

Activity restriction in mild COPD: a challenging clinical problem

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Abstract: Dyspnea, exercise intolerance, and activity restriction are already apparent in mild chronic obstructive pulmonary disease (COPD). However, patients may not seek medical help until their symptoms become troublesome and persistent and significant respiratory impairment is already present; as a consequence, further sustained physical inactivity may contribute to disease progression. Ventilatory and gas exchange impairment, cardiac dysfunction, and skeletal muscle dysfunction are present to a variable degree in patients with mild COPD, and collectively may contribute to exercise intolerance. As such, there is increasing interest in evaluating exercise tolerance and physical activity in symptomatic patients with COPD who have mild airway obstruction, as defined by spirometry. Simple questionnaires, eg, the modified British Medical Research Council dyspnea scale and the COPD Assessment Test, or exercise tests, eg, the 6-minute or incremental and endurance exercise tests can be used to assess exercise performance and functional status. Pedometers and accelerometers are used to evaluate physical activity, and endurance tests (cycle or treadmill) using constant work rate protocols are used to assess the effects of interventions such as pulmonary rehabilitation. In addition, alternative outcome measurements, such as tests of small airway dysfunction and laboratory-based exercise tests, are used to measure the extent of physiological impairment in individuals with persistent dyspnea. This review describes the mechanisms of exercise limitation in patients with mild COPD and the interventions that can potentially improve exercise tolerance. Also discussed are the benefits of pulmonary rehabilitation and the potential role of pharmacologic treatment in symptomatic patients with mild COPD.

Keywords: chronic obstructive pulmonary disease (COPD), small airway dysfunction, dyspnea, physical activity, exercise

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease, characterized by chronic inflammation of the airways and lungs, persistent airflow limitation, and, in many, a progressive decline in lung function. It is associated with significant morbidity and increased mortality,^{1,2} even in patients with mild airflow obstruction. Despite this prospect, the disease often goes undiagnosed and untreated until it has progressed to a point where lung function and quality of life are severely compromised.^{3,4}

The clinical expression of COPD in its early phase of development depends on the integration of several factors, which include: the nature and extent of the physiological impairment; the compensatory responses mobilized to maintain effective pulmonary gas exchange; and the subjective behavioral response to encroachment of

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the respiratory reserve (eg, activity avoidance) (Figure 1). In the current review, the main focus is on smokers with apparently mild airway obstruction but who report persistent activity-related dyspnea.

Physical inactivity is often the consequence of troublesome dyspnea and is considered to be a major contributor to the progression of COPD, which, in turn, has been associated with the development of comorbidities, increased risk for hospitalization and associated health care costs, and increased rates of mortality.^{5,6} Physical inactivity is also considered by some to cause systemic inflammation, which leads to development of comorbidities, such as COPD.^{7,8} By contrast, regular physical activity is known to reduce rates of hospitalization and all-cause and respiratory mortality in patients with COPD,^{6,9} although the impact of physical activity in mild disease is less well understood.

In the past, there has been a perception that mild airway obstruction, as defined by spirometry (ie, post-bronchodilator forced expiratory flow in 1 second [FEV₁]/forced vital capacity <0.7 and FEV₁ >80 % predicted), has few clinical consequences and does not require intervention.¹⁰ However, there is mounting evidence that mild airflow obstruction is associated with a reduction in exercise capacity in patients with COPD.^{5,11,12} Even before patients are aware of their

illness, they often habitually restrict some of their more strenuous activities to avoid unpleasant symptoms, such as dyspnea. Over time, this can lead to a spiral of worsening symptoms, deconditioning, and exercise intolerance as patients become progressively more sedentary,¹³ and provides a compelling rationale for consideration of early intervention.

Smoking cessation is the pivotal and most effective intervention in patients with COPD.^{14,15} It is also well established that pharmacologic treatment, together with nonpharmacologic interventions, can effectively reduce the intensity of dyspnea and improve exercise capacity in moderate-to-severe COPD,^{1,16,17} although this is not well documented in mild disease.

This review summarizes the importance and benefits of encouraging physical activity and exercise in mild COPD, with a focus on alternative outcome measurements, such as small airway dysfunction and exercise abnormalities, which are already apparent in the mild stage of the disease.^{10,11,18,19} Also discussed are the potential benefits for patients with mild COPD of smoking cessation, regular physical activity, and pulmonary rehabilitation (PR), in combination with pharmacologic treatment, which have already been shown to improve dyspnea, quality of life, exercise endurance, and functional capacity of patients with more advanced disease.²⁰

