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RESEARCH ARTICLE

Dynamic airway function during exercise in COPD assessed via impulse oscillometry before and after inhaled bronchodilators

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Abstract

Assessing airway function during exercise provides useful information regarding mechanical properties of the airways and the extent of ventilatory limitation in COPD. The primary aim of this study was to use impulse oscillometry (IOS) to assess dynamic changes in airway impedance across a range of exercise intensities in patients with GOLD 1–4, before and after albuterol administration. A secondary aim was to assess the reproducibility of IOS measures during exercise. Fifteen patients with COPD (8 males/7 females; age = 66 ± 8 yr; prebronchodilator FEV_1 = 54.3 ± 23.6%Pred) performed incremental cycle ergometry before and 90 min after inhaled albuterol. Pulmonary ventilation and gas exchange were measured continuously, and IOS-derived indices of airway impedance were measured every 2 min immediately preceding inspiratory capacity maneuvers. Test-retest reproducibility of exercise IOS was assessed as mean difference between replicate tests in five healthy subjects (3 males/2 females). At rest and during incremental exercise, albuterol significantly increased airway reactance (X_5) and decreased airway resistance (R_5, R_5–R_{20}), impedance (Z_5), and end-expiratory lung volume (60% ± 12% vs. 58% ± 12% TLC, main effect P = 0.003). At peak exercise, there were moderate-to-strong associations between IOS variables and IC, and between IOS variables and concavity in the expiratory limb of the spontaneous flow-volume curve. Exercise IOS exhibited moderate reproducibility in healthy subjects which was strongest with R_5 (mean diff. = −0.01 ± 0.05 kPa/L/s; ICC = 0.68), R_5–R_{20} (mean diff. = −0.004 ± 0.028 kPa/L/s; ICC = 0.65), and Z_5 (mean diff. = −0.006 ± 0.021 kPa/L/s; ICC = 0.69). In patients with COPD, exercise evoked increases in airway resistance and decreases in reactance that were ameliorated by inhaled bronchodilators. The technique of exercise IOS may aid in the clinical assessment of dynamic airway function during exercise.

NEW & NOTEWORTHY This study provides a novel, mechanistic insight into dynamic airway function during exercise in COPD, before and after inhaled bronchodilators. The use of impulse oscillometry (IOS) to evaluate airway function is unique among exercise studies. We show strong correlations among IOS variables, dynamic hyperinflation, and shape-changes in the spontaneous expiratory flow-volume curve. This approach may aid in the clinical assessment of airway function during exercise.

bronchodilator; cardiopulmonary exercise test; dynamic airway compression; reactance; resistance

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway inflammation and remodeling which decreases airway caliber and increases flow resistance, primarily in the small airways (1). The resulting expiratory flow limitation (EFL) is exacerbated on exertion by damaged airways that collapse under modest intrathoracic pressures (2). Expiratory flow limitation is usually followed by compensatory increases in end-expiratory lung volume (EELV) (3). Such lung hyperinflation mitigates EFL and preserves neuromechanical coupling of the respiratory system (4) but compromises mechanical-ventilatory efficiency, evokes tidal volume constraint, and increases the work of breathing (4). Dynamic hyperinflation in COPD may also be a consequence of a shortened respiratory duty cycle which results in an inability to exhale to relaxation volume, compounded by premature airway closure during expiration (5). The ability to assess airway function during exercise is, therefore, a crucial step in understanding the mechanisms of exercise intolerance that contribute to impaired quality of life in COPD (6).

There are numerous methods for monitoring dynamic changes in airway function. For instance, expiratory flow

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limitation has been assessed during exercise using forced vital capacity (FVC) maneuvers (7, 8), but the technique has been criticized on the basis that subjects may not be able to perform maximal efforts during periods of elevated ventilation (9). Moreover, because airway diameter is dependent on lung volume (10), forced expiratory maneuvers during exercise may lead to the inaccurate assessment of flow resistance. Other studies have measured pulmonary resistance during exercise by measuring expiratory flow at the mouth simultaneously with dynamic changes in transpulmonary pressure (7). However, not only do these measures require the invasive placement of esophageal and gastric catheters, but exercise may also disrupt the linear relationship between transpulmonary pressure and flow (11). Previously, this laboratory reported that the progressive fall in intrabreath flow during expiration could be quantified by measuring shape changes in the spontaneous expiratory flow-volume (SEFV) curve, wherein flow limitation manifested as concavity in the expiratory limb and concomitant decreases in the rectangular area ratio (RAR) (12–14). In COPD patients, this progressive concavity was ameliorated by bronchodilator therapy (13), which itself correlated with increased exercise tolerance (15). Nevertheless, despite conferring useful information on exercise-induced changes in small airway function, assessing shape changes in the SEFV curve does not provide a direct measure of airway resistance.

Impulse oscillometry (IOS) uses oscillating pressures from sound waves, applied at the mouth, to obtain data on the mechanical properties of conducting airways. The technique provides information on respiratory impedance (Zrs), which comprises respiratory resistance (Rs) and reactance (Xrs). In addition to being noninvasive and simple to perform, the use of multiple oscillation frequencies makes it possible to distinguish between impedance in the proximal (>20 Hz) and distal (<15 Hz) airways (16). In COPD, resting IOS is more sensitive than spirometry for monitoring airway obstruction and the effect of bronchodilator therapy (17–19), and predicts low exercise tolerance in moderately severe patients with COPD (20). Due to the confounding effects of lung volume on airway resistance (21), IOS has been used almost exclusively under resting conditions. However, Seccombe et al. (22) observed that changes in resistance and reactance in asthmatics following an exercise challenge were not unduly influenced by changes in ventilation. They also showed that IOS-derived measures of airway resistance associated closely with the FEV_1 criteria for exercise-induced bronchoconstriction (>10% postexercise decrease) (22). To our knowledge, only Mansfield et al. (23) have used IOS to assess respiratory impedance in asthmatics "during" exercise, but their measures were limited to an oscillation frequency of 9 Hz that confers limited information on the small airways which are the main site of airflow limitation in COPD (24). The IOS method might, therefore, provide complementary mechanistic insights into airway function when EFL develops progressively during exercise. Moreover, exercise-associated changes in airway resistance and reactance and their association with dynamic hyperinflation and exercise limitation in COPD remain unexplored. Such temporal data on the independent and combined effects of exercise and bronchodilators on airway function may inform our understanding of COPD pathophysiology.

The primary aims of this study were to use impedance oscillometry to assess dynamic changes in airway function during incremental exercise in a group of patients with COPD, and to evaluate the effect of inhaled bronchodilators on exercise-associated changes in respiratory impedance. In accordance with previous data (13), we expected bronchodilator medication to relieve EFL and SEFV curve concavity. We additionally hypothesized that there would be mutual correlations among airway impedance, dynamic hyperinflation, and RAR. Given the paucity of data on the use of IOS during exercise, a secondary aim was to assess the reproducibility of the technique during incremental cycle ergometry.

METHODS

Participants

Fifteen patients with COPD (8 males/7 females; age = 66 ± 8 yr; height = 1.69 ± 0.09 m; mass = 79.3 ± 18.1 kg) with Global Obstructive Lung Disease (GOLD) (25) spirometry stage 1 (n = 4; 1 male), stage 2 (n = 4; 1 male), stage 3 (n = 5; 2 males), and stage 4 (n = 1; female), and preserved ratio impaired spirometry (PRISm) (n = 1; male) (26) volunteered to participate in the experimental trials (Table 1). Inclusion criteria for participants with COPD were a postbronchodilator forced expiratory volume in one second (FEV_1) < 80% predicted, age between 40 and 80 yr (inclusive), stable symptoms (no exacerbations within 4 wk), and free from other known comorbidities. The patient group comprised current (n = 3) and former (n = 12) smokers with a group mean of 47.0 ± 45.4 pack yr (range = 14–204 pack yr). Five healthy subjects with

Table 1. *Resting pulmonary function in patients with chronic obstructive pulmonary disease (COPD) (pre- vs. postbronchodilator) and in healthy subjects*

