Exercise intolerance in severe COPD: A review of assessment and treatment

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By Nathaniel Marchetti, DO [1] and Gerard J. Criner, MD [2]

Abstract: Exercise intolerance is common in persons with chronic obstructive pulmonary disease and can result from multiple physiologic factors, including dynamic hyperinflation, gas exchange abnormalities, and pulmonary hypertension. In the initial assessment, keep in mind that many patients underestimate the degree of their impairment. The 6-minute walk test is very useful in assessing the degree of exercise intolerance; when more extensive assessment is indicated, cardiopulmonary exercise testing (CPET) is the gold standard. CPET is particularly useful for defining the underlying physiology of exercise limitation and may reveal other causes of dyspnea, such as myocardial ischemia or pulmonary hypertension. Strategies for improving exercise tolerance range from the use of bronchodilators and supplemental oxygen to participation in a pulmonary rehabilitation program. (J Respir Dis. 2006;27(5):208-218)

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible. Airflow obstruction results from chronic airway inflammation, mucus plugging, and destruction of lung parenchyma that causes the loss of elastic recoil and early airway closure during exhalation.

COPD is a major cause of morbidity and mortality. Most patients do not seek medical attention until they notice exercise intolerance, which is one of the first and most common symptoms of COPD. Patients are often trapped in a downward spiral, because their dyspnea and exercise intolerance lead to a sedentary lifestyle, resulting in deconditioning and worsening exertional dyspnea (Figure 1).

In this article, we will review the physiology of exercise intolerance in persons with COPD. We will also describe the clinical evaluation and then offer a plan for effective management.

**PHYSIOLOGY OF EXERCISE INTOLERANCE**

COPD is a heterogeneous disease, and multiple factors contribute to exercise intolerance. The most important of these are dynamic hyperinflation and peripheral skeletal muscle weakness. Other factors include gas exchange abnormalities and pulmonary hypertension.

Patients with COPD often have other smoking-related diseases, such as hypertension and heart disease, which also contribute to exercise intolerance. **Dynamic hyperinflation**

The forced expiratory volume in 1 second (FEV₁), which is used to measure the severity of airflow obstruction, was initially considered the most important test of the potential for ventilatory limitation during exercise. However, this theory is being disproved. Evidence indicates that FEV₁ is highly predictive of exercise intolerance if FEV₁ and oxygen uptake (V.O₂) are normalized to age, height, sex, and weight. O'Donnell and associates showed that improvement in exercise performance in patients who have taken nebulized ipratropium is not associated with FEV₁, but correlates best with the change in inspiratory capacity.

If the degree of airway obstruction, as measured by FEV₁, is not a good predictor of exercise intolerance in persons with COPD, what causes the ventilatory limitation that occurs during exertion? Investigators have been exploring the concept of dynamic hyperinflation. Hyperinflation tends to develop secondary to expiratory flow limitations in persons with lung disease. During physical exertion, minute ventilation (Ve) increases to meet the metabolic demands of exercise by increasing the tidal volume, then the respiration rate.

In obstructive lung disease, the increased tidal volume and respiration rate lead to a decreased expiratory time, which intensifies hyperinflation. Because total lung capacity (TLC) does not change during exercise, dynamic hyperinflation produces a larger functional residual capacity at the expense of the inspiratory reserve volume and capacity. The degree of hyperinflation that develops during physical activity can be reliably quantitated by measuring the decline in inspiratory capacity during cardiopulmonary exercise testing (CPET).

O'Donnell and Webb showed that the perceived level of dyspnea (assessed by the Borg scale)
during exercise was linked most closely to the development of dynamic hyperinflation. They also found that during CPET, inspiratory capacity decreased by 0.37 L in patients with COPD and increased by 0.17 L in age-matched persons without COPD. As exercise progressed and inspiratory capacity further declined, end-inspiratory and end-expiratory lung volumes increased. Because TLC remains steady during maximal exercise in patients with COPD, the increase in end-expiratory lung volume prevents Ve from rising as a result of increased tidal volume. The need for increased Ve is not met, and the patient must stop exercising prematurely (Figure 2). One study found that inspiratory capacity declined faster and V.O₂ was lower in a subgroup of patients with emphysema (low carbon monoxide-diffusing capacity [DICO] and high baseline hyperinflation). Dynamic hyperinflation also places the inspiratory muscles at a mechanical disadvantage by forcing them to contract at a shorter operating length and to overcome a larger intrinsic positive end-expiratory pressure to initiate a breath. The inspiratory muscles are forced to operate as a respiratory pump while they work against higher inspiratory loads. Dynamic hyperinflation appears to occur during daily activities as well as during heavy exertion. One study noted dynamic hyperinflation during a 6-minute walk test in patients with severe COPD (mean FEV₁, 45% of predicted). The change in inspiratory capacity correlated with the degree of breathlessness (as measured by the Borg dyspnea and the modified Medical Research Council scales).

