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Cardiopulmonary function alterations in mild and moderate SARS-CoV-2 patients: a longitudinal comparison of pre-infection and early recovery phases

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Abstract

The purpose of this study is to compare and analyze the changes of CPET and pulmonary function indexes in patients with mild and moderate SARS-CoV-2 before infection and in the early recovery period, and to explore the influence of SARS-CoV-2 on cardiopulmonary fitness and its pathogenesis. Clinical data of 39 cases are collected, and paired analyses of CPET and pulmonary ventilation parameters before and after infection are performed using software SPSS. Bivariate correlations are analyzed for days post-infection, VO_{2peak} decline rate, VO_{2peak}/kg after infection, AHRR decline rate, and residual symptom count. The results show that VO_{2peak}, VO_{2peak}/kg, and AT significantly decreased after infection. The VE/VCO_2 slope increased, while $PetCO_2$, VE_{peak}, and VE/VCO_2 minimum showed reductions. FVC, FEV1, and FEV1/FVC remained unchanged. OUES significantly declined, along with AHRR and HR_{peak}, although no significant differences are observed in HR_{rest}, HRR-1 min, and HRR-2 min. The number of residual symptoms is significantly correlated with VO_{2peak}/kg and its decline rate, but not with infection duration. Additionally, the decline rate of VO_{2peak}/kg is strongly associated with post-infection time and post-infection VO_{2peak}/kg. VO_2/HR and power also decreased significantly. Moreover, after SARS-CoV-2 infection, cardiopulmonary function, including cardiac chronotropic and muscle function, is significantly impaired in mild and moderate patients. Residual symptoms are closely linked to cardiopulmonary function. Given the large proportion of mild and moderate cases, these findings offer valuable insights for developing targeted interventions to prevent further symptom progression and improve cardiopulmonary health in this population.

Keywords Cardiopulmonary fitness, Mild and moderate SARS-CoV-2, Early recovery phase

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Introduction

The novel coronavirus pneumonia is an infectious disease caused by SARS-CoV-2 infection, which has the characteristics of rapid spread and strong infectivity [1]. Since 2020, the coronavirus disease 2019 (COVID-19) has spread worldwide, causing a global pandemic and millions of deaths [2]. Mild and moderate SARS-CoV-2 infection patients may be asymptomatic or only show fever, cough, etc., while severe cases may occur acute respiratory distress syndrome, multiple organ dysfunction and even death [3]. After recovery from acute infection period of SARS-CoV-2, there are still lingering symptoms. Studies have shown that 87.4% of those who have recovered have at least one symptom that persists, particularly fatigue and dyspnea [4, 5]. Symptoms that appear even 3 months after infection in some patients, persist for at least 2 months, and cannot be explained by other diagnoses [6]. These symptoms may be new after recovery from an acute infection, or they may have been present since the beginning of the disease and may relapse. Long-term symptoms of COVID-19 can involve multiple respiratory, cardiovascular, neurological, blood, urinary, and exercise systems, including dyspnea, fatigue, anxiety, joint pain, cardiovascular related diseases, and kidney tissue damage. These symptoms appear not only in severe patients, but also in mild and moderate patients.

A large number of studies have shown that some patients with mild to moderate SARS-CoV-2 infection still have some residual symptoms during recovery, mainly manifested as reduced exercise ability, fatigue and chest tightness. Most of these symptoms are associated with decreased cardiorespiratory fitness.

Cardiorespiratory fitness (CRF) is a comprehensive measure of the body's physiological ability to absorb oxygen from the environment, transport oxygen to working tissues, and use oxygen to support vigorous activity [7]. CRF or exercise ability directly reflects the overall function of multiple organs. Therefore, it is an important indicator to measure the overall health and the body's response ability to internal and external stressors, and reflects the health status and prognosis of patients. For the same type of patients, higher CRF has a better prognosis [7]. The American Heart Association published a scientific statement in 2016 advocating for the use of CRF as a clinical vital sign [7]. Some data show that high CRF has a certain protective effect against the serious consequences of SARS-CoV-2 infection.

Maximum VO_2 is not only the gold standard for CRF and aerobic capacity, but also a strong predictor of all-cause and case-specific mortality and morbidity [8]. The study showed that as the peak metabolic equivalent increased, the predicted probability of hospitalization declined steadily, with its lowest point approaching 13METs. For every MET increase in exercise capacity, the chance of hospitalization decreased by 13% [9].

