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REVIEW

Airflow obstruction and exercise

Christopher B. Cooper*

David Geffen School of Medicine, University of California, Los Angeles, USA

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Pulmonary disease;
Chronic obstructive;
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Anabolic agents

Summary
The primary abnormality in chronic obstructive pulmonary disease (COPD) is chronic airway inflammation which results in airflow limitation. Disease progression is usually depicted as an accelerated decline in FEV_1 over time. However, COPD patients also manifest progressive static hyperinflation due to the combined effects of reduced lung elastic recoil and increased airway resistance. Superimposed on static hyperinflation are further increases in operational lung volumes (dynamic hyperinflation) brought on during exercise, exacerbations or tachypnea.

An important consequence of exertional dyspnea is activity limitation. COPD patients have been shown to spend only a third of the day walking or standing compared with age-matched healthy individuals who spend more than half of their time in these activities. Furthermore, the degree of activity limitation measured by an accelerometer worsens with disease progression. COPD patients have been shown to have an accelerated loss of aerobic capacity (VO_2max) and this correlates with mortality just as is seen with hypertension, diabetes and obesity. Thus physical inactivity is an important therapeutic target in COPD.

Summarizing; airflow obstruction leads to progressive hyperinflation, activity limitation, physical deconditioning and other comorbidities that characterize the COPD phenotype. Targeting the airflow obstruction with long-acting bronchodilator therapy in conjunction with a supervised exercise prescription is currently the most effective therapeutic intervention in earlier COPD. Other important manifestations of skeletal muscle dysfunction include muscle atrophy and weakness. These specific problems are best addressed with resistance training with consideration of anabolic supplementation.

* Tel.: +1 310 825 4440; fax: +1 310 206 8211.
E-mail address: ccooper@mednet.ucla.edu

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Contents

''All parts of the body which have a function, if used in moderation and exercised in labours in which each is accustomed, become thereby healthy, well-developed, and age more slowly, but if unused and left idle they become quickly liable to disease, defective in growth, and age more quickly.'' Hippocrates. Circa 450 BC.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. The reported incidence of COPD is believed to dramatically underrepresent the total burden of the disease because typically the diagnosis is not established until patients become symptomatic. At this point, the condition is usually moderately advanced, as COPD is known to begin decades before symptoms manifest.[1] COPD is the fourth-leading cause of death in the USA and Europe, and COPD mortality in females has more than doubled over the last 40 years.[2] Interestingly, due to a widespread misperception that COPD primarily affects males, there is evidence of a diagnostic gender bias: in that when physicians are presented with patients with the same age and history but different gender, they diagnose COPD more frequently in men than women.[3]

The spiral of decline in COPD is characterized by progressively decreased physical functioning and progressive symptoms that eventually require hospital admission as the disease progresses. Patients often are unable to work and may become socially isolated, sleep deprived, and depressed.[4] Adding to these stressors is the continuous fear of exacerbations, which seem to contribute to the progressive decline in lung function, physical status and quality of life.[4]

Manifestations of COPD are highly variable, with significant differences in functional capacity, dyspnea, and involuntary weight loss from patient to patient.[5] Each of these clinical features, individually and collectively, contribute to the COPD phenotype. Inactivity, deconditioning, and muscle atrophy all lead to a decrease in functional capacity. Hyperinflation, hypoxemia, anxiety, and increased ventilatory drive contribute to dyspnea but also deconditioning can exacerbate dyspnea by increasing the ventilatory requirement for a given level of exercise. The additional work of breathing required to overcome the increased airway resistance can significantly increase the oxygen consumption of the respiratory muscles, increasing metabolic rate and contributing to involuntary weight loss.[6] Finally, muscle disuse and atrophy result in loss of lean body mass, whilst malnutrition further exacerbates involuntary weight loss. The common contributory feature of all of these patient outcomes is physical inactivity. Thus physical inactivity is an important therapeutic target in COPD.

