Follow-up of Cardiopulmonary Responses Using Submaximal Exercise Test in Older Adults with Post-COVID-19

The running title: Cardiopulmonary Responses in Post-COVID-19

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ABSTRACT

Background: Data on cardiopulmonary fitness in older adults in the longer term after coronavirus disease 2019 (COVID-19) are of interest as the time required for the full recovery of physical fitness after COVID-19 remains unclear. Some studies have reported that patients do not recover physical fitness for up to 6 or 12 months after COVID-19, whereas other studies have observed full recovery after 12-months. Therefore, this study evaluated and compared the cardiopulmonary responses induced by the 6-minute walk test (6MWT) and 1-minute sit-to-stand-test (STST) results at 3, 6, and 12 months in older adults with and without COVID-19.

Methods: This study included 59 older adults with and without a history of COVID-19. The cardiopulmonary response parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse oxygen saturation (O₂ sat), rate of perceived exertion (RPE), and leg fatigue were evaluated in the participants after 6MWT and 1-min-STST assessments. Results: Post-COVID-19, older adults showed statistically significant differences in HR, SBP, DBP, O₂ sat, RPE, leg fatigue, 6MWT time, and 1-min-STST step numbers at 3, 6, and 12 months (P < 0.001). Moreover, older adults showed statistically significant differences in HR, SBP, DBP, RPE, leg fatigue, O₂ sat, and 6MWT distance at 3 months post-COVID-19 compared with those in older adults without COVID-19 (P < 0.001). Conclusion: While older adults showed recovery of cardiopulmonary response parameters according to 6MWT and 1-min-STST findings at the 12-month follow-up post-COVID-19, these results of these measurements did not return to the values observed in older adults without COVID-19.

Keywords: Exercise test; Geriatrics; Physical exertion; Post-Acute COVID-19 Syndrome
Introduction

The respiratory system is the major target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 infection causes coronavirus disease 2019 (COVID-19), the symptoms of which include inflammation in the respiratory tract with the subsequent spread of inflammation to various organs such as the brain, kidney, and stomach (2, 3). Moreover, individuals who have recovered from COVID-19 also show respiratory system impairment (4, 5). Dyspnea and fatigue are the most common symptoms in individuals recovering from COVID-19 and result in reduced physical fitness and difficulty returning to normal daily life (4-7).

The time required for the recovery of physical fitness after COVID-19 remains unclear. Some studies have reported that patients did not recover physical fitness for up to 6 or 12 months post-COVID-19, (8, 9) whereas other studies observed that patients had recovered their physical fitness by 12 months post-COVID-19 (10, 11). These controversial results may be attributed to differences in COVID-19 severity, the methods of evaluating physical fitness, and treatments and exercise programs. Moreover, several studies demonstrated impaired functioning of various systems among older adults with COVID-19, resulting in increased risks of death (12, 13) and multi-organ dysfunction after hospital discharge (14). A previous study reported pulmonary dysfunction, weakness, and fatigue in older adults at 6 months post-COVID-19 (15). Moreover, the follow-up cardiopulmonary fitness levels at 3, 6, and 12 months post-COVID-19 using submaximal exercise tests in older adults have not been investigated.

