HHS Public Access

Author manuscript

Respir Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Respir Med. 2015 October ; 109(10): 1287–1292. doi:10.1016/j.rmed.2015.09.003.

Right Ventricular Diastolic Function and Exercise Capacity in COPD

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Abstract

Background—Decreased exercise capacity in chronic obstructive pulmonary disease (COPD) is incompletely explained by pulmonary pathologic and physiologic abnormalities. We evaluated the extent to which right ventricular diastolic function (RVDF) is associated with exercise capacity in COPD.

Methods—Fifty-one patients with COPD were evaluated by echocardiography, spirometry, and the 6 minute walk test (6MWT). RVDF was assessed using 4 echocardiographic parameters: 1) the ratio of tricuspid valve (TV) early (E) and late (A) inflow velocities (TV E/A) 2) TV early tissue Doppler velocity (TV e') 3) TV deceleration time (DT) and 4) the ratio of TV E and e' velocities (TV E/e'). Multiple linear regression was used to examine the extent to which these parameters were associated with 6MWT distance. All models adjusted for age, sex, post-bronchodilator FEV_1/FVC, resting heart rate, and use of supplemental O_2 during 6MWT. A regression model was calculated for each of the 4 markers of RVDF.

Results—Forty-seven percent of the sample had GOLD stage III or IV COPD. All 51 subjects had preserved left ventricular ejection fraction (LVEF, mean = 71.7%, SD = 7.8%). A higher TV E/A ratio was associated with increased 6MWT distance (p = 0.001). TV e', TV DT and TV E/e' did not have a statistically significant association with 6MWT distance in regression models.

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Conclusions—In a cohort with moderate to severe COPD and normal LVEF, TV E/A was associated with 6MWT distance after adjusting for relevant demographic and medical covariates. RV diastolic dysfunction may independently contribute to exercise intolerance in COPD.

Keywords

COPD; right ventricle; exercise; diastolic function

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States, accounting for $32 billion in national medical expenditures.[1] The significant healthcare burden of COPD is further demonstrated by its association with decreased exercise capacity.[2,3] Although exercise intolerance in COPD has traditionally been attributed to pulmonary factors including increased mechanical loading of inspiratory muscles, dynamic hyperinflation, increased ventilatory demand, abnormal gas exchange, dynamic airway compression, and peripheral muscle dysfunction, increasing evidence implicates COPD-related right ventricular (RV) structural changes as contributing causes to diminished functional capacity. In a group of patients with moderate COPD and mildly elevated estimated pulmonary pressures, RV wall thickness predicted six minute walk test (6MWT) distance independent of lung function, age, sex, or body mass index.[4] While RV remodeling in COPD is classically associated with cor pulmonale, RV hypertrophy can be present in COPD in the absence of pulmonary hypertension.[5] Furthermore, recent population-based studies reported that emphysema is associated with a cardiac phenotype characterized by reduced RV volume and preserved systolic function.[6,7] Decreased RV chamber size and associated hypertrophy may predispose to RV ventricular diastolic dysfunction.[26] In this way, RV diastolic dysfunction may be a potential novel pathophysiologic explanation for reduced exercise capacity in COPD.

Using pulsed wave and tissue Doppler echocardiography, RV diastolic function (RVDF) can be assessed using a combination of indices including the ratio of early (E) and late (A) trans-tricuspid inflow velocities (TV E/A), early TV annular tissue Doppler velocity (TV e'), and the TV E/e' ratio.[14] Although left ventricular diastolic dysfunction (LVDD) is associated with reduced functional capacity in COPD, the role of RVDF in COPD exercise intolerance is unknown.[8] We hypothesized that individual echocardiographic markers of RVDF would correlate with 6MWT distance in a COPD cohort with both normal and impaired RVDF.

