Cardiopulmonary exercise testing in post-COVID-19 patients

Kenneth Nugent MD

ABSTRACT

Patients with prior COVID-19 infection can have residual symptoms and significant disability. In particular, some patients have abnormal lung function with reduced volumes and diffusion capacities. However, some patients have relatively normal lung function and chest x-rays but have significant dyspnea. These patients have been evaluated using cardiopulmonary exercise testing (CPET) to determine their peak O_2 consumption and their cardiac and respiratory responses during standardized testing. In general, these studies demonstrate that the level of impairment correlates with the severity of the initial infection. In addition, some patients have little or no improvement in their VO_2 over time. This test can provide some insight as to exact system limitations resulting in impairment. Six-minute walk tests provide alternative approaches for evaluating patients when CPET testing is not available. Most patients who have had prior COVID infection improve with standard pulmonary rehabilitation.

Keywords: COVID-19 infection, dyspnea, cardiopulmonary exercise testing, rehabilitation

INTRODUCTION

Patients with prior COVID-19 infections can have several outcomes. Some patients recover completely and are asymptomatic; others have definite residual lung disease with abnormal pulmonary function tests and/or chest imaging. In addition, some patients have chronic constitutional symptoms, such as fatigue and persistent dyspnea.[1] The routine outpatient evaluation of these patients would include oxygen saturation measurements, pulmonary function tests, and chest x-rays. Some patients may need CT scans to evaluate the pulmonary vessels for residual emboli and to evaluate the lung parenchyma for chronic fibrosis. Evaluation of patients with normal standard pulmonary function testing and chest x-rays who report persistent dyspnea with important physical limitation can be difficult. One approach is to use cardiopulmonary exercise testing (CPET).

Corresponding author: **Kenneth Nugent**
Contact Information: Kenneth.Nugent@ttuhsc.edu
DOI: 10.12746/swrccc.v12i52.1329

Cardiopulmonary exercise testing provides a comprehensive assessment of both cardiac responses and ventilatory responses during exercise.[2] Important measurements include O_2 consumption, CO_2 production, heart rate, blood pressure, tidal volume, respiratory rate, and minute ventilation. The initial interpretation analyzes the peak O_2 consumption in relationship to the predicted O_2 consumption. Peak levels below 80% predicted are generally considered abnormal. Analysis of ventilatory responses to exercise includes the measurement of the respiratory rate and the tidal volume, which are the components of the minute ventilation. Patients with pulmonary limitations have reduced levels of minute ventilation during exercise plotted against either O_2 consumption or the workload (Watts) set on the exercise equipment (either a treadmill or cycle ergometer). Patients with respiratory disorders frequently have decreased tidal volumes and increased respiratory rates during standardized exercise tests. In addition, they have increased ratios of minute ventilation to either O_2 consumption or CO_2 production and can have desaturation during the exercise. This testing has been used in several studies in patients who had prior COVID infection who are being evaluated to determine whether or not they have reduced exercise capacity.

CPET TESTING IN POST-COVID PATIENTS

TIME AFTER COVID-19 INFECTION

Skjorten et al. (2021) reported CPET results in 156 patients who had been discharged from the hospital following COVID-19 infection.[3] This testing was done 3 months posthospitalization. Peak oxygen uptake less than 80% of predicted was observed in 49 patients (31%). Ventilatory efficiency was reduced in 24 (15%), breathing reserve was less than 15% in 25 (16%), and oxygen pulse was less than 80% of predicted in 28 (18%). Fifty-nine patients had dyspnea based on an mMRC score ≥1, and these patients had reduced peak VO_2, reduced maximum heart rates, and increased VE/VCO_2 ratios. In patients requiring ICU care, the mean VO_2 peak percent predicted was lower than patients who did not require ICU care. This study demonstrates that approximately one third of patients have the peak VO_2 less than 80% of predicted following hospitalization and that patients with dyspnea had lower exercise capacities.

