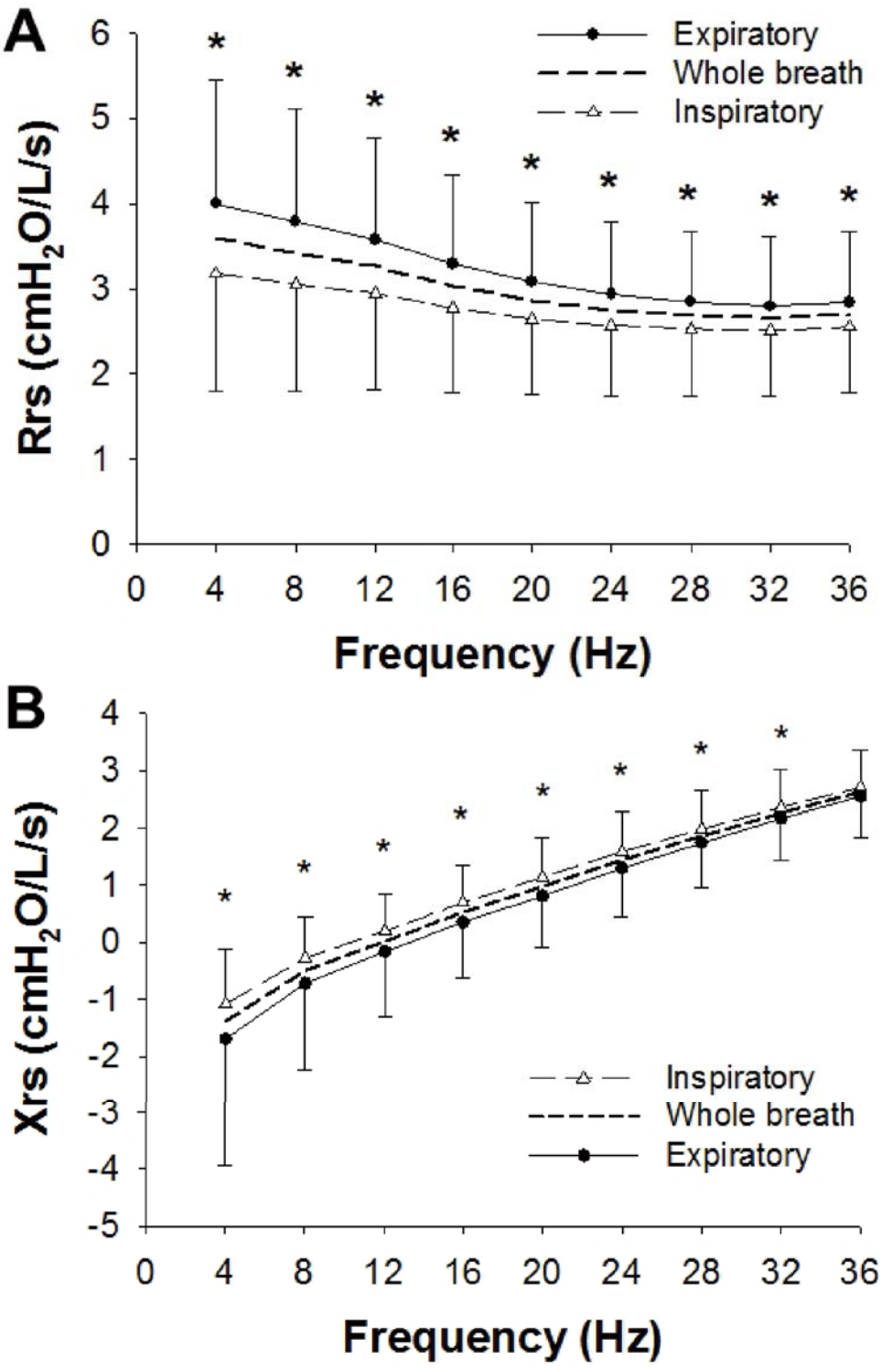
A
Rrs (cmH2O/L/s)
Expiratory
Whole breath
Inspiratory
Frequency (Hz)
B
Xrs (cmH2O/L/s)
Inspiratory
Whole breath
Expiratory
Frequency (Hz)

