*LITERATURE REVIEW*

# Exercise Intolerance in COPD: A Review of the Pathophysiology and Clinical Assessment

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## ABSTRACT

**Introduction:** Chronic obstructive pulmonary disease (COPD) frequently presents with significant impairments that contribute to reduced functional capacity and exercise intolerance, ultimately leading to compromised activity performance. Therefore, this study aimed to describe the pathophysiology and clinical assessment of exercise intolerance in COPD.

**Methods:** Data used were procured through a thorough search of published literature, conducted using both PubMed and Google Scholar search engines. Literature was included when published in the last 10 years, written in English, and available in full-text format. The types of literature used were books, original articles, narrative or systematic reviews, and case reports.

**Results:** A total of 33 pieces of literature were identified and used to provide explanations for the sub-topics under discussion. Out of the total pieces, 22 elucidated the pathophysiology of the topic, while the remaining 12 focused on the clinical assessment.

**Conclusion:** Shortness of breath and leg fatigue were common symptoms of exercise intolerance found in COPD. These symptoms were associated with impairment of the body functions such as the respiratory, cardiovascular, peripheral muscles, neuromuscular, and psychological. Furthermore, physical inactivity caused worsening exercise intolerance, which could be evaluated using the Borg scale. The cardiopulmonary exercise test was recommended to assess exercise intolerance in COPD patients and some field analyses such as walk and step tests could also be carried out.

**Keywords:** chronic obstructive pulmonary disease, exercise intolerance, functional capacity.

## ABSTRAK

**Latar Belakang:** Penyakit Paru Obstruksi Kronis (PPOK) sering muncul dengan gangguan fungsional signifikan yang menghasilkan penurunan kapasitas fungsi dan intoleransi latihan. Ganguan tersebut menghasilakn tampilan aktivitas yang buruk. Review ini bertujuan untuk menggambarkan patofisiologi dan penilaian klinis dan intoleransi latihan pada PPOK.

**Methods:** Data yang digunakan pada ulasan ini dikumpulkan melalui literatur yang telah di kumpulkan dari dan di cari melalui PubMed and Google Scholar as the search engine. Literature was included if published in the last 10 years, written in English, and available in full-text format. The type of literature were books, original articles, narrative or systematic reviews, and case reports.

**Hasil:** Sembilan puluh enam subjek memenuhi kriteria inklusi dan eksklusi. Kepatuhan memulai program RJ setinggi 94,6% pada kelompok BPAK dan 100% pada kelompok IKP. Lima puluh subjek (67,56%) pada kelompok BPAK dan enam belas (72,72%) pada kelompok IKP menjalani sesi latihan sebagaimana terjadwal. Sebanyak 57 subjek (77,02%) pada kelompok BPAK dan 16 subjek (72,72%) dari kelompok IKP menyelesaikan 12 sesi latihan, tanpa memandang waktu yang diperlukan untuk menuntaskannya.

**Simpulan:** Secara keseluruhan, kepatuhan mengikuti program RJ fase II pada kelompok BPAK dan IKP cukup tinggi. Kepatuhan untuk memulai dan menjalani program RJ fase II pada kelompok IKP lebih tinggi dari kelompok BPAK.

**Kata kunci:** bedah pintas arteri koroner, intervensi koroner perkutan, kepatuhan, rehabilitasi jantung.



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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) causes chronic airflow limitation due to airway obstruction and parenchymal damage (emphysema). This disease often appears with significant functional impairments including shortness of breath, fatigue, and exercise intolerance, which can affect a quality of life (QoL) and lead to depression or social isolation. Furthermore, functional impairments can lead to exercise intolerance and decreased activity performance. [1-3]

A study in stable COPD patients found an association between high dyspnoea scores and low maximum exercise capacity. Low exercise

capacity can interfere with daily activities.[4] Functional capacity, exercise tolerance, and exercise capacity are often used interchangeably to describe an ability to perform daily activities requiring aerobic metabolism. Furthermore, aerobic metabolism is determined by maximum oxygen uptake (VO2 max) used during muscle contraction, and its impaired functional capacity leads to exercise intolerance.[5]