Ingul et al. (2022) studied 180 patients who have been hospitalized with COVID-19 infections 3 months after discharge using the CPET; 177 had repeat testing at 12 months.[4] Eighty-six patients (47%) had a mMRC ≥1. Forty patients (23%) had exercise intolerance defined as a VO_2 peak less than 80% of predicted at 12 months. Based on their analysis, the explanations for these exercise limitations included circulatory impairment (N = 11) ventilatory impairment (N = 7), deconditioning (N = 19), and dysfunctional breathing (N = 3). Peak VO_2 and oxygen pulse increased between 3 and 12 months in these patients. These results indicate that these patients' exercise tolerance improved between 3- and 12-months following hospitalization and that over 75% of these patients have normal cardiac and respiratory parameters measured by CPET.

INFECTION SEVERITY–HOSPITAL-BASED MANAGEMENT VERSUS OUTPATIENT MANAGEMENT

Guerreiro et al. (2024) studied 42 patients with COVID infections who did not require hospitalization and 37 patients who did require hospitalization 3 months after their infection. Fifty-eight patients (73%) had chronic dyspnea, and 21 (27%) had chronic fatigue.[5] These two symptoms were more frequent in ambulatory patients than hospitalized patients. Thirty-nine patients had abnormal CT scans with ground glass opacities in 20, bands in 16, and reticulation in 12. Twelve patients who required hospitalization had abnormal spirometric testing, and 18 patients had abnormal carbon monoxide diffusion capacities. There was no difference in peak VO_2 between the hospitalized patients and the nonhospitalized patients. Tidal volume in relationship to the minute ventilation was lower in patients who did not require hospitalization, but the slope of VE/VCO_2 was higher than normal in both groups. Overall, there was no difference in the exercise capacity between these two groups of patients, but patients who did not require hospitalization had a reduced or less efficient ventilatory responses to exercise. The explanation for this is uncertain.

Noureddine et al. (2023) studied 60 patients using CPET testing 12 months after hospitalization with severe COVID-19 infections which required ICU care.[6] Thirty patients (50%) had persistent dyspnea. Fifty subjects (84%) had abnormal CT scans with reticulation (N = 42), bronchiectasis (N = 35), and ground glass opacities (N = 29). The peak VO_2 was 21.8 ± 5.2 mL/kg/min (98.0% predicted), the peak VO_2 pulse was 12.9 ± 3.1 ml/beat (103.7 ± 19.9 % predicted), the VE/VCO_2 slope was 37.2 ± 6.7, and the Vd/Vt was 0.29 (0.25–0.35). Twelve patients had a reduced peak exercise capacity, less than 85% of predicted. These patients had longer ICU stays, 29.7 ± 13.1 days versus 19.1 ± 11.3 days. The primary limitations in these 12 patients were ventilatory (N = 6) and physical deconditioning (N=6). Patients with a normal peak VO_2 had an increased VE/VCO_2 slope. The authors concluded that ICU length of stay was a significant predictor of peak VO_2. The patients in this study had increased dead space ventilation, and this could reflect pulmonary vascular disease associated with COVID infections.

Holley et al. (2023) reviewed CPET results in 45 patients with prior COVID-19 infections who had exercise intolerance and dyspnea.[7] Four patients had restrictive patterns on spirometry, one patient had mild obstruction, and two patients had abnormal diffusion capacities. The average LV ejection fraction was 62.1% ± 2.3%. Fourteen patients (out of 35 with studies) had abnormal findings on computed tomography, including airway abnormalities and ground glass opacities. The average peak VO_2 was 84.2 ± 2.3% of predicted; 25 subjects had abnormal values. The average values for VE/VCO_2 slopes were increased, and 18 had abnormal values. Based on the pre-established criteria, 22 subjects had deconditioning, 19 had dysfunctional breathing, and 5 patients had respiratory limitation. Some subjects fell into more than 1 category; for example, 8 subjects had both deconditioning and dysfunctional breathing. This study demonstrates that patients with prior COVID-19 infection can have abnormal pulmonary function tests, abnormal computed tomography scans, and reduced exercise capacity. The explanation for these changes in exercise capacity are complex and include abnormal ventilation, deconditioning, and dysfunctional breathing.

