Prevalence and prognostic importance of exercise limitation and physical inactivity in COPD

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Exercise capacity should be assessed in all patients with COPD. Exercise intolerance appears to be a stronger predictor of mortality than low physical activity levels. Maximising exercise capacity should be a key goal of pulmonary rehabilitation. https://bit.ly/3vII1ap

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Abstract

Exercise limitation and physical inactivity are separate, but related constructs. Both are commonly present in individuals with COPD, contribute to disease burden over and above the respiratory impairments, and are independently predictive of adverse outcomes. Because of this, clinicians should consider assessing these variables in their patients with COPD. Field tests of exercise performance such as the 6-min walk test and the incremental and endurance shuttle walk tests require limited additional resources, and results correlate with negative outcomes. Laboratory measures of exercise performance using a treadmill or cycle ergometer assess exercise capacity, provide prognostic information and have the advantage of explaining physiological mechanisms (and their interactions) underpinning exercise limitation. Limitations in exercise capacity (*i.e.* "cannot do") and physical inactivity (*i.e.* "do not do") are both associated with mortality; exercise limitation appears to be the more important driver of this outcome.

Background

This review will use definitions of physical activity and exercise endorsed by the US Centers for Disease Prevention and Control, with the former referring to bodily movement produced by skeletal muscles and resulting in energy expenditure, and the latter referring to "a subcategory of physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is the objective" [1]. In this review, we will focus on the prevalence and prognostic importance of exercise limitation and physical activity. The interplay of factors behind exercise limitation and physical inactivity in COPD and interventions for improving exercise capacity and physical activity are discussed elsewhere in this issue of *Breathe* [2, 3].

Exercise intolerance and physical inactivity are common manifestations of COPD. A large proportion of people with COPD show a decreased capacity to perform bouts of moderate and high intensity exercise due to symptoms of breathlessness and/or muscle fatigue. In the recent population-based Canadian Cohort Obstructive Lung Disease (CanCOLD) study, over 30% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometry grades 2–4 showed a peak oxygen uptake ($\dot{V}_{O_2}$) below the lower limit of normal [4]. Furthermore, in a sample referred for pulmonary rehabilitation (PR), almost 90% of patients showed decreased exercise capacity [5].

Unsurprisingly, patients with COPD also have significantly lower levels of physical activity compared with healthy age-matched controls, independent of cultural background, geographic area and the method used to assess physical activity [6]. Findings from systematic reviews indicate a significant decrease in duration and intensity of physical activity in these patients (57% and 75% of the values observed in healthy adults) [7], and a significantly lower number of steps per day compared with most other chronic diseases (*i.e.* a median of 2237 steps per day) [8]. Furthermore, most people with COPD do not meet the recommended physical activity guidelines, as only about one-third achieve at least 30 min of moderate physical activity at least 5 days per week [9–11].

Measuring exercise capacity and physical activity

Since exercise testing is fundamental for accurately quantifying cardiorespiratory fitness and for identifying mechanisms underlying exercise intolerance, it is recommended for patients with COPD. Exercise tests have been categorised into either field walking tests or laboratory tests, with the latter usually performed using a treadmill or cycle ergometer [12]. Field tests are sub-categorised into self-paced tests, such as the 6-min walk test (6MWT), and externally paced tests such as the incremental and endurance shuttle walk tests. Field tests are easily administered, require only minimal additional resources, have established minimum clinically important differences (MCID), and a robust ability to predict subsequent healthcare utilisation and mortality [13]. With respect to field tests of exercise performance in general and the 6MWT in particular, attention to methodology as proposed by official guidelines is required to produce reliable and reproducible results [13, 14]. Laboratory measurements of exercise capacity allow for measurement of complex physiological and metabolic data and their interactions, as the peak $\dot{V}_{O_2}$ measurement integrates respiratory as well as cardiovascular and muscular anomalies of patients. For example, maximal exercise testing can reveal limitations of the ventilatory system (often as a combination of reduced ventilatory capacity and increased ventilatory needs) as a major cause of impaired exercise capacity, especially in those with severe airflow obstruction [15]. However, gas exchange abnormalities, peripheral and respiratory muscle dysfunction, and cardiovascular impairment can also potentially have a role in exercise limitation [15, 16], and can be determined from this type of testing. This is of importance, since physiological systems strongly influence each other – malfunctioning of one system will increase the stress on the other systems.