**Skeletal muscle dysfunction**

COPD has been associated with skeletal muscle weakness and dysfunction. Whether this is related to the systemic effects of COPD, associated medications (corticosteroids), or chronic deconditioning secondary to a sedentary lifestyle is unclear.

One of the first studies to address these concerns showed a significant correlation between quadriceps force generation and hand force grip with maximum V.O₂ obtained during CPET. Bernard and colleagues later showed that cross-sectional area and quadriceps strength were significantly reduced in 34 patients with COPD, compared with 16 age- and sex-matched healthy controls. However, the ratio of quadriceps strength to cross-sectional area was similar. This suggests that muscle weakening is related to atrophy rather than myopathy.

More recently, investigators examined contractile leg fatigue during a constant-workload exercise routine in patients who had received nebulized placebo or ipratropium. Nine of the 18 patients experienced contractile fatigue of the quadriceps after exhaustive exercise. Treatment with ipratropium improved the FEV₁ but did not prolong endurance. The remaining 9 patients, who had no contractile muscle fatigue, had improved endurance during exercise after receiving ipratropium. Exercise limitation was related more to peripheral muscle dysfunction than to ventilatory limitation in half the patients.

**Gas exchange abnormalities**

Severe COPD is characterized by gas exchange abnormalities, especially hypoxemia. The mechanisms of hypoxemia in COPD involve ventilation-perfusion mismatch and hypoventilation. Data generated by the National Emphysema Treatment Trial were analyzed to assess the ability of DICO to predict the need for oxygen supplementation during low-level exercise in 1071 patients. If DICO was less than 20% of predicted, patients were 9 times more likely to require supplemental oxygen while walking at 1 mph on a treadmill than those with a DICO greater than 35% of predicted. In this study, patients received oxygen if their oxyhemoglobin saturation fell below 90%.

**Hypercapnia**

Hypercapnic respiratory failure at rest is a well-known consequence of COPD, especially in persons with inspiratory muscle weakness and increased inspiratory loads (lower FEV₁ or obesity). Hypercapnia has also long been known to occur during exercise, but the mechanism is only beginning to emerge.

Montes de Oca and Celli demonstrated that respiratory muscle strength is similar between eucapnic and hypercapnic patients during maximal CPET. They concluded that hypercapnia during exercise was related to the lung's inability to increase ventilation, not to respiratory muscle weakness.

Dynamic hyperinflation may be the mechanism for exercise-induced hypercapnia. In 20 patients with severe COPD, dynamic hyperinflation and hypercapnia developed at maximal exercise. The best correlates of the change in PaCO₂ were the changes in oxygen saturation and in end-expiratory lung volume, expressed as a percentage of TLC.

During the hyperoxic challenge at rest, about half of the patients retained carbon dioxide. These patients were well matched for lung function, resting PaCO₂, and ventilatory mechanics, but the resting room air PaCO₂ was significantly lower in the retainer group. Dynamic hyperinflation developed during exercise in retainers and nonretainers, but the retainers reached this mechanical limitation earlier and tended to have lower VeMAX and carbon dioxide output (V.CO₂) (Figure 3).
Thus, exercise-induced hypercapnia and dynamic hyperinflation may be related. **Cardiovascular limitations**

Patients with COPD are at high risk for other smoking-related cardiovascular diseases. Hypertensive heart disease, diastolic dysfunction, congestive heart failure and, especially, coronary artery disease (CAD) can affect exercise tolerance. Patients with COPD are candidates for CAD screening via risk factor assessment, history, and physical examination. Any suspicion of CAD calls for appropriate evaluation. **Pulmonary hypertension**

