AGORA
RESEARCH LETTER

Long-term change in reactance by forced oscillation technique correlates with FEV1 decline in moderate COPD patients

To the Editor:

Since the landmark study of the natural history of chronic obstructive pulmonary disease (COPD) by Fletcher and Peto [1], lung function decline has been an issue of great concern and an important therapeutic target. The annual decline in forced expiratory volume in 1 s (FEV_1) is generally used as a marker of disease progression. A review of large longitudinal studies found that the mean rate of FEV_1 decline was highest at Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II (47–79 mL·year^{-1}), indicating the need for treatment at earlier stages of the disease [2].

The forced oscillation technique (FOT) is a noninvasive method that is used to measure respiratory system resistance (R_{rs}) and reactance (X_{rs}) during tidal breathing. Its clinical application has recently progressed worldwide with the spread of commercially available broadband frequency FOT devices. Because correlations between forced oscillatory parameters and spirometric indices are modest, complementary use of both tests may provide useful information regarding lung function [3]. In this study, we assessed whether there would be a long-term change in forced oscillatory parameters and whether the initial FOT index levels could predict the rate of change in these parameters, the so-called "horse-racing effect" [4], in a cohort of patients with COPD.

We retrospectively collected clinical data of outpatients who underwent FOT and spirometry on the same day at a 5-year interval at Shizuoka General Hospital (Shizuoka, Japan) between 2010 and 2015. Subjects included 24 male patients (mean values: age 75 years, body mass index 21.9 kg·m^{-2}, smoking history 68 pack-years, FEV_1 1.65 L and FEV_1 z-score −3.18). All patients satisfied the GOLD definition of COPD and had been receiving medication, including long-acting muscarinic antagonists, long-acting β_2-agonists, inhaled corticosteroids or sustained-release theophylline. COPD grading was based on the GOLD classification and FEV_1/height^2 (L·m^{-2}) [5]. The patients were clinically stable and had no exacerbations for ⩾1 month before the examination. Broadband frequency FOT and spirometry were performed using MostGraph-01 and CHESTAC-33 (Chest M.I., Tokyo, Japan), respectively. We used R_{rs} at 5 and 20 Hz (R_5 and R_{20}, respectively) and the difference between R_5 and R_{20} (R_5–R_{20}) as indicators of the frequency dependence of R_{rs}. In addition, we used X_{rs} at 5 Hz (X_5), which reflects elastic and inertial properties of the lung; resonant frequency (F_{res}), where X_{rs} crosses zero and the elastic and inertial forces are equal in magnitude and opposite; and a low-frequency reactance area (AX), which is an integral of X_5 to F_{res}. Oscillatory indices were expressed as mean values during a respiratory cycle. To determine pulmonary function while receiving daily treatment, medications were not withdrawn before FOT and spirometry, and measured data were expressed as post-bronchodilator values. FEV_1 z-scores were derived from the Global Lung Function Initiative reference equations that adjust for age, sex, height and race [6]. The FOT indices were normally distributed after transforming into natural log (R_5, R_{20}, F_{res} and AX), square root (R_5–R_{20}) or exponential (X_5) values. R_{rs} and X_{rs} z-scores were derived from the reference values of MostGraph measures for the middle-aged and elderly Japanese population (n=784) who participated in annual health check-ups [7]. Comparisons between baseline and after 5 years were made using the paired t-test. Correlations between variables were performed using Pearson's correlation coefficient. A p-value of <0.05 was considered significant. EZR (version 1.27; Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for statistical analyses.

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TABLE 1 Changes in forced expiratory volume in 1 s (FEV_1) and respiratory system reactance (X_{rs}) indices over a 5-year interval

