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Research Article

Relationship of Change in 6-Minute Walking Test to Baseline Lung Hyperinflation in Patients with Chronic Obstructive Pulmonary Disease (COPD) Undergoing Pulmonary Rehabilitation

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Abstract

Rationale: While quality of life has been shown to improve with participation in moderate intensity exercise programs, there is conflicting data on the magnitude of improvement in exercise capacity based on lung function deficit in patients undergoing pulmonary rehabilitation (PR), particularly with respect to lung volumes. Exertional dyspnea has been shown to correlate more strongly with lung hyperinflation, as expressed by a reduction in inspiratory capacity (IC) than with FEV_1.

Objective: To assess the relationship between change in exercise capacity as measured by the 6-minute walk distance (6MWD) and pre-PR complete lung functions in individuals with COPD GOLD stage 3/4.

Methods: Retrospective assessment of lung function, including inspiratory capacity (IC), and change in 6MWD (Δ6MWD) in 33 patients with stable COPD completing a supervised 8-week outpatient pulmonary rehabilitation program. Primary outcome measure was change in 6MWD (Δ6MWD) after completion of PR.

Results All 33 patients (25 male) completed the 8-week program. Median 6MWD was 313 m and 363 m at the outset and end of the program, respectively ($p<0.01$). We found a significant correlation between the pre-rehabilitation 6MWD and IC/TLC ($p=0.006$), more so amongst patients who needed supplemental oxygen during exercise (based on decrease in pulse oxygen saturation below 88% while breathing room air) ($p=0.004$). Patients who needed oxygen during exercise had significantly lower FEV_1 and D_LCO values (both associations $p<0.001$). We found no significant correlation between 6MWD and baseline FEV_1 and D_LCO. There was a strong positive correlation between Δ6MWD and D_LCO ($p<0.003$), and between Δ6MWD and IC/TLC ($p<0.025$), but not between Δ6MWD and FEV_1.

Conclusion Improvement in exercise capacity as assessed by Δ6MWD is greater in patients with less, not greater, baseline lung hyperinflation and greater gas transfer capacity, with little influence by FEV_1.

Keywords: Chronic Obstructive Pulmonary Disease; Lung Hyperinflation; Six-Minute Walk Test; Pulmonary Rehabilitation; Expiratory Flow Limitation; Exercise Limitation

Background

Chronic obstructive pulmonary disease (COPD) results in impairment of ventilatory function and dyspnea leading to a sedentary lifestyle, limited physical function, and diminished quality of life [1-3]. Comprehensive pulmonary rehabilitation programs (PRs) comprised of exercise training and education have proven effective in the treatment of COPD. In addition to reduced exercise capacity, individuals with COPD exhibit an inability to perform activities of daily living, diminished social interaction, and reduced quality of life [3-5].

The six-minute walk distance (6MWD) is a potentially useful biomarker of disease. The test is influenced by the severity of lung compromise and by extrapulmonary manifestations of the condition, such as muscular weakness, weight loss, pulmonary vascular disease, or depression. The test allows patients to be self-paced and to rest when dyspnea becomes intolerable. It is also an important predictor of survival [3, 6]. Patients with a 6MWD less than 350 m have an increased risk of death and hospitalization. Conversely, improved 6MWD has been reported after pulmonary rehabilitation [3]. Polkey et al [6] showed that a decline in 6MWD of 30 meters represented a minimal clinically important difference (MCID) in 6MWD as relevant to worsening clinical status in patients with a wide range of severity of COPD in whom no intervention was applied. While quality of life has been shown to improve with participation in moderate intensity exercise programs, there is limited data on the relationship of magnitude of improvement in exercise capacity based on severity of baseline lung function deficit in patients undergoing pulmonary rehabilitation (PR). Current recommendations for PR referral depend heavily on baseline FEV_1; however, exertional dyspnea has been shown to correlate only weakly with FEV_1 and is more closely related to lung hyperinflation [6-8], although some investigators have found that airflow limitation is a more important cause of dyspnea than static hyperinflation [9]. We hypothesized that patients with the worst lung function, and in particular, those with greater magnitude of lung hyperinflation (i.e. lowest IC/TLC) would be most likely to exhibit improvement in exercise tolerance at the completion of the 8-week program.