	COPD			
	Pre-BD	Post-BD	*P*	Healthy
TLC, L	6.05 (1.76)	5.95 (1.71)	0.237	6.05 (1.56)
FVC, L	3.28 (1.46)	3.48 (1.45)	<0.001	4.30 (1.48)
FVC, %Pred	88.1 (26.8)	93.9 (24.2)	0.002	101.8 (14.2)
FEV_1, L	1.50 (0.77)	1.68 (0.79)	<0.001	3.14 (1.04)
FEV_1, %Pred	54.3 (23.6)	60.8 (23.1)	<0.001	96.2 (14.9)
FEV_1/FVC, %	46.9 (16.4)	49.8 (16.5)	<0.001	73.6 (5.4)
IC, L	2.46 (1.19)	2.59 (1.09)	0.054	2.88 (0.78)
IC, %Pred	95.7 (34.6)	102.6 (33.9)	0.111	112.0 (40.3)
FRC/TLC, %	59.4 (14.7)	56.9 (11.0)	0.068	52.0 (7.9)
s*R*aw, kPa/s/L	19.6 (16.1)	12.2 (9.3)	0.002	4.68 (1.38)
D_{LCO}, mL/min/mmHg	13.2 (5.4)	13.3 (4.4)	0.314	21.7 (9.0)
AX	2.10 (1.77)	1.31 (1.35)	0.004	1.46 (0.09)
Fres, Hz	22.8 (6.4)	19.0 (5.6)	0.001	9.8 (2.5)
R_5, kPa/L/s	0.49 (0.15)	0.40 (0.11)	0.009	0.26 (0.04)
R_5–R_{20}, kPa/L/s	0.16 (0.11)	0.12 (0.10)	0.006	0.02 (0.02)
X_5, kPa/L/s	−0.24 (0.15)	−0.19 (0.12)	0.007	−0.08 (0.02)
Z_5, kPa/L/s	0.52 (0.20)	0.45 (0.15)	0.006	0.27 (0.05)

Data are means (SD). n = 15. AX, reactance area; BD, bronchodilator; D_{LCO}, diffusing capacity for carbon monoxide; Fres, resonant frequency; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; R_5, resistance at 5 Hz; R_5–R_{20}, resistance at 5 Hz minus resistance at 20 Hz; s*R*AW, specific airway resistance; TLC, total lung capacity; X_5, reactance at 5 Hz; Z_5, impedance at 5 Hz. Reference values for spirometry were taken from the NHANES III study (27); reference values for lung volumes were taken from Wanger et al. (28); reference values for D_{LCO} were taken from MacIntyre et al. (29).

normal lung function (3 males/2 females; age = 57 ± 12 yr; height = 1.71 ± 0.02 m; mass = 75.7 ± 8.4 kg) volunteered to participate in the reproducibility trials (Table 1). The study was approved by the Institutional Review Board of the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center and was conducted in accordance with the Declaration of Helsinki. All subjects abstained from intense exercise for 48 h, consumption of alcohol and caffeine for 12 h, and food intake for 3 h before testing.

Experimental Overview

Participants attended the laboratory on two occasions (separated by ≥48 h) to complete the experimental protocol illustrated in Fig. 1. At the first visit, participants provided written, informed consent, completed two respiratory-related questionnaires, had a resting electrocardiogram (ECG), and performed pre- and postbronchodilator pulmonary function tests (PFTs). Before *visit 2*, participants were asked to refrain from any bronchodilator medication for 2 days. At the second visit, participants performed prebronchodilator PFTs, followed by a ramp-incremental cardiopulmonary exercise test (CPET) on a cycle ergometer during which we assessed pulmonary ventilation and gas exchange, IOS-determined metrics of airway impedance (resistance and reactance), and operating lung volumes. After the CPET, participants received 400 μg albuterol (inhaled through a spacer) and then repeated the CPET following 90-min rest.

Questionnaires

To evaluate the impact of COPD on health status, participants completed the COPD assessment test (CAT) by rating eight different respiratory-related symptoms (cough, phlegm, chest tightness, breathlessness, activities, confidence, sleep, and energy) on a severity scale of 0–5 (31). Tallied scores of 0–10 were interpreted as "low impact," 11–20 as "medium impact," 21–30 as "high impact," and 31–40 as "very high impact" (30, 31). To evaluate health-related quality of life, participants completed the St. George's respiratory questionnaire (SGRQ) (6) comprising 50 items divided into three subscales: symptoms (eight items), activity (16 items), and impacts (26 items). The overall score, and those for each subscale, were calculated using algorithms that adjusted for missing data, and ranged from "0" (no impairment) to "100" (maximum impairment) (32).

Resting Pulmonary Function

Spirometry and plethysmography.

Forced vital capacity and FEV_1 were assessed using spirometry (Vmax Encore, V. 29-7, VIASYS; CA) expressed in absolute values and as percentages of predicted norms (27). Total

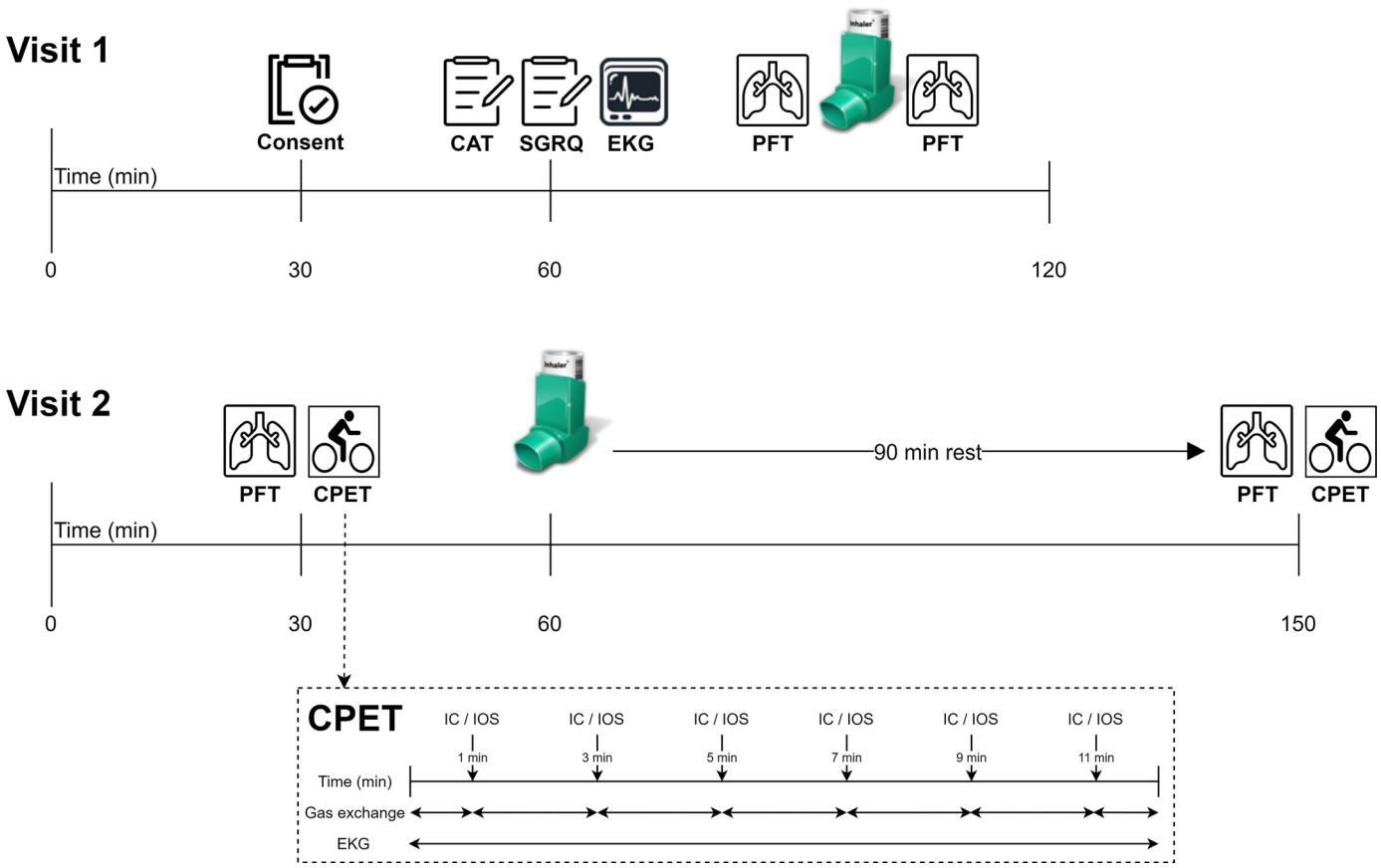

Figure 1. Illustration of the experimental protocol. Tests conducted with COPD patients and healthy subjects were identical except that inhaled bronchodilators were omitted from the latter. CAT, COPD assessment test; CPET, cardiopulmonary exercise test; PFT, pulmonary function tests; SGRQ, St. George's respiratory questionnaire.

lung capacity (TLC) (28) and diffusing capacity for carbon monoxide (D_{LCO}) (29) were determined using an integrated system which included body plethysmography (AutoBox 6200 D, Vmax Encore, V. 29-7). Maximum voluntary ventilation (MVV) was estimated as $FEV_1 \times 40$ (33). Pulmonary function tests were carried out in accordance with recommended standards (28, 29, 34).

