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Evaluation of Exertional Ventilatory Parameters Using Oscillometry in COPD

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Background: Oscillometry is a tool to measure respiratory impedance that requires minimal patients' effort. In patients with chronic obstructive pulmonary disease (COPD), the correlation of respiratory impedance at rest with exertional ventilatory parameters, including exercise tolerance, has scarcely been reported. In addition, the utility of oscillometric parameters might differ between the inspiratory and expiratory phases due to airflow obstruction during expiration, but the hypothesis had not been validated. The aim of the present study was to investigate whether oscillometric parameters are associated with exertional ventilatory parameters in patients with COPD.

Methods: Fifty-five subjects with COPD who attended clinics at the National Hospital Organization Osaka Toneyama Medical Center performed spirometry, oscillometry, and cardiopulmonary exercise testing (CPET) within 2 weeks. The correlations between parameters of spirometry, oscillometry, and CPET were analyzed using Spearman's rank correlation coefficient, univariate, and multivariate analyses.

Results: Respiratory reactance had better correlations with the CPET parameters than respiratory resistance. Moreover, inspiratory reactance at rest correlated with the CPET parameters stronger than expiratory reactance. In particular, inspiratory resonant frequency (Fres-ins) correlated with peak oxygen uptake ($r_S=-0.549$, $p<0.01$) and dead space to tidal volume ratio at peak exercise ($r_S=0.677$, $p<0.01$) and the best predicted expiratory tidal volume (V_T ex) at peak exercise of all the oscillometric parameters ($r_S=-0.679$, $p<0.01$). However, the correlation between Fres-ins and V_T ex at peak exercise became weak in subjects with severe and very severe COPD during exercise.

Conclusion: Measurement of respiratory reactance is useful for the effortless evaluation of not only exertional ventilatory parameters but exercise tolerance in patients with COPD. The correlation of respiratory impedance with exertional ventilatory parameters can become weak in patients with advanced COPD; thus, the measurement of oscillometry might not be appropriate for evaluating exertional ventilatory parameters of patients with advanced COPD.

Keywords: dyspnea, dynamic hyperinflation, airflow obstruction, resonant frequency, tidal volume

Introduction

Globally, chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death and a major cause of morbidity.[1] Improving exercise tolerance or better physical activity would result in the better prognosis in COPD patients.[2] Exercise tests, including 6-minute walk testing (6MWT) and cardiopulmonary exercise testing (CPET), are the gold standard for evaluation of exercise tolerance.[3–5] 6MWT is common and easier to perform than CPET, but CPET can

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evaluate exertional ventilatory parameters more precisely.[4,5] Often, however, the tests cannot be performed in patients with dysmobility, making the evaluation of exertional ventilatory parameters difficult. Therefore, effortless evaluations of exertional ventilatory parameters are needed in the patients. As methods easy to evaluate exertional ventilatory parameters, pulmonary function tests, including spirometry and oscillometry, might be important.[6,7]

Oscillometry, which involves measurements of within-breath changes in respiratory impedance, measures respiratory resistance (Rrs) and respiratory reactance (Xrs). Rrs represents the sum of airway resistance and viscous resistance of the lung and thoracic tissue,[8] while Xrs is considered to reflect the elastance and inertia of the respiratory system.[9] Measurement of respiratory impedance using oscillometry is less time-consuming and requires minimal patients' cooperation.[10] In fact, oscillometry can be used to evaluate patients with severely advanced COPD who are unable to perform even spirometry.[10]

In patients with COPD, Rrs and resonant frequency (Fres) correlate negatively and Xrs at a lower frequency of oscillation correlates positively with forced expiration volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio.[11] Since peripheral airway obstruction becomes more severe during expiration,[12] these oscillometric parameters change dynamically during respiratory cycle. In particular, Rrs becomes higher and Xrs shifts to a more negative direction in the expiratory phase.[13,14] Moreover, when airflow obstruction develops, expiratory flow at a given lung volume reaches its maximal value despite increasing expiratory driving pressure; this is called expiratory flow limitation (EFL).[15–17] EFL during exercise promotes dynamic hyperinflation and contributes to a rapid and shallow breathing pattern.[15,18] Xrs is normally thought to reflect the elastic and inertial properties of the respiratory system in patients without EFL.[19] In patients with EFL, however, oscillatory signals cannot pass through the points of airway obstruction and reach the alveoli; thus, Xrs reflects the mechanical properties of airways proximal to the choke points which are much stiffer than the periphery and becomes more negative.[19]

As other pathophysiology in COPD patients, ventilatory inefficiency during exercise are reported.[16,20] In patients with ventilatory inefficiency, dead space to tidal volume ratio (V_D/V_T) becomes higher during exercise.[20–22] Ventilatory inefficiency is one of the components that affect exercise tolerance in COPD,[23] but the correlation between ventilatory inefficiency and oscillometric parameters had not been investigated.

The above observations suggest that the utility of oscillometric parameters might differ between the inspiratory and expiratory phases. However, the association between each inspiratory and expiratory oscillometric parameter and ventilatory CPET parameters has never been thoroughly investigated, although the association of oscillometry with 6MWT and CPET has been previously reported.[24,25] In addition, the utility of each oscillometric parameter for evaluating and predicting exertional ventilatory parameters, including ventilatory inefficiency and exercise tolerance, has not been investigated in patients with COPD. The information obtained from oscillometry might be clinically useful for assessing the mechanisms of exercise impairment and the effects of interventions.

The aims of the present study were as follows: (1) to investigate inspiratory and expiratory oscillometric parameters that are associated with exertional ventilatory parameters in COPD patients; and (2) to confirm the utility of oscillometry in COPD patients with various airflow obstructions.

Methods
Subjects
A total of 105 patients with COPD who attended clinics at National Hospital Organization Osaka Toneyama Medical Center or participated in several ethically approved research studies on COPD, between August 2015 and July 2019 were screened in the study. The patients were confirmed to have a FEV_1/FVC ratio of <0.70 after using a bronchodilator and were diagnosed with COPD based on their spirometry, smoking history, and symptoms including chronic cough, sputum, and dyspnea. The patients therefore satisfied the definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[26] Only COPD patients who underwent spirometry, oscillometry, and CPET were included. Their drug regimens were not changed within 4 weeks before the measurements in this study. Patients were excluded if they were not clinically stable or had exacerbations, defined as increased dyspnea associated with a change in the quality and quantity of sputum, for at least three months before the present study. Patients were excluded if they had malignant tumors, severe heart disease, or bronchial asthma (ie a history of bronchial asthma, or respiratory symptoms that i) occur

variably over time and vary in intensity, ii) occur at night or on waking, or iii) are triggered by exercise, including CPET). The qualified 55 symptomatic subjects who met the study criteria [modified Medical Research Council (MRC) dyspnea scale ≥1] were evaluated using the examinations described in the following sections.

Study Design

The subjects were evaluated using all three evaluation methods, oscillometry, spirometry, and CPET, within, at most, a 2-week time period when the subjects' clinical symptoms were stable. If oscillometry and spirometry were performed on the same day, spirometry was performed after oscillometry. Short-acting β_2-agonists were not used for more than 12 hours before these tests in all subjects. Long-acting antimuscarinic agents (LAMA) and long-acting β_2-agonists (LABA) were not withdrawn before the measurements of oscillometry, spirometry, and CPET. The Institutional Review Board of National Hospital Organization Osaka Toneyama Medical Center approved the study protocols and chose an opt-out system to obtain subjects' informed consent (approval number, TNH-2,019,037).