Methods

The records of 173 patients participating in a standard pulmonary rehabilitation program at the outpatient physical therapy department at Los Angeles County-University of Southern California medical center were reviewed. The PR program included periodic encouragement from medical and allied health staff for adherence in the program, educational support, and nutritional, smoking cessation and psychological counseling, as needed. The study was approved by the institutional review board of USC (HS-13-00423). Inclusion criteria were patients 18-80 years of age with COPD, GOLD stage 3 or 4 [2]. Patients with primary cardiovascular and musculoskeletal disorders were excluded. The diagnosis of COPD was based on American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (ACP/ACCP/ATS/ERS) recommendations [1]. All patients continued their medications, including long-acting beta-agonists, tiotropium and inhaled corticosteroids, as prescribed.

Spirometry, lung volumes by body plethysmography and gas transfer measurements were performed while seated with a Collins GS/PLUS or DSII/PLUS system (Warren Collins; Braintree, MA). The cut-off point of FEV_1/FVC for COPD was 0.7. Pre-PR (baseline) inspiratory capacity (IC), total lung capacity (TLC), and single breath carbon monoxide diffusion capacity (D_LCO) were recorded for each patient. IC/TLC was computed as an index for lung air trapping. Predicted values for post-bronchodilator FEV_1, FVC and FEV_1/FVC were from Schoenberg et al [10], for subdivisions of lung volume from Crapo et al [11], and for DLCO from Cotes et al [12]. The 6 minute walking distance test was conducted in a 40 meter hallway in accordance with guidelines of the American Thoracic Society [13]. Change in 6MWD (Δ6MWD) before and after the 8-week program (pre- and post-PR data) was used as a measure of improvement in exercise capacity. Responders to the PR program were defined as the significant Δ6MWD, consisting of an increase in walked distance greater than 30 m after PR, considered as a minimal clinically important difference (MCID) [6].

The primary outcome measure was the change in 6MWD (Δ6MWD) after completion of a standard, supervised 8-week pulmonary rehabilitation program. Exclusion criteria were respiratory conditions other than COPD, and patients who experienced acute respiratory decompensation during participation in the rehabilitation program. Pulmonary function testing and pulse oximetry during rest and exercise (while breathing room air) were assessed at start and completion of the pulmonary rehabilitation program at 8 weeks. We assessed which baseline lung function variables are most closely associated with (and likely to predict) improvement in the 6 MWD in patients with moderate to severe COPD undergoing a standard 8-week, 2 days/wk PR program. Changes in health-related quality of life (HRQL) were assessed by the St. George's questionnaire, a 76-item instrument that measures HRQL in 3 domains: respiratory symptoms, impairment of activities, and the psychosocial impact of disease, plus a summary total score [14]. Lower scores indicate better health status, and a change

of 4 points in total score (out of 100) is considered clinically meaningful. Data of only those patients who completed the 8-week PR program were analyzed.

Statistics

Pre- and post-rehabilitation data comparisons of lung function and 6MWD were conducted by analysis of variance (ANOVA) [15]. Relationships between baseline lung function data, 6MWD and Δ6MWD, and between changes in lung function and Δ6MWD were analyzed by Pearson correlation. Statistical significance was identified as a p-value of 0.05.

The results of this study were presented in part in abstract form at the American Thoracic Society International Conference in May 2014 [16].

Results

Of the 173 patients participating in the PR program, 73 had stable moderate-to-severe COPD and were enrolled in a supervised 8-week pulmonary rehabilitation program between 2006 and 2013. Of the 73 recruited patients, complete pre- and post- data was available in 32. The remaining patients were unable to complete the program because of acute COPD exacerbation, other acute illness, motivation deficit, or lack of transportation to bring them to the facility on a consistent basis.