Impulse oscillometry.

Airway resistance (Rrs) at 5 Hz (R_5) and 20 Hz (R_{20}), reactance (Xrs) at 5 Hz (X_5), the integrated area of low-frequency reactance (AX) from 5 Hz to resonant frequency (Fres), and respiratory impedance at 5 Hz (Z_5) were each assessed using IOS (Masterscreen IOS Digital, Jaeger; Leibnizstrasse, Germany). During resting measures, participants were seated, had the nose occluded, and were asked to maintain tidal breathing while external pressure was applied to their cheeks by the investigator.

Cardiopulmonary Exercise Test

Participants completed two identical ramp incremental exercise tests on an electromagnetically braked cycle ergometer (Excalibur Sport PFM, Lode; Groningen, The Netherlands). Following seated rest for 3 min, exercise commenced with unloaded cycling (0 W) for 3 min, after which the power output was increased in a ramp fashion by 5 W·min^{-1} (for participants with FEV_1 ≤1.0 L) or 10 W·min^{-1} (for participants with FEV_1 >1.0 L). The work rate increment for healthy subjects ranged from 10–20 W·min^{-1} depending on the anticipated fitness level. The test continued to the limit of tolerance (determined as the point at which the participant exhibited intolerable dyspnea or was unable to maintain a crank cadence >50 rev·min^{-1} despite verbal encouragement) and was designed to elicit an exercise duration of 8–12 min. Minute ventilation ($\dot{V}_E$) and gas exchange ($\dot{V}O_2$, $\dot{V}CO_2$) were measured breath-by-breath via metabolic cart (Vmax Encore, VIASYS), transcutaneous partial pressure of CO_2 ($PtcCO_2$) was measured at the earlobe using a heated sensor (TOSCA 500, Radiometer, Avantor; Lancashire, UK), and heart rate (f_C) via 12-lead electrocardiogram (GE Cardiosoft V. 6.73, VIASYS). The ratio of pulmonary deadspace to tidal volume (V_D/V_{Ttc}) was calculated post hoc (35). Every 2 min, IOS metrics and inspiratory capacity (IC) were recorded. Peak CPET variables were calculated as the 30 s mean before peak exercise.

Operating lung volumes.

Inspiratory capacity maneuvers were performed during exercise to determine the magnitude of dynamic hyperinflation (4, 36), based on the assumption that TLC remains unchanged. Inspiratory capacity maneuvers were performed in triplicate at rest, once during unloaded cycling, and every 2 min during the incremental ramp commencing at the first minute. Maneuvers were performed following several spontaneous tidal breaths to establish a stable end-expiratory lung volume (EELV). End-expiratory lung volume was calculated by subtracting IC from TLC. End-inspiratory lung volume (EILV) was calculated as the sum of EELV and tidal volume (V_T). Both EELV and EILV were expressed as a percentage of TLC.

Exercise impulse oscillometry.

Impulse oscillometry was used to assess changes in airway resistance and reactance during exercise, and to determine the effects of inhaled bronchodilators on these variables. To accomplish this, participants were asked to continue cycling but switch from breathing through the mouthpiece used for recording gas exchange to that used for IOS. During each IOS measurement, external pressure was applied by the investigator to the participant's cheeks. Following the automated IOS assessment (~20 s), participants switched back to the gas exchange mouthpiece.

Spontaneous expiratory flow-volume loop.

To assess the SEFV loop for concavity a breath-by-breath geometric analysis was performed on the airflow signal using custom-written software in IGOR Pro (Wavemetrics; OR). Briefly, the algorithm isolated the expiratory limb of the loop and defined the reference rectangle using two anchoring points: *1*) the maximum expiratory flow ($\dot{V}_{max}$); and *2*) the point at which flow rapidly turned toward "zero" and transitioned from expiration to inspiration ($\dot{V}_{EE}$) (12). The rectangular area ratio (RAR) was defined as the ratio of the integrated area under the SEFV curve between the two anchors to the entire area of the rectangle. A RAR <0.5 reflects concavity in the descending limb of the expiratory curve, whereas value >0.5 reflects convexity (12).

Reproducibility of Exercise IOS

Given that lung function in respiratory disease can be unstable (37) and confounded by intraindividual day-to-day perturbations in the lung function response to β-2 agonists (38), we opted to assess exercise IOS reproducibility in healthy subjects. Test-retest data were collected from five individuals during two incremental exercise tests which followed the same protocol as that implemented with our patients (bronchodilators excluded).

Data Processing

For the SEFV analysis, the analog flow signal obtained from the metabolic cart was digitized at 100 Hz with a 16-bit analog-to-digital converter (National Instruments, USB-6002 DAQ Module; TX) and then stored on a personal computer. These data were later analyzed using custom-written code and adapted to IGOR Pro (Wavemetrics), as previously described (12). The SEFV data were processed to produce 10 s intervals and then aligned with gas exchange and the IOS measures. Exercise IOS measures were compared between pre- and postbronchodilator values at rest, during exercise at 0 W (unloaded), at 6, 4, and 2 min before intolerance (P6, P4, and P2, respectively), and at peak exercise. Impulse oscillometry data were further analyzed relative to the respective ventilatory demand, determined as $\dot{V}_E/MVV$.

Statistics

Statistical analyses were performed using IBM SPSS Statistics v24 (IBM; IL). Exercise IOS measures (AX, Fres, R_5, R_5–R_{20}, X_5, and Z_5) and operating lung volumes (EILV and EELV) pre- and postbronchodilator were compared at increasing $\dot{V}_E/MVV$, using a two-way repeated-measures ANOVA.

Table 2. *Peak physiological responses to cardiopulmonary exercise tests in patients with chronic obstructive pulmonary disease (COPD) (pre- vs. postbronchodilator) and in healthy subjects [initial cardiopulmonary exercise test (CPET)]*

	COPD			Healthy
	Pre-BD	Post-BD	*P*	
W_{peak}, W	76 (35)	80 (33)	0.793	119 (36)
f_{Cpeak}	117 (18)	121 (18)	0.571	132 (25)
$\dot{V}O_{2peak}$, L/min	1.28 (0.44)	1.32 (0.42)	0.287	1.57 (0.60)
$\dot{V}CO_{2peak}$, L/min	1.39 (0.57)	1.43 (0.52)	0.284	1.92 (0.74)
$\dot{V}_{Epeak}$, L/min	46.6 (19.3)	50.2 (17.6)	0.023	57.0 (21.2)
$\dot{V}_E/\dot{V}O_2$	36.3 (6.4)	38.1 (6.3)	0.019	35.6 (1.9)
$\dot{V}_E/\dot{V}CO_2$	34.5 (5.8)	35.9 (6.5)	0.045	29.3 (1.2)
$\dot{V}_E$/MVV, %	82.7 (19.7)	77.6 (16.2)	0.158	45.5 (6.6)
V_T, L	1.36 (0.46)	1.49 (0.52)	0.010	2.08 (0.64)
f_R, br/min	30.6 (5.8)	28.8 (6.0)	0.015	28.0 (5.9)
V_D/V_{Ttc}	0.28 (0.13)	0.29 (0.13)	0.818	0.24 (0.06)
P_{ETCO_2}, mmHg	36.7 (5.3)	35.1 (5.0)	0.359	37.4 (1.6)
$PtcCO_2$, mmHg	41.9 (7.8)	40.8 (5.3)	0.693	39.5 (2.5)
RAR	0.52 (0.09)	0.53 (0.09)	0.125	0.62 (0.39)
AX, kPa/L	3.31 (2.44)	2.32 (2.17)	0.014	0.25 (0.25)
Fres, Hz	28.2 (7.4)	24.8 (7.7)	0.011	13.9 (4.2)
R_5, kPa/L/s	0.67 (0.18)	0.56 (0.20)	0.011	0.33 (0.05)
R_5–R_{20}, kPa/L/s	0.29 (0.17)	0.23 (0.18)	0.048	0.04 (0.03)
X_5, kPa/L/s	−0.21 (0.27)	−0.19 (0.18)	0.673	−0.05 (0.04)
Z_5, kPa/L/s	0.69 (0.20)	0.57 (0.18)	0.017	0.34 (0.05)