Methods

The study was approved by the National Jewish Health (NJH) Institutional Review Board (IRB; #2278A). Former smokers participating in the COPDGene Study (clinicaltrials.gov identifier NCT 000608764) were recruited for an independent single-center study (K23 HL095658) evaluating the relationship between cardiovascular function and cognitive function in COPD. Subjects were required to be between 55 and 85 years old, have a minimum of a 10 pack-year smoking history, and have Global Initiative on chronic Obstructive Lung Disease (GOLD) I-IV COPD.[31] Exclusion criteria included a combination

of criteria taken from the COPDGene study as well as the cognitive function substudy and included other lung disease (except asthma), COPD exacerbation within the past month that required treatment with antibiotics or systemic corticosteroids, previous surgical excision of at least one lung lobe, active cancer under treatment, suspected lung cancer, metal in chest, recent eye surgery, heart failure, clinically-significant hypertension, renal failure, recent chest or abdominal surgery, inability to use albuterol, history of chest radiation therapy, and major neurological/psychiatric illness.[9]

Of the 234 COPDGene subjects who were screened for enrollment, 49% (114/234) met eligibility criteria, and 104 were subsequently scheduled for visits. The most common reasons for ineligibility at the time of screening were: cancer or other medical condition (26%), substance use disorder (24%), exclusionary cardiovascular condition (24%), and neurological/psychiatric illness (15%). Three of the 104 subjects who attended the first study visit were withdrawn from further participation (2 for clinically-significant hypertension at the time of their initial study visit and 1 for a medication change after visit 1).

The 101 subjects from the single-center study who completed all measures including echocardiography were considered for inclusion in the current analyses. Because we sought to evaluate the association of RVDF with exercise tolerance among patients with COPD, 38 subjects were excluded due to absence of GOLD I-IV COPD, leaving 63 individuals with COPD for analysis. Given that smoking can acutely and chronically alter vascular and myocardial function, the current analyses included only former smokers with non-smoking status confirmed by urine cotinine assays. Consequently, 2 individuals were excluded due to evidence of current smoking based on positive cotinine test results. Because of the potential for coronary artery disease to confound RV function, 7 individuals were excluded due to a history of previous myocardial infarction, percutaneous coronary intervention, and/or coronary artery bypass grafting surgery. In addition, one individual was excluded due to presence of a permanent pacemaker, one due to inability to do the six minute walk due to a torn tendon, and one due to a lower leg amputation that was likely to affect walk distance. Consequently, data from 51 subjects were used in analyses.

Procedures and Measures

Post-Bronchodilator Spirometry—Because COPD severity was determined using the ratio of forced expired volume in one second (FEV_1) and forced vital capacity (FVC), all subjects underwent pre- and post-bronchodilator spirometry using the EasyOne spirometer (ndd Medical Technologies Inc., Andover, MA) in accordance with ATS guidelines.[10,31] After baseline spirometry, two puffs of albuterol (180 μg) were administered from a metered dose inhaler with a spacer. After 20 minutes the subjects were prompted to perform three additional acceptable FVC maneuvers. Any results of questionable quality (EasyOne spirometer rating of C or below) were reviewed by a study pulmonologist (BJM). Previous spirometry results were utilized for one individual due to suboptimal quality of current testing. Post-bronchodilator spirometry was used in the analysis.

6MWT—Six minute walk testing was performed in accordance with ATS guidelines.[11] Subjects were instructed to utilize supplemental oxygen during the 6MWT as prescribed by

their provider for normal activity. Resting SpO_2 (measured on supplemental oxygen as previously prescribed by the individual's provider) and resting heart rate were obtained after subjects had been seated quietly for 5 minutes immediately prior to the 6MWT.

Supine Resting Arterial Blood Pressure—Prior to echocardiography, brachial artery blood pressure was measured after 10 minutes of rest in the supine position under quiet, comfortable ambient conditions. Blood pressure was measured in triplicate and averaged.

Echocardiogram—Data acquisition was performed by one of two sonographers using a Vivid 7 ultrasound system (General Electric Medical Systems, Milwaukee, WI, USA) equipped with a 3-MHz transducer. Using pulsed-wave Doppler echocardiography, right and left ventricular filling parameters were obtained including early (E) and late (A) tricuspid valve (TV) and mitral valve (MV) filling peak velocities, E/A ratio, and E wave deceleration time (DT) as previously described.[12,15] Lateral and septal tricuspid and mitral annulus early (e') and late (a') tissue Doppler diastolic velocities were also obtained. RV diastolic dysfunction was defined as either stage I (TV E/A < 0.8, TV E/e' > 6, and DT > 120 ms) or stage II (TV E/A = 0.8–2.1, TV E/e' > 6, and DT > 120 ms). LVDD was defined as per American Society of Echocardiographic guidelines.[13] Measurements of left and right ventricular function and structure, tricuspid annular plane systolic excursion (TAPSE), RV systolic pressure (RVSP), and right atrial pressure (RAP) were measured/estimated as previously described.[13,14,15] Echocardiographic measurements were confirmed by a blinded reader (HDW).