Physical activity measurement in daily life falls into two categories: 1) subjective methods, including questionnaires and diaries; and 2) direct assessments from mechanical or electronic motion detectors, including pedometers and accelerometers [17]. Subjective measures, which are inexpensive and easy to use, are frequently used in epidemiological studies and large clinical trials; their major limitation is recall bias [6]. Mechanical assessment of steps per day using pedometers is inexpensive and can provide feedback to patients as part of collaborative self-management interventions to increase activity. Direct measurements of movements using accelerometers are valid and more accurate measures of physical activity and can also estimate intensity [6]. Two aspects of physical activity, amount (*e.g.* step counts per day) and intensity (*e.g.* time in the moderate-to-vigorous physical activity (MVPA) range) are important variables. Time spent "not moving, while awake" (*i.e.* sedentary behaviour) is a separate construct and important to prognosis [18]. Finally, physical activity experience was introduced as a concept to capture both the amount and the difficulties experienced with physical activity [19]. This concept is captured by PROactive tools, but to date, these have had limited application in daily clinical practice, possibly due to time constraints, lack of awareness or limited resources.

Prognostic implications of exercise limitation and physical inactivity

Exercise limitation and physical inactivity are not only undesirable in COPD they also appear to mediate other negative outcomes associated with this disease [20–22]. The underlying mechanisms by which reduced exercise tolerance leads to increased mortality in COPD involve a combination of physiological, pathological and systemic factors, including ventilatory limitation, gas exchange abnormalities, skeletal muscle dysfunction and systemic inflammation. Several studies have demonstrated that a low exercise capacity, as assessed by peak $\dot{V}_{O_2}$ during a cardiopulmonary exercise test (CPET) (<593–654 $mL \cdot min^{-1}$ or <10.5–14.6 $mL \cdot kg^{-1} \cdot min^{-1}$), is a highly significant predictor of mortality, independent of forced expiratory volume in 1 s and age [23–26]. In addition, CPET-derived variables reflective of pulmonary gas exchange provide prognostic value in COPD. These include minute ventilation ($\dot{V}_E$)/carbon dioxide production ($\dot{V}_{CO_2}$) nadir ⩾34 or $\dot{V}_E/\dot{V}_{CO_2}$ slope ⩾30 [26, 27]. Moreover, factors linked to impaired ventilation (peak ventilation ⩽25.7 $L \cdot min^{-1}$) [26], deconditioning or autonomic dysfunction (slow 1-min heart rate recovery (⩽14 beats)) [28], and severity of hypoxaemia at peak exercise (arterial oxygen tension <60 mmHg) [29] are associated with poor survival.

The prognostic ability of the 6MWT, a measure of functional exercise performance, is demonstrated extensively in COPD. A 6MWT distance <350 m is associated with an increased risk of exacerbation-related hospitalisation, while distances less than a 200–440 m range predict all-cause and respiratory-specific mortality [30–38]. A systematic review indicated 317 m as a critical value for poor prognosis [39]. Several other 6MWT-derived variables, including exercise-induced oxygen desaturation [32, 35, 36, 40], mean walk-speed [35], 6-min walk-work [35], distance–saturation product [35] and the number of unintended stops [34], also predict poor outcomes. Additionally, a longitudinal decrease in 6MWT distance and repeated desaturation over time independently predict mortality [33, 41, 42], and COPD patients who improve their distance on this test by at least 30 m after PR have a better prognosis compared with patients who lack this improvement [43].

The incremental shuttle walk test (ISWT) also predicts hospital readmission and survival [44–46], and a threshold of <170 m is associated with a higher mortality [46]. Additionally, a change in ISWT distance following PR of ⩾50 m is associated with improved survival [47]. Finally, other simple measures of functional exercise capacity, such as sit-to-stand test [48–52], the short physical performance battery [53, 54] and the gait speed test (4 m) [54–56], predict exacerbation-related hospitalisation and mortality.

Given the evidence that exercise tests appear to be better predictors of prognosis than, for example, spirometry, it is recommended to include a measure of exercise capacity in the assessment of patients with COPD. Although practical and easy-to-perform tests are desirable, especially in primary care settings, it is important to highlight that the choice of the exercise test should depend on the population. For example, the more simple measures, such as the sit-to-stand test, short physical performance battery or gait speed test, might be less predictive in younger patients and those who are at earlier stages of the disease.

Several studies have consistently demonstrated the prognostic value of reduced daily physical activity levels in risk of exacerbations, exacerbation-related hospitalisations and all-cause mortality in COPD, even after controlling for relevant confounding factors [34, 37, 38, 57–65]. A threshold of <4000 steps per day appears to separate those patients with increased mortality risk [38, 66]. Patients with COPD who are less active over the first week following hospital discharge for an exacerbation are more likely to be readmitted within 30 days [67, 68], and the reduction in the level of physical activity after an exacerbation is an important predictor of mortality in the following year [69]. While the amount of regular physical activity associated with reductions in COPD-related hospitalisations appears to be relatively small, equivalent to 2 h per week of walking or cycling [6], causality between increased activity and healthcare utilisation has not been determined. Longitudinal studies of prognostic implications on changes in physical activity are limited, but data suggest that prolonged low physical activity levels or a decrease in physical activity over time are related to an increased risk of exacerbations and mortality [64, 65, 70, 71].