Measurement of Respiratory Impedance Using Oscillometry

Respiratory impedance was measured at rest with broadband oscillometry using a commercially available device (Mostgraph-01, Chest MI Co, Ltd, Tokyo, Japan). The methods were performed according to the standard recommendations.[8] Partitioned (inspiratory and expiratory) and average oscillometric parameters and were measured. Differences between inspiratory and expiratory phases (Δ) were calculated regarding all oscillometric parameters. As indicators of the frequency dependence of Rrs, Rrs at 5 and 20 Hz (R5 and R20, respectively) and the difference between R5 and R20 (R5-R20) were used. In addition, Xrs at 5 Hz (X5), Fres, and a low-frequency reactance area (ALX) were used as indicators of respiratory reactance. Fres indicates the point where Xrs becomes more dominated by inertial rather than elastic forces, and ALX is defined as the integral of X5 to the Fres.

CPET

Symptom-limited exercise tests were performed using an electrically-braked cycle ergometer (CV-1000SS, Lode, Groningen, The Netherlands) using a CPET system (Marquette CASE series T 2001, GE Healthcare, Tokyo, Japan; Aeromonitor AE 310S, Minato Medical Science Co, Ltd, Osaka, Japan).[5] First, pre-exercise resting measurements were taken after reaching a steady-state period during at least 3 min of breathing through a mask. Next, incremental testing was performed by increasing 10W per 2 minutes. Before commencing the CPET, subjects were asked to put in maximum effort in the exercises performed during CPET. CPET was then performed until exhaustion without further encouragement, especially during exercise. The subjects were asked to maintain a cycle ergometer speed of about 60 rpm. The following CPET parameters were measured: expiratory tidal volume (V_T ex), V_D/V_T, mean expiratory flow [V_T ex/expiratory time (Te)], breathing frequency (f_R), minute ventilation (V'_E), V'_E/V'_{CO2}, inspiratory duty cycle (Ti/Ttot), and oxygen uptake (V'_{O2}). These data were measured breath-by-breath and collected as 30 s averages at rest, during exercise at 2 min intervals, and at the end of exercise. In addition, dyspnea intensity (10-point modified Borg category-ratio scale) was evaluated at rest, at the last 15 s of each exercise stage, and at the end of exercise.

Spirometry

The subjects underwent spirometry using the CHESTAC 8800 spirometer (Chest MI, Inc, Tokyo, Japan) before CPET according to the recommendations of the American Thoracic Society.[27] Predicted vital capacity and predicted FEV_1 were calculated according to the formula developed by the Japanese Respiratory Society.[28]

Statistical Analysis

The subjects were grouped into the GOLD stage I and II subgroup (Subgroup A) and the GOLD stage III and IV subgroup (Subgroup B). The Mann–Whitney U-test was used for comparison of various parameters among the subgroups. Spearman's rank correlation coefficient (r_S) and univariate analyses were used for bivariate correlation analysis of the parameters of respiratory impedance and CPET. Multiple stepwise linear regression analysis was performed to detect the variables of oscillometry that were significant determinants of V_T ex, V_T ex/Te, f_R, V'_E, and V'_{O2}. After detecting the most significant oscillometric determinants, univariate and multivariate analyses were performed for interaction analyses. These statistical analyses were performed using EZR Version 1.38 (based on R Version 3.5.2 and R commander Version 2.5–1,

Saitama, Japan).[29] In all analyses, $p<0.05$ was taken to indicate statistical significance.

Results
Baseline Characteristics

Among 55 subjects included in the present study, 16 subjects were GOLD stage I or II and 39 subjects were GOLD stage III or IV (Table 1). There were no differences between the subgroups in age, body mass index, and smoking history. As for oscillometry, expiratory impedance showed wider variation than inspiratory impedance (Table 2). Resistance parameters, Fres, and ALX were higher and X5 was more negative in Subgroup B (Table 3 and Figure 1). Thus, respiratory impedance variously correlated with the severity of airflow obstruction.

Regarding CPET (Table 4), V'_{O2} at rest was higher in Subgroup A (Table 5). At peak exercise, V_T ex, V_T ex/Te,

Table 1 Subjects' Baseline Characteristics (n=55)

Age, Years, n	73.49 (5.56)	61–83
Sex, male/female	54/1	
BMI, kg m^{-2}	20.9 (3.2)	14.7–25.8
Cigarette smoking, pack years	56.5 (26.5)	11–141
GOLD stage I/II/III/IV, n	6/10/29/10	
GOLD category A/B/C/D, n	10/29/0/16	
mMRC dyspnea scale 0/1/2/3/4, n	0/10/22/12/11	
Medications		
LAMA, n	53	
LABA, n	43	
ICS, n	22	
Triple therapy, n	21	
Spirometry		
FEV_1, L	1.24 (0.62)	0.41–3.73
% FEV_1, % predicted	47.10 (22.96)	16.7–141.8
FVC, L	3.01 (0.89)	1.24–5.39
% FVC, % predicted	89.4 (23.7)	39.4–159.9
FEV_1/FVC, %	40.35 (11.17)	21.2–69.2
VC, L	3.05 (0.81)	1.68–5.31
%VC, %	84.45 (19.73)	48.40–146.30
IC, L	1.92 (0.52)	0.92–3.08
IRV, L	0.96 (0.44)	0.19–1.79
ERV, L	1.13 (0.47)	0.33–2.85
V_T, L	0.96 (0.32)	0.29–1.77

Note: Data are presented as the mean (SD) and the minimum and maximum values, unless otherwise stated.
Abbreviations: BMI, body mass index; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroids; IRV, inspiratory reserve volume; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; mMRC dyspnea scale, modified Medical Research Council dyspnea scale; SD, standard deviation; VC, vital capacity; V_T, tidal volume.

Table 2 Results of Baseline Respiratory Impedance at Rest (n=55)

R5, cmH$_2$O/L/s		
Inspiratory	3.62 (1.30)	1.20–6.96
Expiratory	4.88 (2.19)	1.53–13.83
Average	4.25 (1.64)	1.54–10.04
ΔR5	−1.26 (1.50)	−7.59–1.19
R20, cmH$_2$O/L/s		
Inspiratory	2.74 (0.80)	1.13–4.75
Expiratory	3.32 (1.28)	1.44–7.94
Average	3.03 (0.96)	1.49–6.08
ΔR20	−0.58 (0.91)	−3.76–0.77
R5-R20, cmH$_2$O/L/s		
Inspiratory	0.89 (0.60)	−0.07–2.80
Expiratory	1.56 (0.99)	0.01–5.89
Average	1.23 (0.74)	0.01–3.96
ΔR5-R20	−0.68 (0.71)	−3.86–0.52
X5, cmH$_2$O/L/s		
Inspiratory	−1.29 (0.85)	−3.55 - −0.16
Expiratory	−3.64 (3.12)	−12.56 - −0.08
Average	−2.47 (1.89)	−7.54 - −0.13
ΔX5	2.36 (2.58)	−0.16–10.05
Fres, Hz		
Inspiratory	14.53 (5.81)	5.91–30.60
Expiratory	20.08 (7.81)	5.56–34.28
Average	17.31 (6.47)	5.74–32.18
ΔFres	−5.55 (4.65)	−18.51–1.04
ALX, cmH$_2$O/L/s × Hz		
Inspiratory	9.32 (9.12)	0.54–42.08
Expiratory	33.74 (33.57)	0.29–145.30
Average	21.53 (20.14)	0.46–83.41
ΔALX	−24.41 (28.24)	−123.78–0.92

Note: Data are presented as the mean (SD) and the minimum and maximum values, unless otherwise stated.
Abbreviations: ALX, low-frequency reactance area; Δ, difference between inspiratory and expiratory phases; Fres, resonant frequency; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; SD, standard deviation; X5, respiratory system reactance at 5 Hz.