Hyperinflation is central in the pathophysiology of COPD

Hyperinflation, which can occur even in mild to moderate cases,[7] explains many of the pathophysiological manifestations of COPD and also correlates with important patient-reported outcomes, such as dyspnea, declining exercise performance, and reduced quality of life.[8]The exertional dyspnea leads to limitation of daily activities which begins insidiously but progresses relentlessly over time. COPD patients with an average age of 64 years have been shown to spend only a third of the day walking or standing compared with age-matched healthy individuals who spend more than half of their time in these activities.[9] The worsening inactivity leads to an accelerated decline in aerobic performance with disease progression. COPD patients have been shown to have a faster decline in aerobic capacity.[10] Furthermore, in this cohort of 150 male COPD patients, the reduced aerobic capcity correlated with increased mortality.[10] The same phenomenon is seen with hypertension, diabetes and obesity.[11]

Spirometry is important to establish the diagnosis of COPD and should be considered in symptomatic patients with a history of significant exposures such as tobacco smoking (GOLD). Spirometry detects airflow limitation which has been defined as a low FEV_1/forced vital capacity (FVC) ratio less than 70%.[11] Spirometry also provides a measure of the forced expiratory volume in 1 s (FEV_1) which has been used in several published guidelines to stage COPD severity (ATS/ERS, BTS, CTS).[12–14] Although FEV_1 serves a useful purpose in the diagnosis and staging of COPD,[15] this measure correlates poorly with exercise performance[16] and patient-reported outcomes such as dyspnea and quality of life.[17] For example, in the National Emphysema Treatment Trial (NETT) which enrolled aproximately 1200 subjects, FEV_1 significantly correlated with

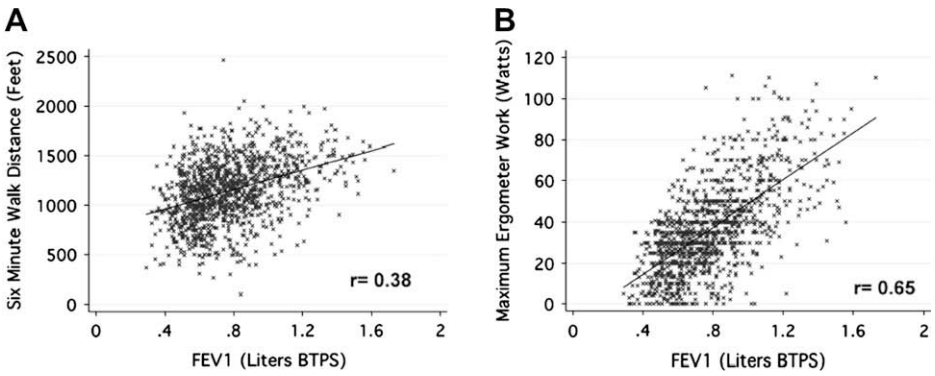

Figure 1 Relationship between FEV_1 and exercise performance in NETT. Data from the National Emphysema Treatment Trial (NETT). (Right) Relation between forced expiratory volume in 1 s (FEV_1) and maximum oxygen consumption (VO_2max). A correlation was found ($r = 0.65$), but the range of possible values for (VO_2max) varied widely at a given level of FEV_1. (Left) The relation between FEV_1 and functional exercise capacity as measured by 6-min walk distance. In this case there is no meaningful correlation.[18] (Figure originally appeared in Ref. 8. Reproduced with permission.)

maximum exercise capacity ($r = 0.65$), however, a given value of FEV_1 can be seen to be poorly predictive of exercise capacity (Fig. 1, panel B). Furthermore, FEV_1 showed no correlation with 6-min walking distance ($r = 0.38$), a measure of functional exercise capacity.[18] These data also confirm our clinical experience that once FEV_1 is reduced to 35% of predicted, exercise capability is highly variable: some patients experience minimal physical limitations, while others are not able to walk. It can be argued, therefore, that clinicians should look beyond the FEV_1 to assess and manage COPD.

The central connection between lung function measures, exercise capabilities, and COPD symptoms appears to be not FEV_1, but the pathophysiologic phenomenon of hyperinflation. Hyperinflation, is usually defined as the elevation of total lung capacity (TLC), functional residual capacity (FRC) or end expiratory lung volume (EELV) and residual volume (RV). For accuracy, these volumes should be measured by body plethysmography. It has been shown that as FEV_1 declines, hyperinflation increases (Fig. 2).[16] Given that static hyperinflation is a progressive phenomenon and a fundamental factor in disease progression, assessment of the development and extent of hyperinflation may in fact be a better indicator of disease progression than FEV_1.

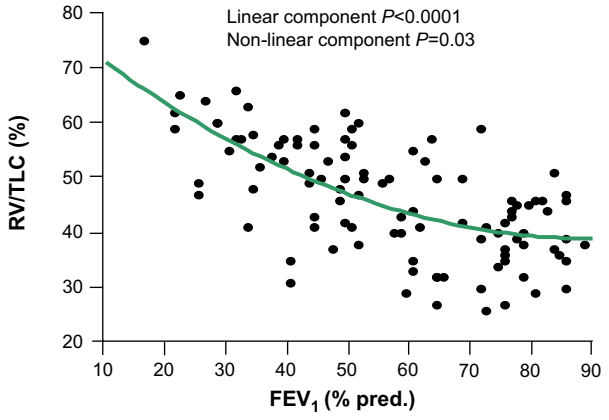

Figure 2 Hyperinflation and FEV_1. Foglio et al.[16] (Figure originally appeared in Ref. 8. Reproduced with permission.)