	Total	GOLD classification				FEV_1/height^2 classification $L{\cdot}m^{-2}$			
		I	II	III	IV	>0.5	⩽0.5 to >0.4	⩽0.4 to >0.3	⩽0.3
Subjects n	24	5	9	6	4	14	4	3	3
FEV_1 z-score									
Baseline	−3.18	−0.55	−2.48	−4.52	−6.05	−1.82	−4.18	−5.22	−6.19
After 5 years	−3.56*	−0.96	−3.25*	−4.54	−6.03	−2.38*	−4.25	−5.45	−6.26
Change per year	−0.08	−0.08	−0.15	−0.05	0.004	−0.11	−0.01	−0.05	−0.02
X_5 z-score									
Baseline	−1.06	−0.33	−0.45	−1.62	−2.48	−0.41	−1.55	−1.95	−2.50
After 5 years	−1.53*	−0.51	−1.28*	−2.08	−2.54	−1.01*	−1.91	−2.37	−2.59
Change per year	−0.09	−0.05	−0.16	−0.09	−0.01	−0.12	−0.07	−0.08	−0.02
F_{res} z-score									
Baseline	1.18	0.45	0.42	1.81	2.87	0.45	1.52	2.41	2.94
After 5 years	1.89*	0.80	1.45*	2.56	3.23	1.25*	2.12	3.05	3.42
Change per year	0.14	0.07	0.21	0.15	0.07	0.16	0.12	0.13	0.10
AX z-score									
Baseline	1.00	0.37	0.40	1.53	2.34	0.40	1.35	1.95	2.40
After 5 years	1.50*	0.59	1.17	2.01	2.60	1.00*	1.73	2.30	2.75
Change per year	0.10	0.04	0.16	0.10	0.05	0.12	0.08	0.07	0.07

Data are presented as mean, unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; X_5: X_{rs} at 5 Hz; F_{res}: resonant frequency; AX: low-frequency reactance area. *: $p<0.05$ *versus* baseline.

FEV_1 and X_{rs} indices, including X_5, F_{res} and AX, significantly changed at the 5-year interval (mean absolute values: FEV_1 1.65–1.40 L, X_5 −1.48–−2.08 $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$, F_{res} 12.34–15.87 Hz and AX 10.81–17.01 $cmH_2O{\cdot}L^{-1}$). Changes in FEV_1 and X_{rs} z-scores by COPD grading system are shown in table 1. The changes per year for all parameters appear highest at GOLD stage II; however, this did not reach statistical significance. For the data graded by FEV_1/height^2, there is a trend for less annualised change in X_5, F_{res} and AX moving from group 1 through to group 4, which is not seen in the GOLD classification. There were no significant changes in R_{rs} indices, including R_5, R_{20} and R_5-R_{20} over 5 years. There was a significant correlation between change in FEV_1 and X_{rs} (correlation coefficient: X_5 0.410, F_{res} 0.422 and AX 0.434). Concerning the horse-racing effect, there was no correlation between the initial FEV_1 level and the rate of change in FEV_1, regardless of whether analysed by absolute value or z-score. However, there was a negative correlation between the initial X_{rs} z-scores and the rate of change in X_{rs} z-scores (correlation coefficient X_5 −0.546, F_{res} −0.411 and AX −0.591). No correlation was observed between the initial absolute X_{rs} levels and the rate of change in absolute X_{rs}.

In this study, X_{rs} indices changed significantly over 5 years, and there was a significant correlation between changes in FEV_1 and X_{rs}. This is the first study to indicate that the lung function decline in patients with COPD affects not only spirometry but also FOT. This suggests that X_{rs} indices, including X_5, F_{res} and AX, measured during tidal breathing, are markers of lung function decline in patients with COPD. The lack of significant changes in R_{rs} indices over 5 years may be explained by the previous finding that X_{rs} indices were more sensitive to the increased severity of COPD than R_{rs} indices [8]. The relationship between the FEV_1 level and the rate of change in FEV_1 has been termed the horse-racing effect, meaning that the lower the level of function, the greater the rate of decline [4]. In this study, we found a negative correlation between the initial X_{rs} z-scores and the rate of change in X_{rs} z-scores, suggesting that the measurement of X_{rs} leads to the early detection of lung function decline in patients with COPD. The lack of significant correlation between the FEV_1 level and the rate of change in FEV_1 could potentially be explained by the limited sample size. Altogether, the results obtained by FOT correlate with those obtained by spirometry, but they are not identical. This indicates that FOT is not a surrogate test for spirometry, but should be used concomitantly. In older patients who have difficulty in undergoing a spirometry test, FOT would be particularly useful. Additional larger prospective studies are required to confirm whether X_{rs} is useful as a marker of lung function decline and can be used as a therapeutic target in COPD.

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