V'_E, V'_{O2}, and Ti/Ttot ($p<0.01$) were higher in Subgroup A (Table 5). These data showed that Subgroup A had better exercise tolerance than Subgroup B. Moreover, given that V_D/V_T at rest and peak exercise was higher in Subgroup B (Table 5), the results showed ventilatory inefficiency and low oxygen uptake during exercise in subjects with severe airflow obstruction. However, no significant difference was observed in f_R between the two subgroups, perhaps because of its wide variation (Figure 2). Whilst, f_R correlated positively with V_T ex/Te and V'_E at peak exercise, but not with V_T ex among all subjects (Supplementary Figure 1).

Table 3 Results of Baseline Respiratory Impedance at Rest in the Various GOLD Stages (Stages I–IV) (n=55)

Parameter	GOLD Stages I, II (n=16)		GOLD Stages III, IV (n=39)		p
R5, cmH$_2$O/L/s					
Inspiratory	2.70 (1.25)	1.20–6.24	4.00 (1.14)	1.96–6.96	**
Expiratory	4.26 (2.88)	1.53–13.83	5.14 (1.83)	2.24–11.82	*
Average	3.48 (2.03)	1.54–10.04	4.57 (1.36)	2.10–9.14	**
ΔR5	−1.56 (1.82)	−7.59–0.02	−1.13 (1.36)	−5.64–1.19	NS
R20, cmH$_2$O/L/s					
Inspiratory	2.18 (0.73)	1.13–4.21	2.97 (0.71)	1.71–4.75	**
Expiratory	3.01 (1.54)	1.44–7.94	3.45 (1.15)	1.78–7.36	NS
Average	2.59 (1.10)	1.49–6.08	3.21 (0.85)	1.75–5.94	**
ΔR20	−0.83 (0.97)	−0.37–0.18	−0.48 (0.88)	−3.76–0.77	NS
R5-R20, cmH$_2$O/L/s					
Inspiratory	0.52 (0.54)	−0.07–2.03	1.04 (0.56)	0.25–2.80	**
Expiratory	1.25 (1.38)	0.01–5.89	1.69 (0.77)	0.14–4.46	**
Average	0.89 (0.94)	0.01–3.96	1.04 (0.56)	0.29–3.20	**
ΔR5-R20	−0.73 (0.93)	−3.86–0.52	−0.65 (0.62)	−2.53–0.42	NS
X5, cmH$_2$O/L/s					
Inspiratory	−0.69 (0.53)	−2.19 - −0.16	−1.53 (0.84)	−3.55 - −0.19	**
Expiratory	−1.72 (2.85)	−11.11 - −0.08	−4.43 (2.90)	−12.56 - −0.42	**
Average	−1.20 (1.67)	−6.65 - −0.13	−2.98 (1.74)	−7.54 - −0.49	**
ΔX5	1.03 (2.39)	−0.15–8.92	2.90 (2.48)	−0.16–10.05	**
Fres, Hz					
Inspiratory	9.87 (3.27)	5.91–17.08	16.44 (5.55)	6.58–30.60	**
Expiratory	12.71 (6.37)	5.56–28.20	23.10 (6.20)	10.67–34.28	**
Average	11.29 (4.71)	5.74–22.64	19.77 (5.42)	9.82–32.18	**
ΔFres	−2.84 (3.73)	−11.12–1.04	−6.65 (4.58)	−18.51–0.37	**
ALX, cmH$_2$O/L/s × Hz					
Inspiratory	3.30 (3.43)	0.54–13.25	11.79 (9.59)	0.60–42.08	**
Expiratory	13.41 (26.96)	0.29–97.59	42.07 (32.70)	2.04–145.30	**
Average	8.35 (15.09)	0.46–55.42	26.93 (19.58)	1.93–83.41	**
ΔALX	−10.11 (23.80)	−84.34–0.81	−30.28 (28.08)	−123.78–0.92	**

Notes: Data are presented as the mean (SD) and the minimum and maximum values, unless otherwise stated. *and **p<0.05 and p<0.01 by the Mann–Whitney *U*-test, respectively.
Abbreviations: ALX, low-frequency reactance area; Δ, difference between inspiratory and expiratory phases; Fres, resonant frequency; GOLD, Global Initiative For Chronic Obstructive Lung Disease; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; SD, standard deviation; X5, respiratory system reactance at 5 Hz.

Identification of Oscillometric Parameters That Best Predicted CPET Parameters

Univariate analyses showed that respiratory resistance at rest hardly correlated with CPET parameters at rest, and inspiratory reactance at rest correlated with V_T ex, V_T ex/Te, V'$_E$, and V'$_{O2}$ at rest (Table 6). However, oscillometric parameters at rest variously correlated with CPET parameters at peak exercise except for f_R (Table 7 and Supplementary Table 1). Moreover, V_T ex, V_T ex/Te, V'$_E$, and V'$_{O2}$ showed a stronger correlation with parameters of reactance than resistance, and all the inspiratory oscillometric parameters showed stronger correlation with these CPET parameters than expiratory oscillometric parameters. In addition, multiple stepwise linear regression analysis determined Fres-ins as the parameter with the strongest correlation with V_T ex, V_T ex/Te, V'$_E$, and V'$_{O2}$ (Supplementary Table 2). Therefore, Fres-ins was detected as the most significant determinant of exertional ventilatory parameters, including exercise tolerance. However, the correlation of exertional ventilatory parameters with Fres-ins was weaker than that with FEV$_1$, which included the
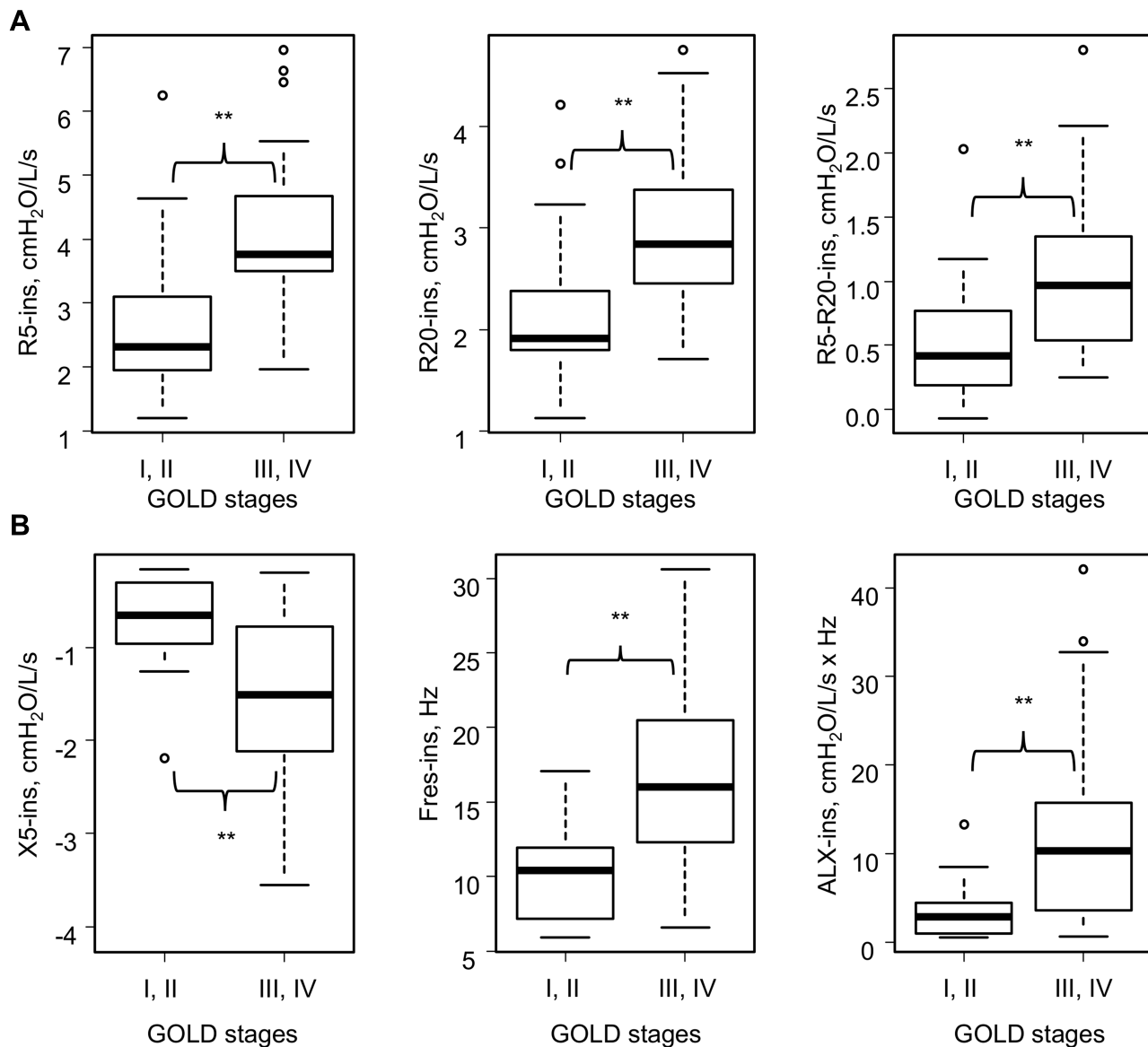
Figure 1 Inspiratory impedance at rest in the various GOLD stages (stages I–IV) (n=55). (**A**) Respiratory resistance and GOLD stages at baseline. (**B**) Respiratory reactance and GOLD stages at baseline. Sixteen subjects were GOLD stage I or II and 39 subjects were GOLD stage III or IV. **p<0.01 by the Mann–Whitney U-test.
Abbreviations: ALX, low-frequency reactance area; Fres, resonant frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; X5, respiratory system reactance at 5 Hz.