Durstenfeld et al. (2022) analyzed 38 studies that reported CPET results in 2160 individuals 3 to 18 months after SARS-CoV-2 infection, including individuals with long COVID symptoms and individuals without these symptoms.[8] The mean peak VO_2 was −4.9 mL/kg/min (95% CI: −6.4 to −3.4) lower in patients with symptoms in comparison to individuals without symptoms. These results were attributed to deconditioning, peripheral limitations with abnormal oxygen extraction, dysfunctional breathing, and chronotropic incompetence. There was no consistent pattern to explain the limitations in these patients, and some patients likely had more than one explanation for exercise limitation. In particular, it is difficult to differentiate deconditioning from reduced oxygen uptake and metabolism in skeletal muscle without invasive studies.

Alternative approaches to evaluation

Cardiopulmonary exercise testing is a relatively complicated test and many hospitals and clinics do not provide these studies. An alternative method to evaluate physical capacity is to use a 6-minute walk test. Wong et al. studied 6-minute walk tests in 225 patients who had had prior COVID infection.[9] They divided these patients into 3 groups based on the severity of the infection, i.e., mild, moderate, and severe COVID infections. The overall walk distance was 447 ± 104 meters. There was a definite decrease in walk distance based on the severity of the COVID infection. In addition, the peak dyspnea score increased in these patients. Al Yammahi et al. used 6-minute walk tests and 2 other protocols to study the activities of daily living in 40 patients who had had prior COVID infection.[10] The Glitter Activities of Daily Living Test requires the participant to perform 9 activities of daily living, which include walking in a circuit, carrying a backpack, going up a 2-step staircase, and moving objects from a shoulder high shelf to a waist high shelf. Subjects complete the circuit 5 times as fast as possible. The Londrina Activities of Daily Living protocol requires the subject to complete 5 activities that are relevant to functional independence during their daily lives. These tests provide information about the participants' functional activity level and changes in blood pressure, heart rate, respiratory rate, O2 saturation, and dyspnea during the testing. This information would provide a baseline before starting a treatment program, including rehabilitation in patients who have had prior COVID infection but would require an organized and equipped study site.

Rehabilitation

Regardless of the explanation(s) for exercise limitation in patients with long COVID, patients and clinicians want to know treatment options. Standard cardiopulmonary rehabilitation programs provide important benefits to patients with either cardiac disease or respiratory disease. Is this approach useful in patients with long COVID? Pouliopoulou et al. (2023) published a systematic review and meta-analysis of rehabilitation interventions in patients with post-COVID-19 conditions.[11] This study included 14 trials with 1244 patients. Seven trials with 389 participants reported improved functional exercise capacity based on 6-minute walk tests, and the patients in the intervention group had an increase of 35.8 ± 6.6 meters in their 6-minute walk tests. Eight trials with 573 participants reported significant changes in dyspnea following the intervention, and five trials with 366 participants reported significant improvement in quality of life. There were no significant changes in FEV1 or FVC. This study demonstrates that physical rehabilitation has the potential to improve functional capacity and quality of life in patients with post-COVID conditions.

Gloeckl et al. (2024) developed practical recommendations based on a literature review and a survey of 14 experts in this field for exercise training in patients with long COVID with or without post-exertional malaise.[12] They classified patients into three groups, including no post-exertional malaise, mild/moderate post-exertional malaise, and severe post-exertional malaise. Recommendations for patients with severe post-exertional malaise include setting limits for both physical and mental activity to avoid overload. Their recommendations do not include suggestions regarding systematic counseling and other neuropsychological techniques.

Other treatment considerations include empiric treatment of postinfectious airway disease and parenchymal lung disease and for cardiac disorders. These trials should have specific outcome goals and limited time frames since improvement may be quite modest.

In summary, in most cases, the best approach to improving physical fitness and reducing symptoms will involve pulmonary rehabilitation and counseling.

Discussion

Some patients recover from COVID-19 infections with no residual symptoms. Other patients have definite chronic lung disease following this viral infection and have abnormal pulmonary function tests and chest radiographs. A third group of patients has persistent and sometimes disabling dyspnea but have normal pulmonary function tests and chest x-rays. These patients can be evaluated using cardiopulmonary exercise testing to determine their peak VO_2. In addition, analyzing the cardiac and respiratory parameters measured during this testing can identify the abnormality most likely causing physical limitation in the patients, especially those with more than one type of limitation. Studies reviewed in this article demonstrate that the severity of the COVID-19 infection influences the residual cardiopulmonary impairment, the time between the infection and testing can affect these results, and the type of impairment is not uniform. Patients can have lung impairment, cardiac impairment, skeletal muscle impairment, and dysfunctional breathing. This testing is not available in many centers, and 6-minute walk tests can provide useful information about the patient's exercise capacity and respiratory response in terms of desaturation during walking. Most patients benefit from rehabilitation, and standard established programs used in pulmonary rehabilitation provide a good approach for most patients.