Figure 4

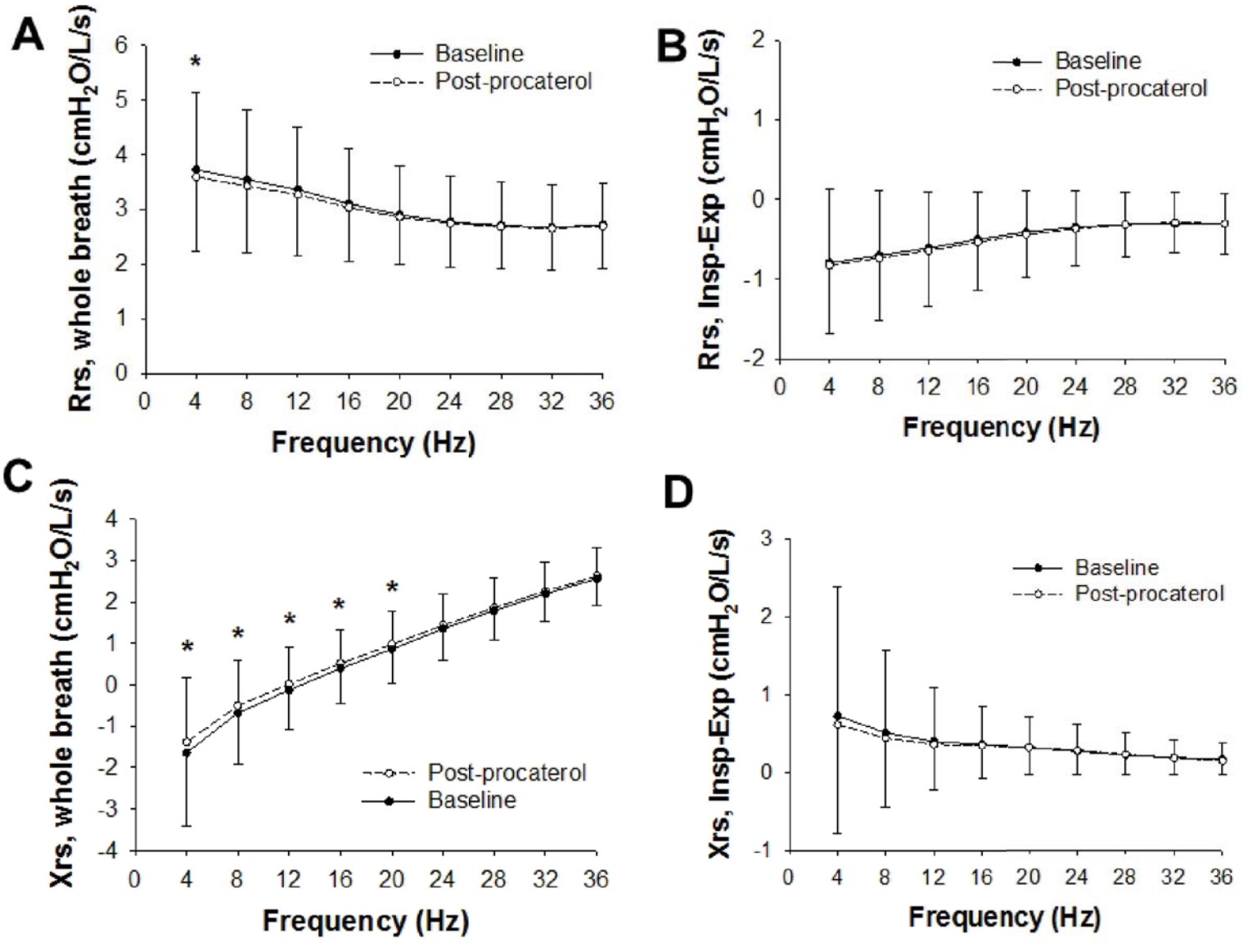
A
Rrs, whole breath (cmH2O/L/s)
Baseline
Post-procaterol
Frequency (Hz)
B
Rrs, Insp-Exp (cmH2O/L/s)
Baseline
Post-procaterol
Frequency (Hz)
C
Xrs, whole breath (cmH2O/L/s)
Post-procaterol
Baseline
Frequency (Hz)
D
Xrs, Insp-Exp (cmH2O/L/s)
Baseline
Post-procaterol
Frequency (Hz)

