Original Article

# Pathophysiology and rehabilitation management of exercise intolerance in COVID-19 patients

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**Abstract:**

**OBJECTIVE:** This review aimed to explore the pathophysiology and rehabilitation management of exercise intolerance in COVID-19 patients.

**METHODS:** We reviewed articles published in 2019-2021 using PubMed, Google Scholar, and CINAHL databases as an electronic database. Data obtained were pathophysiology and rehabilitation management of exercise intolerance in COVID-19 survivors. Types of the article were original articles and systematic or narrative reviews, both published and preprint articles. Articles that were written in English and freely accessible in pdf or HTML format were included.

**RESULTS:** There were 28 articles eligible for this review. Pathophysiology, rehabilitation management, and both pathophysiology and rehabilitation management were explained in 7, 24, and 4 articles, consecutively.

**DISCUSSION:** Exercise intolerance is caused by some pathological processes in the respiratory, cardiovascular, and musculoskeletal systems as a result of systemic inflammation. Fatigue and shortness of breath during the activity were the most common symptom in the early phase of COVID-19 and persisted until the follow-up phase. Hospital admission, especially prolonged use of ventilators and immobilization worsen functional impairment resulting in persistent symptoms. Rehabilitation management begins with a functional assessment consisting of symptom assessment and physical examination of the body systems affected. The goals of rehabilitation management are to increase functional capacity, reduce symptoms, improve the ability to perform daily activities, facilitate social reintegration, and improve quality of life. Exercise is an effective intervention to reach these goals. Several studies recommend breathing, and aerobic exercises, as well as resistance exercises for peripheral and respiratory muscles, to improve symptoms and increase functional capacity.

**Keywords:**

COVID-19, exercise intolerance, functional capacity, pathophysiology, rehabilitation management

Exercise intolerance is the inability to perform exercise caused by various medical conditions such as respiratory, cardiovascular, and injuries or musculoskeletal disorders as well as other medical conditions, including mental and emotional disorders.[1] COVID-19 patients can experience post COVID-19 syndrome, characterized by the presence of postinfection symptoms, especially shortness of breath and fatigue. Around 89.5% and 94.9% of COVID-19 survivors experience symptoms of shortness of breath and fatigue, consecutively.[2]

Exercise intolerance is a complex clinical symptom characterized by a decrease in oxygen consumption during physical activity caused by a decreased ability of the cardiovascular system to supply oxygen, and the inability of skeletal muscles to use the delivered oxygen, or both.[3] In COVID-19, some pathological processes occur in the respiratory, cardiovascular,



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and musculoskeletal systems, which further causes an impaired function.[4]

Previous research found that all patients experienced decreased functional capacity, and shortness of breath, palpitations, as well as dizziness during the exercise test. This study also found that patients experienced syncope and hyperventilation during exercise.[5] Abdallah *et al*. found that fatigue and shortness of breath during the activity were the most common symptoms in the early phase of COVID-19. In addition, both of these symptoms persisted until the follow-up phase. Impaired lung volume and gas exchange as well as decreased functional capacity were found 3–4 months after discharge from the hospital.[6]

Research by Prazao et al. found that patients who recovered from severe COVID-19 had a low cardiorespiratory fitness.[7] The decrease in cardiorespiratory fitness was not only caused by pathologies of respiratory, cardiovascular, and musculoskeletal functions but also caused by impaired function due to inactivity and hospital care, especially the intensive care unit (ICU).[2,7] The decreased cardiorespiratory fitness in severe COVID-19 indicated a poor prognosis.[7]

Research data on exercise intolerance in COVID-19 patients and survivors are still very limited. Based on the pathophysiology that occurs in COVID-19 infection, in future, there may be many COVID-19 survivors with exercise intolerance. It may become a challenging issue to manage by physicians, especially rehabilitation physicians. This review explained about exercise intolerance in COVID-19 survivors, focusing on pathophysiology and rehabilitation management.