The central role of air trapping and hyperinflation in patient functioning and outcomes is illustrated in Fig. 3. At play are two vicious cycles that act to worsen hyperinflation. The first cycle results from activity limitation, leading to deconditioning, defined as the premature accumulation of lactate at low exercise work rates. Lactate from deconditioned muscles effluxes into the bloodstream, increasing carbon dioxide production from bicarbonate buffering, which in turn increases the ventilatory requirement for exercise. Increased ventilatory requirement is a significant factor in worsening air trapping and hyperinflation, which then manifests as increased dyspnea and reduced exercise tolerance. COPD exacerbations worsen airflow obstruction and also cause hyperinflation even before it becomes clinically apparent. The second cycle (Fig. 3) revolves around respiratory rate and available exhalation time. For given values of airway resistance and elastic recoil, when exhalation time is shortened due to increased inspiratory rate there is incomplete lung emptying, i.e. worsened air trapping and hyperinflation. These events can be triggered by anxiety or hypoxemia both of which cause breathing to become rapid and shallow. Understanding Fig. 3 highlights the important therapeutic targets that should lessen hyperinflation and improve patient-reported outcomes. These are to (a) relieve airflow obstruction, (b) prevent exacerbations, (c) improve physical conditioning, (d) correct hypoxemia, and (e) prevent anxiety and panic attacks. These therapeutic approaches are readily recognized as the long-established goals of a traditional pulmonary rehabilitation program.

Lung volume response to exercise

The behavior of operational lung volumes during exercise differs between healthy individuals and those with COPD. When healthy individuals exercise, tidal volume (V_T) expands by virtue of a decrease in the end expiratory lung volume and an increase in the end-inspiratory lung volume. Also, the operational lung volumes (EELV—EILV) remain on the steeper part of the pressure—volume or compliance

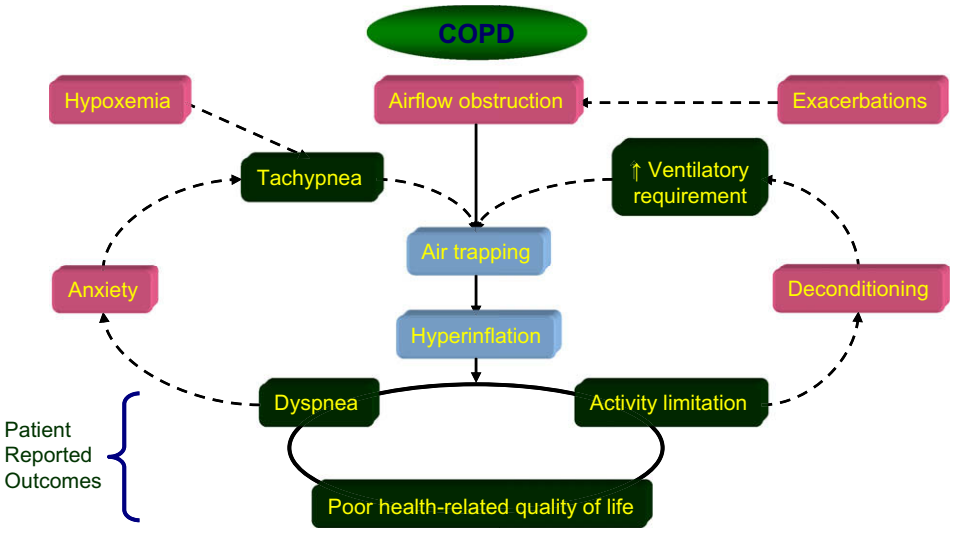

Figure 3 Air trapping links pathophysiology and patient centered outcomes in COPD. Central role of air trapping and hyperinflation in the pathophysiology of chronic obstructive pulmonary disease (COPD). Although related to increased airway resistance, hyperinflation correlates more directly with patient-reported outcomes. Activity limitation leads to deconditioning, which, in turn, increases ventilatory requirement, establishing a cycle of decline leading to worsening hyperinflation. Anxiety and hyopoxemia cause tachypnea, which worsens hyperinflation by allowing less time for exhalation. [Figure originally appeared in Ref. 8. Reproduced with permission.]