Data are means (SD). n = 15. AX, reactance area; BD, bronchodilator; f_C, cardiac frequency; Fres, resonant frequency; MVV, maximum voluntary ventilation; P_{ETCO_2}, partial pressure of end-tidal CO_2; $PtcCO_2$, partial pressure of CO_2 by transcutaneous measurement; RAR, rectangular area ratio; R_5, resistance at 5 Hz; R_5–R_{20}, resistance at 5 Hz minus resistance at 20 Hz; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, CO_2 output; $\dot{V}_E$, minute ventilation; V_D/V_{Ttc}, ratio of physiologic dead space to tidal volume estimated using transcutaneous P_{CO_2} measurement; W, power; X_5, reactance at 5 Hz; Z_5, impedance at 5 Hz.

Bonferroni-adjusted post hoc tests were used in the case of significant interactions. Effect size was estimated using the partial eta-squared (η^2_p) method and categorized as small (<0.01), medium (0.01–0.14), and large (>0.14) (39). The independent associations between peak exercise IOS and RAR, and between peak exercise IOS and IC (grouped for pre- and postbronchodilator) were assessed using Spearman's rank correlation. Test-retest reproducibility of IOS measures were assessed using mean difference (*test 1* − *test 2*), a one-sample *t* test for mean difference versus a hypothesized mean of "0," 95% limits of agreement (95% LoA), and intraclass correlation coefficient (ICC). Data are presented as means (SD) (unless stated), and α level was specified a priori as 0.05.

RESULTS

Questionnaires

The group mean CAT score was 15 ± 6 (range 10–29) which denoted a "medium impact" of COPD on health status. For the SGRQ, total score was calculated as 41 ± 14 (range 18–66) and comprised a symptom score of 49 ± 20 (range 16–74), an activity score of 60 ± 19 (range 30–87), and an impact score of 27 ± 17 (range 2–62).

Pulmonary Function and Exercise Tolerance

Resting pulmonary function is shown in Table 1. Patients with COPD generally exhibited a moderate-to-severe obstructive pattern. Following inhaled albuterol, nearly all group-mean metrics of spirometry, plethysmography, and IOS improved significantly, manifesting as increases in capacities and flows, increases (improvements) in reactance, and decreases in resistance ($P < 0.05$). Diffusing capacity (D_{LCO}) was unaffected by albuterol. Peak physiological responses to CPET are shown in Table 2. Following inhaled albuterol, there were no statistically significant increases in peak power or $\dot{V}O_2$, and no change in the ratio of physiologic dead space to tidal volume (V_D/V_{Ttc}). We did, however, observe a significant reduction in airway resistance (R_5 and R_5–R_{20}; $P < 0.05$) congruent with significant increases in $\dot{V}_E$ and V_T. Patients exhibited poor exercise tolerance, with moderate ventilatory limitation characterized by high end-exercise $\dot{V}_E$/MVV (83% ± 20%), which was not significantly altered by bronchodilator treatment (78% ± 16%). None of the patients desaturated appreciably at end-exercise (Sp_{O_2peak} = 97.0% ± 2.6%; range = 91%–100%).

Reproducibility of Exercise IOS

We assessed the between-trial reproducibility of exercise IOS measures in five healthy adults (Table 1). Lung function in this group was within normal limits (FEV_1 = 96% ± 15% predicted; FEV_1/FVC = 73.6% ± 5.4%). Grouped reproducibility of IOS measures (rest and exercise) is shown in Table 3. Overall, the mean difference between *test 1* and *test 2* was generally low and was not significantly different from a hypothesized mean of "0" for any measure (AX, R_5, R_5–R_{20}, X_5, Z_5; $P > 0.05$) except Fres (P = 0.031). Reproducibility using ICC was moderate for R_5 (r = 0.682, P = 0.002), R_5–R_{20} (r = 0.647, P = 0.004), and Z_5 (r = 0.689, P = 0.003). Mean difference (*test 1* − *test 2*) at rest and for each exercise stage is shown in Table 4. Only the between-test difference in Fres at peak exercise was significantly different from "0" (P = 0.035), showing this measure to

Table 3. *Within-day, between-trial reproducibility of IOS measures in healthy subjects (rest and exercise, all timepoints)*

	Mean Difference (SD)	OS *t* Test	95% LoA	ICC (*P* Value)
AX, kPa/L	−0.02 (0.16)	0.300	−0.33, 0.30	0.212 (0.271)
Fres, Hz	−0.93 (2.63)	0.031	−6.08, 4.22	0.816 (<0.001)
R_5, kPa/L/s	−0.01 (0.05)	0.257	−0.10, 0.09	0.682 (0.002)
R_5–R_{20}, kPa/L/s	−0.004 (0.028)	0.235	−0.059, 0.051	0.647 (0.004)
X_5, kPa/L/s	0.002 (0.036)	0.378	−0.068, 0.073	0.403 (0.095)
Z_5, kPa/L/s	−0.006 (0.021)	0.263	−0.035, 0.046	0.689 (0.003)

Data are means (SD). n = 5. AX, reactance area; Fres, resonant frequency; ICC, intraclass correlation coefficient; LoA, limits of agreement; OS *t* test, one-sample *t* test; R_5, resistance at 5 Hz; R_5–R_{20}, resistance at 5 Hz minus resistance at 20 Hz; X_5, reactance at 5 Hz; Z_5, impedance at 5 Hz.

Table 4. *Mean difference (test 1 − test 2) of impulse oscillometry (IOS) measures by exercise stage in healthy subjects*

	Ax (SD), kPa/L	Fres (SD), Hz	R_5 (SD), kPa/L/s	R_5–R_{20}, (SD) kPa/L/s	X_5 (SD), kPa/L/s	Z_5 (SD), kPa/L/s
Rest	0.006 (0.015)	0.466 (0.753)	0.002 (0.034)	0.012 (0.013)	0.002 (0.011)	0.002 (0.034)
Unloaded (0 W)	0.086 (0.149)	1.718 (3.514)	0.026 (0.053)	0.018 (0.030)	0.010 (0.029)	0.028 (0.048)
Peak −6 min	0.026 (0.206)	0.354 (2.807)	0.030 (0.051)	0.012 (0.031)	0.002 (0.043)	0.030 (0.051)
Peak −4 min	0.002 (0.056)	0.302 (2.632)	0.008 (0.030)	0.008 (0.016)	0.000 (0.021)	0.008 (0.033)
Peak −2min	0.038 (0.128)	2.713 (3.009)	0.000 (0.048)	0.000 (0.028)	0.005 (0.013)	0.003 (0.053)
Peak	0.050 (0.311)	2.038 (1.860)*	0.026 (0.048)	0.020 (0.037)	0.006 (0.073)	0.024 (0.048)

Data are means (SD). n = 5. AX, reactance area; Fres, resonant frequency; R_5, resistance at 5 Hz; R_5–R_{20}, resistance at 5 Hz minus resistance at 20 Hz; X_5, reactance at 5 Hz; Z_5, impedance at 5 Hz; *Significantly different vs. 0 ($P < 0.05$).

be poorly reproducible at elevated ventilations. However, there was no pattern of change in either mean difference (*test 1 − test 2*), 95% LoA, or ICC with increasing $\dot{V}_E$/MVV.