Infected people continue to have multiple symptoms long after recovery, which can eventually lead to exercise intolerance and decreased CRF. The American Heart Association states that the gold standard for direct assessment of CRF is Cardiopulmonary Exercise Testing (CPET). In addition to being the gold standard method for assessing CRF, CPET has many clinical uses and will be a key tool for detecting and understanding the pathophysiology of the lasting effects of Pneumonia [10].

The cause of CRF decline caused by SARS-CoV-2 infection is not clear, and most scholars believe that the impaired motor ability is multi-factorial. SARS-CoV-2 infection is an inflammatory state associated with the release of pro-inflammatory cytokines, and while beneficial, prolonged sustained cytokine production and excess inflammatory mediators, known as"cytokine storms,"can lead to additional damage to vital organs. Persistent mild inflammation after infection may also lead to systemic disease [11, 12]. Viral infections lead directly to basic dysfunction at the cellular and tissue levels. Animal models [13, 14] suggest that inflammatory markers, including IL-6 and TNF, impair chronotropic and endothelial function.

Decreased beta-receptor reactivity is a prominent feature of chronotropic dysfunction, which increases adrenergic activation and thus activates inflammatory pathways[15–17]. Chronic inflammation and adrenergic activation can blunt chronotropic, vascular function, and motor capacity without pathological changes of autonomic nervous system or sinus node [18]. Studies have shown that athletes with persistent symptoms, including exercise intolerance and fatigue, experienced a longitudinal decrease in peak heart rate at 3 months [19].

Therefore, it is necessary to understand the changes of static lung function and cardiopulmonary exercise function in mild patients at the early stage of rehabilitation.

Object and Method

Object

A total of 44 cases of mild patients with SARS-CoV-2 infection who underwent CPET and pulmonary ventilation function testing in the Cardiopulmonary Function Department of Henan Provincial People's Hospital within 1 to 3 months after infection from December 2022 to May 2024 are included, and all of them had undergone CPET and pulmonary ventilation function testing in the department within 1 year before infection. The exclusion criteria are as follows:

1) Combined with chronic diseases affecting cardiopulmonary function, such as heart failure, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary interstitial fibrosis, muscular disease, etc.
2) There are significant changes in lifestyle between the two tests, such as the amount of exercise and weight loss.
3) Under 18 years of age.

Method

Cardiopulmonary exercise test system

QuarkPFT Ergo Omnia 1.6.8 cardiopulmonary exercise test system from COSMED S.R.L is used for the test. Before the test, gas capacity calibration, high, medium and low three-flow rate calibration, air calibration, O_2 and CO_2 two-point system calibration and metabolic simulator calibration are carried out, which are all used for clinical testing [20]. The subjects first complete the static pulmonary ventilation function examination in the seated position, and then the appropriate incremental power is selected according to age, gender, height, weight and estimated functional status to perform the ramp power incremental exercise test, so that the subjects could reach the limit state within 6–12 min, or the modified Bruce exercise regimen is applied with the activity plate [21]. For each patient, the identical exercise protocol with the same intensity increments and duration is strictly followed in both pre-infection and post-infection tests. In addition, the termination criteria standardization is ensured, as shown in Sect."Physiological criteria for determining maximal exercise effort in patients". During the test, subjects'electrocardiograph (ECG), blood pressure, oxygen saturation, gas exchange and symptoms are closely monitored.

According to the 2003 ATS/ACCP Cardiopulmonary Exercise Test Guidelines, the test should be terminated when any of the following conditions occurred [22]:

(1) Chest pain suggests myocardial ischemia;
(2) ECG indicates myocardial ischemia;
(3) Second to third-degree atrioventricular block;
(4) Systolic blood pressure decreases by more than 20 mmHg (1 mmHg = 0.133 kPa);
(5) Hypertension: Systolic blood pressure > 250 mmHg, Diastolic blood pressure > 120 mmHg;
(6) Severe decrease in oxygen saturation: $SpO_2 \leq 80\%$, accompanied by symptoms and signs of severe hypoxemia;
(7) Sudden pallor, limb incoordination, confusion, dizziness, and signs of respiratory failure.