curve for the respiratory system. By contrast, in patients with COPD, as respiratory rate increases during exercise, end expiratory lung volume also increases: a phenomenon called dynamic hyperinflation. A consequence of dynamic hyperinflation is that the operational lung volumes are forced upwards onto the flatter part of the pressure–volume curve, increasing the elastic work of breathing. As a direct consequence of increased EELV, the inspiratory capacity (IC) is decreased. Dynamic hyperinflation is compounded with pre-existing static hyperinflation, worsening dyspnea further and leaving the patient with the feeling that there is no room to breathe. The extent of dyspnea is closely related to the degree of dynamic hyperinflation.[19] Progressive dynamic hyperinflation, which can occur even during simple daily activities such as walking,[20] contributes to ventilatory constraints that limit exercise and contributes to dyspnea intensity.[19]

The medical literature has shown that even in mild cases of COPD there is evidence of hyperinflation. In a study of the effects of mild-to-moderate airflow limitation on exercise capacity as experienced in COPD, 9 control subjects with normal pulmonary function and 12 patients with mild-to-moderate airflow limitation were compared during progressive cycle ergometry.[7] FEV_1 values (% predicted) for the control group were 105% and for the mild COPD group were 72%; aerobic capacity or maximum oxygen intake ($\dot{V}O_2$) was 104% for the control group and 69% for the COPD group. These data show that even in mild cases of COPD, the aerobic capacity is decreased. Comparing rest, to maximal exercise, a significant decrease in end expiratory lung volume ($p < 0.01$) was noted in control subjects, while a significant increase ($p < 0.05$) was found in the COPD group. This increase in end expiratory lung volume experienced by the COPD group reflects dynamic hyperinflation and can be attributed to the effect of even mild airflow limitation on the ventilatory response to exercise.

Dynamic hyperinflation is targeted with therapeutic interventions to improve lung emptying or reduce ventilatory demand in order to produce a clinically meaningful improvement of exercise endurance and symptoms. To determine which resting spirometric parameters best reflect improvements in exercise tolerance and exertional dyspnea in response to acute high-dose anticholinergic therapy in advanced COPD, O'Donnell et al.[21] studied 29 patients with stable COPD and moderate to severe chronic dyspnea who received 500 μg of nebulized ipratropium bromide or placebo. The study reported that inspiratory capacity (TLC–EELV) was the best correlate of exercise performance and argued that this was a representative measure of the degree of hyperinflation. In another study of the effects of bronchodilator therapy on hyperinflation, O'Donnell et al.[22] showed that patients stopped exercise when the inspiratory reserve volume reached a level of approximately 500 ml below total lung capacity regardless of whether they were given salmeterol or placebo. These findings are indicative of a dyspnea threshold during which patients stray off the steep part of the pressure volume curves and experience very unfavorable respiratory system mechanics that lead them to stop exercise. From a clinical standpoint, the objective is to keep people in the mid-range (steeper part) of their compliance curve in order to minimize dyspnea. Interventions that prolong the time needed to reach operational lung volumes that result in dyspnea are believed to improve exercise endurance. These interventions are discussed in the following paragraphs.

Non-pharmacologic interventions

In the context of COPD management in general, there are several important non-pharmacological interventions including avoidance of exposures, vaccinations, structured rehabilitative exercise, oxygen supplementation and several

surgical approaches including lung transplantation. Most of these issues are beyond the scope of this article and have been thoroughly explored in other publications.[12,23] However, important investigation has been undertaken to determine the effects of certain non-pharmacologic interventions on hyperinflation, exercise, and dyspnea (Table 1). Rehabilitative exercise, helium–oxygen breathing, and lung volume-reduction surgery have been shown to impact hyperinflation to some small degree.[24–30] In the study by Porszasz et al.[24] seven weeks of exercise training at target work rates resulted in lower minute ventilation and breathing frequency at the same constant work rate along with increased IC by 133 ml ($p < 0.05$) signifying decreased hyperinflation. An earlier study had demonstrated similar improvements in breathing efficiency (minute ventilation and breathing frequency) after a rehabilitative exercise program.[31] Breathing helium–oxygen mixture as opposed to ordinary air should improve expiratory flow because of the lower gas density and thus reduce air trapping and hyperinflation. One study demonstrated this effect quite convincingly during constant load exercise with reductions in IC reflecting improvement in dynamic hyperinflation.[25] However, another study at rest showed helium–oxygen breathing to have no effect on hyperinflation as compared to bronchodilator therapy.[26] Supplemental oxygen has been shown to be more effective, especially for its effects on dynamic hyperinflation during exercise. For example, Somfay et al.[46] showed improvements in dynamic IC up to 330 ml during exercise breathing 50% oxygen. The efficacy reported for supplemental oxygen is almost certainly due to a slowing of the respiratory rate resulting from higher arterial oxygen partial pressure, which reduces the peripheral chemoreceptor or carotid body component of ventilatory drive.