Median FVC, FEV_1, FEV_1/FVC, TLC and D_LCO in the 32 patients assessed was 71% predicted, 48% predicted , 0.49, 106% predicted, and 58% predicted, respectively (Table 1). Median MRC scale was 1.7. Median 6MWD increased by 42 m (12%) between the outset and end of the program (p<0.01). Median D_LCO in responders (defined as those patients whose 6MWD increased by at least 30 m [4]) and nonresponders was 63% and 46% predicted, respectively (p<0.025); IC/TLC was 0.38 and 0.32, respectively (p <0.05). Figure 1 shows a significant correlation between lung hyperinflation as expressed by baseline IC/TLC and D_LCO (r = 0.6, p< 0.001). Figure 2 shows significant correlation between the baseline 6MWD and IC/TLC (p=0.006); this relationship was even stronger amongst patients who needed supplemental oxygen during exercise (determined by a decrease in pulse oxygen saturation below 88% while breathing room air) (p=0.004). Patients who needed oxygen during exercise had significantly lower IC/TLC (p <0.005), FEV_1 and D_LCO (both associations p<0.001) (Figure 3 a-c). We found no significant correlation between baseline 6MWD and baseline FEV_1 and D_LCO (Figure 4). There was, however, a strongly positive correlation between Δ6MWD and baseline D_LCO (p<0.003, Figure 5), and between Δ6MWD and baseline IC/TLC (p<0.025, Figure 6), but not between Δ6MWD and baseline FEV_1. Mean D_LCO in the responders and non-responders was 63% and 42% predicted, respectively (p <0.05), while mean FEV_1 was 45% and 54% predicted, respectively (p <0.05). Quality of life measured with the SGRQ showed a clinically meaningful improvement in 25 patients (78%). The observed changes in SGRQ ranged from mild deterioration (an increase in ≥4 points in the total score) to a marked improvement (a decrease of ≥12 points).

Table 1. Anthropometric and physiologic features of 32 patients undergoing pulmonary rehabilitation program (PR).

	Median (IQR)	
Age (yr)	60 (9)	
Gender (M/F)	21 /11	
BMI	29 (5)	
FVC (% predicted)	71 (34)	
FEV_1 (% predicted)	48 (17)	
FEV_1/FVC	0.49 (0.18)	
TLC (% predicted)	106 (33)	
IC (% predicted)	83 (41)	
IC/TLC	0.32 (0.18)	
D_LCO (% predicted)	58 (29)	
6MWD (m)		
pre-PR	341 (148)	
post-PR	383 (139)	
Δ6MWD	35 (51)	p <0.05*
SGQR		
Pre-PR	50 (24)	
Post-PR	44 (15)	
ΔSGQR	6 (9)	p <0.05*

*Analysis of variance

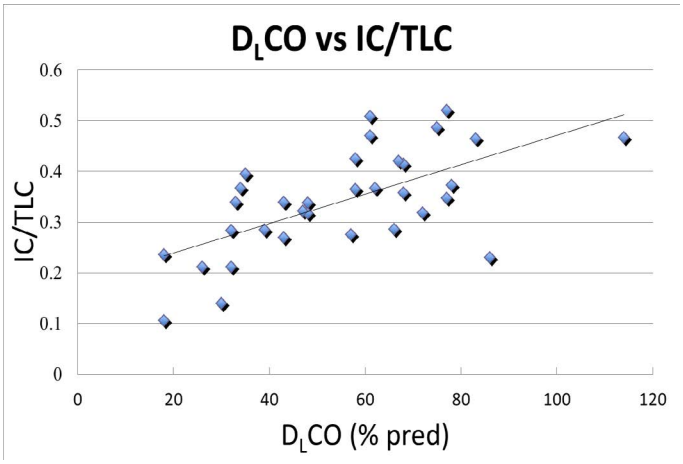

Figure 1. There was a positive correlation between lung hyperinfla-

tion and single-breath carbon monoxide diffusion capacity (r= 0.6, p< 0.001).

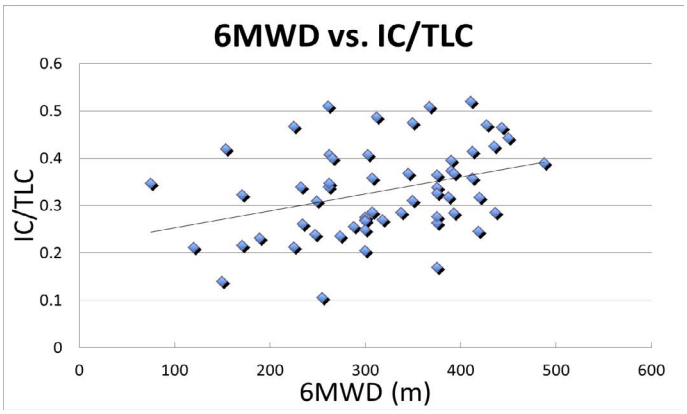

Figure 2. There was a positive correlation between baseline IC/TLC and baseline walked distance (r= 0.34, p= 0.006).