correlation of FEV_1 with V'_{O2} (r_S=0.823, p<0.01) and that with V'_E (r_S=0.903, p<0.01) (Table 7).

Analysis Between Fres-Ins at Rest and CPET Parameters

Comparing CPET parameters at rest with those at peak exercise, V_T ex, V_T ex/Te, V'_E, and V'_{O2} showed stronger correlations with Fres-ins at peak exercise than at rest (Figure 3). Regarding analyses of f_R and Fres-ins, statistical significance was not observed at either rest or at peak exercise.

Moreover, the differences of CPET parameters between at peak exercise and at rest correlated with Fres-ins, including V_T ex (r_S=−0.571, p<0.01), V_T ex/Te (r_S=−0.598, p<0.01), V'_E (r_S=−0.555, p<0.01), and V'_{O2} (r_S=−0.558, p<0.01). This indicated the statistically more significant difference in correlation coefficients at peak exercise compared with at rest during CPET. Therefore, during exercise, the correlation between Fres-ins at rest and CPET parameters became stronger.

In addition, Fres-ins correlated with an index of the ventilatory inefficiency: V_D/V_T at peak exercise (r_S=0.677,

Table 4 Results of Cardiopulmonary Exercise Testing at Peak Exercise and at Rest (n=55)

	At Peak Exercise		At Rest	
Incremental load testing				
V_T ex, mL	1132 (332)	597–2047	696 (169)	354–1192
V_T ex/Te, mL/sec	924 (363)	322–2043	370 (90)	175–660
f_R, breaths/min	29 (5)	16–40	21 (6)	8–32
V'_E, L/min	33.0 (10.6)	14.6–63.9	13.7 (2.5)	6.8–19.1
Ti/Ttot	0.38 (0.08)	0.24–0.68	0.37 (0.07)	0.22–0.62
V'_{O2}, mL/min	711 (236)	313–1218	249 (45)	171–361
V_D/V_T	0.40 (0.05)	0.31–0.50	0.44 (0.04)	0.38–0.54
V'_E/V'_{CO2}	46.6 (7.6)	33.3–72.3	61.6 (8.6)	46.5–81.9

Note: Data are presented as the mean (SD) and the minimum and maximum values, unless otherwise stated.
Abbreviations: f_R, breathing frequency; SD, standard deviation; Te, expiration time; Ti/Ttot, inspiratory duty cycle; V_D, physiological dead space; V_D/V_T, dead space to tidal volume ratio; V'_E, minute ventilation; V'_E/V'_{CO2}, ventilatory equivalent for carbon dioxide; V'_{O2}, oxygen uptake; V_T, tidal volume; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow.

Table 5 Results of Cardiopulmonary Exercise Testing (CPET) at Rest and at Peak Exercise in Various GOLD Stages (Stages I–IV) (n=55)

	GOLD Stages I, II (n=16)				GOLD Stages III, IV (n=39)			
	At peak exercise		At rest		At peak exercise		At rest	
Incremental load testing								
V_T ex, mL	1515 (246)*	1137–2047	739 (145)	488–935	975 (214)	597–1445	679 (177)	354–1192
V_T ex/Te, mL/sec	1297 (296)*	927–2043	383 (56)	292–467	771 (265)	322–1464	366 (102)	175–660
f_R, breath/min	29 (5)	24–40	20 (4)	14–27	29 (5)	16–40	21 (6)	8–32
V'_E, L/min	44.1 (8.3)*	33.0–63.9	14.1 (2.0)	10.4–17.6	28.5 (7.9)	14.6–48.3	13.6 (2.8)	6.8–19.1
Ti/Ttot	0.43 (0.06)*	0.35–0.60	0.38 (0.07)	0.30–0.62	0.36 (0.09)	0.24–0.68	0.36 (0.08)	0.22–0.62
V'_{O2}, mL/min	928 (168)*	696–1218	270 (45)*	171–361	622 (201)	313–1214	240 (42)	173–327
V_D/V_T	0.35 (0.03)*	0.31–0.40	0.42 (0.04)*	0.38–0.49	0.42 (0.04)	0.34–0.50	0.45 (0.04)	0.38–0.54
V'_E/V'_{CO2}	44.9 (6.1)	36.0–54.4	59.5 (8.5)	46.5–78.3	47.2 (8.1)	37.0–72.3	62.5 (8.6)	46.6–81.9

Notes: Data are presented as the mean (SD) and the minimum and maximum values, unless otherwise stated. *$p<0.05$ by the Mann–Whitney U-test comparing with each CPET parameter of subjects with GOLD stages III and IV.
Abbreviations: CPET, cardiopulmonary exercise testing; f_R, breathing frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation; Te, expiratory time; Ti/Ttot, inspiratory duty cycle; V_D, physiological dead space; V_D/V_T, dead space to tidal volume ratio; V'_E, minute ventilation; V'_E/V'_{CO2}, ventilatory equivalent for carbon dioxide; V'_{O2}, oxygen uptake; V_T, tidal volume; V_T ex, expiratory tidal volume; V_T ex/Te; mean expiratory flow.