Effects of bronchodilators on respiratory mechanics during exercise

Bronchodilators work to relieve hyperinflation and dyspnea by relaxing airway smooth muscle thus reducing airway resistance and increasing expiratory flow at a given lung volume. To test the efficacy of tiotropium in achieving the goal of sustained reduction in lung hyperinflation in patients with COPD, a double-blinded, placebo-controlled, parallel-group study was conducted in 187 patients randomized to receive either 18 μg of tiotropium or placebo.[32] Spirometry, plethysmographic lung volumes, cycle exercise endurance and the intensity of exertional dyspnea at 75% of each patient's maximal work capacity were compared. The study showed that inspiratory capacity increased 0.33 L with treatment; in contrast, residual volume and functional residual capacity decreased, thereby reducing hyperinflation both at rest and during exercise. Because improved inspiratory capacity permitted greater expansion of tidal volume, exercise endurance was prolonged by 21% following treatment, compared to placebo.[32]

The effects of bronchodilators on static and dynamic hyperinflation, exercise endurance, and dyspnea in the setting of COPD are well documented in the medical literature (Table 2),[26–33] but the exact mechanisms by which bronchodilators improve exercise performance are unclear. Notably, by altering lung mechanics, bronchodilatory therapy has been reported to change patient perceptions of symptoms during exercise.[33] Whereas prior to treatment patients reported that breathlessness limited their physical activity, following treatment they were more likely to report limitation due to leg fatigue.[33] This finding has been described as a ''shift in the locus of symptom limitation'' at maximum exercise. Relief of dyspnea seems to expose the significant contribution of skeletal muscle dysfunction, discussed earlier, in the limitation of physical activity, which must be addressed together with lung mechanics in the clinical management of the COPD patient.

While it is known that bronchodilators reduce operational lung volumes in the resting state (static hyperinflation), until recently their effects on dynamic hyperinflation were unclear. One hypothesis was that because bronchodilators induced lower static lung volumes at rest, it took longer for dynamic hyperinflation to occur, thereby extending the dyspnea limit and prolonging exercise endurance. O'Donnell et al.[32] have shown this hypothesis to

Table 1 Effects of non-pharmacological interventions on hyperinflation, exercise and dyspnea.

Intervention	Author	*n*	Baseline FEV_1 (%)	Δ Static IC[a] (mL)	Δ Dynamic IC[b] (mL)	Δ Exercise endurance	Δ Dyspnea	*p* value
Oxygen	Somfay et al.[46]	10	31	−31	+330[c]	+618 s[c]	↓	<0.05 vs. room air
Exercise training	Porszasz et al.[24]	24	36	NM	+133	+696 s	NM	<0.05 vs. pre-training
LVRs	Fishman et al.[27]	608	27	NM	NM	↑>10 W	NM	<0.02 vs. no surgery
	Appleton et al.[28]	29	28	NM	NM	+126 m	↓	<0.01 vs. BL (dyspnea only)
	Miller et al.[29]	93	15–40	NM	NM	+45 m	NM	<0.05 vs. BL
Heliox	Palange et al.[25]	12	37	−80	+200	+288 s	↓	<0.001 vs. air
	Pecchiari et al.[26]	22	41–61	+20	NM	NM	NM	<0.05
BLVR	Hopkinson et al.[30]	19	28	NM	+170	+170	↓	0.03 vs. no surgery (exercise only)

NM = not measured; BLVR = bronchoscopic lung volume reduction. [Source: Ref. 8. Reproduced with permission].

[a] Measured during body plethysmography as TLC–FRC.

[b] Measured at isotime during constant load sub-maximal exercise.

[c] Measured with 50% inspired oxygen concentration.

Table 2 Effects of bronchodilators on hyperinflation, exercise and dyspnea.