Figure 5

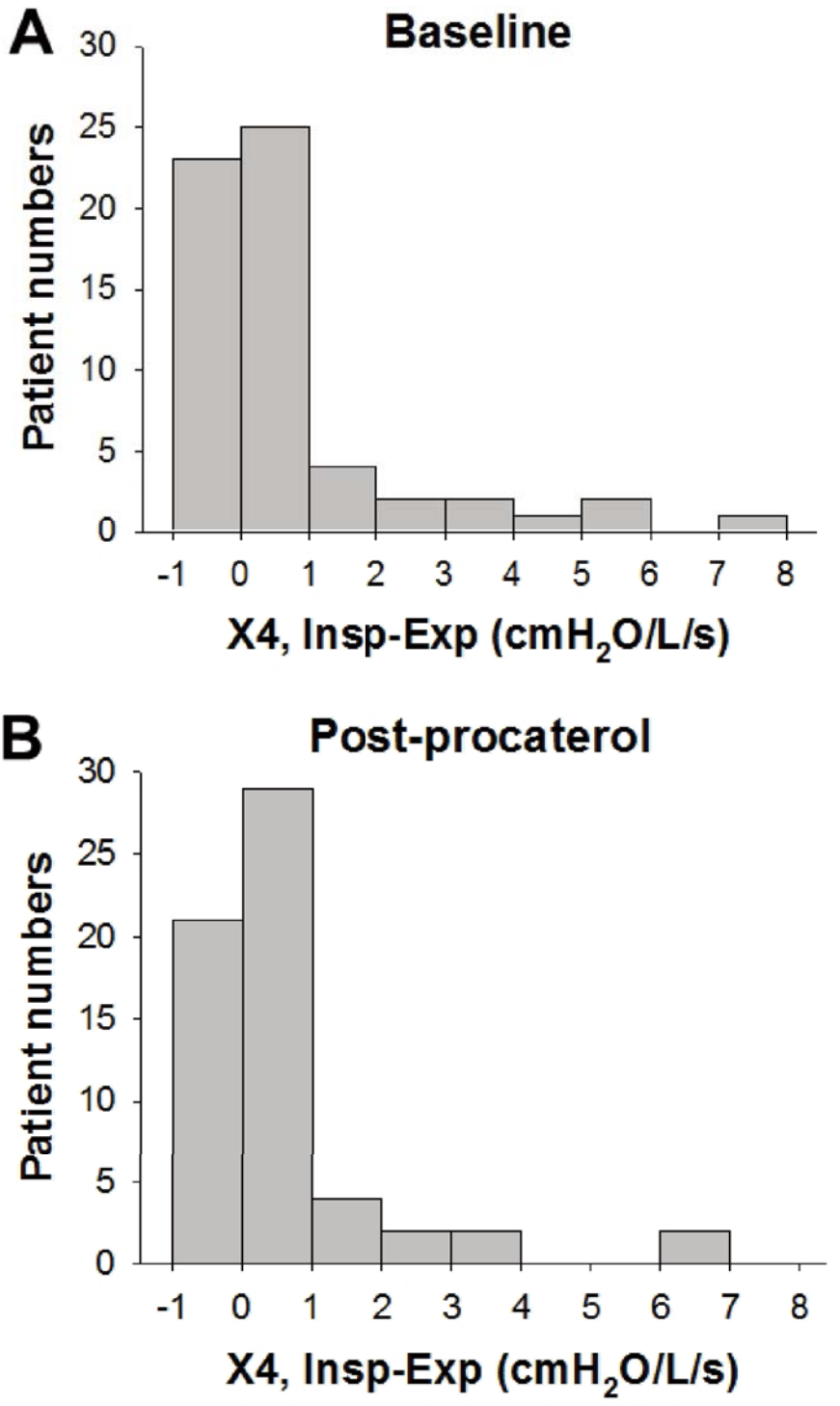
A
Baseline
Patient numbers
30
25
20
15
10
5
0
-1
0
1
2
3
4
5
6
7
8
X4, Insp-Exp (cmH2O/L/s)
B
Post-procaterol
Patient numbers
30
25
20
15
10
5
0
-1
0
1
2
3
4
5
6
7
8
X4, Insp-Exp (cmH2O/L/s)