Subjects completed the walk, spirometry and echocardiography testing over 2 study visits most often separated by 2 days (mode=2 days, median=5 days), and 94% of the sample completed the visits within 2 weeks of each other. To determine potential comorbid conditions that might contribute to RV diastolic dysfunction, all subjects were asked to provide self-reported medical history of hypertension, diabetes, obstructive sleep apnea, diuretic use, and use of supplemental oxygen at rest, with activity, and with sleep. A dichotomous variable was calculated to indicate whether each participant had none versus one or more of the following conditions: hypertension, diabetes, or obstructive sleep apnea.

Data Analysis

Data were analyzed using SPSS Statistics 22.0 (SPSS Inc., Chicago, IL). Demographic and clinical characteristics of the sample were summarized using means and standard deviations for continuous variables and number and percentage of subjects for categorical variables. The association between each marker of RVDF and 6MWT distance was first examined via bivariate correlations. Next, multivariate linear regression was used to examine the extent to which each marker of RVDF was associated with 6MWT distance after adjusting for relevant demographic and clinical covariates. Covariates were selected as follows: 1) age and sex were selected *a priori* due to their association with RVDF and 2) additional covariates were included in the regression models if the bivariate correlation with 6MWT distance indicated a trend toward statistical significance (defined as $p < 0.10$).[33] The following were considered as potential covariates: body mass index (BMI), systolic blood pressure, diastolic blood pressure, post-bronchodilator FEV_1/FVC, comorbidity score (none

versus one or more of the following conditions: hypertension, diabetes, obstructive sleep apnea), smoking history (pack-years), resting SpO_2 prior to 6MWT, resting heart rate prior to 6MWT, use of oxygen during the 6MWT, and presence or absence of LVDD. Four regression models were calculated: one for each marker of RV diastolic function (TV E/A, TV e', TV DT, and TV E/e'). In each model, all independent variables were entered simultaneously. Regression coefficients and significance tests for each independent variable reflect the effect of that variable after accounting for the effect of all other independent variables in the model. Significance tests were two-sided with a significance level of 0.05.

Results

Subject Characteristics

The mean age of subjects was 69.6 years old (SD = 6.7), and the majority of subjects were male (58.8%) (*see* Table 1). The vast majority of the subjects had GOLD Stage II (47.1%), III (23.5%), or IV (23.5%) with a mean FEV_1/FVC of 50.6% (SD = 12.6). The majority of subjects had normal RVDF (n = 37, 86.0%), with 14% demonstrating either Stage I (n = 4, 9.3%) or Stage II (n = 2, 4.7%) RV diastolic dysfunction. On the other hand, LVDD was present in 57.1% (n = 28) of subjects. LV systolic function was normal (LVEF M = 71.7%, SD = 7.8) with normal LV size (LVIDD M = 4.5 cm, SD = 0.6). Subjects demonstrated a reduced average walk distance (M = 389.1 meters, SD = 99.7).[32] The distance walked was normally distributed in this sample. Only 39.2% (N=20) of subjects used resting supplemental oxygen therapy, while 60.7% (N=31) used oxygen with activity and/or with sleep.

RV Diastolic Function and 6MWT Distance

To assess the association between individual markers of RVDF and exercise tolerance, we first examined the bivariate correlation between each marker and 6MWT distance (*see* Table 2). TV E/A ratio had a statistically significant correlation with walk distance ($r = 0.40$, $p < 0.01$), as did TV e' ($r = 0.32$, $p < 0.05$).