Intervention	Author	*n*	Baseline FEV_1 (%)	Δ Static IC* (mL)	Δ Dynamic IC†	Δ Exercise endurance	Δ Dyspnea	*p* value
Theophylline	Chrystyn et al.[47]	33	29	+190	NM	+56 m	↓	<0.001 vs. PLA
Albuterol	Belman et al.[52]	13	39	+350	NM	NM	↓	<0.05 vs. PLA
	Newton et al.[48]	281 SH	52	+220	NM	NM	NM	<0.001 vs. BL
		676 MH	78	+110	NM	NM	NM	NS vs. BL
Salmeterol	O'Donnell et al.[32,33,49]	23	42	+330	+170	+90 s	↓	<0.05 vs. PLA
Ipatropium	O'Donnell et al.[50]	29	40	+450, +330	+390, +290	+168, +66 s	↓	<0.05 vs. PLA
Tiotropium	Celli et al.[51]	81	43	+350	NM	NM	NM	<0.01 vs. PLA
	O'Donnell et al.[32,33,49]	187	44	+230	+180	+105	↓	<0.05 vs. PLA
	Maltais et al.[34]	261	43	+220, +150	+220, +140	+235 s, +171 s	↓ ↓	<0.01 vs. PLA

*IC measured during body plethysmography as total lung capacity minus functional residual capacity. †IC measured at isotime during constant load submaximal exercise. MH = moderately hyperinflated (TLC = 115%–133% predicted); SH = severely hyperinflated (TLC > 133% of predicted); NM = not measured. For those studies involving exercise, static IC measurements are reported after administration of bronchodilator but before exercise. For the Maltais study, the first values represent changes 2.25 h following administration of tiotropium and the second values represent changes at 8 h. [Source: Ref.[8] Reproduced with permission.]

be true by measuring inspiratory capacity at various stages during sub-maximal constant work rate exercise tests and demonstrating an increase with bronchodilator treatment. Increases in inspiratory capacity increased exercise endurance time by 21% as compared to placebo, and dyspnea decreased by 0.9 ± 0.3 units on the modified Borg scale.[32] A more recent study confirmed these findings by showing comparable improvements in endurance time for submaximum constant work rate post-treatment.[34] Additionally, this study showed significant, but reduced effects of treatment 8 h post-dose. Collectively, these studies demonstrate conclusively that improvements in hyperinflation, particularly with increases in inspiratory capacity, do correlate with improvements in exercise endurance and reductions in dyspnea upon exertion — effects that have not correlated with FEV_1 measurements alone. These studies provide compelling evidence of the need to consider disease progression in COPD not simply in terms of a continuing decline in FEV_1,[15] but also as a progressive decline in exercise performance linked to the symptoms that accompany dynamic hyperinflation.

Exercise and disease progression in COPD

Although activity monitors are available for use in COPD patients, most are impractical to use in daily medical practice. In the clinical trial setting, however, one device, a triaxial accelerometer (DynaPort Activity Monitor; McRoberts BV, The Hague, Netherlands), was used successfully to compare physical activity patterns between patients with COPD and age-matched healthy subjects.[20] COPD patients spent nearly half as much time walking compared to healthy individuals (44 ± 26 vs. 81 ± 26 min/day; $p < 0.0001$) and significantly less standing time (191 ± 99 vs. 295 ± 109 min/day; $p < 0.0001$). Movement intensity during walking was also decreased (1.8 ± 0.3 vs. 2.4 ± 0.5 m/s^2; $p < 0.0001$).[9] Stated differently, healthy subjects spent more than half of their time walking or standing, but the COPD patients spent less than one third of their time walking and standing, and therefore much more time sitting or lying around. When these activity data were related to the stage of disease severity, the most dramatic decline in activity level was noted between healthy individuals and those patients with COPD of GOLD stages 1 and 2 [F. Pitta, personal communication]. This suggests a strong need for focused research on the early pathophysiology of COPD that leads to the decline in activity level, and the resulting deleterious health consequences.

Increases in mortality associated with physical inactivity were reported by Myers et al. who studied 6213 men over the course of six years.[11] After adjustment for age, the peak exercise capacity measured in metabolic equivalents (MET) was the strongest predictor of the risk of death among both normal subjects and those with cardiovascular disease. Exercise capacity, in fact, was a better predictor of mortality than established risk factors for cardiovascular disease. Each 1-MET increase in exercise capacity conferred a 12% improvement in survival.[11] These findings support results from an earlier study assessing exercise capacity as a predictor of mortality specifically in the setting of COPD. Among 144 COPD patients who were followed for five years, 31 died. VO_2max was reported to be the best predictor of mortality, independent of FEV_1 measures and patient age.[10] These findings have prompted a call to action to address the serious global problem of physical deconditioning, to which the COPD patient is particularly susceptible. The prescription of exercise has been incorporated into COPD guidelines,[20,35] which have been used to construct a therapy model based on staging of COPD, shown in Fig. 4. Pulmonary rehabilitation, with a focus on exercise training of the legs, acts to break the vicious cycle of physical deconditioning, which through increased lactic acidosis in turn increases the ventilatory requirement during exercise, increases breathlessness, decreases exercise capacity, and further worsens the physical deconditioning caused by COPD.[36] Equally important as initiating a rehabilitation program is maintaining it; without ongoing exercise maintenance, functional exercise capacity and quality of life in COPD patients have been shown to decline towards the end of one year, returning towards baseline exercise capacity and worse quality of