Physiological criteria for determining maximal exercise effort in patients

Meet one or more of the following conditions:

(1) The oxygen uptake at peak exercise (VO_{2peak}) reaches the expected value and/or the platform is observed;
(2) The predicted maximum power is reached;
(3) The predicted maximum heart rate is reached;
(4) There is evidence of ventilation restriction, that is, peak exercise ventilation at or above the maximum voluntary ventilation;
(5) While there is no respiratory exchange rate (RER) value that defines maximum effort, a value greater than 1.15 is more likely to be associated with near maximum or maximum effort;
(6) The Borg score of the exhausted patient is 9–10 on a scale of 0–10;

All 39 patients achieve the best effort standard.

Main monitoring indexes

Main indexes of CPET: VO_{2peak}, VO_{2peak}/kg, anaerobic threshold (AT), a minute ventilation/a minute carbon dioxide production slope (VE/VCO_2 Slope), $\Delta VO_2/\Delta WR$, maximum oxygen pulse (VO_{2peak}/HR), Oxygen-uptake efficiency slope (OUES), Partial pressure of end-tidal carbon dioxide ($PetCO_2$), lowest ventilatory equivalent for carbon dioxide ($VE/VCO_{2\ lowest}$), lowest ventilatory equivalent for oxygen ($VE/VO_{2\ lowest}$), Peak heart rate (HR_{peak}), rest heart rate (HR_{rest}), recovery period 1-min heart rate (HRR-1 min), maximal exercise ventilation (VE_{peak}), and peak respiratory rate (RF_{peak}).

Main indexes of static lung ventilation function: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC).

Other indexes: Number of residual symptoms, adjusted HR reserve (AHRR $[HR_{peak} - HR_{rest}]/[220 - age - HR_{rest}]$), VO_{2peak}/kg decline rate, change rate after AHRR infection compared with before infection, infection days.

The units and explanations of all indexes are shown in Table 1.

Statistical analysis

SPSS 21.0 statistical software is used to analyze the experimental data. The measurement data of normal distribution is presented as mean ± standard deviation ($\overline{x} \pm s$), the measurement data of non-normal distribution is presented as median (interquartile) [M (Q25-Q75)], and the count data is presented as percentage or component ratio (%). The main parameters of CPET and the main parameters of static lung function of the test data are tested for normality. The parameters with normal distribution are compared before and after infection using paired t-test, while those without normal distribution are tested by rank-sum test. $P < 0.05$ is considered statistically significant. Bivariate correlation analysis is performed on the number of lingering symptoms, AHRR, VO_{2peak}/kg decline rate, AHRR decline rate, and infection days.

Table 1 The units and explanations of indexes

Indexes	Unit	Explanation
VO_{2peak}	ml/min	Maximum oxygen uptake measured during exercise, reflecting overall cardiopulmonary capacity
VO_{2peak}/kg	ml/(kg·min)	Oxygen consumption per kilogram of body weight; a key measure of aerobic fitness and cardiopulmonary function
VO_2@AT	ml/min	Oxygen uptake at the anaerobic threshold (AT), where anaerobic metabolism supplements energy production, marked by increased lactate and L/P ratio in blood and muscle
VE/VCO_2 Slope	–	Slope of minute ventilation to CO_2 output from exercise onset to AT or RC point; reflects ventilator—perfusion efficiency
$\Delta VO_2/\Delta WR$	ml/(min·W)	Represents the efficiency of aerobic work, expressed as the increase in oxygen uptake (VO_2) relative to the increase in workload (WR). It quantifies the amount of oxygen consumed per unit of work performed. The normal range is (10.2 ± 1.0) ml/(min ·W)
VO_{2peak}/HR	ml/beat	Known as oxygen pulse, this parameter is calculated by dividing peak oxygen uptake (VO_{2peak}) by the heart rate (HR) measured at the same time point. It reflects the amount of oxygen delivered per heartbeat, influenced by peripheral oxygen extraction and cardiac stroke volume. It is a recognized indicator of cardiovascular efficiency
OUES	–	A submaximal parameter reflecting the efficiency of oxygen uptake relative to ventilation. OUES (Oxygen Uptake Efficiency Slope) is calculated by the logarithmic relationship between oxygen consumption (VO_2) and minute ventilation (VE) during incremental exercise. It is commonly used to evaluate cardiorespiratory fitness and endurance performance, particularly in patients with cardiovascular or pulmonary conditions
$PetCO_2$	mmHg	End-tidal CO_2 pressure; reflects alveolar ventilation and ventilation-perfusion matching
VE/$VCO_{2\ lowest}$	–	Minimum ventilation required to eliminate 1L of CO_2 during exercise; indicates ventilatory efficiency
VE/$VO_{2\ lowest}$	–	Minimum ventilation required to consume 1L of O_2 during exercise; indicates ventilatory demand per oxygen unit
HR_{peak}	bpm	Peak heart rate recorded during exercise testing
HR_{rest}	bpm	Resting heart rate measured before exercise
HRR-1 min	bpm	Heart rate recovery at 1 min post-exercise; calculated as the difference between HR_{peak} and HR at 1 min of recovery
VE_{peak}	L/min	Peak minute ventilation achieved during maximal exercise
RF_{peak}	breaths/min	Peak respiratory frequency during exercise
FVC	L	Forced vital capacity; the maximal volume of air forcibly exhaled after full inhalation
FEV1	L	Forced expiratory volume in the first second; the volume of air exhaled during the first second of forced expiration
FEV1/FVC	%	Ratio of FEV_1 to FVC; used to assess airway obstruction, typically ≥ 70–80% in healthy individuals
AHRR	%	Adjusted heart rate reserve = $(HR_{peak} - HR_{rest})/(220 - age - HR_{rest})$; reflects cardiovascular responsiveness