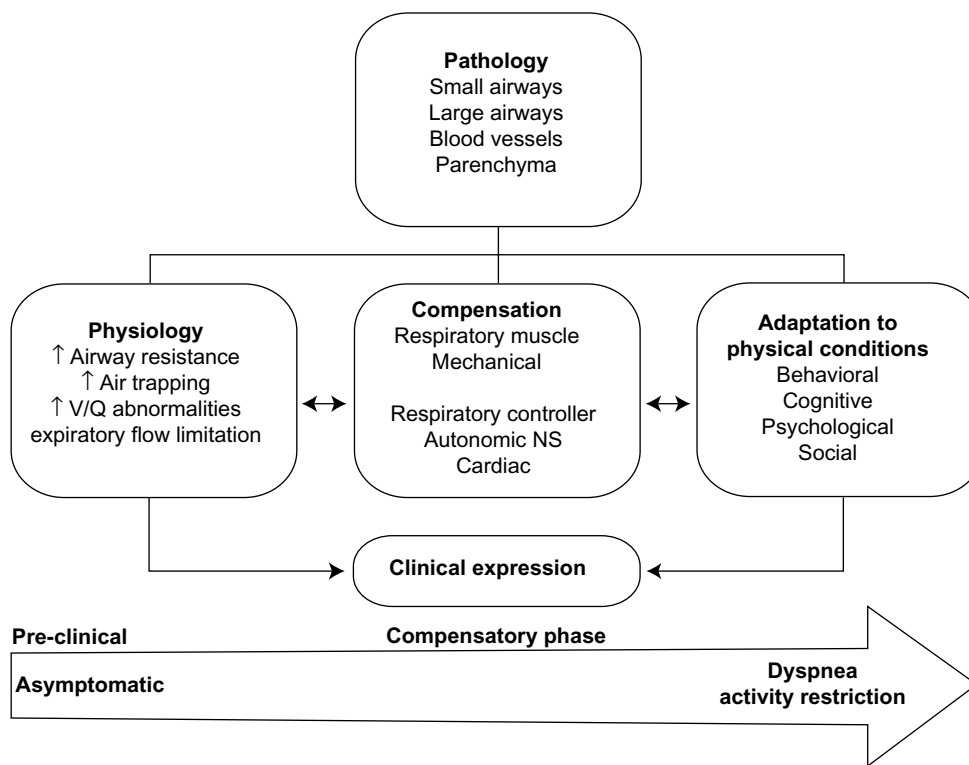


Figure 1 Characterization of mild chronic obstructive pulmonary disease.

Abbreviations: NS, nervous system; V/Q, ventilation/perfusion.

Exercise abnormalities in COPD

Exercise and activity limitation are already apparent in patients at the mild stage of COPD (Global initiative for chronic Obstructive Lung Disease [GOLD] 1),^{1,10,11,18} with exercise tolerance becoming increasingly compromised with disease progression.^{5,21} Exertional dyspnea and leg discomfort are common exercise-limiting symptoms in patients with COPD, including symptomatic patients with mild airflow obstruction.^{11,18} Both symptoms result from a complex interaction of factors, such as baseline respiratory mechanical dysfunction,²² individual susceptibility to leg muscle fatigue,²³ type of exercise,^{24–26} and bronchodilation status,^{27–29} the consequences of which vary from patient to patient. As dyspnea and leg fatigue worsen, the patient leads a more sedentary lifestyle in order to avoid these symptoms, resulting in skeletal muscle deconditioning, exercise intolerance, and poor quality of life.¹³

Mechanisms of exercise limitation in mild symptomatic COPD

Patients with mild COPD exhibit a diverse range of structural abnormalities of the lungs and airways, including airway wall thickening, pulmonary gas trapping, emphysema, and vascular dysfunction.^{30–32} As a result, these patients display substantial heterogeneity in airways resistance and conductance, pulmonary gas trapping, resting (static) lung hyperinflation, and integrity of the alveolar–capillary gas exchange interface.³³ Recent evidence has also shown that dynamic hyperinflation (during exercise) occurs in many patients with mild COPD, independently of whether patients have resting hyperinflation.³⁴ Understanding the structure–function relationships in the lungs and airways may assist understanding of exercise limitations in COPD.