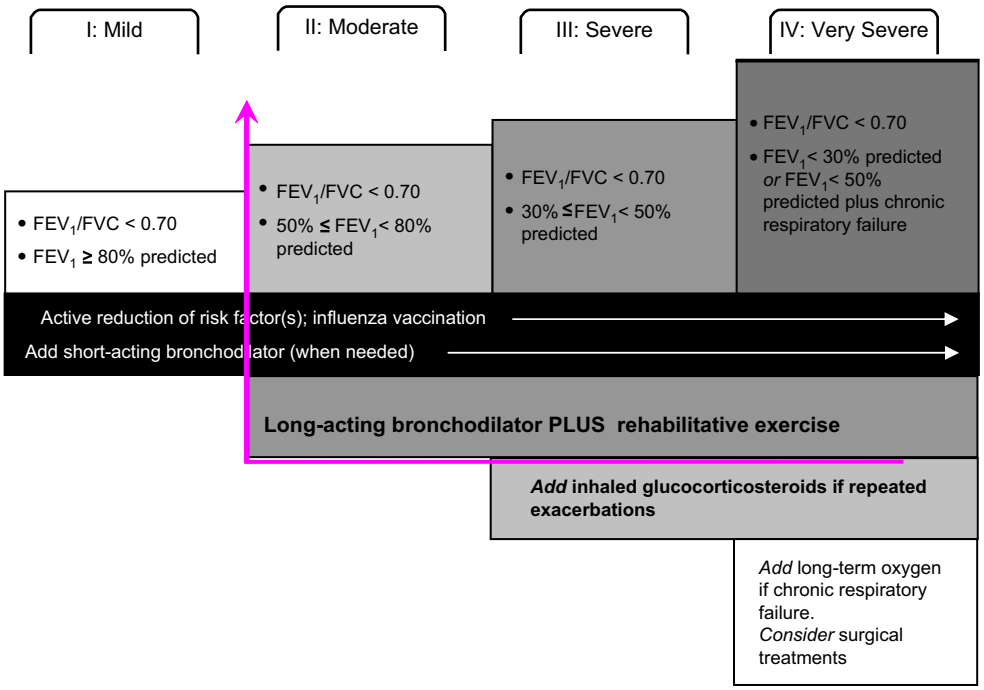

Figure 4 Therapy based on staging of COPD. The ATS/ERS Task Force and original GOLD Guidelines were used together to construct a therapy model based on the staging of COPD. For all patients with COPD ($FEV_1/FVC < 0.70$), it is recommended that risk factors be avoided and influenza vaccinations be given. At stage I (mild), short-acting bronchodilators should be added to risk-factor avoidance and vaccination. Stage II (moderate) calls for the addition of a regular prescription of one or more long-acting bronchodilators; at this time rehabilitative exercise should also be added to therapeutic intervention. At stage III (severe), it is recommended that, along with other therapies mentioned, an inhaled corticosteroid also be prescribed if there are repeated exacerbations. At stage IV (very severe), supplemental O_2 should be used to counter chronic hypoxemia and surgery (LVRS or lung transplantation) can be considered, in carefully selected cases. [Source: Global Intiative for Chronic Obstructive Lung Disease: Executive Summary.[20] Reproduced with permission.]

life.[37] Pulmonary rehabilitation, therefore, should be for life.

The exercise paradigm, however, needs to change for patients with earlier COPD. Hospital-based programs, which are high cost and resource intensive, are not appropriate for these patients. Further, these patients may be working and therefore not available during traditional hospital-based rehabilitation hours. Pulmonary medicine can learn much from the discipline of cardiology, which has restructured programs and resources for myocardial infarction patients to accommodate work schedules and other demands of daily living. The author of this paper is undertaking studies of how the use of personal trainers in health clubs in Los Angeles impacts the health, outcomes, and survival of COPD patients who embark on a physical training program at an early stage of disease. Of particular interest is the impact on comorbidities that typically occur as a result of physical inactivity, such as hypertension, atherosclerosis, dyslipidemia, obesity, glucose intolerance, and depression. We are eager to report the outcome of these trials in the years ahead.