Results

General clinical data

A total of 44 patients are collected, including one juvenile and three patients who participated in exercise rehabilitation treatment between two tests. One patient is terminated due to spasm of the right lower extremity and RER less than 1.05. Finally, 39 patients are enrolled. There are 21 males (53.8%) and 18 females (46.2%), with an average age of 44.9 ± 2.5 (18–76) years. The average Body Mass Index (BMI) is 23.50 ± 0.46, 16.69–29.71 kg/m^2.

Comparison of CPET indexes before and after infection

Figure 1 shows the comparison of CPET indexes before and after infection. VO_{2peak}, VO_{2peak}/kg, AT, $\Delta VO_2/\Delta WR$, VO_{2peak}/HR, OUES, power, AHRR are significantly higher before infection than after infection. VE/$VCO_{2\ lowest}$ and VE/VCO_2 Slope are significantly higher after infection than before infection. $PetCO_2$ and VE_{peak} are significantly lower after infection than before infection. Peak HR is significantly lower after infection than

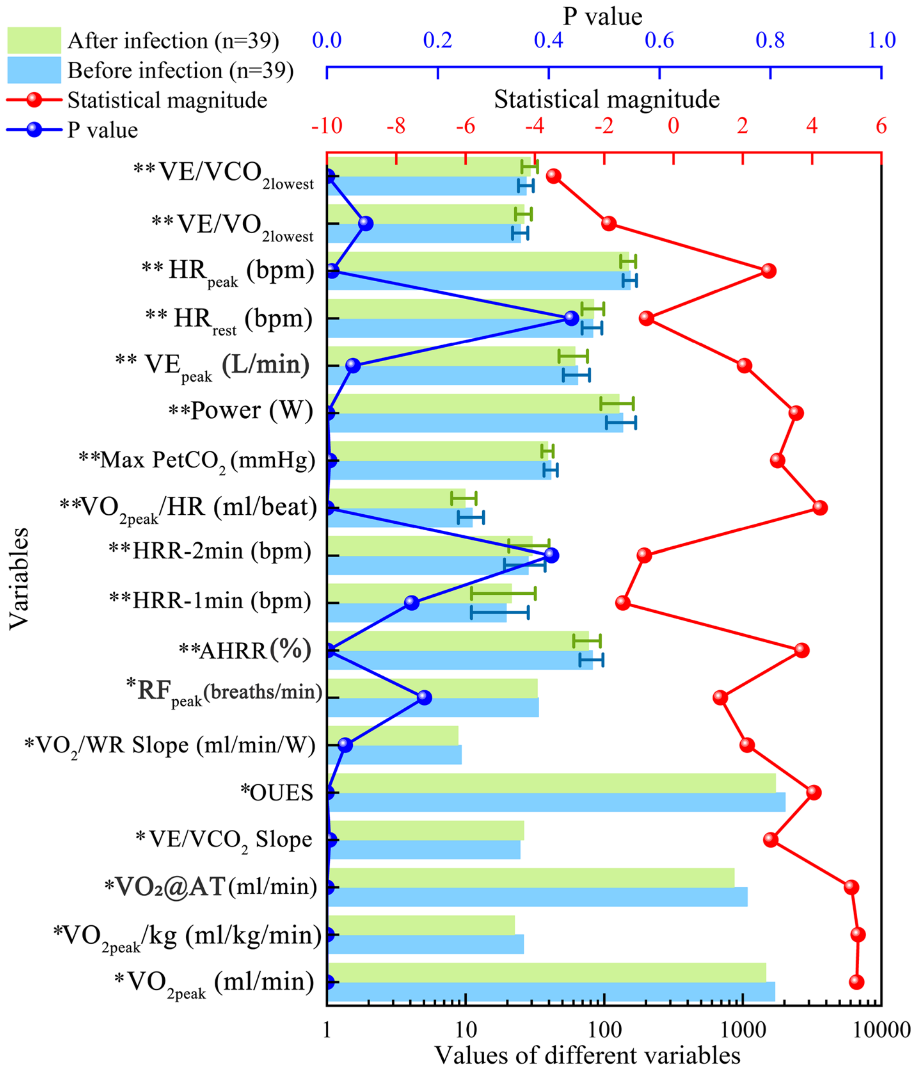

Fig. 1 Comparison of CPET parameters before and after infection, where ** represents normal test and * represents rank sum test

before infection. There is no statistical difference in other CPET indexes before and after infection. Detailed data can be found in Table S1 in the supplementary materials. Coincidentally, the Sliz D team study showed [23] that mild SARS-CoV-2 infection in 49 elite athletes also led to a decrease in VO_{2peak}. Some scholars