Small airway dysfunction

The small airways, ie, those <2 mm in diameter, are the major sites of obstruction in patients with COPD.³⁵ Narrowing, occlusion, and loss of small airways have been confirmed from resected lung specimens, even in patients with mild COPD, using quantitative computed tomography,^{19,35,36} and are associated with enhanced inflammatory and repair responses, as well as a build-up of inflammatory mucus exudates in some patients.³⁶ Recent findings suggest that these changes precede the onset of centrilobular emphysema.¹⁹

Persistent expiratory flow limitation (EFL) is the defining feature of COPD. It occurs when expiratory flow cannot be increased because it is already at maximum during spontaneous tidal breathing at that lung volume. EFL arises due to the combined effects of airway narrowing, diminished lung

elastic recoil, airway–parenchyma uncoupling, and dynamic airway collapse.^{37–39} The relative contribution of each of these factors to EFL in patients with mild COPD varies from patient to patient and is difficult to quantify conclusively.^{38,40}

Ventilation/perfusion (V_A/Q) abnormalities

Patients with mild-to-moderate COPD commonly exhibit abnormal V_A/Q mismatch while breathing at rest, despite a largely preserved FEV_1 .^{41–43} Resting alveolar-to-arterial oxygen tension gradient has been shown to be abnormally widened (>15 mmHg) in patients with mild-to-moderate COPD who have regional low V_A/Q ratios.^{41,42} In patients with emphysematous destruction, high V_A/Q ratios (and wasted ventilation) may be dominant. Such patients exhibit a decreased surface area for gas exchange, as evidenced by a reduced diffusing capacity of the lung for carbon monoxide, and small vessel disease, both of which have been demonstrated in patients with mild COPD.^{30,41–44} These abnormalities likely contribute to a higher ventilatory requirement during exercise in patients with mild COPD (Figure 2).

Responses to exercise in mild COPD

High ventilatory demand

Peak oxygen consumption ($V'O_2$) and minute ventilation (V'_E) are reduced, and perceived dyspnea is increased during incremental exercise to tolerance in patients with mild COPD compared with healthy controls.^{10,11,18,45,46} By contrast, ventilatory equivalent for carbon dioxide ($V'_E/V'CO_2$) output is consistently higher during cycle^{10,11,18} and treadmill exercise test⁴⁶ in this patient population. This abnormality may reflect an impaired ability to reduce higher physiologic dead space during exercise in patients with mild COPD, an altered set-point for arterial partial pressure of carbon dioxide, or a combination of the two. However, significant arterial O_2 desaturation (>5%) has not been reported during incremental cycle exercise,^{10,11,18,45} suggesting that compensatory increases in V'_E and normal increase in cardiac output, ensure an improved V_A/Q relationship during exercise in these patients.^{41,42,47} In some patients, earlier metabolic acidosis, as a result of skeletal muscle deconditioning, provides an added stimulus to V'_E during exercise.^{11,18}

Impairment of dynamic respiratory mechanics

In addition to higher ventilatory requirements, dynamic gas trapping and mechanical constraints on tidal volume (V_T) expansion may contribute to reduced peak $V'O_2$ and V'_E in patients with mild COPD.^{10,11,18,45} Exercise-induced gas trapping occurs through a combination of tachypnea

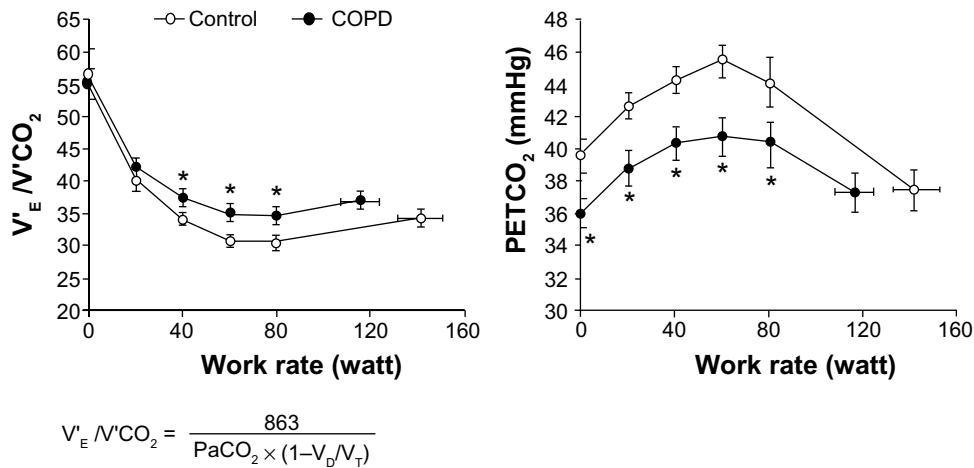


Figure 2 Ventilatory insufficiency in mild chronic obstructive pulmonary disease. $V'_E / V'CO_2$ (left) and $PETCO_2$ (right) in response to symptom-limited incremental cycle exercise in patients with mild COPD and healthy controls (Mean \pm SE) at rest, 20, 40, 60, and 80 watt during exercise and at peak exercise ($*P < 0.05$) COPD versus control at a standardized work rate (watt).