Exercise IOS

Average IOS measures at the respective $\dot{V}_E$/MVV during incremental exercise in patients with COPD, before and after inhaled bronchodilators, are shown in Fig. 2. Two female patients with GOLD stage 3 (73 yr) and 4 (65 yr), respectively, were unable to exercise beyond unloaded cycling (0 W). Both were excluded from the temporal analysis (i.e., IOS responses and operating lung volumes during exercise; n = 13) but were retained for the independent correlational analysis (i.e., IOS vs. RAR and IOS vs. IC at peak exercise; n = 15).

AX.

There was a statistically significant main effect of bronchodilator on AX [$F_{(1,12)}$ = 25.56, $P < 0.001$, η^2_p = 0.68, Fig. 2*A*], showing that AX was lower postbronchodilator (2.14 ± 0.38 vs. 1.44 ± 0.27 kPa·L^{-1}). There was no main effect of ventilatory demand [$F_{(1.54,18.42)}$ = 3.04, P = 0.083, η^2_p = 0.20] and no condition × ventilation interaction [$F_{(2.48,29.74)}$ = 0.35, P = 0.752, η^2_p = 0.03].

Fres.

There was a statistically significant main effect of bronchodilator on Fres [$F_{(1,12)}$ = 24.96, $P < 0.001$, η^2_p = 0.68, Fig. 2*B*], showing that Fres was lower postbronchodilator (23.9 ± 1.9 vs. 20.6 ± 1.9 Hz). There was a main effect of ventilatory demand [$F_{(2.76,33.08)}$ = 10.29, $P < 0.001$, η^2_p = 0.46], showing that Fres was higher at peak exercise (P = 0.003), and at P2 (P = 0.029) when compared to rest. There was no condition × ventilation interaction [$F_{(2.76,33.16)}$ = 0.296, P = 0.812, η^2_p = 0.02].

R_5.

There was a statistically significant main effect of bronchodilator on R_5 [$F_{(1,12)}$ = 22.04, P = 0.001, η^2_p = 0.65, Fig. 2*C*], showing that R_5 was lower postbronchodilator (0.55 ± 0.06 vs. 0.48 ± 0.04 kPa·L·s^{-1}). There was a main effect of ventilatory demand [$F_{(1.99,23.84)}$ = 6.96, P = 0.004, η^2_p = 0.37], showing that R_5 was higher at peak exercise (P = 0.010), at P2 (P = 0.005), at P4 (P = 0.009), and during unloaded exercise (P = 0.008) when compared with the rest. There was no condition × ventilation interaction [$F_{(2.49,29.93)}$ = 1.28, P = 0.298, η^2_p = 0.10].

R_5–R_{20}.

There was a statistically significant main effect of bronchodilator on R_5–R_{20} [$F_{(1,12)}$ = 14.26, P = 0.003, η^2_p = 0.54, Fig. 2*D*], showing that R_5–R_{20} was lower post-bronchodilator (0.21 ± 0.04 vs. 0.17 ± 0.03 kPa·L·s^{-1}). There was a main effect of ventilatory demand [$F_{(1.60,19.19)}$ = 6.34, P = 0.011, η^2_p = 0.35], showing that R_5–R_{20} was higher at peak exercise (P = 0.015), at P2 (P = 0.013), at P4 ($P < 0.001$), at P6 (P = 0.003), and during unloaded exercise (P = 0.004) when compared with the rest. There was no condition × ventilation interaction [$F_{(2.61,31.32)}$ = 0.34, P = 0.766, η^2_p = 0.03].

X_5.

There was a statistically significant main effect of bronchodilator on X_5 [$F_{(1,12)}$ = 12.03, P = 0.005, η^2_p = 0.50, Fig. 2*E*], showing that X_5 was higher postbronchodilator (−0.21 ± 0.02 vs. −0.17 ± 0.01 kPa·L·s^{-1}]. There was no main effect of ventilatory demand [$F_{(1.40,16.78)}$ = 0.224, P = 0.722, η^2_p = 0.02], and no condition × ventilation interaction [$F_{(5,60)}$ = 0.54, P = 0.748, η^2_p = 0.04].

Z5.

There was a statistically significant main effect of bronchodilator on Z5 [$F_{(1,12)}$ = 26.18, $P < 0.001$, η^2_p = 0.69, Fig. 2*F*], showing that Z5 was lower postbronchodilator (0.60 ± 0.06 vs. 0.51 ± 0.05 kPa·L·s^{-1}). There was a main effect of ventilatory demand [$F_{(1.62,19.44)}$ = 5.04, P = 0.022, η^2_p = 0.30], showing that Z5 was higher at P2 (P = 0.044), at P4 (P = 0.004), at P6 (P = 0.037), and during unloaded exercise (P = 0.005) when compared with the rest. There was no condition × ventilation interaction [$F_{(2.34,28.03)}$ = 0.78, P = 0.489, η^2_p = 0.06].

Operating Lung Volumes

Operating lung volumes (EELV and EILV) at rest and during exercise in patients with COPD, before and after inhaled bronchodilators, are shown in Fig. 3.

EELV.

There was a statistically significant main effect of bronchodilator on EELV [$F_{(1,12)}$ = 13.24, P = 0.003, η^2_p = 0.52], showing that EELV was lower postbronchodilator (60 ± 12 vs. 58% ± 12% TLC]. There was a main effect of ventilatory demand [$F_{(2.11,25.37)}$ = 17.73, $P < 0.001$, η^2_p = 0.60], showing that EELV increased above resting values at P4 (P = 0.015), at P2 (P = 0.010), and at peak exercise (P = 0.001). There was no condition × ventilation interaction [$F_{(5.0,60.0)}$ = 0.94, P = 0.465, η^2_p = 0.07].

EILV.

There was no statistically significant main effect of bronchodilator on EILV [$F_{(1,12)}$ = 0.06, P = 0.811, η^2_p = 0.01]. There was