## Pathophysiology of Exercise Intolerance in COVID-19

Exercise intolerance occurs due to low functional capacity which represents the inability of the cardiovascular and respiratory systems to provide oxygen for muscle contraction during physical activities. Functional capacity, exercise tolerance, exercise capacity, cardiorespiratory fitness, and cardiorespiratory endurance are terms that are usually used interchangeably.[8,9] Functional capacity values can be measured or predicted by determining the maximum oxygen uptake (VO2 max), quantitatively and qualitatively.[10]

VO2 max can be predicted by the 6-min walk test (6MWT), and other exercise tests using a treadmill or cycle ergometer. An accurate and reliable exercise test to determine exercise tolerance is Cardiopulmonary Exercise Testing (CPET), which measured oxygen consumption (VO2) by blood gases analysis. CPET outcomes varied including Metabolic Equivalents (METs), exercise workload, blood pressure response, and heart rate.[8-10] Sawant *et al*. assessed the response of COVID-19 patients to the 1-min sit-to-stand test related to the number of repetitions, oxygen saturation, heart rate, and rating of perceived exertion to describe functional capacity.[10] A review by Vaidya *et al*. concluded that sit-to-stand test was a kind of field test that could indicate functional capacity and exercise tolerance.[11]

Factors affecting exercise intolerance in COVID-19 are damage to the respiratory, cardiovascular, and peripheral musculoskeletal systems. These factors are schematically described in Figure 1.

Inflammation in COVID-19 causes damage to the vascular endothelium which can lead to pulmonary edema. Lung tissue biopsy revealed bilateral diffuse alveolar lesions with exudates and cellular fibromyxoids. In addition, prolonged use of a ventilator results in secondary lung injury which also causes edema, lung inflammation, impaired surfactant function, as well as decreased lung compliance, and gas exchange causes hypoxemia. Impaired respiratory function is exacerbated by the consolidation of the lung parenchyma resulting in changes of alveolar walls to become fibrotic tissue in the process of tissue healing.[2,4]

Damage to the cardiovascular system is caused by an imbalance between high metabolic demands and low cardiac reserve, systemic inflammation, and thrombogenesis, or cardiac injury caused by direct viral invasion of the myocardium. High concentrations of cytokines and inflammatory markers are associated with macrophage infiltration into the myocardial interstitial tissue which can lead to myocarditis. Myocarditis leads to myocardial injury, heart failure, cardiogenic shock, and malignant arrhythmias that may persist after the acute phase. Cardiac injury is known more severe in patients with comorbidities such as hypertension, diabetes mellitus, and cardiovascular diseases as well as the use of ventilators during acute infection.[4,12]

The incidence of thromboembolism in COVID-19 patients is about 22%. COVID-19 patients with hypercoagulability have a higher risk for thromboembolic events such as pulmonary thromboembolism and stroke. A significant increase in the D-dimer value is an important marker for the development of deep vein thrombosis and is associated with the development of intravascular hypercoagulability. Coagulation abnormalities can occur due to interactions between immobilization, systemic inflammation, platelet activation, endothelial dysfunction, and venous stasis.[4] Another vascular disorder is disseminated intravascular coagulation which increases the risk of death. This disorder occurs due to an