Exercise intolerance refers to the incapability to attain or maintain the level of exercise intensity expected for individuals with comparable age, body composition, and gender. This impairment is attributed to the dysfunction of one or more major bodily systems, such as the respiratory, cardiovascular, or peripheral muscular systems. [6, 7]

A considerable percentage of individuals diagnosed with COPD, specifically at least 15%, exhibit diminished functional capacity and subpar performance in various activities, such as ambulation, quality of sleep, and rest. These individuals may also struggle with routine tasks related to home management, recreation, and other day-to-day activities. Furthermore, basic daily activities may even trigger feelings of fatigue and shortness of breath among individuals with moderate to severe COPD. A recent study showed that 30% of moderately affected individuals were more likely to remain confined to their homes, even during stable periods. However, this percentage increased to nearly 50% during exacerbations.[3]

Zamzam et al. reported an association between decreased QoL and the severity of COPD. Decreased QoL occurs because patients have difficulties in socializing, hence, they become frustrated and angered.[8] Decreased exercise capacity also affects QoL, as an independent predictor of increased mortality in patients.[9]

The enhancement of exercise tolerance has become one of the primary objectives of COPD management since the variable has significant ramifications on the physical, psychological, and overall QoL.[8] Therefore, this study describes exercise intolerance in COPD patients with a focus on pathophysiology and clinical assessment.

## METHODS

Data utilized for this study were obtained from literature searched using PubMed and Google Scholar as the search engine. Literature was included when published from 2006 to 2021, written in English, and available in full-text format. Meanwhile, the type of literature were original articles, narrative or systematic reviews, and case reports. The results were presented in the form of text, figures, and tables.

## RESULT

A total of 33 literature were found and used to explain sub-topics, where 22 and 12 explained pathophysiology and clinical assessment, respectively.