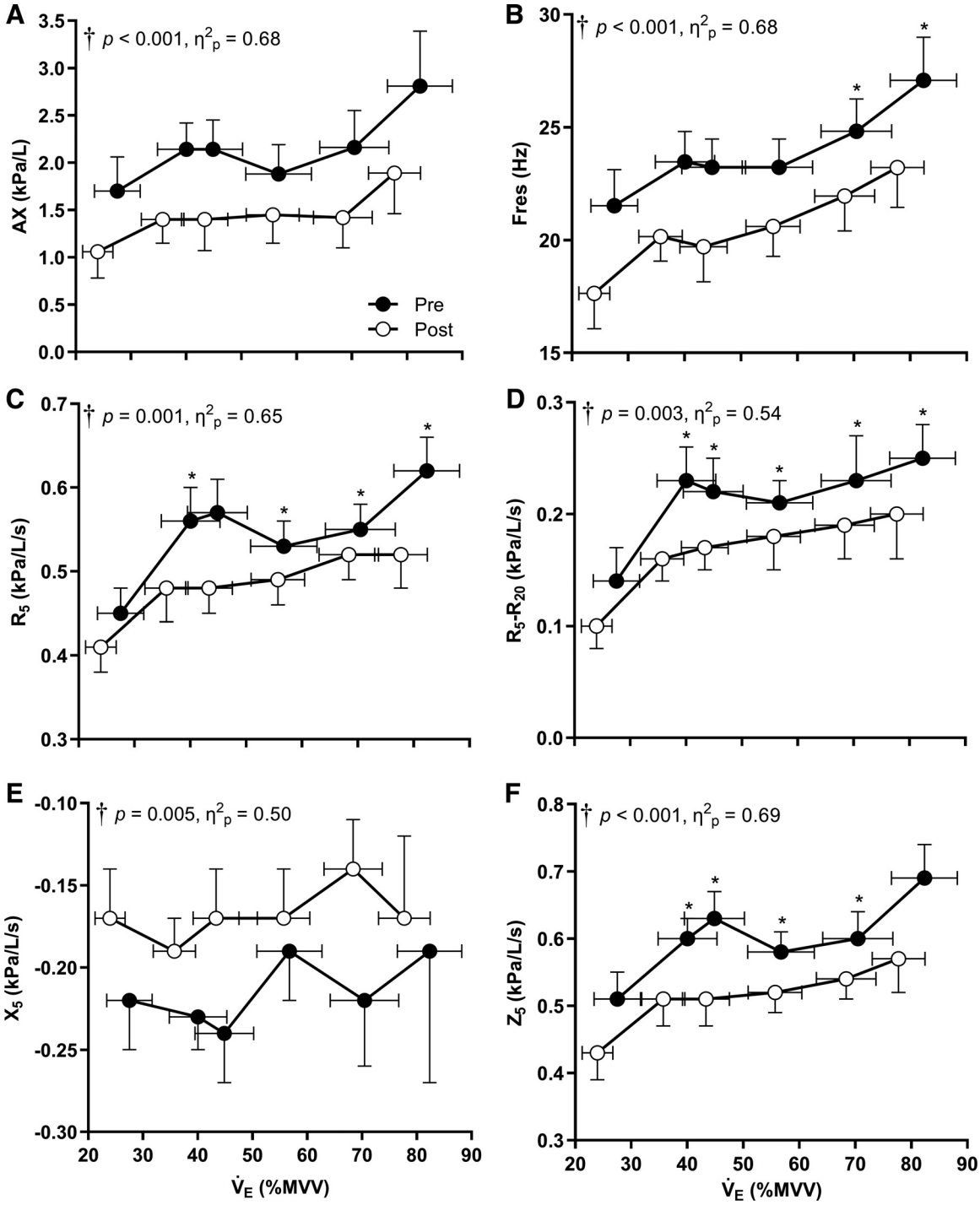

Figure 2. Impulse oscillometry in patients with chronic obstructive pulmonary disease (COPD) during incremental exercise before and after inhaled albuterol; AX (*A*), Fres (*B*), R_5 (*C*), R_5–R_{20} (*D*), X_5 (*E*), and Z_5 (*F*) as a function of $\dot{V}_E$/MVV. ●, prebronchodilator; ○, postbronchodilator. Data are means ± SE (illustrating uncertainty in the mean temporal response) ($n = 13$). †Statistically significant main effect of bronchodilator. *Significantly different versus rest ($P < 0.05$).

a main effect of ventilatory demand [$F_{(2.12,25.48)} = 55.30$, $P < 0.001$, $\eta^2_p = 0.82$], showing that EILV increased above baseline during unloaded exercise ($P = 0.027$), at P6 ($P = 0.005$), at P4 ($P < 0.001$), at P2 ($P < 0.001$), and at peak exercise ($P = 0.001$). There was a statistically significant condition × ventilation interaction [$F_{(2.41,28.880)} = 9.69$, $P < 0.001$, $\eta^2_p = 0.45$], but post hoc tests revealed interactions at any given $\dot{V}_E$/MVV.

Correlations

Exercise IOS versus expiratory flow-volume configuration.

Associations between RAR and AX, Fres, R_5, X_5, R_5–R_{20}, and Z_5 at peak exercise (pre- and postbronchodilator) are shown in Fig. 4. Spearman's rank correlations show a strong

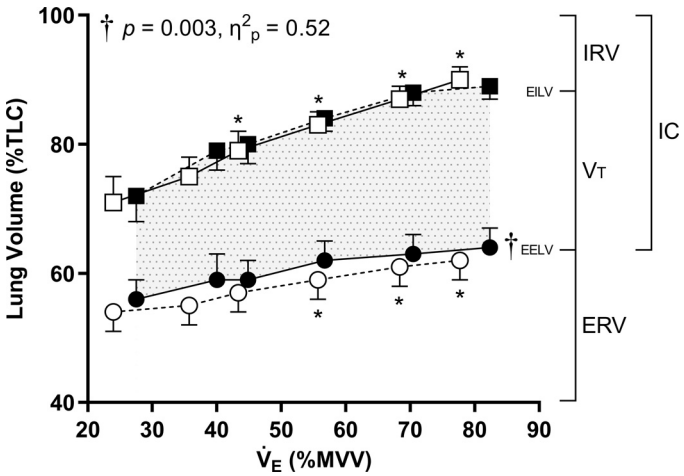

Figure 3. Operating lung volumes (EELV and EILV) in patients with chronic obstructive pulmonary disease (COPD) as a function of $\dot{V}_E$/MVV during incremental exercise before and after inhaled albuterol. ●■, pre-bronchodilator; ○□, postbronchodilator. Data are means ± SE (illustrating uncertainty in the mean temporal response) (n = 13). †Statistically significant main effect of bronchodilator (EELV only). *Significantly different vs. rest (P < 0.05). EELV, end-expiratory lung volume; EILV, end-expiratory lung volume; ERV, expiratory reserve volume; IRV, inspiratory reserve volume; V_T, tidal volume; IC, inspiratory capacity.

negative correlation between RAR and AX (r = −0.733; P < 0.001, Fig. 4*A*), between RAR and Fres (r = −0.652; P < 0.001, Fig. 4*B*), between RAR and R_5 (r = −0.539, P < 0.001, Fig. 4*C*), between RAR and R_5–R_{20} (r = −0.688; P < 0.001, Fig. 4*D*), and a strong positive correlation between RAR and X_5 (r = 0.559; P = 0.001, Fig. 4*E*). There was a moderate negative correlation between RAR and Z5 (r = −0.307, P < 0.001, Fig. 4*F*).

Exercise IOS versus inspiratory capacity.
Associations between IC and AX, Fres, R_5, X_5, R_5–R_{20}, and Z_5 at peak exercise (pre- and postbronchodilator) are shown in Fig. 5. Spearman's rank correlations show a strong negative correlation between IC and R_5 (r = −0.598; P < 0.001, Fig. 5*C*), between IC and R_5–R_{20} (r = −0.542; P = 0.002, Fig. 5*D*), and a moderate negative correlation between IC and AX (r = −0.424; P = 0.019, Fig. 5*A*), and between IC and Z5 (r = −0.35, P = 0.002, Fig. 5*F*). There was no significant correlation between IC and either Fres (Fig. 5*B*) or X_5 (Fig. 5*E*).

DISCUSSION

The primary aims of this study were to use impedance oscillometry to assess dynamic changes in airway function during incremental exercise in a group of patients with COPD, and to evaluate the effect of inhaled bronchodilators on exercise-associated changes in respiratory impedance. We made several important findings: *1*) incremental exercise statistically increased airway resistance in patients with COPD; *2*) inhaled bronchodilators significantly decreased resistance and increased (improved) reactance at rest and during exercise in COPD, but without significantly improving exercise capacity/tolerance; and *3*) IOS variables showed strong correlations with changes in operating lung volumes and flow-volume loop configuration. In line with our secondary aim, we demonstrated moderate test-retest reproducibility of IOS-derived airway resistance and net impedance during exercise in healthy subjects. Collectively, these data may have important implications for the clinical assessment of airway function in obstructive lung disease.

Respiratory Impedance during Exercise in COPD

We observed that respiratory resistance increased with increasing ventilatory demand in patients with COPD (Fig. 2). At peak exercise, resistance in the distal airways was significantly reduced following inhaled albuterol (R_5 = 0.67 ± 0.18 vs. 0.56 ± 0.20 kPa·L^{-1}·s^{-1}; R_5–R_{20} = 0.29 ± 0.17 vs. 0.19 ± 0.18 kPa·L^{-1}·s^{-1}) without a significant reduction in $\dot{V}_E$/MVV (83% ± 20% vs. 78% ± 16%; P = 0.158). Several studies have assessed airway resistance during exercise indirectly using forced expiratory efforts (7, 8), and others have assessed pulmonary resistance using ratios of expiratory flow and intrathoracic pressures (7, 40). Mansfield et al. (23) used a modified IOS device to assess airway function at an oscillation frequency of 9 Hz, and Eisenberg et al. (41) used body plethysmography (interrupter technique) to assess airway resistance at a single work rate of ~75 W. Thus, to our knowledge, ours is the first study to employ multiple frequencies to assess resistance and reactance in both the distal and proximal airways across a range of exercise intensities to intolerance.