$p<0.01$). However, FEV_1 correlated with V_D/V_T at peak exercise stronger than Fres-ins ($r_S=-0.715$, $p<0.01$) (Table 7).

Correlation Between Fres-Ins at Rest and CPET Parameters at Peak Exercise

As indicated by the scatter plots of Fres-ins and V_T ex, V_T ex/Te, V'_E, and V'_{O2} (Figure 3), the correlations between the various parameters can be considered nonlinear and exponential. Therefore, analyses between Fres-ins and the natural logarithms of these CPET parameters were performed. Fres-ins correlated negatively and linearly with the natural logarithms of the CPET parameters (Figure 4). Combined with the results of Figure 1, which indicated

that Fres-ins correlated positively with the GOLD stages, these analyses using logarithmic conversion implied that the correlation between Fres-ins and the CPET parameters becomes weak in advanced stages of COPD.

Discussion

The present study highlights four major findings regarding the correlation between respiratory impedance and exertional ventilatory parameters: 1) inspiratory rather than expiratory oscillometric parameters correlated with exertional ventilatory parameters stronger; 2) Fres-ins at rest correlated with exertional ventilatory parameters and reflected exercise tolerance in COPD subjects; 3) Fres-ins correlated with ventilatory inefficiency during exercise; and 4) the correlation between respiratory impedance and
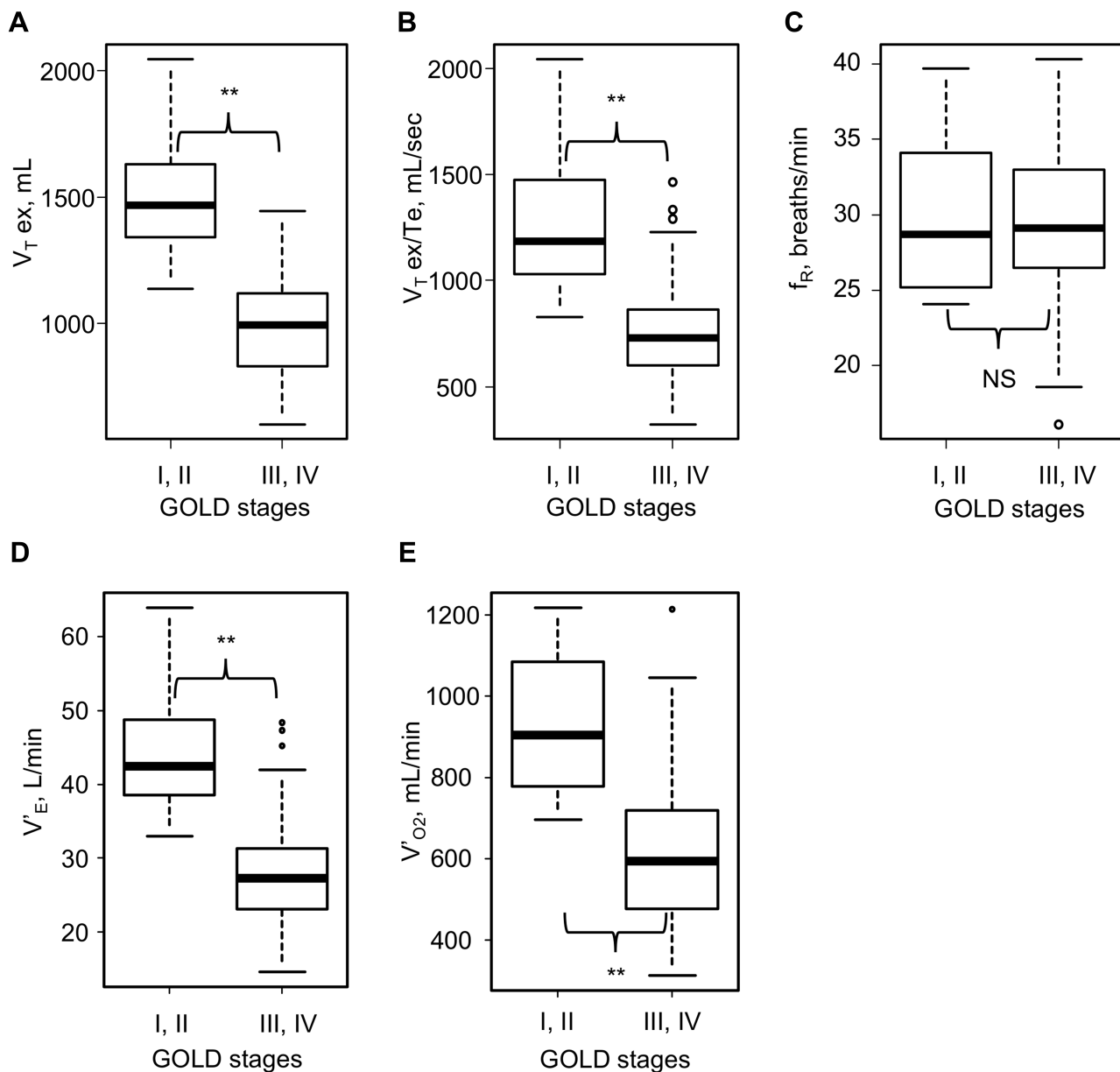
Figure 2 Results of cardiopulmonary exercise testing at peak exercise in the various GOLD stages (stages I–IV) (n=55). (**A**) Expiratory tidal volume at peak exercise in the various GOLD stages. (**B**) Mean expiratory flow (V_T ex/Te) at peak exercise in the various GOLD stages. (**C**) Breathing frequency (f_R) at peak exercise in the various GOLD stages. (**D**) Minute ventilation (V'_E) at peak exercise in the various GOLD stages. (**E**) Oxygen uptake (V'_{O2}) at peak exercise in the various GOLD stages. $**p < 0.01$ by the Mann–Whitney U-test.
Abbreviations: f_R, breathing frequency; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NS, not significant by the Mann–Whitney U-test; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow.

exertional ventilatory parameters became weak in subjects with severe airflow obstruction. To the best of our knowledge, this is the first study to evaluate exertional ventilatory parameters using respiratory impedance at rest.

In COPD patients, inspiratory reactance at rest, particularly Fres-ins, better correlated with ventilatory parameters at peak exercise than those at rest. During exercise, due to the combination of decreased elastic recoil pressure and increased airway resistance, patients with

COPD require a longer expiratory time to enable complete expiration of tidal volume.[30] However, the simultaneous increase in f_R results in a short expiratory time, which is insufficient for COPD patients to exhale their entire tidal volume due to airflow obstruction, leading to dynamic hyperinflation.[18] Accordingly, oscillometric parameters correlate variously with spirometric parameters including FEV_1,[31] which reflects the severity of airflow obstruction. However, oscillometry has not been considered a surrogate

Table 6 Spearman's Rank Correlation Coefficient Between Parameters of Respiratory Impedance at Rest, Spirometry, and Cardiopulmonary Exercise Testing at Rest (n=55)