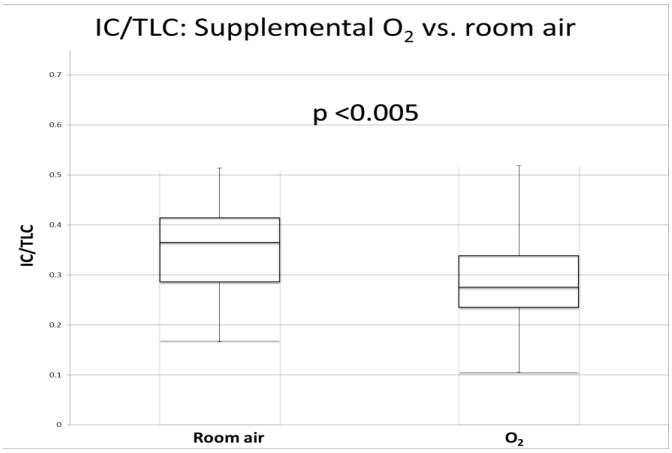

Figure 3a.

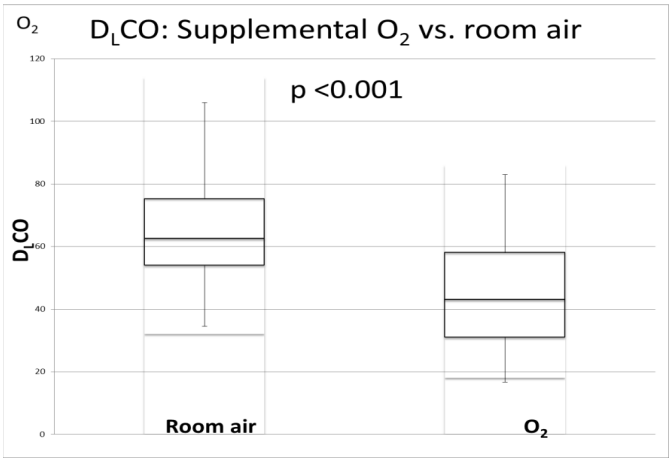

Figure 3b.

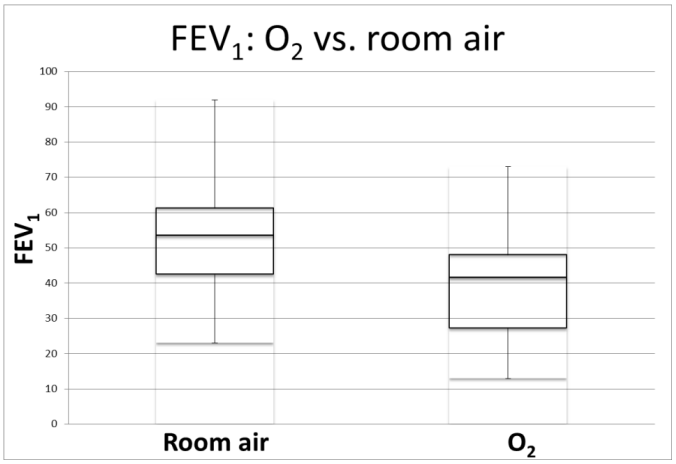

Figure 3c.

Figure 3. (a-c): Physiologic variables in patients breathing room air and those receiving supplemental oxygen. Boxes and whiskers represent medians, 25th and 75th quantiles, and outliers. There was no significant difference in FEV_1 amongst cohorts.

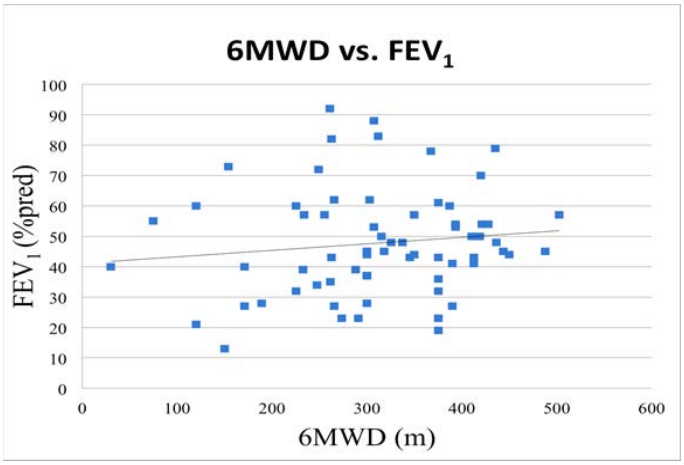

Figure 4. There was no correlation between baseline forced expiratory volume and baseline walked distance (r= 0.12, p= 0.3).