The high airway resistance exhibited by patients with COPD at rest is assumed to be due to airway remodeling, mucus secretions, and/or chronic airway inflammation (2). During exercise, however, our data show that dynamic changes in airway resistance in COPD result from a balance among various interrelated mechanisms, which are mediated by both ventilatory demand and albuterol administration. For example, at increasing levels of $\dot{V}_E$/MVV, airway patency would be expected to be retained owing to the passive component of parenchymal tethering (42) and the positive effects of exercise-induced bronchodilation (43), thereby reducing airway resistance. However, at higher ventilatory demands (presumably when the equilibrium radius of the airway smooth muscle was surpassed), we observed an increase in airway resistance (Fig. 2), suggesting that other factors (e.g., dynamic airway collapse and mucus secretions) play an increasingly important role. Airway resistance during exercise may be differentially influenced by bronchodilators. Indeed, a postalbuterol fall in EELV (Fig. 3) would be expected to increase airway resistance due to reduced diameter of the small airways (44). However, we observed a net decrease in airway resistance following albuterol administration, and this is consistent with the notion that albuterol-mediated changes in bronchial smooth muscle tone may be the prevailing mechanism underpinning improvements in airway resistance following inhaled bronchodilators during exercise, particularly in chronic bronchitis. Our study is the first to empirically demonstrate this using impulse oscillometry.

It was anticipated that elevated airway resistance during exercise and subsequent expiratory flow limitation would result in shape changes to the spontaneous expiratory flow volume curve and compensatory decreases in IC. Indeed, we observed a negative association between airway resistance

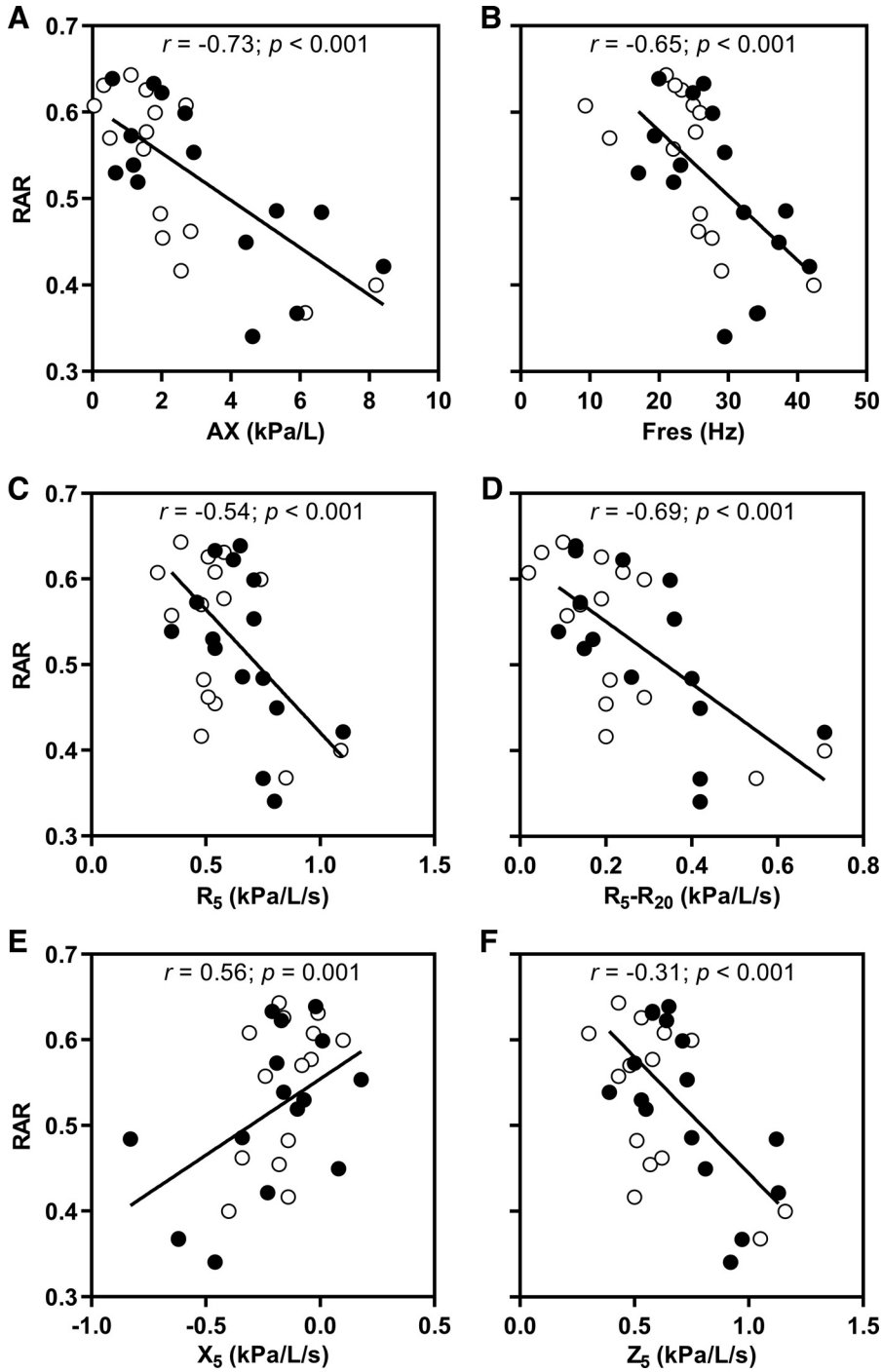

Figure 4. Associations between rectangular area ratio (RAR) and impulse oscillometry (IOS) variables at peak exercise in patients with chronic obstructive pulmonary disease (COPD) (pre- and postbronchodilator; $2 \times n = 15$). AX (*A*), Fres (*B*), R_5 (*C*), R_5–R_{20} (*D*), X_5 (*E*), and Z_5 (*F*). ●, prebronchodilator; ○, postbronchodilator.

and RAR (Fig. 4), and progressive dynamic hyperinflation with increasing ventilatory demand both before and after the administration of inhaled bronchodilators (Fig. 3). The dynamic decreases in IC occurred congruent with changes in airway impedance. Furthermore, IC at peak exercise was correlated with both R_5 and R_5–R_{20} (Fig. 5), which supports the notion that dynamic hyperinflation may have occurred owing to the intensity-mediated increase in airway resistance. Interestingly, we found that albuterol increased IC by ~2% at rest, but increased IC by up to 4% during low-intensity (unloaded) exercise, suggesting bronchodilators may exert a more pronounced effect on operating lung volumes during exercise when airway resistance is greater. We further demonstrate that mitigating airway resistance (and dynamic hyperinflation) at rest using an inhaled bronchodilator, exerts an effect that persists into exercise. Given that dyspnea in COPD is underpinned by a complex relationship among EFL, dynamic hyperinflation (45), and increased neural respiratory drive (46, 47), we would expect diminished respiratory impedance, attenuated dynamic hyperinflation, and an increased RAR in our group of patients with COPD to confer less respiratory distress.