Next, regression models examined the extent to which each marker of RVDF was associated with walk distance after adjusting for relevant covariates. The following variables were selected as covariates because they exhibited a trend toward a statistically significant bivariate association with 6MWT distance: post-bronchodilator FEV_1/FVC, resting heart rate, and use of oxygen during the 6MWT (*see* Table 2). As such, each regression model included age (chosen *a priori*), sex (chosen *a priori*), post-bronchodilator FEV_1/FVC, resting heart rate, use of oxygen during the 6MWT, and one of the markers of RV diastolic function. The model for TV E/A was statistically significant ($F_{(6, 43)} = 7.82$, $p < 0.001$) with an adjusted R^2 of 0.46, indicating that the model accounts for 46% of the variance in 6MWT distance. As shown in Table 3, TV E/A ratio had a statistically significant positive association with distance walked (unstandardized b = 125.47, 95% CI = 54.55 to 196.40, p = 0.001). In other words, for every 1-unit increase in TV E/A ratio, a subject walked an average of 125 meters further after adjusting for all of the covariates in the model. The other significant predictors of distance walked were resting heart rate (unstandardized b = −2.04, 95% CI = −3.59 to −0.49, p = 0.011) and use of oxygen during the 6MWT (unstandardized b

= −77.85, 95% CI = −125.98 to −29.72, p = 0.002). This model was repeated using TV e', TV DT, and TV E/e' in place of TV E/A. None of these other markers of RVDF had a statistically significant association with distance walked (p = 0.117 for TV e', p = 0.871 for TV DT, and p = 0.754 for TV E/e').

Because RVDF can coexist with RV systolic dysfunction, which itself is a known predictor of exercise capacity, we next examined whether the association between TV E/A ratio was significant when also controlling for decreased TAPSE, a marker of RV systolic function. This secondary analysis examined a model in which TAPSE (normal/> 1.6 cm vs. reduced/≤ 1.6 cm) was included as an additional covariate to those included in the initial model.[14] In this model, TV E/A ratio again demonstrated a statistically significant positive association with 6MWT distance (unstandardized b = 134.04, 95% CI = 50.92 to 217.16, p = 0.002). However, TAPSE itself was not a significant predictor of distance walked (unstandardized b = 24.84, 95% CI = −77.68 to 127.36, p = 0.626).

Discussion

The increased recognition of the critical role the RV plays in cardiopulmonary disease has led to growing interest in the investigation of RVDF in the context of pulmonary arterial hypertension, heart failure, and congenital heart disease.[16,17,18] However, little is known about the pathophysiologic implications of RVDF in COPD. To our knowledge, this is the first study to examine the association between RVDF and exercise capacity in COPD. In our COPD subjects, TV E/A velocity was associated with 6MWT distance. This association was identified amongst a relatively small cohort (N = 51), even after adjusting for age, sex, airflow limitation, HR, and use of oxygen during the 6MWT. This finding suggests that there is a strong association between TV E/A and walk distance among individuals with COPD. Furthermore, this association remained significant even after controlling for RV systolic dysfunction, a known confounder for RVDF.

LVDD has been associated with reduced 6MWT distance in COPD and was therefore examined as a potential covariate.[19] Although it was present in 57% of our cohort, LVDD did not have a significant bivariate association with 6MWT distance in our cohort. This finding may be explained by the fact that 93% of individuals with LVDD in our cohort had only Stage I LVDD, an early form of diastolic impairment state that is not typically associated with functional limitation. Our study is further strengthened by the fact that all subjects had preserved LV ejection fraction and had no history of congestive heart failure, effectively excluding the possibility that the presence of LV systolic dysfunction might confound our findings.

The pathogenesis of RV diastolic dysfunction is traditionally thought to result from ventricular-arterial coupling associated with pulmonary hypertension. Chronic pulmonary hypertension-induced elevation in RV afterload increases RV wall stress, leading to progressive RV hypertrophy, chamber enlargement, and impaired relaxation. However, RV diastolic dysfunction is associated with many pathologic phenomena that directly impact RV relaxation including hypoxia, inflammation, microvascular ischemia, systemic hypertension, and obesity.[20,21,22,23,24] In this way, RV diastolic dysfunction may develop as a

consequence of COPD even in the absence of COPD-related pulmonary vascular disease. RV diastolic dysfunction may contribute to reduced exercise tolerance in COPD through reduction in RV preload, and consequently RV stroke volume. The physiologic cost of decreased RV stroke volume may be exacerbated by exercise, and may therefore further explain the association of RV diastolic dysfunction with decreased 6MWT distance.