## EXERCISE INTOLERANCE

### Pathophysiology of Exercise Intolerance in COPD

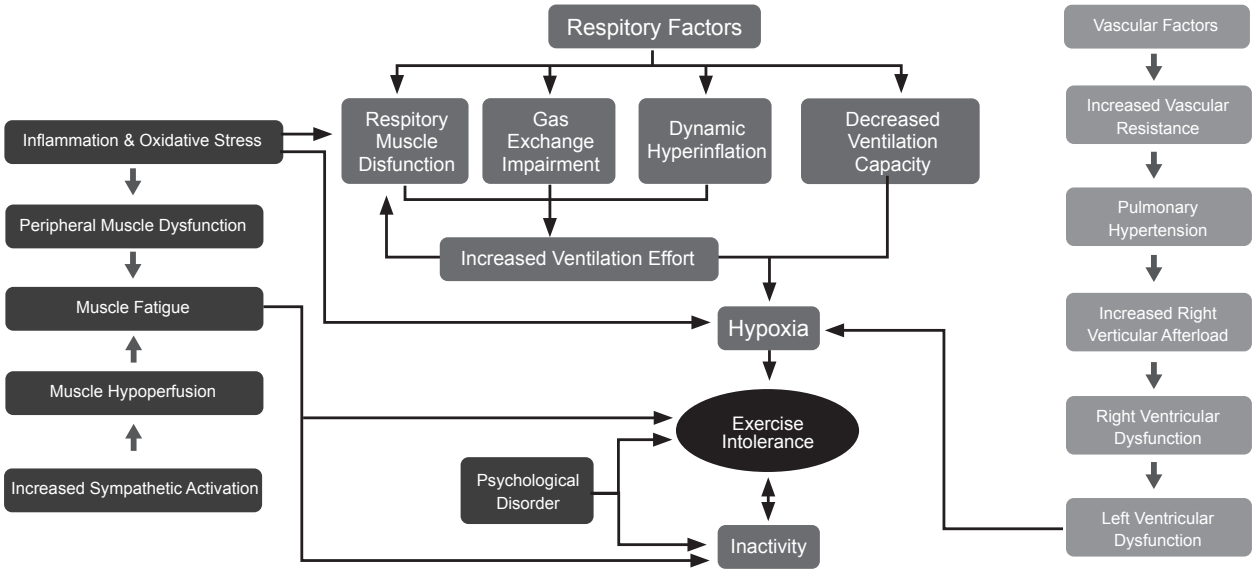


**Figure 1.** Pathophysiology of Exercise Intolerance COPD

Central factors causing exercise intolerance in COPD are ventilation, dynamic hyperinflation, and shortness of breath, while the peripheral factors include muscle atrophy, weakness, and fatigue.[7,10,11] The pathophysiology of exercise intolerance is described schematically in Figure 1. [5, 7, 11]

### Respiratory Factors

In COPD, ventilation is limited due to airway obstruction and decreased lung compliance.[7] Furthermore, ventilatory limitation causes an increase in work of breathing, arterial carbon dioxide ($CO_2$), metabolic acidosis, and the burden of ventilation.[7,12] Hyperinflation or muscle dysfunction also causes the inability of the respiratory system to withstand the workload, resulting in shortness of breath.[7]

Exercise given to COPD patients can increase the work of breathing due to increased oxygen demand and blood flow. In intense exercise, there is a decrease in peak oxygen uptake (VO2 peak) and premature lactic acidosis causing intolerance.[7]

Impairment of gas exchange regulation causes alveolar ventilation/perfusion (VA/Q) mismatch, impaired diffusion, and hypoxemia during exercise causing tissue hypoxia. Meanwhile, hypoxia directly and indirectly increases pulmonary ventilation through peripheral chemoreceptor response, and stimulation of lactic acid production leading to lactic academia.[7]

Lactic acidemia contributes to the failure of muscle to contract and leads to increased pulmonary ventilation due to $CO_2$ production.[7] In severe pulmonary disease patients, arterial oxygen ($O_2$) desaturation may occur during exercise. In addition, low carbon monoxide diffusion capacity can predict the occurrence of arterial

$O_2$ desaturation and acts as the best predictor of exercise capacity.[13] Carbon monoxide diffusion capacity is influenced by diffusion surface area, blood volume in the capillary bed, and distribution of alveolar ventilation. Meanwhile, low diffusion capacity causes increased ventilation work to maintain arterial blood gases and acid-base homeostasis.[9, 11, 14]

Indirect measurement of pulmonary hyperinflation at rest can be conducted by calculating the ratio of inspiratory capacity to total lung. In large-scale population studies, this ratio has been observed to predict all-cause mortality, respiratory mortality, and the severity of the risk of exacerbations. In contrast, serial measurement of dynamic hyperinflation can be achieved by assessing the changes in inspiratory capacity from resting values.[6]

Hyperinflation causes excessive expansion of the thoracic cavity, resulting in overstretching of the respiratory muscles. Mechanically, this is caused by the inability of the muscles to increase their output following the increase in neurological signals. The consequences of these pathological changes are muscle weakness causing hypercapnea, shortness of breath, arterial $O_2$ desaturation, and exercise intolerance. During exercise, the maximal inspiratory pressure is increased due to the respiratory muscles' workload.[7, 15]

Another respiratory muscle dysfunction that causes exercise intolerance is an increase in systemic vascular resistance in diaphragmatic workload. This causes a "stealing" effect of blood from the peripheral muscles, even though there are no convincing data to confirm this theory.[7]