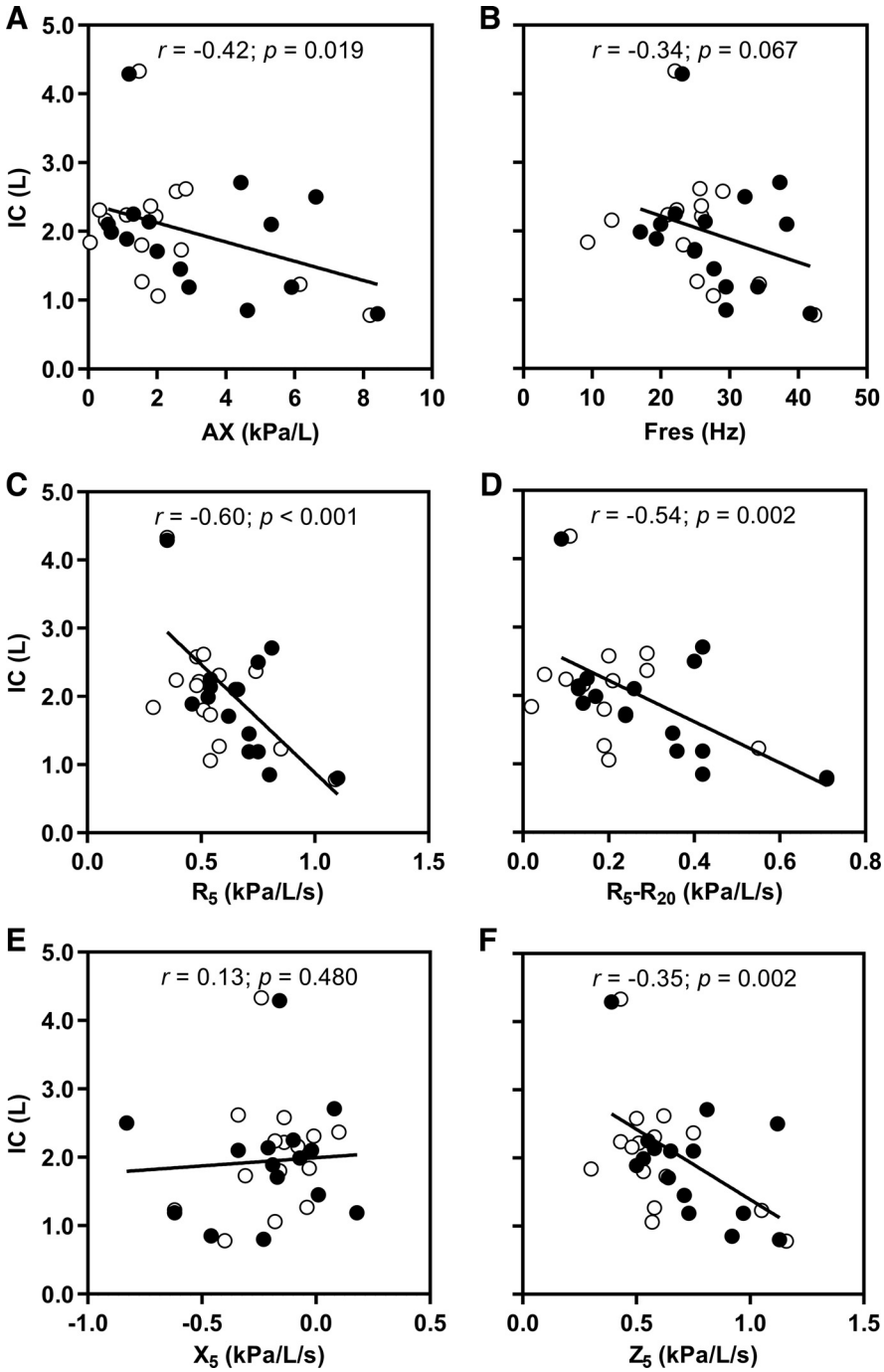

Figure 5. Associations between dynamic hyperinflation (IC) and impulse oscillometry (IOS) variables at peak exercise in patients with chronic obstructive pulmonary disease (COPD) (pre- and postbronchodilator; $2 \times n = 15$). AX (*A*), Fres (*B*), R_5 (*C*), R_5–R_{20} (*D*), X_5 (*E*), and Z_5 (*F*). ●, prebronchodilator; ○, postbronchodilator.

At rest, bronchodilator-mediated changes in airway resistance closely relate to improvements in lung mechanics and dyspnea in COPD (48). Although these positive changes in airway function may be expected to prolong exercise time, there is a poor association between lung function at rest and exercise capacity in COPD. Moreover, short-term improvements in lung function following bronchodilation do not reliably increase exercise capacity (49). Our data reenforce this notion in that, following the administration of a β2 agonist, we observed no change in $\dot{V}O_{2max}$ (1.28 ± 0.44 vs.1.32 ± 0.42 L·min^{-1}), W_{peak} (76 ± 35 vs. 80 ± 33 W), or V_D/V_{Tc} (0.28 ± 0.13 vs. 0.29 ± 0.13) despite improvements in both resting and exercise airway impedance and hyperinflation. The effect of bronchodilator therapy on exercise tolerance is inconsistent (50), and is typically more pronounced in those with more severe spirometric impairments and in those who develop concavity in the SEFV curve (15). We enrolled a heterogenous group of patients with COPD (from mild to very severe) with a range of FEV_1 and SGRQ scores, and this may explain why albuterol failed to improve exercise capacity in this study. A report by Aliverti et al. (51) also showed no improvement in constant-load cycling performance following salbutamol administration in patients with COPD, despite

bronchodilators evoking significant decreases in IC. It should be noted that our exercise protocol of an incremental ramp differs from the constant work rate trials used in most studies, although we also observed amelioration of dynamic hyperinflation. Some of the inconsistency among studies may be explained by differences in the type of drug administered (short- or long-acting, β2 agonists or anticholinergic), differences in study design, and differences in disease severity. Indeed, studies in larger and more homogenous groups of patients with COPD may be warranted.

Technical Considerations for Impedance Oscillometry

To our knowledge, this is the first study to comprehensively assess airway impedance during exercise using IOS. To be confident of accurately detecting changes in airway function, we assessed the test-retest reproducibility of exercise IOS in a small sample of healthy subjects. When comparing the overall responses to the protocol (rest and exercise), mean differences between *test 1* and *test 2* were low, showing values significantly above "0" for Fres alone ($P = 0.031$; Table 3). Moreover, ICC data showed moderate correlation coefficients for R_5 ($r = 0.682$, $P = 0.002$), R_5–R_{20} ($r = 0.647$, $P = 0.004$), and Z_5 ($r = 0.689$, $P = 0.003$; Table 3). When assessing reproducibility by exercise stage, only Fres exhibited a significant one-sample t test at peak exercise, but there was no pattern of change in any other IOS measure with increasing $\dot{V}_E$/MVV. Thus, our preliminary data ($n = 5$) show acceptable measurement reproducibility of resistance (R_5 and R_5–R_{20}) and net impedance (Z_5) at this level of ventilation. This is supported by our observation of a predictable and consistent postbronchodilator change in airway function in our patient group. It should be noted that neither patients with COPD nor controls in our study reached a high absolute $\dot{V}_E$ (50 ± 18 and 57 ± 21 L·min^{-1}, respectively). Given that IOS assessments may be affected by high respiratory pressures and lung volumes, further studies on the validity of exercise IOS at higher rates of ventilation (e.g., in younger and/or more athletic subjects) are warranted. Given the potentially greater variability of IOS in COPD, further reproducibility data in these patients may also prove insightful.

It is pertinent that measures of R_5 and R_5–R_{20} were reproducible. Low oscillation frequencies (e.g., 5 Hz) penetrate deeper into the small airways and lungs, and subtracting R_{20} from R_5 (R_5–R_{20}) represents flow resistance primarily in the distal airways (16) which are the main source of lung resistance in COPD (24, 52). At present, we do not have a clear explanation for why resistance appears to be more reproducible than reactance. Oscillatory impedance is dependent on the volume at which it is measured (53). In a single-compartment model, the relationship between lung volume and resistance is determined by changes in airway geometry, whereas the volume-reactance relationship is underpinned by tissue compliance and gas compression (54). Given the different mechanical factors that govern resistance and reactance, it is reasonable that they might differ in their assessment reproducibility, although further studies to explore this disparity are needed.

Conclusions

This study provides novel data regarding dynamic changes in airway function during exercise before and after bronchodilator administration in patients with COPD. The use of impulse oscillometry to assess flow resistance and reactance allowed for the reporting of a temporal response, and this is a unique feature of our study. Peak IOS variables correlate well with measures of dynamic hyperinflation and indications of expiratory flow limitation in the spontaneous expiratory flow-volume loop, and additionally provide data regarding function of the small airways during exercise. Finally, we show that respiratory resistance and impedance as measured using IOS is reproducible in healthy subjects up to modest levels of ventilation. This approach may aid in the clinical assessment of airway function during exercise.

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DISCLOSURES

H.B.R. reports consulting fees from Omniox Inc., and is involved in contracted clinical research with Boehringer Ingelheim, GlaxoSmithKline, Novartis, AstraZeneca, Astellas, United Therapeutics, Genentech, and Regeneron.

AUTHOR CONTRIBUTIONS

R.C., H.B.R., R.C., W.W.S., and J.P. conceived and designed research; J.P., M.C., F.L., W.Y., C.W., R.C. and A.S. performed experiments; N.B.T., M.C., F.L., W.Y., C.W., A.S., and J.P. analyzed data; N.B.T., M.C., F.L., W.Y., C.W., A.A., H.B.R., R.C., W.W.S., and J.P. interpreted results of experiments; N.B.T., M.C., F.L. and J.P. prepared figures; N.B.T., M.C. F.L., and J.P. drafted manuscript; N.B.T., M.C., F.L., W.Y., C.W., A.A., R.C., H.B.R., R.C., W.W.S., and J.P. edited and revised manuscript; N.B.T., M.C., F.L., W.Y., C.W., A.A., R.C., A.S., H.B.R., R.C., W.W.S., and J.P. approved final version of manuscript.

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