have found through repeated CPET testing [8] that even patients with mild to moderate SARS-CoV-2 infection will cause long-term VO_{2peak} reduction. Other studies have shown that although there are no major symptoms of dyspnea and 6-MWT is within the normal range, CPET is impaired in 35% of patients and VO_{2peak} is lower than 80% [24].

SARS-CoV-2 impaired mitochondrial function and oxygen metabolism homeostasis [25], resulting in decreased skeletal muscle function. Endothelial injury caused by the virus, which is related to the pro-coagulant state and subsequent microthrombosis, leads to multiple organ dysfunction and muscle injury, and endothelial dysfunction is a common pathogenic factor for most clinical symptoms [26]. The impaired metabolic function of skeletal muscle and the blood perfusion capacity of lung and muscle can lead to the decrease of OUES [27], and this study also showed that OUES decreased after infection compared with that before infection.

Comparison of main indexes of static pulmonary ventilation function before and after infection

It can be seen from Fig. 2 that the major parameters of static lung ventilation function, FVC, FEV1 and FEV1/FVC, showed no statistical difference before and after infection. Detailed data can be found in Table S2 in the supplementary materials.

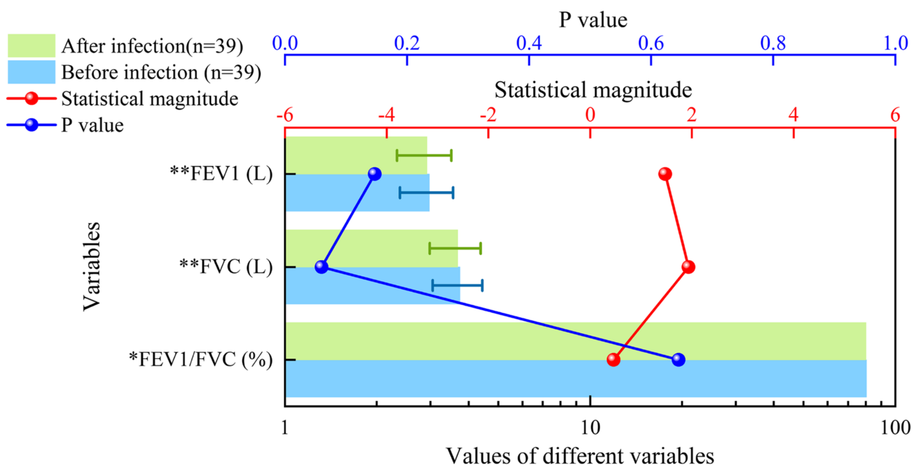

Fig. 2 Static pulmonary ventilation function did not conform to the normal distribution of measurement indexes before and after infection