Table 1 provides an overview of the assessment methods for exercise capacity and physical activity in COPD with advantages/disadvantages and prognostic indicators.

PR interventions to target exercise capacity limitation in COPD

Comprehensive PR includes individualised goal setting based on initial assessments of exercise capacity and physical activity. Assessment should also include non-respiratory factors that limit participation, such as balance problems and frailty [12, 72, 73]. PR for COPD patients provides beneficial and clinically meaningful effects across multiple outcome areas, including increases in exercise capacity [12, 74]. Furthermore, higher intensity exercise, at least in the short run, leads to greater physiological benefits [75]. Thus, the effect of aerobic training is dose dependent, with a higher volume of exercise (duration and intensity) needed for optimal improvement in exercise capacity [76].

Ventilatory limitation during exercise is caused by an imbalance between (lowered) ventilatory capacity associated with expiratory flow limitation and dynamic hyperinflation, and (increased) ventilatory demands due to increased work of breathing, dead space ventilation and early onset of lactic acidosis [77]. In patients experiencing ventilatory limitation during exercise, optimisation of bronchodilator therapy prior to and during PR can increase maximal ventilation and reduce dynamic hyperinflation [12], and is recommended for all patients prior to undertaking PR. This pharmacotherapy is optimised by individualised education on the proficient use of inhalers. In patients with mucus expectoration problems, airway clearance techniques are indicated, but their impact on exercise limitation has not been elucidated [78]. For patients with advanced disease associated with hypercapnic respiratory failure, noninvasive ventilation reduces hypercapnia and improves dyspnoea and exercise tolerance by unloading the inspiratory muscles and reducing work of breathing. Although the implementation of noninvasive ventilation during exercise is

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TABLE 1 Methods of exercise capacity and physical activity assessment with advantages/disadvantages and prognostic value

Assessment method	Advantages	Disadvantages	Outcome	Prognostic value
Exercise capacity: laboratory tests				
Cardiopulmonary exercise test on cycle or treadmill	Gold standard for exercise capacity evaluation No need for a practice test	High costs due to sophisticated equipment and personnel	Peak $\dot{V}_{O_2}$ Peak $\dot{V}_E$ $\dot{V}_E/\dot{V}_{CO_2}$ 1-min heart rate recovery Hypoxaemia at peak exercise	Increased mortality risk: • Peak $\dot{V}_{O_2}$ <593–654 mL·min^{-1} • Peak $\dot{V}_{O_2}$ <10.5–14.6 mL·kg^{-1}·min^{-1} • Peak $\dot{V}_E$ ⩽25.7 L·min^{-1} • $\dot{V}_E/\dot{V}_{CO_2}$ nadir ⩾34 • $\dot{V}_E/\dot{V}_{CO_2}$ slope ⩾30 • 1-min heart rate recovery ⩽14 beats • P_{aO_2} <60 mmHg
Exercise capacity: field tests				
6-min walk test	Easy to perform Inexpensive	Does not provide insight into the mechanisms of exercise limitation	Distance Exercise-induced oxygen desaturation Mean walk-speed 6-min walk-work Distance–saturation product Unintended stops	Increased hospitalisation risk: • Distance <350 m • Oxygen saturation post-test ⩽88% • Mean walk-speed ⩽1.0 m·s^{-1} • 6-min walk-work ⩽27 000 kg·m • Distance–saturation product ⩽310 m·% Increased mortality risk: • Distances less than a 200–440 m range • Oxygen saturation post-test ⩽88–90% • Oxygen saturation >4% reduction • Mean walk-speed ⩽0.9 m·s^{-1} • 6-min walk-work ⩽20 000 kg·m • Distance–saturation product ⩽290 m·%
Incremental shuttle walk test	Easy to perform Requires less technical equipment	Practice test needed Audio signals under copyright	Distance	Increased mortality risk: • Distance <170 m
Endurance shuttle walk test	Easy to perform Requires less technical equipment	Practice test needed Audio signals under copyright	Time	
Physical activity: objective methods				
Accelerometers	Information on type, duration, intensity and frequency of physical activity	More expensive Technical expertise required to analyse and interpret the raw data output	Steps Frequency Intensity Accumulated time Activity type	Increased hospitalisation risk: • VMU <130 *versus* VMU >270 Increased mortality risk: • <4000 steps per day • VMU <130 *versus* VMU >270 • ⩾8.5 h per day sitting time
Pedometers	Low cost Easy to use	Limited to step-based activities No information on intensity, pattern or duration of activities	Steps	Increased mortality risk: • <4000 steps per day
Physical activity: subjective methods				
Questionnaires, diaries	Low cost Easy to use	Recall bias Limited reliability and validity Overestimation of physical activity	Physical activity type Time spent in different activities	Increased hospitalisation risk: • <2 h per week self-reported physical activity • <79 kcal per day *versus* >232 kcal per day Increased mortality risk: • <2 h per week self-reported walking or cycling