Cor pulmonale and pulmonary hypertension are important contributors to exercise intolerance in a subset of patients with COPD. The exact incidence of pulmonary hypertension in patients with COPD is unknown. However, right ventricular (RV) hypertrophy has been documented in 40% of patients with COPD in autopsy series. **20**

Patients with pulmonary hypertension become breathless during exercise because increased RV afterload reduces RV output, diminishing left ventricular (LV) output. This effect is even worse in the presence of RV dilation, which causes the interventricular septum to bow and further impede LV filling. The patient, unable to continue exercising, goes into early metabolic acidosis. **20** Ventilation also becomes less efficient in the presence of pulmonary hypertension because of increased dead space.

Pulmonary artery pressure (PAP) can increase in some patients with COPD during exercise. Kessler and colleagues **21** studied a group of patients with mean PAP of less than 20 mm Hg at rest. During exercise, PAP increased to over 30 mm Hg in 76 of 131 patients with COPD (mean FEV₁, 44% of predicted). Patients who had pulmonary hypertension during exercise were also more likely to have pulmonary hypertension at rest. **22**

**Effect of intrathoracic pressure changes on cardiac function**

During exercise, patients with COPD are affected by pronounced swings in intrathoracic pressures, which become more negative during inspiration and more positive during expiration. These changes can affect cardiac performance in 2 ways:

- Increased negative pleural pressures during inspiration increase blood return to the right side of the heart, causing RV dilation and bowing of the interventricular septum toward the left ventricle. The LV end-diastolic and wedge pressures increase, less blood returns to the left side of the heart, and LV cardiac output declines. **22**

- Negative intrathoracic pressure during inspiration decreases the LV ejection fraction. **23** Cardiac function can be estimated during CPET by calculating the oxygen pulse (V.O₂/heart rate), which reflects the stroke volume. Montes de Oca and colleagues **24** used this technique to examine the effect of intrathoracic pressure changes on cardiac function and found that the pleural pressure became more negative during exercise. The change and absolute nadir of pleural pressure correlated with a drop in oxygen pulse, suggesting that LV function declined during exercise. **ASSESSING EXERCISE TOLERANCE**

The patient's capacity for exercise can be evaluated with a thorough history and physical examination, a 6-minute walk test, and maximal CPET. **History and physical examination**

To get a rough estimate of exercise intolerance, ask the patient what activities he or she can perform. For example, can the patient do light housework, carry grocery bags, or enjoy hobbies? Information about the distance the patient can walk--and why he or she must stop--can also be helpful.

Keep in mind that many patients underestimate their degree of exercise intolerance or gradually diminish their activity level without realizing it. Watching for dyspnea as the patient walks into the office and climbs onto the examining table is especially useful, since the patient's report may be inaccurate. **6-Minute walk test**

The 6-minute walk test is easy to perform and is highly reproducible. It is primarily indicated for assessing the patient's response to treatment, but it is also used to evaluate functional status and prognosis. **25** Unstable angina and myocardial infarction within the past month are the only contraindications to the test. Relative contraindications include heart rate greater than 120 beats per minute, systolic blood pressure greater than 180 mm Hg, and diastolic blood pressure greater than 100 mm Hg. **26**

Detailed instructions for the 6-minute walk test are available from the American Thoracic Society (ATS). **26** The test should be performed indoors along an unobstructed flat hallway that is 30 meters in length. Course layout is a consideration; patients seem able to walk farther on a circular than on a straight course. **27** Patients should wear shoes and clothing appropriate for walking and use any of their customary walking aids, such as a cane or a walker.

The technician counts the number of laps walked and monitors the patient. The patient's oxygen saturation should be monitored and supplemental oxygen provided to maintain an oxygen saturation
of at least 88%. The technician should not provide oral encouragement except for the ATS-approved phrases.\textsuperscript{26} \textbf{Maximal CPET}

CPET is a sophisticated method for evaluating exercise tolerance in patients with any disease that limits physical activity.\textsuperscript{28} It is the gold standard for the assessment of exercise intolerance in patients with COPD. CPET is routinely performed to assess and monitor the patient's exercise tolerance before lung transplantation. It has become extremely important in the evaluation of patients who are scheduled to undergo lung volume reduction surgery (LVRS).