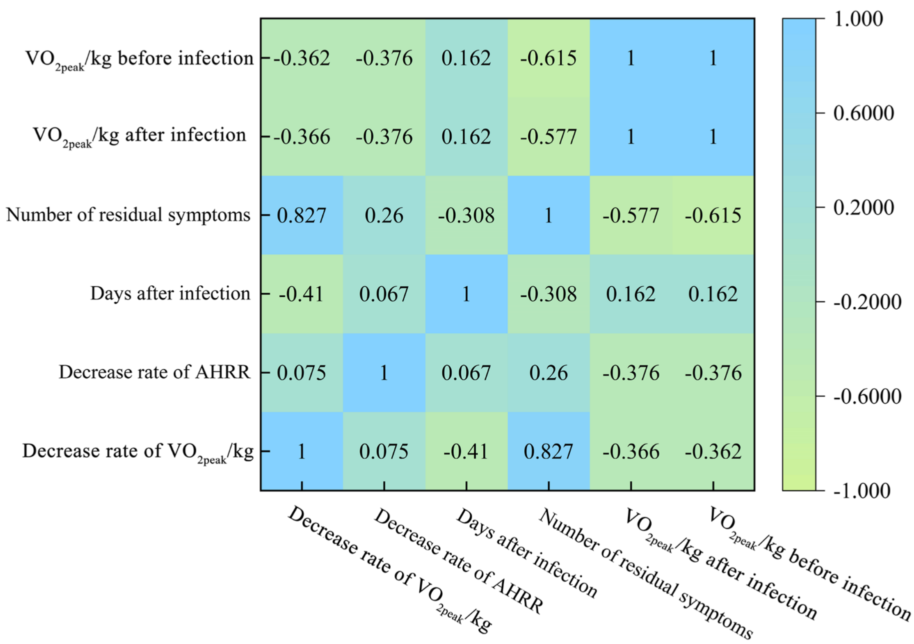

Fig. 3 Bivariate correlation analysis of other indexes

Other indexes

The number of residual symptoms is 2.28 ±2.05, the decrease rate of AHRR is 6.16(0.84–12.76), the decrease rate of VO_{2peak}/kg is 11.52 ±9.37, and the infection days are 45(26–58). The number of residual symptoms is correlated with the decline rate of VO_{2peak}/kg and VO_{2peak}/kg before and after infection, and the decline rate of AHRR is correlated with VO_{2peak}/kg before and after infection. As shown in Fig. 3, the decrease rate of VO_{2peak}/kg is correlated with the number of days after infection, the number of residual symptoms, and VO_{2peak}/kg before and after infection. Detailed data can be found in Table S3 in the supplementary materials.

Analysis of differences in sex variables

As shown in Fig. 4, there are no statistically significant differences in the number of residual symptoms, AHRR decline rate, VO_{2peak}/kg decline rate, VO_{2peak}/kg before and after infection between different genders. Detailed data can be found in Table S4 in the supplementary materials.