Submaximal cardiopulmonary fitness can be evaluated using exercise tests including the 6-minute walk test (6MWT), 1-minute sit-to-stand test (1-min-STST), 6-minute step test, and Chester step test (16-21). These field tests are widely used for assessing cardiopulmonary fitness in individuals with neurological diseases, respiratory diseases, or metabolic syndromes (16). The American Thoracic Society reported that the 6MWT is commonly used to evaluate
submaximal levels of cardiopulmonary fitness (22). The 6MWT has excellent reliability and
validity in patients with chronic obstructive pulmonary disease (23). However, this test requires
a corridor >30 m (22). Therefore, a limitation of 6MWT is that it is mostly used in hospitals
and rehabilitation centers, and not in homes with limited space (24). Therefore, submaximal
cardiopulmonary fitness tests using shorter corridors have been developed, including the 1-min-
STST (17). A previous study reported the positive correlation between the number of steps of
1-min-STST and 6MWT distance and that the 1-min-STST can detect a change in exercise
tolerance similar to the 6MWT (25). In addition, the 1-min-STST is a good test for evaluating
cardiopulmonary fitness levels in patients post-COVID-19 (20). These patients complete the
test in about 90% of cases (20). However, evidence of cardiopulmonary fitness based on the
6MWT and 1-min-STST in the longer term in older adults post-COVID-19 has not been
reported. Therefore, the present study evaluated and compared the cardiopulmonary responses
induced by the 6MWT and 1-min-STST between older adults at 3, 6, and 12 months post-
COVID and those without COVID-19. This study aimed to provide information on alternative
tests that can be used to investigate cardiopulmonary fitness in older adults with a history of
COVID-19, for when 6MWT is not possible. We tested the hypothesis that the
cardiopulmonary response of older adults with a history of COVID-19 would not have
recovered to the values observed in older adults without COVID-19, by the 12-month follow-
up visit.

Methods

Study design and participants

This prospective cohort study evaluated and compared the cardiopulmonary responses
induced by the 6MWT and 1-min-STST at 3, 6, and 12 months between older adults with and
without a history of COVID-19. This study recruited a total of 59 older adults with and without
a history of COVID-19 infection. The sample size was calculated using GPower 3.1, using a
power of 0.95, power analysis with an alpha of 0.05, and an effect size (f) of 0.22 (26). The participants who were recruited were aged ≥60 years, with or without a history of COVID-19, as confirmed by SARS-CoV-2 detection by polymerase chain reaction or-antigen test kit before the investigation. The exclusion criteria included a history of cardiopulmonary diseases such as acute myocardial infarction or asthma, along with musculoskeletal diseases and neurological diseases that could interfere with the testing procedures. All participants had normal body mass index (BMI) values (18.5–24.9 kg/m²), resting pulse oximetry >94%, and resting respiratory <22 beats per minute. All participants provided written informed consent. This study was approved by the Clinical Research Ethics Committee of the University of Phayao, Phayao, Thailand (IRB code 1.3/032/65).

**Procedures**

We evaluated the participants for the baseline demographic data including age, weight, height, BMI, and comorbidities. We assessed their cardiopulmonary responses induced by 6MWT and 1-min-STST at 3, 6, and 12 months. Test sequences were randomly assigned using a website (randomizer.org).

Before starting the 6MWT, the cardiopulmonary parameters were evaluated, including the heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse oxygen saturation (O₂ sat), rate of perceived exertion (RPE), and leg fatigue. Each participant was asked to wear comfortable clothing and shoes. We then instructed the participants to walk as far as possible for 6 min without running within the corridor space of 30 m. The distance completed in each 6MWT was recorded, (22) and the cardiopulmonary parameters were measured and recorded upon test completion.

Before conducting the 1-min-STST, the cardiopulmonary parameters (HR, SBP, DBP, O₂ sat, RPE, and leg fatigue) were measured. The participants were then instructed to sit on a
chair without armrests with a seat height of 46 cm, and to repeatedly stand up until the hips and knees were fully extended and then sit down with the arms folded across the chest as fast as possible for 1 min. We recorded the number of completed actions during the test (20). After completing this test, the cardiopulmonary parameters were measured again and recorded. All tests were performed at 3, 6, and 12 months after COVID-19. A rest period of 30 min was provided between each test.

**Statistical analysis**

The normality of the data distribution was assessed using the Kolmogorov–Smirnov test and kurtosis. All variables had a normal distribution after considering the kurtosis value. Continuous variables are expressed as means and standard deviations. We assessed within-group differences using repeated-measure analysis of variance. A *post hoc* Bonferroni contrast analysis was conducted to determine the significance among the means obtained at the three time points. We used an independent sample t-test to compare cardiopulmonary response parameters between groups. We performed the statistical analyses using IBM SPSS Statistics for Windows, version 26.0, with *P* < 0.05 considered statistically significant.