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Abbreviations: V'_E , minute ventilation; $V'_E / V'CO_2$, ventilatory equivalent for carbon dioxide; $PETCO_2$, partial pressure of end-tidal carbon dioxide; $PaCO_2$, arterial partial pressure of carbon dioxide; V_D , dead space volume; V_T , tidal volume; $V'CO_2$, carbon dioxide output; COPD, chronic obstructive pulmonary disease.

and EFL: end-expiratory lung volume (EELV) increases and inspiratory capacity decreases (Figure 3), which is reflected in the dyspnea slope that was significantly ($P < 0.05$) steeper in patients with GOLD 1 COPD compared with normal

healthy controls (Figure 4).¹¹ Thus, expiratory time becomes insufficient to allow EELV to decline to its natural relaxation volume between breaths and becomes dynamically (rather than statically) determined.

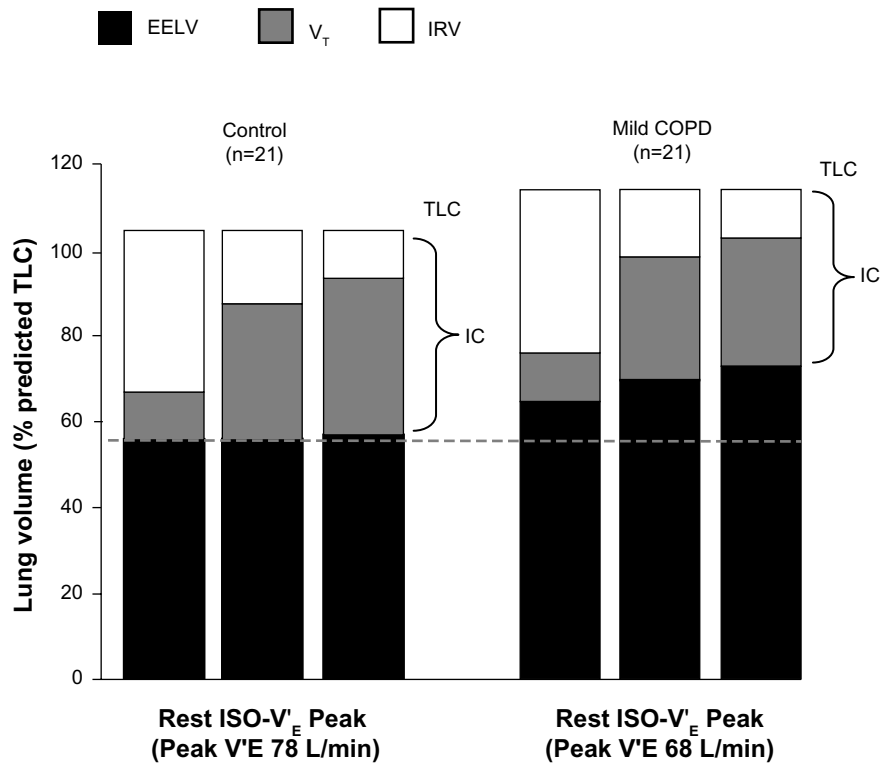


Figure 3 Operating lung volumes during exercise.

Note: Data from Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2008;177(6):622–629. Official Journal of the American Thoracic Society.¹¹

Abbreviations: COPD, chronic obstructive pulmonary disease; EELV, end-expiratory lung volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; ISO- V'_E , isotime minute ventilation; TLC, total lung capacity; V_T , tidal volume.

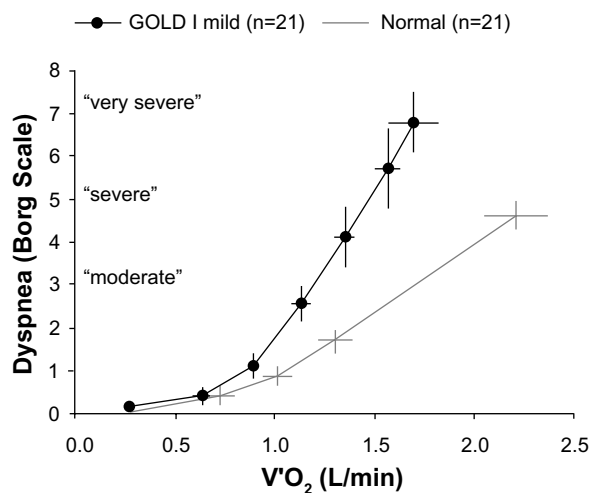


Figure 4 Exertional dyspnea intensity

Notes: Values are means \pm standard error of the mean. Mild > normal slopes ($P < 0.05$). Adapted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2008;177(6):622–629. Official Journal of the American Thoracic Society;¹¹ Borg Scale.⁴⁸
Abbreviations: GOLD, Global initiative for chronic Obstructive Lung Disease; V'O₂, oxygen consumption.