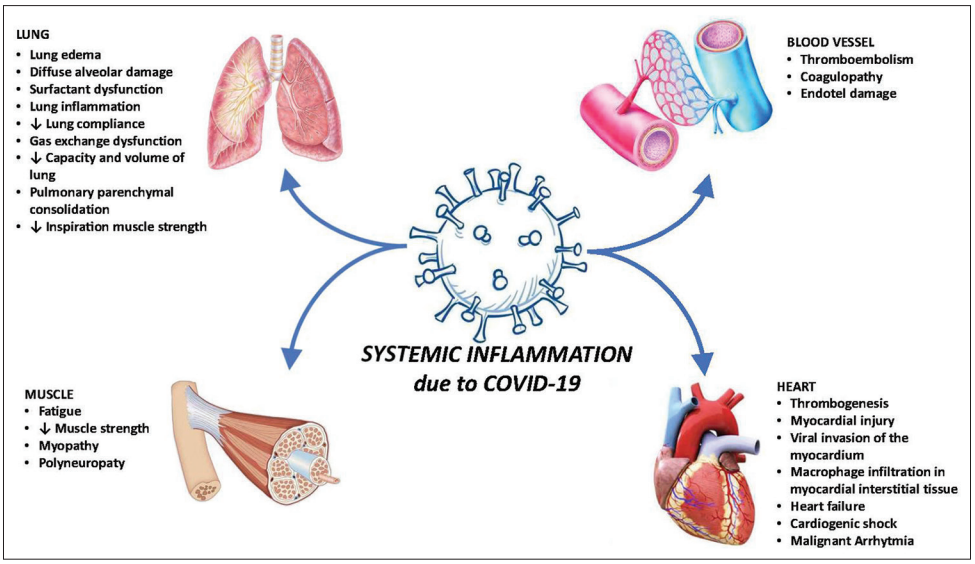


**Figure 1:** Factors affecting exercise intolerance in COVID-19

acute inflammatory response or sepsis that causes tissue endothelial damage to multi-organ failure.[13]

COVID-19 patients may experience chronic fatigue and musculoskeletal disorders after discharge from the hospital. Fatigue is a common symptom experienced from the acute phase and can persist for several months after being discharged from the hospital. The incidence of fatigue in COVID-19 is associated with high levels of interleukin-6 and interleukin-10 in the chronic phase due to a cytokine storm during the acute phase. Musculoskeletal disorders and decreased muscle strength in critically ill patients with long hospital stays can be caused by several things, such as muscle hypoxia, prolonged immobilization, as well as long-term use of steroids and neuromuscular blocking agents that can lead to polyneuropathy or myopathy.[4] Atrophy and loss of muscle mass began in the 1st week of ICU admission and worsened in patients with multi-organ failure, sepsis, or prolonged ICU stay. Other musculoskeletal complications are heterotopic ossification, muscle wasting, prolonged pain, weakness, shortness of breath, as well as decreased ability to walk and to do physical activities.[12]

Research showed that more than 80% of COVID-19 survivors experience various functional limitations. Increased lung restriction may contribute to decreased walking distance and increased shortness of breath or leg fatigue in 6MWT. Approximately 43% of patients had obstructive and 53% had restrictive pulmonary disorders within the 1st year after hospitalization. Patients with persistent shortness of breath showed greater impairment of gas exchange at rest and activity as well as have more severe restrictive pulmonary impairment on spirometry.[14,15]

The marked decrease in cardiorespiratory fitness was found in acute COVID-19 infection. However, in the recovery phase, it is not widely known. Extensive lung damage can impair oxygen diffusion from the lungs to the circulation and causing hypoxemia. Damage to cardiovascular function can also disrupt oxygen delivery to meet the metabolic needs of contracting muscles. Loss of muscle mass also increases the incidence of exercise intolerance in the recovery phase.[16]

Cardiac abnormalities along with prolonged immobilization lead to decreased cardiorespiratory capacity which can reduce the ability to perform daily activities, and may increase the risk of cardiac events after discharge from the hospital. In a study of adverse effects of immobilization on cardiorespiratory fitness, a 30% reduction in cardiorespiratory capacity was found after 3 weeks of bed rest.[4] One previous study found persistent symptoms in 3 months after COVID-19 infection in 2113 patients.[2]