**Results**

The characteristics of older adults with and without a history of COVID-19 are shown in Table 1. Age (*t* = 1.97, *P* = 0.51), weight (*t* = 0.24, *P* = 0.34), height (*t* = 0.37, *P* = 0.99), and BMI (*t* = 0.34, *P* = 0.134) did not differ significantly between the two groups (Table 1). Comparison of 6MWT in older adults with and without recovery from mild COVID-19 at 3, 6, and 12 months showed that older adults without COVID-19 showed no statistically significant differences in HR (*F* = 0.52, *P* = 0.60), SBP (*F* = 1.77, *P* = 1.79), DBP (*F* = 0.89, *P* = 0.42), O₂ sat (*F* = 0.97, *P* = 0.06), RPE (*F* = 0.24, *P* = 0.47), and leg fatigue (*F* = 0.66, *P* = 0.52) values, or 6MWT distance (*F* = 0.02, *P* = 0.98) after cardiopulmonary response testing.
over 3, 6, and 12 months. In contrast, older adults with a history of COVID-19 showed significant differences in cardiopulmonary response parameters at 3, 6, and 12 months \((P < 0.05)\) (Table 2).

After cardiopulmonary response testing, older adults with a history of COVID-19 had significantly increased HR \((t = 5.58, P < 0.001)\), SBP \((t = 5.56, P < 0.001)\), DBP \((t = 7.42, P < 0.001)\), RPE \((t = 9.11, P < 0.001)\), and leg fatigue \((t = 10.15, P < 0.001)\), as well as decreased O₂ sat \((t = 5.50, P < 0.001)\) and 6MWT distance \((t = 4.39, P < 0.001)\) at 3 months compared with those values in older adults without a history of COVID-19 infection. The follow-up at 6 months showed that the differences in cardiopulmonary response parameters between groups were the same as those at 3 months \((P < 0.001)\). At the 12-month follow-up, the differences between groups were the same as those at 3 and 6 months \((P < 0.001)\), except for the O₂ sat, which did not differ significantly between the groups \((P = 0.975)\) (Table 3).

The results of the post-cardiopulmonary testing responses using the 1-min-STST revealed no significant differences in HR \((F = 2.61, P = 0.08)\), SBP \((F = 1.60, P = 0.21)\), DBP \((F = 0.28, P = 0.76)\), O₂ sat \((F = 2.27, P = 0.11)\), RPE \((F = 1.57, P = 10.22)\), leg fatigue \((F = 0.06, P = 0.94)\), and the 1-min-STST results \((F = 2.48, P = 0.09)\) in older adults without COVID-19 compared at 3, 6, and 12 months. In contrast, older adults post-COVID-19 showed significant differences in responses to cardiopulmonary testing at 3, 6, and 12 months \((P < .05)\) (Table 4).

 Compared with older adults without a history of COVID-19, older adults with a history of COVID-19 showed significantly increased HR \((t = 5.32, P < 0.001)\), SBP \((t = 7.58, P < 0.001)\), DBP \((t = 5.03, P < 0.001)\), RPE \((t = 10.68, P < 0.001)\), and leg fatigue \((t = 10.26, P < 0.001)\) and decreased O₂ sat \((t = 6.41, P < 0.001)\) after cardiopulmonary testing, as well as increased 1-min-STST values \((t = 5.15, P < 0.001)\) at 3 months \((P < 0.001)\). Furthermore, the follow-up at 6 months showed that the differences in post-cardiopulmonary testing response...
parameters between groups were the same as those at 3 months ($P < 0.05$). The follow-up at 12 months demonstrated that the differences were the same as those at 3 and 6 months ($P < 0.05$), except for SBP ($P = 0.210$), DBP ($P = 0.099$), $O_2$ sat ($P = 0.581$) and the 1-min-STST result ($P = 0.176$), all of which did not differ significantly between the groups (Table 5).

The results of the present study revealed no differences in characteristics between older adults with and without a history of COVID-19. Additionally, the duration of the recovery from COVID-19 was revealed to have an impact on cardiopulmonary response parameters.