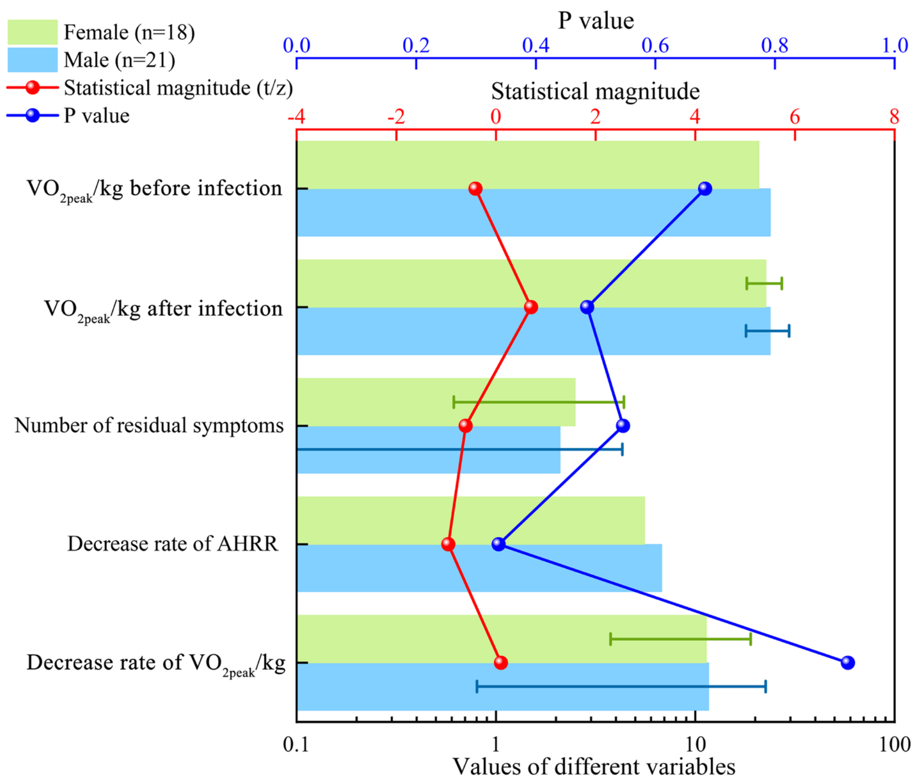

Fig. 4 Analysis of differences in sex variables

Indexes before and after infection in 3 cases of exercise rehabilitation

All the three cases are male, aged 41, 27 and 42, respectively. The relevant parameters before and after infection are displayed in Fig. 5. Detailed data can be found in Table S5 in the supplementary materials. Bruno Ribeiro Baptista, et al. [24] also found that the VE/VCO$_2$ slope is significantly increased in SARS-CoV-2 patients compared with healthy subjects. Some scholars believe that hyperventilation is a possible explanation for long-term exercise intolerance in patients with mild SARS-CoV-2 infection [28]. However, elevated VE/VCO$_2$ slope and hyperventilation cannot be considered as pathological changes in convalescent patients. Our study showed a significant increase in VE/VCO$_2$ slope compared to pre-infection, but no increase in VE$_{peak}$. Compared with before infection, VE/VCO$_2$ Slope decreases significantly in 3 cases, and VE$_{peak}$ decreases in 2 cases. In one case, although VE$_{peak}$ increased by 5.3%, VO$_{2peak}$ increased by 15.2%, and the improvement rate of VO$_{2peak}$/kg is even as high as 31.4%, which increased from 84% of the expected value before infection to 107%. Therefore, the increase in VE$_{peak}$ is due to the significant increase in CRF compared with that before infection and the full utilization of respiratory reserve, rather than pathological changes. This indicates that regular endurance training can improve exercise ventilation efficiency by reducing the sensitivity of peripheral chemoreceptors [29].

Conclusion

In this paper, the changes of CPET and static pulmonary function indexes in patients with mild and moderate SARS-CoV-2 infection before infection and early recovery are analyzed, and the influence of SARS-CoV-2 on cardiopulmonary fitness and its pathogenesis are discussed. The results show that VO$_{2peak}$, VO$_{2peak}$/kg and AT of mild SARS-CoV-2 infection patients in the early recovery period (within 2 months after infection) are significantly decreased after infection. In addition, VO$_{2peak}$/HR and HR$_{peak}$, which reflect cardiac function, are decreased after infection with statistical significance ($P < 0.05$), while HR$_{rest}$, HRR-1 min and HRR-2 min show no statistical difference before and after infection, but AHRR is significantly decreased after infection compared with that before infection, indicating a decline in cardiac function. The decrease of VO$_{2peak}$/HR and HR$_{peak}$ may be related to the heart disease caused by infection, or other system diseases caused by infection may make the heart function of patients not fully mobilized, rather than the heart function is damaged. Moreover, after infection, VE/