## Assessment of Exercise Intolerance in COVID-19

The main symptoms associated with exercise intolerance in COVID-19 are shortness of breath and fatigue.[2] Shortness of breath is caused by hyperventilation and is usually accompanied by tachycardia, chest pain, headache, abdominal pain, nausea, fatigue, and anxiety.[5] Shortness of breath can be examined by Dyspnea Severity Index (DSI) Questionnaire, Modified Medical Research Council Dyspnea Scale, and Numerical Rating Scale on a scale of 0–10.[17,18] Patients with persistent shortness of breath have heavier restrictions on spirometry examination and low diffusing capacity of the lungs for carbon monoxide (DLCO) values. They also had decreased functional capacity, increased

oxygen desaturation, and increased symptoms during 6MWT.[14] Scales that can be used to measure fatigue in post-COVID-19 patients are the Modified Fatigue Impact Scale and the Fatigue Assessment Scale Table 1.[17,18]

Research by Huang *et al*. found pulmonary abnormalities, decreased respiratory muscle strength, and impaired diffusion capacity in more than 50% of patients with COVID-19 in the early convalescent phase. DLCO disturbances, and decreased lung capacity, as well as 6-min walking distance, were also found in severe cases.[19] Another study found symptoms of exercise intolerance in the form of shortness of breath, palpitations, dizziness, syncope, tachycardia, chest pain, and fatigue in most or all of the subjects undergoing the exercise testing or training.[5]

In severe cases of COVID-19 patients, a decrease in the performance of peripheral muscles including respiratory muscles was found.[7] Examination of the musculoskeletal system found a loss of muscle mass in the healing phase.[16] Examination of the inspiratory muscle was carried out by measuring the maximal inspiratory pressure (MIP).[20] Measurement of the MIP is related to the strength of the diaphragm and can predict diaphragmatic weakness before changes are found on spirometry, for example, a decrease in forced vital capacity.[20]

Pulmonary function abnormalities found after COVID-19 infection were significant changes in lung capacity and volume. However, there is no decrease in lung function that was found on spirometry.[16] Total lung capacity and DLCO, as well as prediction of VO2peak, were lower in admitted patients compared to nonadmitted patients.[6]

Electromyography (EMG) examination in severe cases of COVID-19 patients showed high EMG activity with low-power output. This result is caused by the activity of each motor unit that could only activate a low force so that more motor unit recruitment is needed.[7]

A study found that the walking distance of severe COVID-19 patients was lower than nonsevere cases, with 88.4% distance of the predicted value.[19] In CPET, peak oxygen consumption (VO2peak) is below the predicted value within 3 months of recovery.[16] Respiratory mechanics indices including inspiratory capacity and inspiratory reserve volume were lower in admitted patients.[7]

**Table 1: The Modified Medical Research Council Scale**

| Grade | Description of Breathlessness |
|---|---|
| Grade 0 | I only get breathless with strenuous exercise |
| Grade 1 | I get short of breath when hurrying on level ground or walking up a slight hill |
| Grade 2 | On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level |
| Grade 3 | I stop for breath after walking about 100 yards or after a few minutes on level ground |
| Grade 4 | I am too breathless to leave the house or I am breathless when dressing |

## Rehabilitation Management of Exercise Intolerance in COVID-19

Rehabilitation in COVID-19 aims to improve functional capacity and quality of life, facilitate social reintegration after hospitalization, reduce symptoms, and improve the ability to perform daily activities. Intervention to increase exercise tolerance and functional capacity as well as reduce shortness of breath are breathing and aerobic exercises, as well as resistance exercises for peripheral and respiratory muscles.[4]

Conditions that cause exercise to be contraindicated are as follows: (1) body temperature ≥38.0°C, (2) within ≤7 days from the time of being consulted, (3) time from onset of illness with symptoms of dyspnea is ≤3 days, (4) chest X-ray examination shows >50% progress in 24–48 h, (5) oxygen saturation ≤95%, and (6) resting blood pressure <90/60 mmHg or >140/90 mmHg.[21] Preparations before exercise include monitoring body temperature, wearing appropriate sports clothing, and prescribing good exercise, especially determining the intensity and duration under the patient's condition and safety considerations during exercise.[12]