Addition of bronchodilator therapy to exercise rehabilitation

Treatment with tiotropium during pulmonary rehabilitation has been shown to markedly potentiate the beneficial effects on exercise endurance.[38] In a double-blind, placebo-controlled trial, COPD patients participating in 8 weeks of physical rehabilitation at 17 sites were randomized to receive either tiotropium 18 μg daily ($n = 47$) or placebo ($n = 44$). All patients were allowed to use the short-acting bronchodilator albuterol as needed. Exercise endurance was measured using a sub-maximal constant load exercise test on a treadmill ergometer at 75% of maximum work rate. Baseline measurements did not differ significantly between groups. All of the patients improved their exercise endurance as they progressed though eight weeks of structured exercise training using target work rates. However, those patients receiving the long-acting bronchodilator, experienced clinically meaningful improvements in dyspnea and health status compared to patients who underwent physical rehabilitation alone. Mean differences in endurance time (tiotropium minus placebo) prior to physical rehabilitation, at the end of physical rehabilitation, and 12 weeks after physical rehabilitation were 1.65 min ($p = 0.183$), 5.35 min ($p = 0.025$), and 6.60 min ($p = 0.018$), respectively. We are led to the conclusion that improvements in ventilatory mechanics from tiotropium permitted patients to perform their exercise training at a higher intensity thus augmenting the physiological benefits derived from pulmonary rehabilitation.[38]

Exercise training in patients with COPD clearly improves sub-maximal exercise endurance, possibly mediated by

decreased dynamic hyperinflation.[24] However, it is important that exercise rehabilitation focus not only on improving lung function, but also muscle strength. Aerobic activity is of little value to the patient who is unable to get out of bed because of muscle atrophy. The quadriceps, pectoralis major, and latissimus dorsi muscles are all weaker in COPD patients than in control subjects, and quadriceps strength correlates with the degree of airflow obstruction.[39] Resistance training, as a means of improving skeletal muscle strength, is a crucial component of exercise rehabilitation.[40] However, like aerobic training, resistance training should be scientifically based and focused on the larger agonist and antagonist muscle groups, with attention to the overload principle and appropriate progression of the resistance.[41] In men with COPD, who have high prevalence of low testosterone levels, the relative deficiency of testosterone may contribute to muscle atrophy and weakness. There is some evidence to suggest that combining testosterone with resistance training in men with COPD may improve muscle strength,[40] and there have been other studies of anabolic therapies in COPD showing increased fat-free mass and exercise performance.[4,14] Despite these findings, anabolic supplementation is not generally recommended in evidence-based guidelines.[40] Several devices can be used to assist ambulation in severe COPD including portable oxygen systems and also walking frames. The physiological benefits that accrue from using supplemental oxygen have already been discussed. Ambulatory oxygen increases exercise endurance in an experimental setting[42] although longer-term use has not been shown to improve quality of life.[43] Consequently, the widespread use of portable oxygen, especially in non-hypoxemic patients, remains somewhat controversial. Inspiratory pressure support during exercise has been shown to increase endurance time[44] but the cumbersome nature of apparatus for ventilatory assistance will probably limit its practical application.[42] Use of walking frames has not been scientifically evaluated although the addition of occupational therapy to conventional pulmonary rehabilitation program has been shown to improve specific outcomes that relate to activities of daily living.[45]

Conclusions

Approaches to maintaining physical activity in COPD must be centered around the most effective therapies. To date, the medical evidence suggests that the combination of long-acting bronchodilator therapy combined with structured exercise prescriptions is the most beneficial approach. Exercise therapy should begin as early as possible in the disease process. However, current structured programs are primarily hospital-based and are not conducive to use by patients in early stage disease who require more flexible hours and outpatient resources. More severe patients can be assisted in some degree of physical activity with support from lightweight portable oxygen systems, which have been shown to prolong survival[41] and devices to assist in ambulation. The medical evidence reveals that physical activity improves exercise capacity and that this is associated with prolonged survival. The extent to which physical activity decreases exacerbations is unclear but is an area worthy of additional study.

Conflict of interest

Dr Cooper reports receiving grants/research support from Boehringer—Ingelheim, Eumedic, Ltd, Forest Pharmaceuticals, Pfizer Inc, and Spiration, Inc; serving as a consultant for Boehringer—Ingelheim, Emphasys Medical, ROX Medical, and VIASYS; receiving honoraria from Boehringer—Ingelheim, Dey, GlaxoSmithKline, and Pfizer Inc; and serving on the speakers' bureau for Boehringer—Ingelheim, Dey, GlaxoSmithKline, and Pfizer Inc.

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