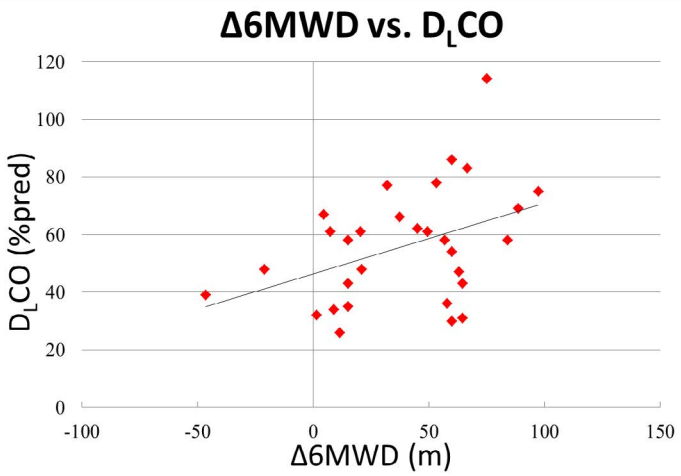

Figure 5. There was a positive correlation between baseline sin-

gle-breath carbon monoxide diffusion capacity and change in six-minute walking distance at completion of the rehabilitation program (r= 0.45, p= 0.01).

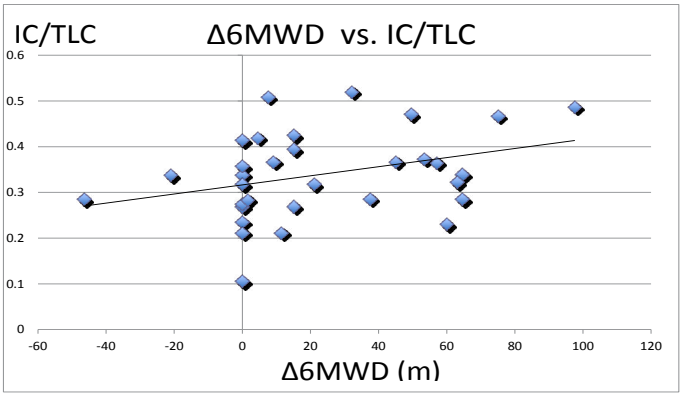

Figure 6. There was a positive correlation between the baseline ratio of inspiratory capacity to total lung capacity and change in six-minute walking distance at completion of the rehabilitation program (r = 0.33, p <0.025).

Discussion

To our knowledge, this is the first study that assessed the relationship between the change in six-minute walking distance and baseline IC/TLC, an index of lung air trapping, in patients undergoing an 8-week pulmonary rehabilitation program. The main findings were: (a) a close correlation between the pre-rehabilitation 6MWD and degree of lung air trapping, more so amongst patients who needed supplemental oxygen during exercise; (b) a strongly positive correlation between post-PR increase in 6MWD and baseline D_LCO, and between increase in 6MWD and IC/TLC, but not between increase in 6MWD and baseline FEV_1, and (c) patients who needed oxygen during exercise had significantly lower baseline FEV_1 and D_LCO values.