Previous studies in healthy individuals have shown that selective stressing of the respiratory system, by adding dead space to the breathing apparatus, results in significant increases in peak V_T and V'_E and a preservation of exercise capacity.^{49–51} By contrast, the ability of patients with advanced COPD to increase V'_E in response to such added chemostimulation is markedly diminished,⁵² and suggests that impaired respiratory mechanics represent the proximate limitation to exercise in COPD. These findings were recently extended to patients with mild COPD.¹⁸ In this latter group, an inability to further increase end-inspiratory lung volume, $V_{T'}$ and V'_E at the peak of exercise in response to dead space loading indicated that the respiratory system had reached its physiological limits at the end of exercise. Moreover, this abnormality occurred in a setting of adequate cardiac reserve. Such critical mechanical constraints on V_T expansion during added dead space breathing were associated with an earlier onset of intolerable dyspnea in patients with mild COPD but not in healthy controls.¹⁸

Mechanical studies have also confirmed that dynamic lung compliance is decreased and pulmonary resistance, rest-to-peak changes in EELV, intrinsic positive end-expiratory pressures, and oxygen cost and work of breathing are increased in symptomatic patients with mild COPD compared with healthy controls.^{11,45}

Cardiovascular impairment

As smoking history is a common risk factor for both COPD and cardiovascular disease, it is not surprising that

patients with COPD display a range of cardiocirculatory abnormalities. Historically, it was widely believed that cardiovascular complications occurred only in patients with advanced disease as a consequence of chronic hypoxemia, eg, pulmonary hypertension and cor pulmonale. More recently, however, it is recognized that cardiovascular dysfunction is a common comorbidity in mild-to-moderate COPD.^{53–59}

In a large Danish population study, the presence of dyspnea and mild airflow obstruction was shown to be an independent predictor of cardiovascular mortality.⁶⁰ Preclinical, mild airflow obstruction is associated with smaller left ventricular end-diastolic volumes and decrements in stroke volume and cardiac output.^{53,54} Minor, increased emphysema is also associated with impaired left ventricular diastolic function and reduced cardiac output.^{54,55} Emphysematous destruction of lung parenchyma and pulmonary capillary beds, endothelial dysfunction, reduced pulmonary blood flow, and increased pulmonary vascular resistance have been suggested as possible underlying mechanisms responsible for these abnormalities.^{53,54}

Skeletal muscle dysfunction

Activity limitation inevitably leads to deconditioning and skeletal muscle dysfunction, manifested as marked declines in muscle mass and strength, which contribute to impaired mobility, poor health status, and further exercise intolerance.^{1,61} There is a growing appreciation that structural and functional abnormalities of the skeletal muscles can develop in patients with mild COPD.^{62–65} Skeletal muscle impairment may, in turn, lead to reduced exercise capacity.¹² Muscle injury,⁶² loss of skeletal muscle oxidative capacity, and diminished endurance⁶³ have been reported in patients with mild-to-moderate COPD and appear to develop in the absence of significant muscle wasting.¹²

Physical inactivity and deconditioning are thought to contribute to skeletal muscle dysfunction, and the initiation of exercise training programs has been shown to improve muscle function;⁶⁶ however, physical inactivity is not thought to be the sole determinant of muscle impairment in mild-to-moderate COPD.⁶³ Muscle impairment worsens with progressive lung function, suggesting the involvement of oxidative stress.⁶³ Active smoking may also play a significant role due to its negative impact on muscle bioenergetics and protein synthesis.⁶³

Assessment of exercise tolerance

Due to the detrimental role of physical inactivity in COPD, a complete patient assessment should include both assessment of usual activity levels and measurement of lung function. Clinical trials of interventions for COPD frequently

assess physical activity using either subjective methods, including patient diaries and questionnaires,⁶⁷ or objective methods, eg, pedometers⁶⁸ or accelerometers.⁶⁷ Subjective methods are inexpensive, easy to administer, and represent the patients' perspective on their functional status. A wide variety of simple questionnaires for quantifying physical activity has been reviewed.⁶⁷ These methods do have their limitations, such as the potential for erroneous reporting, recall bias, and interpretation issues.⁶⁹

Simple assessment of physical activity and symptoms may help reveal the impact of COPD on patients' daily lives. Pedometers count the number of steps taken by detecting vertical movements, but can underestimate slow walking, such as in elderly patients,⁷⁰ and provide no information about the time spent in individual activities or the intensity of the activities performed.⁶⁷ Accelerometers are more technologically advanced than pedometers, and multi-axial devices are able to detect movement in multiple planes of motion.⁷¹ Unlike pedometers, accelerometers are also generally capable of recording and storing information on exercise intensity. Newer devices, incorporating multi-axial accelerometers and multiple physiological sensors, are able to estimate energy expenditure even at the slow walking pace typical of elderly patients with COPD.^{72,73} The significance of assessing physical activity was demonstrated in a recent study, which found that all-cause mortality in patients with COPD was best predicted using objective measures of physical activity.⁷⁴