Conclusion

Cardiopulmonary exercise testing provides a comprehensive approach to evaluate the subject's exercise capacity and determine cardiac responses and respiratory responses to standard workloads. If this testing is not available, a 6-minute walk test can provide important information and should be used to help evaluate the patient's current symptoms, change in status over time, and improvement with either treatment or rehabilitation.

Article citation: Nugent K. Cardiopulmonary exercise testing in post-COVID-19 patients. The Southwest Respiratory and Critical Care Chronicles 2024;12(52): 15–19
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas
Submitted: 6/1/2024
Accepted: 6/27/2024
Conflicts of interest: none

References

1. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 2023;21(3):133–146. DOI: 10.1038/s41579-022-00846-2.
2. Juarez M, Castillo-Rodriguez C, Soliman D, et al. Cardiopulmonary exercise testing in heart failure. J Cardiovasc Dev Dis 2024;11(3):70. DOI: 10.3390/jcdd11030070.
3. Skjørten I, Ankerstjerne OAW, Trebinjac D, et al. Cardiopulmonary exercise capacity and limitations 3 months after COVID-19 hospitalisation. Eur Respir J 2021;58(2): 2100996. DOI: 10.1183/13993003.00996-2021.
4. Ingul CB, Edvardsen A, Follestad T, et al. Changes in cardiopulmonary exercise capacity and limitations 3–12 months after COVID-19. Eur Respir J 2023;61(2): 2200745. DOI: 10.1183/13993003.00745-2022.
5. Guerreiro I, Bringard A, Nehme M, et al. Exercise ventilatory response after COVID-19: comparison between ambulatory and hospitalized patients. Am J Physiol Lung Cell Mol Physiol 2023;325(6):L756–L764. DOI: 10.1152/ajplung.00142.2023.
6. Noureddine S, Roux-Claudé P, Laurent L, et al. Evaluation of long-term sequelae by cardiopulmonary exercise

testing 12 months after hospitalization for severe COVID-19. BMC Pulm Med 2023;23(1):13. DOI: 10.1186/s12890-023-02313-x.

7. Holley AB, Fabyan KD, Haynes ZA, et al. Cardiopulmonary exercise testing in younger patients with persistent dyspnea following acute, outpatient COVID-19 infection. Physiol Rep 2024;12(3):e15934. DOI: 10.14814/phy2.15934.
8. Durstenfeld MS, Sun K, Tahir P, et al. Use of cardiopulmonary exercise testing to evaluate long covid-19 symptoms in adults: a systematic review and meta-analysis. JAMA Netw Open 2022;5(10):e2236057. DOI: 10.1001/jamanetworkopen.2022.36057.
9. Wong AW, López-Romero S, Figueroa-Hurtado E, et al. Predictors of reduced 6-minute walk distance after COVID-19: a cohort study in Mexico. Pulmonology 2021;27(6):563–565. DOI: 10.1016/j.pulmoe.2021.03.004.
10. Al Yammahi RJ, Alaparthi GK, de Sá Ferreira A, et al. Cardiopulmonary response in post-COVID-19 individuals: a cross-sectional study comparing the londrina activities of daily living protocol, 6-minute walk test, and glittre activities of daily living test. Healthcare (Basel) 2024;12(7):712. DOI: 10.3390/healthcare12070712.
11. Pouliopoulou DV, Macdermid JC, Saunders E, et al. Rehabilitation interventions for physical capacity and quality of life in adults with post-COVID-19 condition: a systematic review and meta-analysis. JAMA Netw Open 2023;6(9):e2333838. DOI: 10.1001/jamanetworkopen.2023.33838.
12. Gloeckl R, Zwick RH, Fürlinger U, et al. Practical recommendations for exercise training in patients with long COVID with or without post-exertional malaise: a best practice proposal. Sports Med Open 2024;10(1):47. DOI: 10.1186/s40798-024-00695-8.