CPET is particularly useful for defining the underlying physiology of exercise limitation and may reveal other causes of dyspnea, such as myocardial ischemia or pulmonary hypertension. Because CPET analyzes both pulmonary and cardiac data, it is often used to gauge the relative contribution of the pulmonary and cardiac systems in exercise intolerance. It is also helpful for assessing a patient's response to bronchodilator therapy, pulmonary rehabilitation, or surgery, and the results of CPET can be used to write exercise prescriptions for pulmonary rehabilitation.\textsuperscript{28}

During the test, patients exercise increasingly hard until exhaustion. The cycle ergometer, but not the treadmill, accurately measures the amount of work performed in watts.\textsuperscript{28} Physiologic measurements (V.O\textsubscript{2}, V.CO\textsubscript{2}, respiration rate, tidal volume, Ve) are recorded on a breath-by-breath basis and reported as 20-second averages. Continuous pulse oximetry and ECG monitoring are also performed.

The patient can exercise with an arterial line in place, which allows periodic measurement of arterial blood gas and lactate levels. The inspiratory capacity (tidal volume plus inspiratory reserve volume) can be measured every few minutes, providing an indirect way to measure dynamic hyperinflation.\textsuperscript{11}

The most characteristic feature of COPD on CPET is the development of dynamic hyperinflation, which is suggested by diminishing inspiratory capacity and a blunted increase in tidal volume.\textsuperscript{11}

Patients do not reach maximal heart rate but have a reduced V.O\textsubscript{2, max} and a low respiratory reserve (defined as Vemax/maximum voluntary ventilation [MVV] = 85% or MVV Vemax = 8 L).

The MVV can be measured directly or estimated by multiplying FEV\textsubscript{1} by 35 (obstructive lung disease only).\textsuperscript{28} The dead space, which normally decreases during exercise, remains the same or increases with progressive exercise.

In severe COPD, the increase in dead space elevates levels of PaCO\textsubscript{2} during progressive exercise. Patients usually cannot reach anaerobic threshold; persons with mild to moderate COPD have normal or reduced anaerobic threshold secondary to deconditioning. Arterial desaturation can occur during exercise and is most common in patients with emphysema.\textsuperscript{28}

\textbf{Improving Exercise Tolerance}

There are several ways to improve exercise tolerance in patients with COPD. The goal is to increase the patient's ability to exercise and to decrease exertional dyspnea. Bronchodilators, supplemental oxygen, pulmonary rehabilitation, and surgery all can help patients achieve these results.\textbf{Bronchodilators}

Short- and long-acting B\textsubscript{2}-agonists, as well as short- and long-acting anticholinergic agents, are a mainstay of therapy for patients with COPD. Bronchodilators are easy to administer, relatively inexpensive, and well tolerated. Tiotropium, salmeterol, oxitropium, formoterol, and albuterol have been shown to decrease hyperinflation by decreasing end-expiratory lung volume and thereby increasing inspiratory capacity.\textsuperscript{29,30} Other effects of these agents are summarized in the Table.\textsuperscript{7,31-33}

The effect of bronchodilators on exercise performance has also been studied. In one study, albuterol was shown to significantly decrease dynamic hyperinflation, improve dyspnea, and ameliorate respiratory muscle function during maximal exercise.\textsuperscript{31} There was a significant correlation between the change in breathlessness and the development of dynamic hyperinflation. There was no difference in the maximum work rate achieved between albuterol and placebo.\textsuperscript{31}

In a randomized, double-blind, cross-over study, ipratropium resulted in a 30% improvement in endurance time, with less breathlessness, during constant-work-rate exercise and caused less dynamic hyperinflation.\textsuperscript{7} Improved exercise time correlated best with the change in inspiratory capacity.

O'Donnell and associates\textsuperscript{32} found that tiotropium produced a 21% longer exercise time during constant-work-rate exercise and was associated with less dynamic hyperinflation. The patients receiving tiotropium also had significantly lower functional residual capacity and residual volume, as well as less dyspnea during exercise.

In a randomized, double-blind, placebo-controlled, cross-over study of patients with severe COPD, salmeterol improved both resting and dynamic hyperinflation, as measured by an increase in inspiratory capacity, during constant-work-rate exercise.\textsuperscript{33} Respiratory muscle function improved, but exercise time did not.