Figure 6

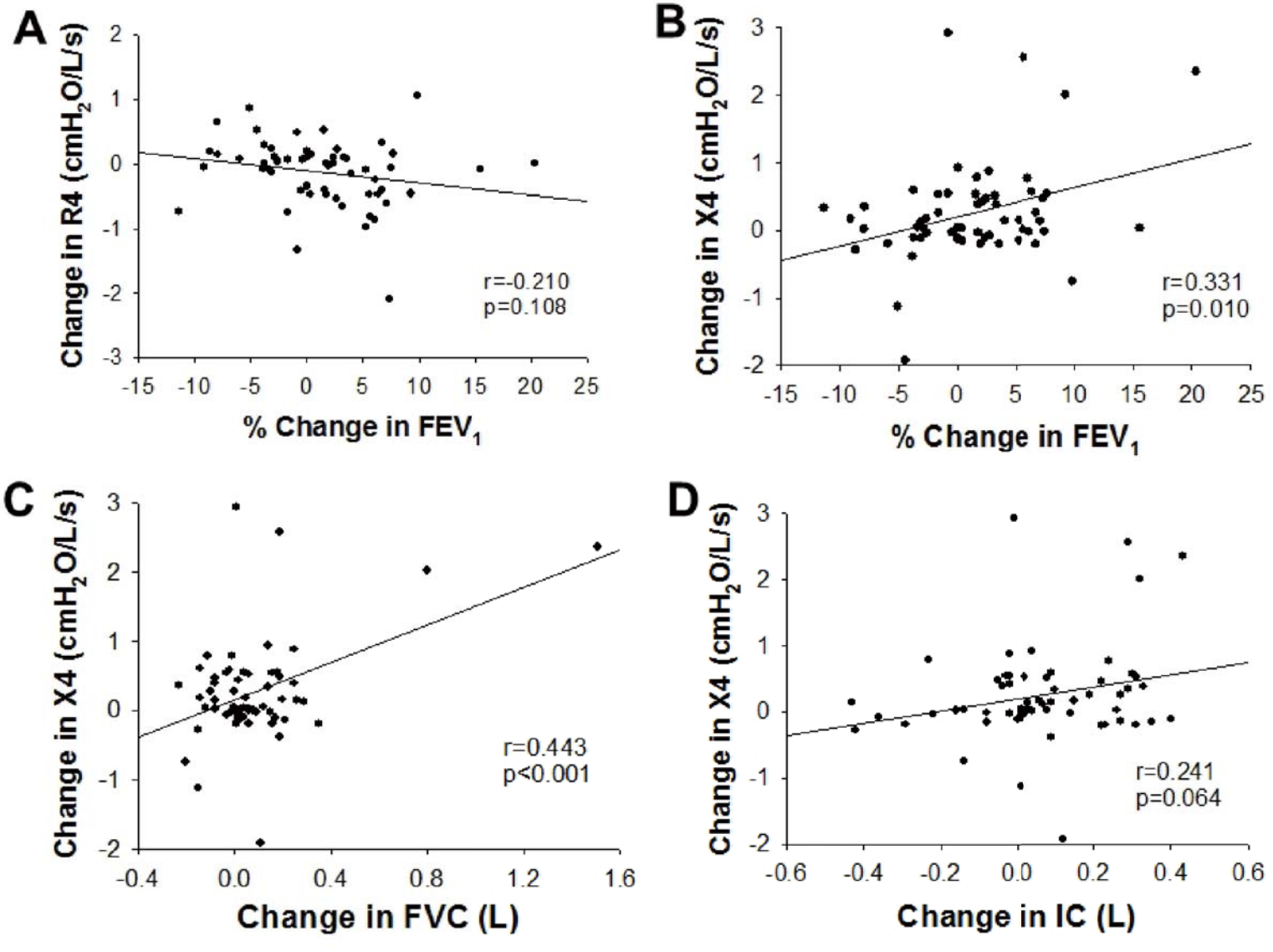
A
Change in R4 (cmH2O/L/s)
% Change in FEV1
r=-0.210
p=0.108
B
Change in X4 (cmH2O/L/s)
% Change in FEV1
r=0.331
p=0.010
C
Change in X4 (cmH2O/L/s)
Change in FVC (L)
r=0.443
p<0.001
D
Change in X4 (cmH2O/L/s)
Change in IC (L)
r=0.241
p=0.064

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.