	V_T ex		V_T ex/Te		f_R		V'_E		V'_{O2}		V_D/V_T	
Oscillometry												
R5												
Inspiratory	−0.260	NS	−0.193	NS	0.236	NS	−0.065	NS	−0.111	NS	0.175	NS
Expiratory	−0.176	NS	−0.048	NS	0.222	NS	0.050	NS	−0.105	NS	0.108	NS
R20												
Inspiratory	−0.223	NS	−0.105	NS	0.252	NS	−0.002	NS	−0.033	NS	0.160	NS
Expiratory	−0.133	NS	−0.051	NS	0.150	NS	0.008	NS	−0.050	NS	0.062	NS
R5-R20												
Inspiratory	−0.247	NS	−0.177	NS	0.220	NS	−0.052	NS	−0.136	NS	0.150	NS
Expiratory	−0.174	NS	−0.140	NS	0.182	NS	−0.031	NS	−0.189	NS	0.094	NS
X5												
Inspiratory	0.365	**	0.246	NS	−0.257	NS	0.152	NS	0.289	*	−0.338	*
Expiratory	0.143	NS	0.119	NS	−0.153	NS	−0.005	NS	0.114	NS	−0.245	NS
Fres												
Inspiratory	−0.356	**	−0.278	*	0.241	NS	−0.148	NS	−0.335	*	0.385	**
Expiratory	−0.174	NS	−0.194	NS	0.155	NS	−0.038	NS	−0.220	NS	0.303	*
ALX												
Inspiratory	−0.372	**	−0.250	NS	0.258	NS	−0.155	NS	−0.296	*	0.314	*
Expiratory	−0.160	NS	−0.109	NS	0.179	NS	0.019	NS	−0.132	NS	0.217	NS
Spirometry												
FVC	0.429	**	0.503	**	−0.093	NS	0.434	**	0.506	**	−0.156	NS
FEV$_1$	0.352	**	0.419	**	−0.136	NS	0.304	*	0.467	**	−0.253	*
FEV$_1$/FVC	0.039	NS	0.131	NS	−0.004	NS	0.006	NS	0.143	NS	−0.180	NS

Notes: *$p<0.05$; **$p<0.01$.
Abbreviations: ALX, low-frequency reactance area; FEV$_1$, forced expiratory volume in 1 second; f_R, breathing frequency; Fres, resonant frequency; FVC, forced vital capacity; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; Te, expiratory time; V'$_E$, minute ventilation; V'$_{O2}$, oxygen uptake; V$_T$ ex, expiratory tidal volume; V$_T$ ex/Te, mean expiratory flow; X5, respiratory system reactance at 5 Hz.

test for spirometry, because these tests do not necessarily evaluate the same breathing conditions and each oscillometric parameter reportedly only fairly or moderately correlates with spirometric parameters.[31,32] Therefore, the correlations between oscillometry and exertional ventilatory parameters also seemed to be moderate. Nevertheless, we assessed the utility of oscillometry because it is particularly useful for assessing the respiratory pathophysiology of COPD and for evaluating the exertional ventilatory parameters of patients who are unable to perform even spirometry.

This study suggested that inspiratory impedance at rest correlates with exertional ventilatory parameters of CPET better than does expiratory impedance. Inspiratory rather than expiratory oscillometric parameters were reportedly less variable.[7] Airways tend to open during inspiration and the pressure pulses can be transmitted to the periphery, but airflow obstruction during expiration was suggested to occur with inhomogeneity in the lung.[7,33] Hence, the more variability of expiratory oscillometric parameters was probably due to the inhomogeneity of airflow obstruction.[7] In addition, in patients with COPD, loss of lung elastic recoil causes EFL, and more negative ΔX5 and higher inspiratory X5 were considered to predict the presence of EFL.[19,34,35] Therefore, subjects in Subgroup B were estimated to have developed EFL compared with Subgroup A subjects (Table 3). Given that the correlation of Fres-ins with CPET parameters became weak in advanced COPD subjects (Figure 4), EFL and/or dynamic hyperinflation might potentially have associated with the inhomogeneity of airflow obstruction. Therefore, inspiratory impedance might be a more useful parameter for evaluating exertional ventilatory parameters in patients with COPD. In addition, oscillometry might be useful for

Table 7 Spearman's Rank Correlation Coefficient Between Parameters of Respiratory Impedance at Rest, Spirometry, and Cardiopulmonary Exercise Testing at Peak Exercise (n=55)

	V_T ex		V_T ex/Te		f_R		V'_E		V'_{O2}		V_D/V_T	
Oscillometry												
R5												
Inspiratory	−0.560	**	−0.487	**	0.111	NS	−0.491	**	−0.404	**	0.480	**
Expiratory	−0.413	**	−0.329	**	0.063	NS	−0.388	**	−0.322	*	0.358	**
R20												
Inspiratory	−0.490	**	−0.426	**	0.113	NS	−0.438	**	−0.327	*	0.384	**
Expiratory	−0.297	*	−0.241	NS	0.020	NS	−0.309	*	−0.207	NS	0.252	NS
R5-R20												
Inspiratory	−0.558	**	−0.459	**	0.136	NS	−0.457	**	−0.432	**	0.510	**
Expiratory	−0.522	**	−0.427	**	0.063	NS	−0.486	**	−0.439	**	0.422	**
X5												
Inspiratory	0.631	**	0.537	**	−0.163	NS	0.520	**	0.516	**	−0.620	**
Expiratory	0.488	**	0.446	**	−0.049	NS	0.463	**	0.419	**	−0.463	**
Fres												
Inspiratory	−0.676	**	−0.586	**	0.138	NS	−0.566	**	−0.568	**	0.677	**
Expiratory	−0.577	**	−0.533	**	0.027	NS	−0.564	**	−0.514	**	0.554	**
ALX												
Inspiratory	−0.658	**	−0.553	**	0.155	NS	−0.541	**	−0.537	**	0.607	**
Expiratory	−0.517	**	−0.463	**	0.057	NS	−0.489	**	−0.445	**	0.437	**
Spirometry												
FVC	0.770	**	0.798	**	0.115	NS	0.756	**	0.718	**	−0.550	**
FEV_1	0.875	**	0.871	**	0.155	NS	0.903	**	0.823	**	−0.715	**
FEV_1/FVC	0.496	**	0.477	**	0.168	NS	0.556	**	0.470	**	−0.453	**

Notes: *$p<0.05$; **$p<0.01$.
Abbreviations: ALX, low-frequency reactance area; f_R, breathing frequency; FEV_1, forced expiratory volume in 1 second; Fres, resonant frequency; FVC, forced vital capacity; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; Te, expiratory time; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow; X5, respiratory system reactance at 5 Hz.

detecting the inhomogeneity of airflow obstruction in COPD. Further investigations are necessary to validate the hypothesis.

The present study indicated that Fres-ins was the best oscillometric parameter for predicting V'_{O2} and V'_E at peak exercise. Given the stronger correlation between Fres-ins at rest and V_T ex at peak exercise than that between Fres-ins at rest and V_T ex at rest (Figure 3), respiratory reactance at rest might correlate with the degree of V_T expansion. Consequently, Fres-ins might have correlated with V'_{O2} at peak exercise, which is calculated using V'_E: the product of V_T ex and f_R. Given that changes in X5 and Fres related to small airway broncho-dilation in COPD,[36] Fres-ins might have reflected airway obstruction and correlated with V_T ex. Further studies to assess the correlation of Fres-ins with V_T ex might be necessary. The present study suggested that respiratory

impedance measured by oscillometry, particularly respiratory reactance at rest, is useful for evaluating exertional ventilatory parameters quantitatively and can be a complementary tool for predicting exercise tolerance, although the utility of oscillometry was not better than that of spirometry.