**Discussion**

This study evaluated and compared the cardiopulmonary responses induced by the 6MWT and 1-min-STST at 3, 6, and 12 months between older adults with and without a history of COVID-19.

Our findings indicate that older adults with a history of COVID-19 had recovered their cardiopulmonary response parameter values based on testing through 6MWT and 1-min-STST by 6 and 12 months. However, these values were not similar to the values observed in older adults without a history of COVID-19, except for $O_2$ sat. Therefore, this finding supported the study hypothesis.

The recovery of cardiopulmonary response parameters among older adults with a history of COVID-19 in this study may be attributed to a history of mild COVID-19. The participants were not admitted to the hospital and had no severe complications from COVID-19, which may have contributed to the faster recovery of these cardiopulmonary responses in these patients. SARS-CoV-2 infection causes long-term respiratory complications (27-31). A previous study reported that patients with severe pneumonia due to COVID-19 not admitted to the hospital showed improved pulmonary function and exercise capacity at 3, 6, 9, and 12 months after infection (10). However, this previous study also reported a decrease in gas
transfer that caused impaired blood-gas exchange, resulting in pulmonary dysfunction in patients with severe COVID-19-associated pneumonia admitted to the hospital (10). Several studies reported similar observations (32-34). Impaired blood-gas exchange occurs due to SARS-CoV-2-activated cardiopulmonary dysfunction (35, 36). Therefore, the saturated O\textsubscript{2} levels in older adults post-COVID-19 in this study had recovered to the values in older adults without COVID-19 potentially because the original infection did not involve pneumonia or hospital admission.

Although we observed that older adults had recovered cardiopulmonary response parameters in the 6MWT and 1-min-STST at 6 months and 12 months post-COVID-19, Betschart et al. reported no significant difference in physical performance levels using the 6MWT at 3 months and 12 months after discharge in patients with mild to severe COVID-19 with hospital admission (37). They proposed that this may be due to the range of comorbidities among patients in their study, which may have caused impaired physical performance before COVID-19, thus affecting the course of their physical performance recovery after COVID-19 (37). Tofiq et al. also reported lower physical function compared with normal reference values based on the results on the chair stand test within 1 min among patients who had recovered from severe COVID-19. In contrast, the physical function parameters after testing using 6MWT did not differ from normal reference values at 6 months. However, at 12 months, many patients still had lower physical fitness than that before COVID-19 (38). The authors suggested that this decreased physical performance could be attributed to decreased muscle strength and endurance due to COVID-19 (38). Moreover, impaired respiratory muscle strength, dyspnea, and decreased work capacity have also been reported in these patients (39). A previous study reported a decreased walking duration 6 months after COVID-19 (9). The impairment of physical function may be due to neuromuscular dysfunction and sustained immobility (40-43). Therefore, these findings suggested that COVID-19 severity and several comorbidities may be related to the recovery of physical function post-COVID-19.
Our study provided information on cardiopulmonary responses based on data from submaximal exercise tests in older adults at three different follow-up times (3, 6, and 12 months) after mild COVID-19. Few studies have reported long-term cardiopulmonary response parameters in this population. Most previous studies reported on these parameters from the onset of COVID-19 (19, 44). Our results demonstrated that while cardiopulmonary response parameters of older adults had partially recovered at 6 and 12 months after COVID-19 onset, they had not returned to the normal values as observed in individuals without COVID-19. Additional longer-term follow-up of these parameters in this patient population is needed to determine if their values fully recover to normal values.

**Study limitations**

The study may be limited by the lack of analysis of additional variables that may impact the cardiopulmonary response parameters of the 6MWT and 1-min-STST, such as patient age, physical activity level, and socioeconomic status. Future studies are needed to assess these variables.

**Conclusion**

While older adults with a history of COVID-19 showed recovered cardiopulmonary response parameters based on the 6MWT and 1-min-STST at 12 months post-infection, the values had not recovered to the values found in older adults without COVID-19. Thus, exercise interventions may be necessary to enhance cardiopulmonary function recovery for patients post-COVID-19. Future randomized controlled trials are needed to assess the effects of such rehabilitation interventions.