Endurance tests using constant work rate (CWR) protocols, ie, cycle ergometer or treadmill, are often used to assess the effects of PR because exercise training has little effect on maximal exercise capacity but can improve endurance.⁷⁵ Furthermore, CWR protocols are gaining popularity because they are able to assess improvements in endurance as a result of PR⁷⁵ and are responsive to the beneficial effects of bronchodilators on symptoms that limit exercise tolerance.^{45,76–79}

Simple assessment of physical activity

Simple assessment of physical activity in patients with COPD is by the use of tools or questionnaires designed to assess a patient's ability to accomplish basic and instrumental activities of daily living,⁸⁰ eg, the well-established London Chest Activity of Daily Living scale (LCADL), which assesses dyspnea during a patient's activities.⁸¹ Interestingly, a recent systematic review has concluded that assessment of activities of daily living should be used more often as a clinical outcome in the management of patients with COPD.⁸²

The modified British Medical Research Council (mMRC) dyspnea scale⁸³ and the COPD Assessment Test (CAT© 2009;

GlaxoSmithKline, Brentford, UK)⁸⁴ are used by the GOLD guidelines for symptom/risk evaluation.¹ Together, these questionnaires represent valuable tools for pulmonologists that can help to provide a clear assessment of an individual's disease severity. The mMRC dyspnea scale uses a simple grading system to assess a patient's level of dyspnea from 0 (only breathless with strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing).⁸³ The majority of patients with mild ($FEV_1 > 80\%$ predicted) airflow obstruction provide a score of 0–1 on the mMRC dyspnea scale.^{12,85} The mMRC dyspnea scale is also used to help calculate the dyspnea arm of the BODE Index: body mass index (B), airflow obstruction (O), dyspnea (D), and exercise tolerance (E),⁸⁶ which is used to predict mortality in COPD. Validation of the BODE Index has shown that a BODE score of 3–4 and mild-to-moderate airflow limitation ($FEV_1 > 50\%$) are associated with a similar survival probability (~0.7).⁸⁷

The CAT is a questionnaire used to measure the overall impact of COPD on a patient's life. It consists of eight items, each scored 0 (no impact) to 5 (very severe impact), giving a total score range of 0–40, where a higher CAT score indicates that COPD is having a more severe impact on a patient's life. In a recent European cross-sectional study, Jones et al⁸⁵ proposed that a CAT score ≥ 10 is clinically meaningful, and showed that patients with mild airflow obstruction already display significant health status impairment (CAT score ~16). While the total CAT score does not provide a specific evaluation of dyspnea and activity limitation, it can help to identify patients in whom these two symptoms are perceived as problematic.

6-minute walking distance test (6MWT)

The 6MWT is a practical method of assessing exercise tolerance and tracking functional changes in patients with COPD. Requiring little more than a 100-foot hallway and a stopwatch, the 6MWT measures the distance that a patient can walk on a flat, hard surface over 6 minutes. In contrast to tests that focus on a single component of physical function, the 6MWT evaluates the integrated response of pulmonary, cardiovascular, and muscular components.

Because the 6MWT is self-paced and dependent on patient motivation, the test measures submaximal exercise tolerance rather than exercise capacity.⁸⁸ However, because most activities are performed at submaximal levels, the 6MWT is believed to provide useful information regarding activities of daily living, in that patients with a severely impaired 6-minute walking distance are likely to have very low physical activity levels in daily life.²¹ It is also better tolerated than other walking tests.⁸⁹

Results of the 6MWT have been correlated with health status, dyspnea at rest, maximum exercise capacity, and mortality.^{90–92} The 6MWT distance speed is generally similar between patients with mild COPD and healthy controls.⁹³ However, Díaz et al¹² recently showed that the 6MWT distance is significantly reduced in dyspneic patients with mild COPD, compared with non-dyspneic patients and smoker controls.

Incremental (ISWT) and endurance (ESWT) shuttle walking tests

Similar to the 6MWT, the ISWT is a field-based walking test, which does not require expensive equipment. However, unlike the 6MWT, the ISWT is externally paced and walking speed is incrementally increased each minute until the patient is limited by symptoms. The ISWT was developed to provide a field-based equivalent of the more advanced laboratory-based tests that measure peak exercise capacity.^{94,95} A variation of the ISWT, the ESWT is conducted at a constant pace (80%–85% of peak effort based on a prior ISWT) and continues until the patient is limited by symptoms.⁹⁶ A number of studies have demonstrated that the ESWT is responsive to the effects of bronchodilators on exercise tolerance^{26,97,98} and may have better discriminative properties than the 6MWT.⁹⁷

There is a paucity of studies that have evaluated ISWT and ESWT in patients with mild COPD. In one small study, Boer et al⁹⁹ suggest that there is no significant difference in ISWT distance between patients with mild COPD and smoker controls, despite a significant difference between patients with moderate COPD and smoker controls.