$\dot{V}_{O_2}$: oxygen uptake; $\dot{V}_E$: minute ventilation; $\dot{V}_{CO_2}$: carbon dioxide production; P_{aO_2}: arterial oxygen tension; VMU: vector magnitude unit.

rather complex and labour intensive, it can improve exercise-induced symptoms of dyspnoea in a subset of patients [79].

Patients who show clinically relevant exercise-induced oxygen desaturation will probably be prescribed oxygen supplementation during exercise. Evidence supporting the use of oxygen to enhance exercise training effects in COPD is mixed, probably due to the differences in exercise training intensity among trials [79]. Similarly, patient responses to continuous nasal high-flow oxygen therapy are highly variable [80]. Of note, even those COPD patients without apparent oxygen desaturation might benefit from oxygen supplementation during exercise. This beneficial effect appears to be mediated through reduced ventilation and dynamic hyperinflation, resulting in increased exercise capacity [81].

Patients with impaired inspiratory muscle strength and/or endurance are at risk of developing respiratory muscle fatigue during exercise, especially when this is combined with marked dynamic hyperinflation. As inspiratory muscle fatigue during exercise is difficult to assess, a baseline evaluation of inspiratory muscle function may provide useful information in some patients. In patients with inspiratory muscle impairment, targeted inspiratory muscle training can be a useful an add-on or stand-alone intervention to optimise endurance exercise capacity, although the results are mixed [82–84].

While some COPD patients reach "healthy" cardiovascular exercise limitation (*e.g.* by reaching the age-predicted maximal heart rate), cardiovascular comorbidities such as ischaemic heart disease and heart failure may impair the cardiovascular response during exercise. The use of β-blockers in this population has a direct impact on the cardiovascular exercise response and hyperinflation, with the characteristic increased intrathoracic pressures, may also impact on cardiac output during exercise by lowering stroke volume as a consequence of impaired venous return to the right atrium. Exercise training can improve cardiovascular output [85], although it is unclear whether this effect is directly due to improved cardiac function or whether it is related to reduced ventilatory requirements or improved dynamic hyperinflation, resulting in a better end-diastolic volume and stroke volume [86].

Skeletal muscle dysfunction is highly prevalent in patients with COPD and is characterised by both quantitative and qualitative deterioration of the muscle tissue. Besides muscle atrophy, muscle dysfunction is characterised by a fibre shift towards type II fibres, decreased number and function of mitochondria, and decreased capillarisation, compromising the aerobic muscle metabolism during exercise. Individually targeted exercise training can result in increased muscle cross-sectional area, a reduced proportion of type IIx fibres and metabolic improvements (*e.g.* increased oxidative capacity, reduced exercise-induced lactate production), therefore reducing the reliance on anaerobic muscle pathways for a given exercise intensity. This not only reduces skeletal muscle limitation, it also reduces ventilation and cardiovascular requirements during exercise [87].

Do improvements in exercise capacity or physical activity drive the mortality benefit of PR?

Among the multitude of benefits of PR, perhaps the most valued is its potential to decrease mortality. However, whether it is its ability to increase physical activity (what people actually do) or physical fitness (exercise capacity: what people are capable of doing) that leads to a mortality benefit is unclear. A 2011 paper by Waschki *et al*. [62], titled "Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study", clearly gives the impression that physical activity is the most important determinant of mortality in COPD. However, in their analysis of 4-year mortality in a cohort of 170 COPD patients, receiver operating characteristic (ROC) analysis showed the coefficient for baseline physical activity level was only slightly higher than for 6-min walk distance (area under the ROC of 0.81 *versus* 0.77, respectively). It is not surprising that cross-sectional studies such as this have difficulty distinguishing between physical activity and exercise capacity as mortality determinants, as the two measures are intercorrelated: more active people tend to be more fit.