All classes of bronchodilators have been shown to improve exercise tolerance in patients with COPD.
The most common approach to initiating bronchodilator therapy is to follow the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Short-acting bronchodilators, such as albuterol and ipratropium (or a combination of the two), are recommended on an as-needed basis. Long-acting bronchodilators are recommended once the patient’s disease progresses beyond GOLD stage II disease (FEV<sub>1</sub> between 50% and 80% of predicted). Available agents include the long-acting β<sub>2</sub>-agonists (formoterol or salmeterol) and the anticholinergic agent tiotropium. A long-acting anticholinergic agent is a reasonable choice for a patient who primarily has exercise intolerance, because it has been shown to provide the greatest improvement in exercise performance. If a single agent does not provide adequate relief or if the patient’s disease progresses to GOLD stage III/IV disease, a second long-acting agent can be added. It must be emphasized that these are only guidelines. Individual patient needs, such as drug cost, adverse reactions, and response to the prescribed medication, must be carefully considered. Patient progress can be assessed subjectively with patient interviews or more objectively with serial 6-minute walk testing or CPET.

**Pulmonary rehabilitation**

Now a standard of care for patients with COPD, pulmonary rehabilitation improves exercise tolerance and eases dyspnea. Ample data have documented the effectiveness of lower extremity training, such as treadmill walking or cycling, for improving exercise performance. Most studies have involved older persons (aged 60 to 70 years) with mild to moderate COPD who exercised 3 times a week for up to 24 weeks. Results showed that performance could be improved by exercising at 60% of maximum versus 30% of the maximum obtainable work rate. Upper extremity exercise does not consistently improve exercise tolerance. Also, the duration of benefits once the patient completes rehabilitation is unclear. Evidence suggests that patients return to near-baseline exercise performance 1 year after completing 8 weeks of rehabilitation—even if they received weekly telephone calls and underwent monthly supervised rehabilitation sessions. Patients should undergo pulmonary rehabilitation when they have dyspnea, reduced exercise tolerance, or restriction in their desired activities. The patient's symptoms and level of disability—not the patient's physiologic lung function (FEV<sub>1</sub>)—determine when rehabilitation is started. Typically, patients experience these symptoms at GOLD stages II through IV; this is when the GOLD guidelines recommend that pulmonary rehabilitation be instituted.

**Other modalities**

Other methods of improving exercise tolerance include exercising with oxygen and exercising while air is blown toward the patient's face. Supplemental oxygen appears to benefit patients who do not have hypoxemia during exercise as well as those who do. Early data show that supplemental oxygen not only prolongs endurance time but also allows the diaphragm to perform more ventilatory work, which unloads the accessory muscles of respiration. Patients have less dyspnea, a reduced respiration rate, increased Ve, and less dynamic hyperinflation.

All of these benefits occur acutely while the patient is exercising. However, because the effect of hyperoxia on long-term exercise performance is unknown, exercise with supplemental oxygen cannot be recommended at this time. Patients with COPD often seek relief from dyspnea by sitting near a fan that is blowing air toward their face. We examined the effect this would have on exercise performance. Patients were able to exercise 30% longer, with significantly less dyspnea. As with oxygen, the effect of air blown toward the patient's face occurs only acutely and the long-term benefits, if any, are not known. Further studies are needed to determine whether oxygen or air blown toward the patient's face will allow patients to train more intensely.

**Surgery**

Surgical procedures are the last resort for persons who have advanced COPD. LVRS improves mortality and quality of life for patients with upper lobe-predominant emphysema and a low exercise capacity. Studies show that exercise performance improves significantly for all patients after LVRS, but the change is most evident in persons who have upper lobe predominance and low exercise capacity. A comparison between LVRS and medical treatment showed that patients undergoing LVRS had a significantly longer 6-minute walk test, as well as a higher maximum V.O<sub>2</sub>, tidal volume, and Ve on CPET. LVRS might improve exercise performance by significantly reducing dynamic hyperinflation. We have also shown that LVRS improves diaphragm strength and exercise tolerance. Clearly, LVRS is an important therapy for a subset of persons with severe COPD. It can improve exercise tolerance and increase the patient’s chances for survival. The effect of LVRS on exercise performance is probably secondary to a reduction in dynamic hyperinflation during exertion.
References


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