Laboratory cardiopulmonary exercise testing

Although laboratory tests of exercise performance are not widely available, they can be very useful in evaluating the nature and extent of physiological impairment on an individual basis and can help in the planning of personalized treatment. Incremental cycle and treadmill tests represent the gold standard for the evaluation of integrated physiological responses to the stress of physical activity. These tests are particularly valuable for the investigation of disproportionate dyspnea and/or unexplained exercise intolerance in patients with mild airway obstruction. Consistent abnormalities in mild COPD include: increased dyspnea and leg discomfort ratings (as measured using the Borg Scale⁴⁸); decreased peak oxygen uptake and work rate; increased ventilatory inefficiency; increased gas trapping (as measured by serial inspiratory capacity measurements); and a relatively rapid shallow breathing pattern with an early plateau of \dot{V}_{T^*} ^{10,11,18,45,100}

In some patients, cardiac abnormalities or increased arterial oxygen desaturation are uncovered.

Therapy of COPD

At present, smoking cessation is the only intervention that has been conclusively shown to slow the progression of COPD^{14,15} and should be implemented in all patients as early as possible,¹ but a recent systematic review of studies in mild-to-moderate COPD (patients with $FEV_1 \geq 50\%$ predicted) has shown that, in addition to smoking cessation, pharmacologic and nonpharmacologic treatment initiated in the early stages of the disease can also have a beneficial effect on disease symptoms and prognosis.¹⁰¹ Nonetheless, relieving symptoms and improving exercise tolerance are increasingly recognized as important goals of treatment for COPD, and benefits can be achieved using both pharmacologic and nonpharmacologic interventions.^{1,16,17}

Pharmacologic therapy

Maintenance therapy of COPD with long-acting bronchodilators can significantly reduce the impact of the disease.^{102–104} In patients with COPD and persistent activity-related dyspnea, it is important to first achieve sustained bronchodilation and lung deflation to reduce dyspnea, allowing patients to engage more in activities of daily living.

The GOLD guidelines¹ assign patients with COPD to four separate groups (A–D) on the basis of combined assessment of airflow limitation, symptoms, and exacerbation risk, and provide recommendations for initial pharmacologic treatment based on these groups (Table 1). To date, there is insufficient evidence for recommendations for the pharmacologic treatment of patients with few symptoms and at low risk (group A).

For patients with spirometrically confirmed COPD who report persistent activity-related dyspnea, the initial goal is to reduce EFL in order to address lung hyperinflation and dyspnea. By virtue of their ability to relax airway smooth muscle tone, all classes of bronchodilators enhance lung emptying and increase inspiratory capacity.^{27,105–107} The majority of clinical studies of bronchodilators for COPD have been conducted in patients with more severe airflow limitation (GOLD 3 and GOLD 4, groups C and D), and their efficacy in improving lung function, symptoms, and exercise tolerance is well established in these patients.^{27–29,76–78,106} However, there is an increasing body of evidence on the pharmacological treatment of patients with mild-to-moderate COPD that supports treatment at the early stages of the disease.^{108,109}

Table 1 Global initiative for chronic Obstructive Lung Disease recommendations for initial pharmacologic management of chronic obstructive pulmonary disease (COPD)

Patient group	Recommended First Choice	Alternative Choice	Other possible treatments**
Initial Pharmacologic Management of COPD*			
A	Short-acting anticholinergic prn <i>or</i> Short-acting beta ₂ -agonist prn	Long-acting anticholinergic <i>or</i> Long-acting beta ₂ -agonist <i>or</i> Short-acting beta ₂ -agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic <i>or</i> Long-acting beta ₂ -agonist	Long acting anticholinergic and long-acting beta ₂ -agonist	Short-acting beta ₂ -agonist <i>and/or</i> Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta ₂ -agonist <i>or</i> Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta ₂ -agonist <i>or</i> Long-acting anticholinergic and phosphodiesterase-4 inhibitor <i>or</i> Long-acting beta ₂ -agonist and phosphodiesterase-4 inhibitor	Short-acting beta ₂ -agonist <i>and/or</i> Short-acting anticholinergic Theophylline
D	Inhaled corticosteroid + long-acting beta ₂ -agonist <i>and/or</i> Long-acting anticholinergic	Inhaled corticosteroid + long-acting beta ₂ -agonist and long-acting anticholinergic <i>or</i> Inhaled corticosteroid + long-acting beta ₂ -agonist and phosphodiesterase-4 inhibitor <i>or</i> Long-acting anticholinergic and long-acting beta ₂ -agonist <i>or</i> Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting beta ₂ -agonist <i>and/or</i> Short-acting anticholinergic Theophylline

Notes: *Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference; **medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns.