Special considerations for providing exercise to COVID-19 patients are as follows: (1) COVID-19 patients who experience severe sore throat, myalgia, shortness of breath, general fatigue, chest pain, cough, and fever should avoid exercise with an intensity of >3 METs for 2–3 weeks after these symptoms disappear; (2) if there are mild symptoms related or unrelated to COVID-19, then activity should be limited to light activity (≤3 METs). However, sedentary behavior should be prevented. Increase rest periods if symptoms worsen. Exercise with high intensity and long duration should be avoided; and (3) asymptomatic COVID-19 patients should continue to exercise as usual with due observance of government regulations regarding restrictions. Patients with mild or moderate cases who wish to exercise after recovery can start with light stretching and strengthening exercises for 1 week before engaging in targeted cardiovascular exercise. Patients with severe cases should be given exercise with a pulmonary rehabilitation approach.[12]

At present, there are no specific guidelines to provide exercise in COVID-19 patients or survivors with exercise

intolerance. However, several studies recommend exercise as an effective intervention in reducing symptoms and increasing functional capacity. Exercise is aimed at correcting functional impairment due to pathological changes in COVID-19.[22,23]

A review by Jimeno-Almazán *et al*. explained the benefits of exercise in post-COVID-19 patients, such as improvement of symptoms of shortness of breath and other respiratory functions such as increased oxygen uptake, lung function, as well as improvement of oxidative stress. Exercise can also increase mitochondrial biogenesis, vascularization, and cardiovascular function as well as decrease blood pressure and normalize dis-autonomy. Increased muscle mass, muscle strength, intermuscular coordination, and tolerance to exercise, as well as improvements in neurological, immune, and psychological functions, are also found in the provision of exercise.[22]

The aerobic exercise recommended for COVID-19 patients adheres to the same principles as an exercise in patients with cardiovascular diseases. Exercise with a duration of 150 min/week of moderate-vigorous intensity divided into 3–5 sessions is prescribed individually based on clinical and functional assessments. The recommended intensity is 70%–85% of the peak heart rate obtained in the exercise test. Monitoring of vital signs and oxygen saturation should be performed during exercise to prevent adverse events. Exercise is increased gradually according to patient tolerance.[5] Consider intermittent exercise in patients with significant fatigue.[5,21] Zhu *et al*. recommend aerobic exercise for COVID-19 patients in the recovery phase in the form of walking up and downstairs, walking indoors, as well as dancing. Exercise is done for at least 6 weeks, 5 times a week, 30–60 min in duration, and starting at a low intensity. The intensity is increased by 10% every week until it reaches the limit of 70% of the maximum heart rate.[24] Other types of exercise that can be given to patients after severe cases of COVID-19 are walking, brisk walking, slow jogging, and swimming. The intensity of the exercise starts from the low intensity with a progression of intensity or duration of exercise. The frequency of exercise is 3–5 times a week and the duration is 20–30 min.[21] A systematic review by Alawna *et al*. explained that COVID-19 patients were given aerobic exercise for 20–60 min by cycling or walking, exercise intensity 55%–80% VO2 max, or 60%–80% maximum heart rate. This exercise should be repeated 2–3 sessions/week. Exercise at this dose can improve immune function without producing fatigue and is said to be safe and did not trigger adverse events.[25]

The recommended resistance exercises for COVID-19 survivors are multi-joint exercises to increase the strength and hypertrophy of the muscles being trained. Several factors that need to be considered in administering resistance training are as follows: (1) low-volume exercise can increase the feasibility and safety of most COVID-19 survivors including patients with cardiometabolic disease and the elderly with frailty syndrome and (2) it is recommended to avoid high-intensity exercise for long periods.[23]