The identified association between RVDF and exercise tolerance raises the possibility that RV diastolic dysfunction may be a therapeutic target unto itself. Although not expressed in normal myocardium, phosphodiesterase 5 (PDE5) is markedly upregulated in conditions associated with RV hypertrophy, a known marker of RV diastolic dysfunction.[25] Accordingly, treatment with PDE5 inhibitors in PH patients improves echocardiographic parameters of RV diastolic dysfunction.[26,27] However, it is unclear whether the ability of PDE5 inhibitors to improve RV diastolic function in PH is a result of decreased RV afterload, direct effects on RV lusitropy, or a combination of both. Future clinical studies are required to test the impact of PDE5 inhibitors on both RV diastolic function and exercise capacity in RV diastolic dysfunction populations including COPD. Furthermore, because COPD-associated hyperinflation is associated with reduced right atrial and RV filling, bronchodilator therapies should also be considered for candidate interventions in RV diastolic dysfunction studies.[28]

We acknowledge that our study is limited by multiple factors. First, RV diastolic dysfunction (as defined American Society of Echocardiography guidelines) was present in only 14% of the cohort, limiting the ability to draw significant conclusions about the association between RV diastolic dysfunction and 6MWT distance among those with severe RV diastolic dysfunction. However, RV diastolic dysfunction represents a spectrum of abnormalities in not only TV inflow velocities and patterns but also myocardial relaxation velocities. Consequently, RV diastolic dysfunction is defined by not only TV E/A but also TV DT and E/E'. Because alterations in flow may precede changes in tissue mechanics in RV diastolic dysfunction, a decrease in TV E/A ratio may be present prior to changes in TV e' velocity (and therefore TV E/e') in early stage disease.[29] In this way, TV E/A may be an early marker of RV diastolic impairment prior to the development of overt RV diastolic dysfunction as currently defined. Future efforts will attempt to enroll a larger RV diastolic dysfunction cohort in order to evaluate a composite of RV diastolic parameters for a more comprehensive diastolic assessment and correlation with 6MWT distance.

Because our study design did not utilize right heart catheterization to conclusively exclude PH prior to enrollment, it is conceivable that PH was present amongst some study subjects. Therefore, the identified associations between 6MWT distance and TV E/A could in part reflect those of exercise capacity and PH. However, it is worth noting that our cohort demonstrated relatively normal values for multiple echocardiographic markers of PH, including RVSP, RV minor and RA major dimensions, and TAPSE, suggesting PH is less likely to be a confounder in our analysis.

As a highly preload dependent chamber, any assessment of RVDF reflects loading conditions in that moment. Therefore variable loading conditions may confound the ability to correlate echocardiographic markers of RV diastolic dysfunction with 6MWT distance

performed at different time points.[30] When compared to the relatively preload-independent tissue Doppler velocities, variable loading conditions are more relevant when evaluating trans-valvular inflow velocities (i.e., TV E and A) as was done in this study. Although subjects with a prior diagnosis of coronary artery disease were excluded from enrollment, functional studies were not performed as part of screening to identify undiagnosed ischemia that in turn may confound associations with 6MWT distance. Despite these limitations, our findings support an independent association between RVDF and exercise tolerance in COPD. These results suggest additional investigation into the role of RVDF in exercise tolerance in COPD may ultimately reveal a novel, and possibly treatable, pathophysiologic process.

Acknowledgments

We thank Ann Depew, M.A. and Christina Schnell, B.A. for assistance with participant recruitment and Trudi Madigan, Ronnie Calzada, Steven Belcher, and James Thorpe for assistance with data collection. Thank you Anne Hunting and Lyndsay Lev, B.S. for administrative support. Research reported in this publication was supported by the National Institutes of Health (NIH) grants K23 HL095658, R01 HL089897, and the NIH/NCATS Colorado CTSI Grant Number UL1 TR001082. Contents are the authors' sole responsibility and do not necessarily represent official NIH views. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Colorado. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

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Table 1

Study cohort demographic and clinical characteristics (N=51)