In addition, the present study suggested that respiratory reactance correlated with ventilatory inefficiency. In Subgroup B, increased V_D/V_T at peak exercise showed ventilatory inefficiency during exercise (Table 5). This was also supported by the prolonged expiratory time and the shallow breathing pattern (Table 5). Moreover, the correlation between Fres-ins and V_D/V_T indicated that Fres-ins might be used as a surrogate marker for ventilatory inefficiency during exercise because V_D/V_T is a common marker of ventilatory inefficiency.[16,20] Fres-ins might potentially be useful as an index easy to measure
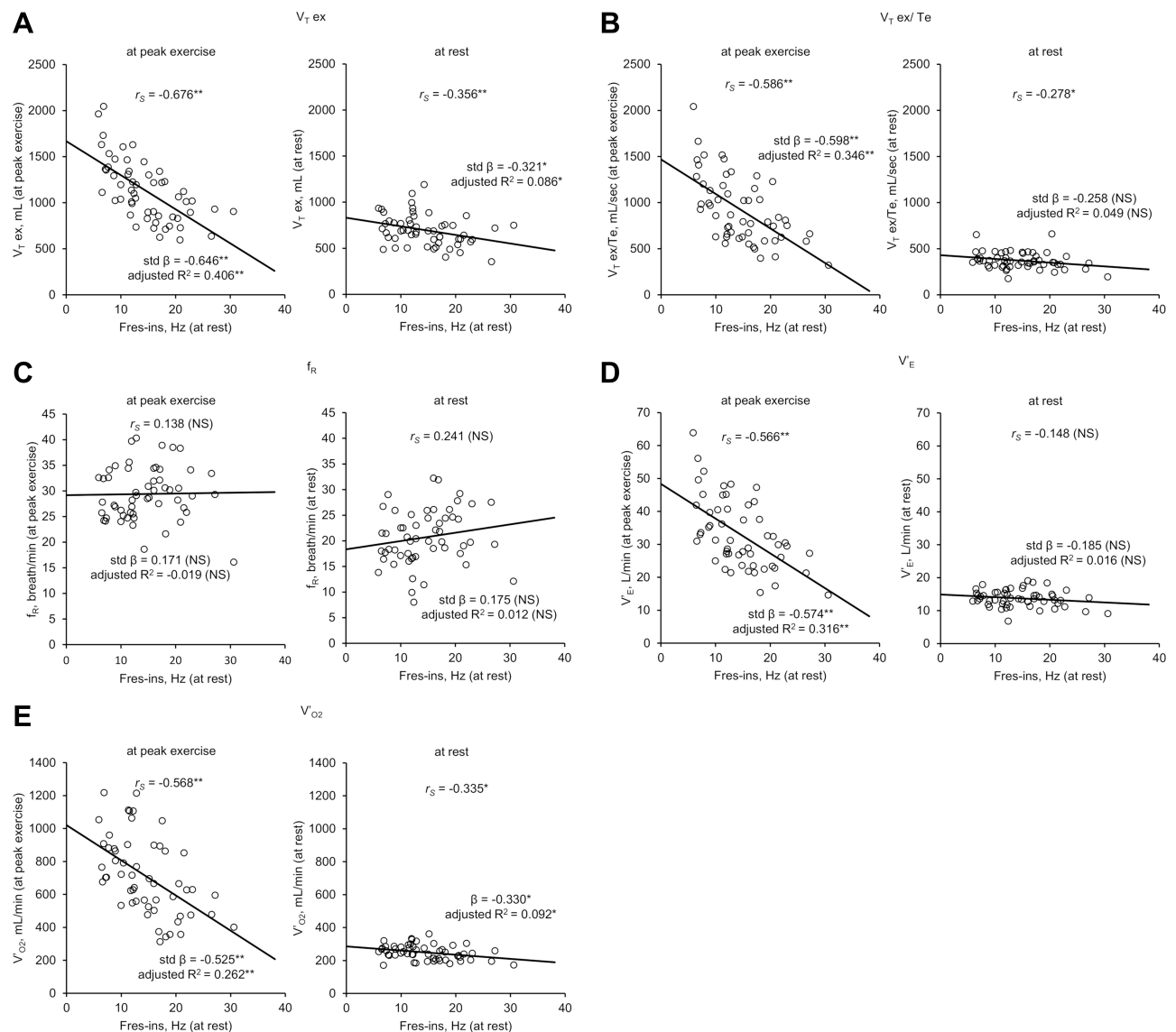
Figure 3 Results of univariate analyses and Spearman's rank correlation coefficient analyses between inspiratory resonant frequency (Fres-ins) at rest and ventilatory parameters of cardiopulmonary exercise testing (CPET) (n=55). In each figure, the graphs on the left show the results of Fres-ins at rest and CPET ventilatory parameters at peak exercise, while those on the right show the results of Fres-ins at rest and ventilatory parameters at rest, respectively. (**A**) Fres-ins and expiratory tidal volume (V_T ex). (**B**) Fres-ins and mean expiratory flow (V_T ex/Te). (**C**) Fres-ins and breathing frequency (f_R). (**D**) Fres-ins and minute ventilation (V'_E). (**E**) Fres-ins and oxygen uptake (V'_{O2}). *$p<0.05$; **$p<0.01$.

Abbreviations: CPET, cardiopulmonary exercise testing; f_R, breathing frequency; Fres-ins, inspiratory resonant frequency; NS, not significant; R^2, R-squared; r_S, Spearman's rank correlation coefficient; std β, standardized regression coefficient estimate; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow.

for adding or choosing interventions to improve ventilatory inefficiency in patients with COPD, although further studies are needed.[37] The present study first showed that oscillometric parameters correlated with ventilatory inefficiency during exercise and indicated the potential role of respiratory impedance for effortlessly assessing exertional ventilatory parameters qualitatively in COPD patients.