In general, recommendations for resistance training are as follows: (1) low volume of exercise (3–6 sets per muscle group per week), (2) multi-joint exercises are better than single-joint exercises, (3) training sessions should not exceed 45 min, (4) the number of repetitions ≤6, (5) the length of the interval between sets is about 3 min, (6) controlled movement speed (2 s in each concentric and eccentric phase), and (7) preferably in the afternoon or evening.[23] Santana *et al*. recommend resistance training after discharge with progressive resistance training in 2–3 weeks with 8–12 repetitions for the upper and lower extremities.[26]

Respiratory rehabilitation in COVID-19 patients consists of forced expiratory and coughing exercises as well as inspiratory muscle exercises. The duration of the respiratory rehabilitation program depends on the patient's clinical condition and comorbidities. Some studies recommend 6–8 weeks of exercise episodes to maximize the benefits of exercise. One study found that lung function and quality of life improved in older adults who recovered from COVID-19 after 6 weeks. Research by Abodonya *et al*. found that inspiratory muscle training with an inspiratory muscle trainer (IMT) device 2 sessions per day, 5 times a week, and carried out for 2 weeks after weaning from the ventilator, got an increase in inspiratory muscle function which was marked by an increase in MIP. Inspiratory muscle training is also said to reduce the length of ventilator use and improve lung function.[20] Another study found that in addition to improving lung function, exercise with IMT can improve DSI scores, shorten the length of hospital stays, and improve quality of life.[20]

Seyller *et al*. recommend breathing exercises with incentive spirometry as part of the protocol for managing mild to moderate COVID-19 patients.[27] One technique used for breathing exercise are as follow (a) respiratory breathing: deep breaths inhale through the nose, hold for 2 seconds, then exhale slowly through a whistle. Repeat the exercise for 15 minutes; (b) long breathing exercise: stand straight, relax muscles, take a deep breath, feel the air enter the lower abdominal cavity, then exhale slowly, the slower the better, fully feel the process of expelling air from the lungs, trachea, and nasal cavity. Exercises are performed 10-20 times daily; (c) bend and exhale exercise: stand with the feet shoulder-width apart, cross both arms in front of the chest, exhale slowly as bending

forward, and inhale as both arms fall and stretch them out to both sides. This exercise should be done every day at least 20 times.[28]

The criteria for termination of exercise are if the following conditions occur: (1) oxygen saturation <88%–93%; (2) heart rate <40 beats per min or >120 beats per min; (3) systolic blood pressure <90 mmHg and >180 mmHg; (4) body temperature >37.2°C; (5) respiratory symptoms and fatigue that worsen during exercise and do not decrease with rest; and (6) symptoms such as chest pain or chest tightness, difficulty breathing, severe cough, dizziness, headache, blurred vision, palpitations, excessive sweating, and instability.[29]

## Summary

Exercise intolerance in COVID-19 is caused by damage to the respiratory, cardiovascular, and musculoskeletal systems due to a systemic inflammatory process. Pathology of these systems results in functional disturbances characterized by symptoms of shortness of breath and fatigue that persist until the recovery phase. Hospital admission, especially prolonged use of ventilators, and immobilization worsen functional impairment resulting in persistent symptoms.

Rehabilitation management begins with a functional assessment consisting of symptom assessment and examination of cardiovascular, respiratory, as well as musculoskeletal functions. COVID-19 patients show lower levels of cardiorespiratory fitness, especially in severe cases.

The goals of rehabilitation management are to increase functional capacity, reduce symptoms, improve the ability to perform daily activities, facilitate social reintegration, and improve quality of life. There are no specific guidelines for providing exercise to COVID-19 patients with exercise intolerance, but several studies recommend exercise as an effective intervention in reducing symptoms and increasing functional capacity.

The exercise aims to improve functional impairment due to pathology arising from COVID-19. Several studies recommend breathing, and aerobic exercise, as well as a resistance exercise for peripheral and respiratory muscles to improve symptoms and increase functional capacity.

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### Conflicts of interest
There are no conflicts of interest.

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