**Vascular Factors**

Vascular factors as the cause of exercise intolerance are pulmonary hypertension resulting from increased resistance and right ventricular dysfunction with an increase of right ventricular afterload.[7,9] Right ventricular hypertrophy can lead to right ventricular failure when untreated. Furthermore, left ventricular filling is also impaired, and the ability of the heart to fulfill exercise requirements is reduced. The occurrence of left and right ventricular dysfunction results in the limitation of physical activity. Myocardial dilatation and hypertrophy can also cause tachyarrhythmias. In addition, Faludi et al. showed that right ventricular diastolic function and its filling pressure affected functional capacity and led to impairment of oxygen delivery as well as metabolic acidosis.[7, 9, 16-18]

**Peripheral Muscle Dysfunction**

Many factors considered a potential cause of peripheral muscle dysfunction are cigarette smoking, muscle disuse, drugs, oxidative stress, systemic muscle inflammation, hypoxia, and hypercapnea. Table 1 summarizes the structural abnormalities of skeletal muscles in COPD patients.[19] Furthermore, peripheral muscle dysfunction causes fatigue which is characterized by the inability to perform work at a certain intensity, or maintain the force required during contraction to meet the needs of physical activity. Decreased muscle endurance is mainly found in patients with advanced COPD. Serres et al. also reported a positive relationship between muscle endurance and COPD severity.[19-22]

**Table 1. Structural Abnormalities of Skeletal Muscles in COPD Patients**

| Structural Abnormalities of Skeletal Muscles in COPD |
|---|
| • Low mitochondrial density and synthesis |
| • High mitochondrial degradation |
| • Low oxidative enzyme activity |
| • A shift of muscle fiber type (towards a more glycolytic profile) |
| • Low muscle capillary |
| • An imbalance between muscle protein synthesis and breakdown |
| • Muscle atrophy |

During exercise, peripheral muscles are very sensitive to any changes in $O_2$ delivery. Metabolites such as hydrogen ions (H+), inorganic phosphate, and lactic acid accumulate more quickly when the supply of $O_2$ is reduced and caused impaired contractility. Furthermore, insufficient $O_2$ transport during exercise causes muscles to tire easily.[22] There is also the manifestation of deoxyribonucleic acid damage and reduced mitochondria due to oxidative stress in COPD. Decreased physical activity is caused by changes in the distribution of fibers and a reduction in capillary density that cause muscles susceptible to fatigue in performing an exercise with high- intensity.[7, 11, 12]

Peripheral muscle fatigue is also caused by increased degradation due to inflammation which leads to wasting.[20] Meanwhile, chronic inflammation increases muscle oxidative stress by increasing reactive oxygen species, directly causing damage and degradation of protein. The study by Couillard et al found that oxidative stress occurred in the quadriceps muscle characterized by an increase in lipid and protein peroxidation.[23]

Malnutrition causes a decrease in enzyme capacity and the availability of energy substrates in muscle. About 30% of COPD patients in outpatient clinics experienced weight loss due to decreased caloric intake and chronic inflammatory effects. Similarly, the use of corticosteroids, specifically during exacerbations, affects skeletal muscle through decreased contractile protein, increased protein breakdown, decreased growth factors, decreased glycolytic activity, and sarcomere atrophy.[7]

**Neuromuscular Factors**

In COPD, there is an increase in sympathetic activity in the muscles, resulting in negative effects such as inflammation, anabolic catabolic imbalance, apoptosis, cardiomyocyte injury, decreased number of type 1 muscle fibers, impaired endothelial function, and dyspnea. Excessive sympathetic outflow results in muscle hypoperfusion leading to hypoxia. Meanwhile, sympathetic muscle activity at rest is negatively correlated with the VO2 peak. In healthy muscles, vasoconstrictive activity can be overcome, and when there is a sympathovagal imbalance,

vasoconstriction of blood vessels increases and causes a decrease in blood flow and non-oxidative metabolism.[24, 25]

**Psychological Factors**

Anxiety and depression are reported in about 40% and 20% of COPD patients. These variables cause an increase in shortness of breath symptoms that worsen hyperinflation and decrease exercise tolerance and QoL.[7] There is also a relationship between depression and admission rate due to COPD exacerbations. Exacerbations also affect physical activity levels, but the study cannot be concluded. Hormonal changes such as over-activity of the hypothalamic-pituitary-adrenocortical axis or dysregulation of the autonomic nervous system also occur during depression.[26]