The correlation between respiratory impedance and exertional ventilatory parameters can become weak in patients with advanced COPD. In the present study, the more reduced V_T ex/Te in Subgroup B implied that airflow obstruction during exercise became more severe (Table 5). Moreover, as described above, subjects in Subgroup B were estimated to have developed more severe EFL than those in Subgroup A. In addition, the exponential correlations between Fres-ins at rest and CPET parameters at peak exercise showed that the correlations between oscillometry and CPET became weak in COPD subjects
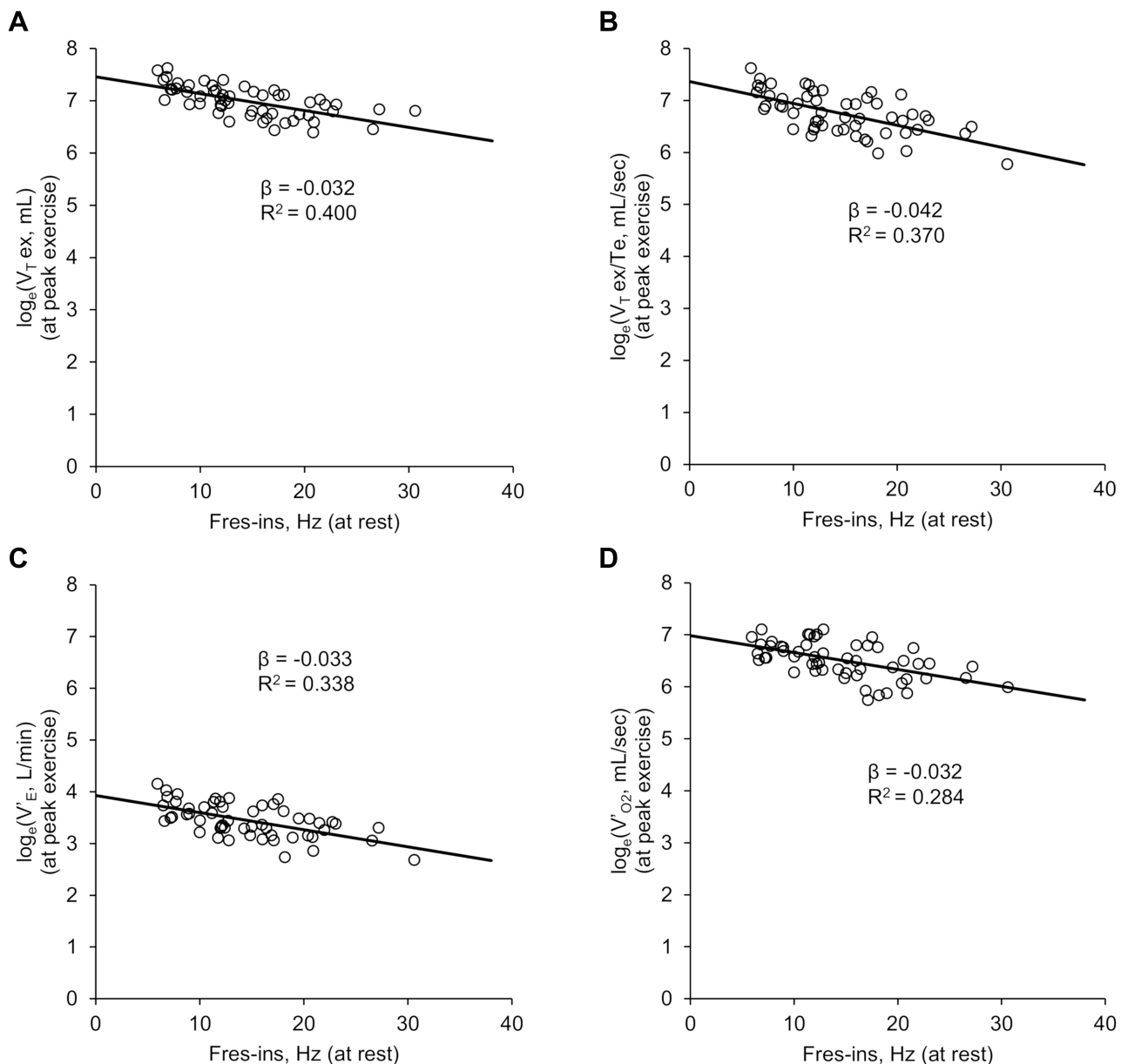
A

$\beta = -0.032$
$R^2 = 0.400$

x-axis: Fres-ins, Hz (at rest)
y-axis: $\log_e(V_T ex, mL)$ (at peak exercise)

B

$\beta = -0.042$
$R^2 = 0.370$

x-axis: Fres-ins, Hz (at rest)
y-axis: $\log_e(V_T ex/Te, mL/sec)$ (at peak exercise)

C

$\beta = -0.033$
$R^2 = 0.338$

x-axis: Fres-ins, Hz (at rest)
y-axis: $\log_e(V'_E, L/min)$ (at peak exercise)

D

$\beta = -0.032$
$R^2 = 0.284$

x-axis: Fres-ins, Hz (at rest)
y-axis: $\log_e(V'_{O2}, mL/sec)$ (at peak exercise)

Figure 4 Results of Spearman's rank correlation coefficient and univariate analyses of the correlation between inspiratory resonant frequency (Fres-ins) at rest and ventilatory parameters of cardiopulmonary exercise testing (CPET) at peak exercise (n=55).Interaction analyses were performed for Fres-ins and natural logarithms of exertional ventilatory parameters of CPET. All the analyses were statistically significant (p<0.01). (**A**) Fres-ins and expiratory tidal volume (V_T ex). (**B**) Fres-ins and mean expiratory flow (V_T ex/Te). (**C**) Fres-ins and minute ventilation (V'_E). (**D**) Fres-ins and oxygen uptake (V'_{O2}).
Abbreviations: β, unstandardized regression coefficient estimate; CPET, cardiopulmonary exercise testing; Fres-ins, inspiratory resonant frequency; R^2, R-squared; V'_E, minute ventilation; V'_{O2}, oxygen uptake; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow.

with severe airflow obstruction (Figure 4). Given these results, oscillometry might not be appropriate for evaluating exertional ventilatory parameters in advanced COPD patients with EFL because wide variations in respiratory reactance level at rest decrease the accuracy of evaluation. The present study included a small number of subjects and was a single-center study; thus, further investigations are needed to validate the hypothesis and to verify the clinical utility of oscillometry in patients with advanced COPD.

The present study had some limitations. First, it was a single-center investigation and some selection bias might have affected the findings. Second, this study included a small number of subjects. In particular, only one female subject was included in the study. In addition, the number

of COPD subjects with each GOLD stage was small. Hence, a larger study population is required to validate the results. Third, this study did not include a healthy control group because only symptomatic subjects who underwent oscillometry, spirometry, and CPET were evaluated retrospectively.

In conclusion, respiratory reactance at rest, particularly Fres-ins, was able to estimate exertional ventilatory parameters of CPET. Inspiratory reactance is useful for effortlessly predicting exertional ventilatory parameters both quantitatively and qualitatively in patients with COPD, but oscillometry might not be appropriate to evaluate exertional ventilatory parameters in patients with advanced COPD with EFL. Further investigations of oscillometry to accurately evaluate exertional ventilatory parameters and to improve the clinical utility are necessary.

Abbreviations

ALX, low-frequency reactance area; β, unstandardized regression coefficient estimate; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; Δ, difference between inspiratory and expiratory phases; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 second; f_R, breathing frequency; Fres, resonant frequency; Fres-ins inspiratory resonant frequency; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IC, inspiratory capacity; ICS, inhaled corticosteroids; IRV, inspiratory reserve volume; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonists; R^2, R-squared; R20, respiratory resistance (Rrs) at 20 Hz; R5, Rrs at 5 Hz; R5-R20, difference between R5 and R20; Rrs, respiratory resistance; r_S, Spearman's rank correlation coefficient; SD, standard deviation; std β, standardized regression coefficient estimate; Te, expiratory time; Ti/Ttot, inspiratory duty cycle; VC, vital capacity; V_D, physiological dead space; V_D/V_T, dead space to tidal volume ratio; V'_E, minute ventilation; V'_E/V'_{CO2}, ventilatory equivalent for carbon dioxide; V'_{O2}, oxygen uptake; V_T, tidal volume; V_T ex, expiratory tidal volume; V_T ex/Te, mean expiratory flow; X5, respiratory reactance (Xrs) at 5 Hz; X5-ins, inspiratory X5; Xrs, respiratory reactance.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary material file.

Ethics Approval and Consent to Participate

The present study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of NHO Osaka Toneyama Medical Center (approval number, TNH-2,019,037). The Institutional Review Board of NHO Osaka Toneyama Medical Center chose an opt-out system to obtain subjects' informed consent.

Author Contributions

YY contributed to conceptualizing and designing the study, data collection and analysis, and wrote the manuscript. KM cared for all the subjects, contributed to conceptualizing and designing the study, data analyses, and revision of the manuscript. TM, KF, YO, HK, KT, and KY contributed to collecting subject data and revising the manuscript. MM and HK contributed to data interpretation and design of the study. All the authors reviewed and approved the submission of the final manuscript.

Disclosure

The authors declare no conflicts of interest in association with the present study.

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