Variable	Mean (SD)	N (%)
Age (years)	69.6 (6.7)	
Sex		
Male		30 (58.8)
Female		21 (41.2)
BMI	27.5 (5.1)	
Systolic blood pressure (mmHg)	127 (11)	
Diastolic blood pressure (mmHg)	76 (8)	
Supplemental Oxygen Use		
Rest		20(39.2)
Activity		31(60.7)
Sleep		31(60.7)
Diuretic use		15 (29.4)
Post-Bronchodilator FEV_1 (% predicted)	50.3 (20.6)	
Post-Bronchodilator FEV_1/FVC (%)	50.6 (12.6)	
GOLD Stage		
I		3 (5.9)
II		24 (47.1)
III		12 (23.5)
IV		12 (23.5)
Chronic Bronchitis (n=50)		7(14.0)
Comorbidity		
None		23(45.1)
Hypertension		24 (47.1)
Diabetes		4 (7.8)
Obstructive sleep apnea		10 (19.6)
Smoking History (pack-years)	57.8 (32.5)	
6 Minute Walk Testing		
Distance, (meters)	389.1 (99.7)	
Resting SpO_2 Prior to 6 Minute Walk Test	92.5 (2.8)	
Resting Heart Rate Prior to 6 Minute Walk Test (BPM)	77.8 (14.2)	
Use of Oxygen During 6 Minute Walk Test		
No		22 (43.1)
Yes		29 (56.9)
Right Ventricular Diastolic Function		
Normal		37 (86.0)
Stage I		4 (9.3)
Stage II		2 (4.7)
TV E/A Ratio (n=50)	1.1 (0.3)	
TV E (cm/s) (n=50)	42.2 (9.0)	

Variable	Mean (SD)	N (%)
TV A (cm/s) (n=50)	40.1 (9.4)	
TV e' (n=45) (cm/s)	10.3 (2.1)	
TV DT (ms) (n=50)	230.7 (75.4)	
TV E/e' (n=44)	4.2 (0.9)	
Right Ventricular Structure and Systolic Function		
RV Minor (cm)	3.6 (0.6)	
RA Major (cm)	4.5 (0.7)	
TAPSE (n=45)		
Normal (> 1.6 cm)		42 (93.3)
Reduced (≤ 1.6 cm)		3 (6.7)
Right ventricular systolic pressure (mmHg) (n=32)	39.5 (14.7)	
Right atrial pressure (n=49)		
3 mmHg		45 (91.8)
8 mmHg		4 (8.2)
Left Ventricular Size and Systolic Function (n=51)		
Left ventricular ejection fraction (%)	71.7 (7.8)	
Left ventricular internal dimension diastole (cm)	4.5 (0.6)	
Left Ventricular Diastolic Function (n=49)		
Normal		21 (42.9)
Stage I or Stage II		28 (57.1)

Table 2

Bivariate correlations with distance walked during 6 minute walk test

Predictor	Correlation Coefficient
Markers of Right Ventricular Diastolic Function	
TV E/A ratio	0.40**
TV e'	0.32*
TV DT	0.24†
TV E/e'	−0.06
Potential Covariates	
Age (years)	−0.16
Sex	0.20
BMI	−0.01
Systolic blood pressure (mmHg)	0.12
Diastolic blood pressure (mmHg)	0.11
Post-bronchodilator FEV_1/FVC	0.34*
Comorbidity	−0.06
Smoking history (pack-years)	−0.19
Resting SpO_2 prior to 6MWT	−0.04
Resting heart rate prior to 6MWT (BPM)	−0.27†
Use of oxygen during 6 minute walk test	−0.55**
Left ventricular diastolic dysfunction	0.02

Notes: Pearson correlation coefficients are reported, with the following exception: point biserial correlation coefficients are reported for dichotomous predictors (i.e., sex, comorbidity, use of oxygen during 6 minute walk test, and left ventricular diastolic dysfunction).

† $p<0.10$

* $p<0.05$

** $p<0.01$

Table 3

Results of regression model for association between TV E/A ratio and distance walked during 6MWT

Predictor	Unstandardized b (95% CI)	p
Age (years)	−2.23 (−5.43 to 0.98)	0.169
Sex		0.149
Male	Reference	
Female	31.57 (−11.73 to 74.86)	
Post-Bronchodilator FEV_1/FVC	0.49 (−1.41 to 2.38)	0.607
Resting heart rate prior to 6MWT (BPM)	−2.04 (−3.59 to −0.49)	0.011
Use of Oxygen During 6 Minute Walk Test		
No	Reference	
Yes	−77.85 (−125.98 to −29.72)	0.002
TV E/A ratio	125.47 (54.55 to 196.40)	0.001

Note: n=50 for this model due to missing data for TV E/A ratio for 1 subject.