Table 2. Pulmonary function test results at baseline and after procaterol inhalation

	Baseline	Post-procaterol	P value
VC, L	3.41 ± 0.75	3.46 ± 0.73	<0.001*
VC, % predicted	105.4 ± 18.4	107.6 ± 17.6	0.001*
IC, L	2.13 ± 0.51	2.19 ± 0.51	0.015*
FVC, L	3.27 ± 0.76	3.36 ± 0.73	0.004*
FVC, % predicted	101.9 ± 19.6	104.4 ± 17.9	0.004*
FEV_1, L	1.79 ± 0.58	1.80 ± 0.57	0.240
FEV_1, % predicted	76.5 ± 23.4	77.1 ± 22.6	0.269
FEV_1/FVC, %	54.1 ± 10.9	53.4 ± 11.5	0.271
PEF, L/s	5.59 ± 1.90	5.59 ± 1.84	0.623
FEF_{25-75}, L/s	0.726 ± 0.417	0.717 ± 0.384	0.987
FEF_{25-75}, % predicted	24.7 ± 14.1	24.2 ± 12.5	0.938

*Significant difference between baseline and post-procaterol values compared by paired *t*-test ($p < 0.05$). Data are mean ± SD (n=60).

Table 3. Correlations between pulmonary function test results and respiratory impedance at baseline

	R4, whole breath		X4, whole breath	
	r	P-value	r	P-value
VC	-0.623	<0.001*	0.676	<0.001*
VC, % predicted	-0.474	<0.001*	0.598	<0.001*
IC	-0.319	0.013*	0.493	<0.001*
FVC	-0.642	<0.001*	0.709	<0.001*
FVC, % predicted	-0.506	<0.001*	0.635	<0.001*
FEV_1	-0.638	<0.001*	0.678	<0.001*
FEV_1, % predicted	-0.424	<0.001*	0.515	<0.001*
FEV_1/FVC	-0.319	0.013*	0.396	0.002*
PEF	-0.590	<0.001*	0.638	<0.001*
FEF_{25-75}	-0.475	<0.001*	0.435	<0.001*
FEF_{25-75}, % predicted	-0.391	0.002*	0.368	0.004*

Values (r) are Spearman's rank correlation coefficients. *Significant correlation ($p < 0.05$). Rrs and Xrs at 4 Hz (R4 and X4) during a whole breath before procaterol administration (baseline) were analyzed (n=60).

Table 4. Correlations between changes in pulmonary function test results and respiratory impedance before and after procaterol

	Change in R4, whole breath		Change in X4, whole breath	
	r	P-value	r	P-value
Change in IC	-0.217	0.335	0.241	0.064
Change in FVC	-0.189	0.149	0.443	<0.001*
Change in FEV_1	-0.168	0.200	0.135	0.304
% change in FEV_1	-0.210	0.108	0.331	0.010*
Change in PEF	-0.124	0.345	0.194	0.137

Values (r) are Spearman's rank correlation coefficients. *Significant correlation ($p < 0.05$). Changes in Rrs and Xrs at 4 Hz (R4 and X4) during a whole breath before and after procaterol inhalation were analyzed (n=60).

Table S1. Correlations between pulmonary function test results and respiratory impedance after procaterol administration

	R4, whole breath		X4, whole breath	
	r	P-value	r	P-value
VC	-0.558	<0.001*	0.556	<0.001*
VC, % predicted	-0.396	0.002*	0.454	<0.001*
IC	-0.300	0.020*	0.403	0.001*
FVC	-0.600	<0.001*	0.568	<0.001*
FVC, % predicted	-0.506	<0.001*	0.480	<0.001*
FEV_1	-0.617	<0.001*	0.627	<0.001*
FEV_1, % predicted	-0.424	<0.001*	0.494	<0.001*
FEV_1/FVC	-0.315	0.014*	0.418	0.002*
PEF	-0.566	<0.001*	0.638	<0.001*
FEF_{25-75}	-0.467	<0.001*	0.425	<0.001*
FEF_{25-75}, % predicted	-0.398	0.002*	0.372	0.003*

Values are Spearman's rank correlation coefficients (r). *Significant correlation ($p < 0.05$). Rrs and Xrs at 4 Hz (R4 and X4) during a whole breath after administration of procaterol were analyzed (n=60).

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 β_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.

Highlights

- The usefulness of FOT to evaluate bronchodilator responses is unclear in COPD.
- We assessed responses to procaterol by FOT and spirometry.
- Zrs specifically Xrs parameters are sensitive to acute responses to procaterol.