**Physical Inactivity**

Physical inactivity due to shortness of breath, fatigue, peripheral muscle dysfunction, and psychological factors caused the worsening of exercise intolerance. Mazzarin et al. reported that there is a relationship between inactivity as measured by the number of steps per day and the exercise capacity of COPD patients.[23] The incidence of exacerbations in moderate-grade COPD patients caused patients to become more inactive.[27, 28]

**Clinical Assessment of Exercise Intolerance in COPD**

Symptoms and signs of exercise intolerance include chest pain, shortness of breath, cold sweats, dizziness, and leg fatigue before, during, and after exercise. The occurrence of exercise intolerance during training or testing indicates termination. It also determines risk stratification, which is the cardiovascular events during exercise training or testing.[7]

**Borg Scale**

Dyspnea and fatigue are the two main symptoms in COPD patients assessed through recall or real-time. A real-time evaluation of symptoms only answers the question of how hard the dyspnea or fatigue was experienced during the test. The visual analog and Borg scales are the most commonly used tools to assess dyspnea or fatigue during the test.[7]

The Borg scale is a very simple numerical list used to assess the Rating of Perceived Exertion (RPE). Patients are asked to rate exertion during the activity by combining all sensations of physical stress and fatigue. They are told to ignore other factors such as shortness of breath or leg fatigue, by trying to focus on the sensations of exertion and this scale ranges from 6-20, as shown in Figure 2. Compared to other linear scales as the visual analog, the RPE shows the same sensitivity and reproducibility of results [(29)]. The Borg scale is also used to assess shortness of breath and limb fatigue in a Category Ratio (CR) of 1-10 and is referred to as the Borg CR10, as shown in Figure 2. [30, 31]

| Score | Borg RPE | Score | Borg CR10 Scale |
|---|---|---|---|
| | Level of Exertion | | Level of Exertion |
| 6 | No exertion et all | 0 | No exertion et all |
| 7 | | 0.5 | Very, very slight (just noticeable) |
| 7.5 | Extremely light | 1 | Very slight |
| 8 | | 2 | Slight |
| 9 | Very light | 3 | Moderate |
| 10 | | 4 | Somewhat severe |
| 11 | Light | 5 | Severe |
| 12 | | 6 | |
| 13 | Somewhat hard | 7 | Very severe |
| 14 | | 8 | |
| 15 | Hard (heavy) | 9 | Very, very severe (almost maximal) |
| 16 | | 10 | Maximal |
| 17 | Very hard | | |
| 18 | | | |
| 19 | Extremely hard | | |
| 20 | Maximal exertion | | |

RPE indicates Rating of Perceived Exertion, and CR10 indicates Category Ratio 10.

**Figure 2. Borg RPE and Borg CR10 Scale**

**Cardiopulmonary Exercise Testing (CPET)**

The level of exercise capacity and intolerance is clinically determined by the CPET test, which is a non-invasive technique to evaluate the integrative functions of the cardiovascular, respiratory, hematopoietic, metabolic, and neuropsychological systems during maximal exercise. This test is considered a gold standard to assess exercise capacity and objectively determine intolerance. Furthermore, it allows the evaluation of metabolic and cardiorespiratory responses during maximal or peak exercise.[7, 32]

The variable used to assess exercise capacity with CPET is peak $O_2$ uptake (VO2 peak). The VO2 peak value is the highest value obtained at the end of the exercise test until exhaustion. In this state, no $O_2$ uptake can be identified (plateau VO2) and the VO2 peak is considered the maximum (VO2 max). Meanwhile, a VO2 max of less than 85% of the predicted value is considered abnormal. Another variable to predict exercise intolerance with CPET is the inspiratory capacity (IC), which is the maximum amount of air exhaled after normal breathing. The decrease occurred due to dynamic hyperinflation and increasing in end respiratory lung volume during exercise.[15, 32]