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Abbreviation: prn, pro re nata.

The effects of short-acting bronchodilators on exercise tolerance have been examined in symptomatic patients with mild airflow limitation (equivalent to group B).^{45,110} Despite modest improvements in airway function, operating lung volumes, and dyspnea intensity, short-acting agents yield no significant improvements in exercise endurance. Correspondingly, the GOLD guidelines¹ view long-acting bronchodilators as superior to short-acting bronchodilators for patients in group B; however, this recommendation is based on expert consensus opinion rather than evidence from clinical trials.

The results from a study by Casaburi et al; unpublished data, 2014 ClinicalTrials.gov identifier: NCT01072396) indicated that tiotropium significantly improved exercise duration compared with placebo in patients with GOLD 2 COPD (although not in patients with GOLD 1 COPD), and this improvement was associated with significant improvements in dynamic lung hyperinflation. This study has the

largest cohort to date on which the effects of bronchodilator treatment in patients with mild-to-moderate COPD (48 patients with GOLD 1 COPD and 78 patients with GOLD 2 COPD) have been assessed. Further investigations are clearly warranted into the benefits of bronchodilator treatment in mild COPD and the long-term effects of bronchodilators on physical activity.

Pulmonary rehabilitation

Every effort should be made to inform patients with COPD about the benefits of physical activity due to its correlation with all-cause mortality. Exercise training improves skeletal muscle function to reduce ventilatory requirements, leading to reductions in dynamic hyperinflation and exertional dyspnea.²⁰ Thus, exercise training may interrupt the cycle of decline leading to inactivity. Exercise training serves as the cornerstone of PR, which also includes patient assessment, self-management education, nutritional intervention,

and psychosocial support.¹¹¹ Multiple guidelines for COPD recommend PR for all symptomatic patients, regardless of disease severity.^{1,17,20} These recommendations are based on evidence for improvement in dyspnea, quality of life, exercise endurance, and functional capacity, for which PR is stronger than almost any other therapy in COPD;²⁰ PR has also been shown to have a beneficial effect in reducing levels of anxiety and depression, which are common comorbidities also seen in mild-to-moderate COPD.^{1,112,113}

Despite these recommendations, there have been few studies to evaluate the benefits of PR in patients with mild COPD. The findings of an early systematic review suggested that physical activity can significantly improve physical fitness in patients with mild-to-moderate COPD.¹¹⁴ However, no improvements to health-related quality of life or dyspnea were reported. A more recent systematic review indicated there were significant, positive effects of PR on exercise capacity and quality of life in patients with mild COPD.¹¹⁵ Nevertheless, the impact of PR on health care resource use and lung function in patients was inconclusive. Together, these findings suggest that patients with mild COPD may benefit from PR programs as a part of their disease management, but further prospective studies are required.

Conclusion

Accumulating evidence suggests that pathological changes leading to exercise limitation are present even in symptomatic patients with mild COPD, and such patients show evidence of impairment in the form of increased exertional dyspnea and leg discomfort.^{1,10,11,18} Although the mechanisms of this impairment are multifactorial, abnormal ventilatory mechanics linked to EFL, lung hyperinflation, ventilatory inefficiency, and exertional dyspnea are central to the process.^{5,10–12,18,19} Patients adapt to exertional dyspnea by decreasing physical activity, beginning with nonessential leisure activities, and progressing to include basic activities of daily living. This reduction in physical activity leads to deconditioning, which not only worsens dyspnea, but also negatively affects health status and prognosis.¹³

Pulmonologists have a range of tools, including the 6MWT, ISWT, ESWT, laboratory-based tests including the CWR test, and physical activity assessments (eg, questionnaires^{80,83,86,116} and pedometers and accelerometers^{67,68,71–73}) by which to measure levels of physical activity in symptomatic mild COPD patients. In addition, a range of pharmacologic^{27,76–78,106} and nonpharmacologic (smoking cessation, exercise training, and PR) treatments are available to manage COPD,^{1,16,17} although their potential benefits in mild disease are inconclusive. This review highlights recent evidence that exercise

intolerance and activity limitation are apparent even in mild disease,^{10,11,18} with the reasonable hope that early intervention can help reduce disease progression in these patients, thereby reducing morbidity and mortality and, consequently, the need for hospitalizations and associated health care costs. Additional prospective clinical trials are urgently needed to determine if earlier introduction of pharmacotherapy is effective in patients with mild COPD.

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