The average severity of airflow limitation observed in this study (FEV_1 48% predicted) is similar to that reported in other studies involving patients with moderate to severe COPD undergoing PR [5, 17]. Chen et al [18] found that 6MWD correlated with RV/TLC in severe and very severe COPD patients. Other studies have shown strong correlations amongst dynamic hyperinflation, neurochemical dissociation, and the Borg dyspnea scale in patients with COPD [8]. With increase in end-expiratory lung volume, the diaphragm loses its ability to generate inspiratory pressure because of decrease in its appositional area with respect to the chest wall, shortening of its resting length, and increase in its Laplace radius [19]. To compensate for this change in the muscle's effectiveness, there is increased respiratory drive [20] and activation of inspiratory muscles and phasic activation of expiratory muscles [21]. This would explain the finding of a positive correlation between increase in the 6MWD and baseline IC/TLC. Findings by other workers have been inconsistent and sometimes conflicting. Altenburg et al [22], using cluster analysis, described a group of COPD patients exhibiting a larger improvement in walking capacity (as assessed by shuttle walk test) associated with high TLC, RV/TLC and low FEV_1 values. Plankeel et al [23] found that patients with significant ventilatory limitation experienced marked increase in walk distance following PR. Zanini et al [24] similarly demonstrated greater response to PR in patients with higher numbers of exacerbations, dyspnea levels and leg fatigue, lower FEV_1, FEV_1/FVC, D_LCO, and higher RV and RV/TLC values. By contrast, others reported improvement in 6MWD to be directly related to FEV_1 and SGRQ [25, 26]. Garrod and colleagues [27] did not find any relationship between baseline lung function and change in 6MWD in a heterogeneous group of COPD patients participating in either outpatient or home-based PR. Reasons for these conflicting findings include several factors, including heterogeneity of presenting symptoms, functional impairment and quality of life amongst patients, and differences in the intensity of the PR program. For example, our PR program is similar to those of others in terms of duration (8 weeks) and frequency of weekly sessions (2 per week). Other programs are more intensive (up to 12 weeks, 5 days a week, with fixed groups of patients, 8-10 at a time) [23, 26]. The finding of multiple factors determining responses to a PR program thus renders prediction of improvement based on a single variable problematic. It also suggests that every symptomatic patient should be considered for pulmonary rehabilitation [1, 3].

It might be expected that patients with the most severe airflow limitation would be the most dyspneic. Yet, some patients with severe airway obstruction, as reflected by the FEV_1 have few symptoms, while others with minimal flow limitation exhibit severe dyspnea. Use of the negative expiratory pressure technique during quiet tidal breathing has demonstrated that expiratory flow limitation (EFL) at rest is associated with lower IC [28]. Since maximal tidal volume correlates with IC during exercise, patients with EFL at rest exhibit an increase in end-expiratory lung volume and a further decrease in IC with concomitant exercise limitation. By contrast, in non-EFL patients IC is usually normal, and FEV_1/FVC is the sole predictor of exercise limitation [29]. This is mainly due to the fact that a low FEV1/FVC ratio is associated with a maximal expiratory flow-volume curve with an upward concavity with little expiratory flow over the resting tidal volume range. Thus patients without EFL at rest but with a low FEV_1/FVC are more likely to exhibit EFL during exercise than patients who have a normal FEV_1/FVC. In this connection, lung hyperinflation also reflects the degree of emphysematous destruction, resulting in reduction of surface area available for gas exchange as well as capillary bed volume, components of gas transfer across the alveolar-capillary membrane, hence the direct correlation between IC/TLC and D_LCO. This finding would also explain the requirement for supplemental oxygen in patients with lower values of IC/TLC, D_LCO and FEV_1.

Our study had a number of limitations. The dropout rate in our program was 56%, higher than reported in other PR programs (11%-31%) [26,30]. One explanation for this low completion rate is that virtually all patients in our population were indigent and, as such, most of them had limited financial and social resources, with limited access to transportation (many had to rely on public means to travel long distances, a hindrance in patients with advanced disease). Secondly, others had been discharged from the hospital after a serious illness and still convalescing. A third factor was that our facility is an acute tertiary care institution without a dedicated inpatient PR center, as is available in other facilities [26]. All patients, however, exhibited a high impact of respiratory disease on health status, with the majority experiencing limited response to prior medical management. Patients who were referred and enrolled typically demonstrated the following characteristics: (a) moderate to very severe airflow limitation (GOLD stage 3/4); (b) a moderately to severely impaired quality of life as defined by a SGRQ total score of 25 or more; and (c) at least one annual hospitalization for acute respiratory illness or failure. Furthermore, four patients were still smoking at the time of enrollment in the PR program. All were able to quit smoking by the time of completion of PR, although data with respect to continuation of tobacco abstinence after completion of the PR program was not available.

Conclusions and Future Directions

Improvement in exercise capacity as assessed by increase in 6MWD is greater in patients with less baseline lung hyperinflation and greater gas transfer capacity, with little influence by FEV_1. Since FEV_1 has been shown to correlate less strongly with dyspnea than with lung hyperinflation, future studies should address specifically the effects of PR on lung hyperinflation in patients with different presentations of airflow limitation. It may be that individuals with phenotypic characteristics of emphysema (who exhibit greater degree of hyperinflation) benefit less from PR than patients who possess features predominantly characteristic of chronic bronchitis or the asthma/COPD overlap syndrome [31, 32].

Conflicts of interest

The authors have no conflicts to declare.

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