It is hard to imagine a clinical trial that would directly answer this question. There is, however, evidence that can be brought to bear. The only interventional studies involve an animal model: rats bred differentially for high and low aerobic fitness. The median lifespan for low exercise capacity rats was 28–45% shorter than high exercise capacity rats [88]. A second study found that increasing the amount of voluntary aerobic exercise (by selective breeding or housing with wheels in cages) did not result in extended lifespan in mice, seeming to contradict a direct link between energy expenditure and lifespan [89]. Non-interventional studies in humans have relevance. In a Veteran's Administration cohort of 8171 men, exercise capacity (based on an incremental treadmill test) was associated with mortality and remained a strong predictor even after adjusting for physical activity (based on a questionnaire) [90]. While physical inactivity predicted mortality, the association was eliminated after adjusting for exercise capacity. In a second study, 31 818 men and 10 555 women completed an activity questionnaire and performed a maximal treadmill test [91]. In long-term

follow-up, physical inactivity was associated with mortality among men, but this association was eliminated after adjustment for exercise capacity. No significant association between physical inactivity and mortality was observed in women. In the same study, exercise capacity was inversely associated with mortality in both men and women, and the associations remained significant after adjustment for physical activity. However, both studies are limited by using subjective measures of physical activity, and as people tend to over-report their physical activity level, this might affect the true association between physical activity and mortality. However, findings from a recent study using accelerometer-derived physical activity appear to confirm the association between exercise capacity and survival in patients with COPD: patients with a preserved exercise capacity had a significantly lower 6-year all-cause mortality risk compared with patients with a reduced exercise capacity, regardless of physical activity level [38].

The evidence cited above seems to suggest that exercise capacity appears to have a tighter relationship to mortality than physical activity. However, it does not tell us whether an intervention that increases either exercise capacity or physical activity would reduce mortality, as only indirect evidence can be mustered to suggest causality. Recently published evidence has shown a substantial mortality benefit from analysis of a US Medicare database [92]. Comparing those who participated in PR within 3 months of a COPD hospitalisation to those who did not, 1-year survival was 37% better in those who participated in PR. This might infer that the driver of the mortality benefit in the post-hospitalisation period must be ubiquitous to a wide range of US PR programmes. But the study as such does not ascertain the direct link between improved survival and increased exercise tolerance, as the benefits may be linked to other benefits of taking part in PR, such as better self-management skills or improved medical management, *etc*.

In fact, improvements in exercise capacity are a reliable outcome of PR programmes. In an unusual declaration, a Cochrane review stated that additional randomised clinical trials comparing PR to conventional care in COPD are not warranted based on the consistently demonstrated improvement in health-related quality of life and exercise capacity [93]. In contrast, rehabilitation-induced improvements in objectively measured physical activity have been examined in a substantial number of studies. The results are decidedly mixed, with roughly half of reports failing to find significant improvements in physical activity [94]. Among participants in individual programmes, changes in physical activity are very heterogeneous [64, 95, 96]. It might be inferred that an intervention that yields inconsistent and modest physical activity improvement is unlikely to induce a substantial mortality benefit.

More direct substantiation would, of course, be of help. However, if improving exercise capacity is, indeed, the main driver of the mortality benefit of PR, it follows that maximising exercise capacity gains through exercise training should be a key goal of PR programmes.

Conclusions and future directions

Exercise intolerance and physical inactivity are known treatable traits for patients with COPD and both contribute to disease burden and are predictive of adverse outcomes. Because of this, healthcare professionals should consider assessing these variables in patients with COPD. Physical activity can be assessed subjectively by questionnaires or diaries, or objectively by motion detectors. Exercise tests are categorised into either field walking tests (*e.g.* 6MWT, ISWT, endurance shuttle walk test) or laboratory tests (such as treadmill endurance time). Field tests of exercise performance require limited additional resources; laboratory measures of exercise performance have the advantage of explaining physiological mechanisms (and their interactions) underpinning exercise limitation. Although limitations in exercise capacity (*i.e.* "cannot do") and physical inactivity (*i.e.* "do not do") are both associated with mortality, limitations in exercise capacity appear to be the more important driver of this outcome. Therefore, improving exercise capacity should be a primary objective of PR programmes. However, future studies on the prognostic implications of longitudinal changes in exercise capacity and physical activity in patients with COPD are highly needed.

Key points

- Exercise and physical activity are separate constructs.
- Exercise capacity should be assessed in all patients with COPD; this can be determined using field or laboratory tests.
- Although both are related to prognosis in the COPD patient, exercise intolerance (reduced capacity) appears to be a stronger predictor of mortality than low physical activity levels.
- Maximising exercise capacity should be a key goal of PR programmes.

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