**Field Test**

Field tests such as the 6-minute walk (6MWT), three-minute step (3MStepT), and sit-to-stand can also be used to determine exercise capacity. There are numerous benefits to these tests, including their ease of administration, minimal equipment requirements, non-laboratory setting, and ability to accurately assess pulmonary rehabilitation progress.[7, 33]

**Six-Minute Walk Test (6MWT)**

This test is recommended to assess functional capacity and evaluate treatment response in a COPD rehabilitation program. Previous studies reported that 6MWT results were reliable in patients with severe and very severe cases.[29,34] The 6MWT offers several advantages, such as its cost-effectiveness, ease of administration, and suitability for evaluating exercise tolerance levels. The test has some drawbacks, such as the inability to objectively determine the precise cause of exercise limitations, the need for prior familiarization, the relatively long time required to complete the test, and the need for a 30-meter corridor. However, monitoring of blood pressure, heart rate, and oxygen saturation before and after the test can provide an index of functional capacity. A walking distance of 6 minutes (6MWD) is used to determine the functional capacity.[35]

There is a strong association between 6MWD and COPD clinical outcomes because the test can describe both pulmonary and extra-pulmonary manifestations of the complication. A study of longitudinal changes in subjects with severe COPD for over 2 years, found an increase in survival. In subjects who did not survive, there was a significant decrease in 6MWD by 40 meters compared to survived subjects with more than 1 year (22 meters) without a parallel change in forced expiratory volume of 1 second (FEV1). The distance covered in this test is considered a good predictor of mortality. Meanwhile, distances of less than 350 meters are associated with increased mortality in COPD.[29, 34]

**Three-Minute Step Test (3MStepT)**

This test is performed by stepping up and down on the platform for 3 minutes. Beaumont et al. found a correlation between 6MWD and 3MstepT and concluded that 3MstepT was valid to measure exercise capacity in COPD patients. After the 3MstepT, there is a higher heart rate and greater leg fatigue observed, while a lower oxygen saturation is noted in 6MWT. The advantages of field tests include their ease of administration, minimal space requirements, relatively short duration, and simple equipment needs (such as a 15 cm high platform). Moreover, 6MWT is typically well tolerated by COPD patients.[33]

**Sit to Stand Test (STST)**

Versions of STST are varied, ranging from a few seconds to several minutes. All STST versions have been tested in COPD patients, and the most frequently used is the 1-min STST.[36] Furthermore, Janssens et al. found that the value of the 5R-STST in COPD patients was lower than in healthy subjects of the same age.[37] The 5R-STST identifies impairment of exercise capacity and mobility. Another study by Puhan et al. reported a lower 1- minute STST performance in subjects who died within 2 years than in survivors. Meanwhile, subjects that cannot conduct more than 12 repetitions in 1 minute have a lower metabolic power and can predict the risk of

death.[38] The shorter, medium, and longer version of the STST provides information on leg strength and coordination, muscle endurance, and exercise capacity and tolerance, respectively.[36]

## CONCLUSION

COPD patients are often experiencing intolerance characterized by an inability to achieve and maintain the intensity of the exercise by people with the same condition. Shortness of breath and leg fatigue are common symptoms of exercise intolerance found in COPD. In addition, respiratory dysfunctions such as impaired ventilation, impaired gas exchange, dynamic hyperinflation, and muscle dysfunction cause exercise intolerance. Right and left ventricular dysfunction as well as pulmonary hypertension can also result in this complication. Structural changes in the muscles can cause patients to experience fatigue easily during exercise. Furthermore, neuromuscular and psychological factors can exacerbate this condition. Clinically, the Borg scale is a useful tool for evaluating symptoms of exercise intolerance. CPET is recommended as the best test to assess functional capacity, and field tests such as 6MWT, STST, and 3MstepT can also be adopted.

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