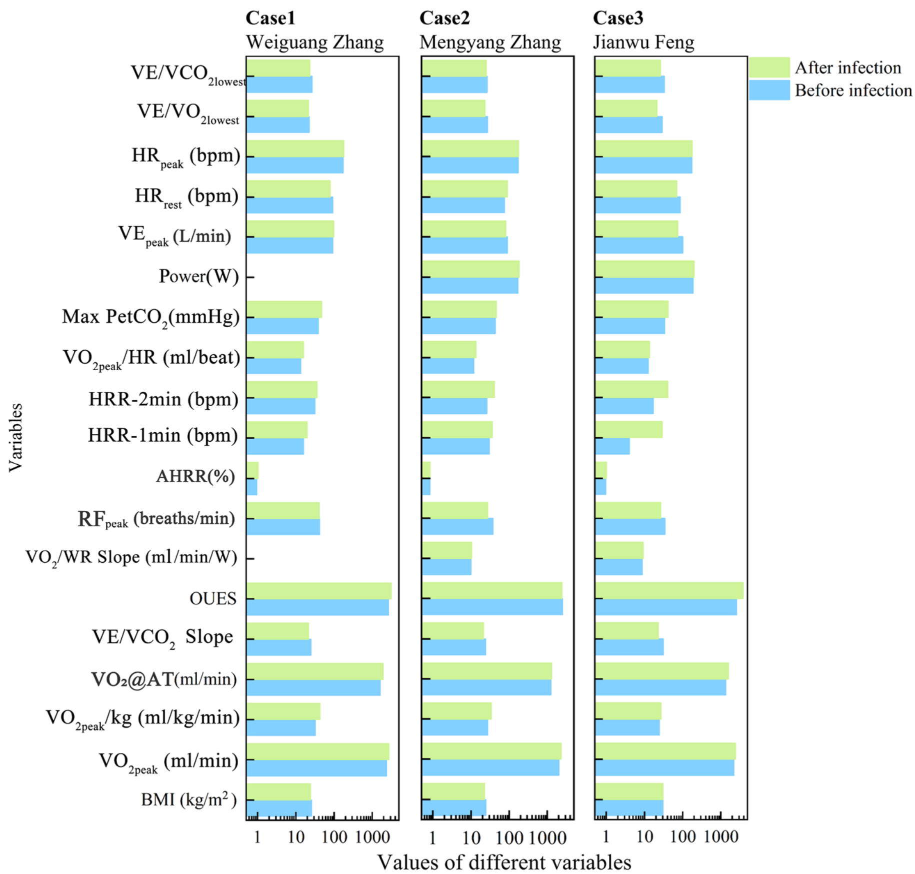

Fig. 5 Indexes before and after infection in 3 cases of exercise rehabilitation

VCO_2 slope and VE/VCO_2 minimum values significantly increase, PetCO2 and VE_{peak} decrease, but there is no significant difference in resting FVC, FEV1 and FEV1/FVC. It is suggested that SARS-CoV-2 has no obvious damage to resting ventilation function in patients with mild and moderate infection, but there may be hyperventilation or ventilatory dysfunction in patients under stress. We also found that the number of residual symptoms after infection is correlated with the decline rate of VO_{2peak}/kg and VO_{2peak}/kg before and after infection, and the decline rate of AHRR is correlated with VO_{2peak}/kg before and after infection. The decrease rate of VO_{2peak}/kg is correlated with the number of days after infection, the number of residual symptoms, and the VO_{2peak}/kg before and after infection. The CRF of 3 patients participating in exercise rehabilitation has improved, indicating that scientific exercise and higher CRF have a certain protective effect on SARS-CoV-2 infection. In the current era of SARS-CoV-2 virus and human coexistence, people should be encouraged to scientific fitness to enhance people's defense ability against the virus and reduce the damage to human beings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02777-9.

Additional file1

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Declaration Ethics approval and consent to participate This manuscript represents core research and has not yet been published or submitted anywhere. All the data sources were cited properly. The Ethics Committee of Henan Provincial People's Hospital approved this research study (2021 Ethical Approval No. 21). The authors declare to obey all the academic ethical standards. Consent for publication The authors declare that the contents of this article has not been published previously. All the authors have contributed to the work described, read and approved the contents for publication in this journal. All the authors have no conflict of interest with the funding entity and any organization mentioned in this article in the past three years that may have influenced the conduct of this research and the findings. Availability of data and materials The datasets and materials used in the current study are available from the corresponding authors upon request. Competing interests All authors disclosed no relevant relationships. This work was supported by the Zhengzhou Collaborative Innovation Major Project (Zhengzhou University, 518-23240003/518-23240004). Authors'contributions Yijing Feng: Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing-original draft Jinyi Xu: Data curation, Formal analysis, Funding acquisition, Investigation, Resources, Software, Supervision, Validation, Visualization, Writing-original draft Xianglin Lian: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Validation, Writing-review & editing Xiaoju Zhang:

Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Writing-review & editing Informed Consent All the authors who made contributions to this paper are included and aware of the content of this paper.

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Yijing Feng: Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing-original draft Jinyi Xu: Data curation, Formal analysis, Funding acquisition, Investigation, Resources, Software, Supervision, Validation, Visualization, Writing-original draft Xianglin Lian: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Validation, Writing-review & editing Xiaoju Zhang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Writing-review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the medical ethics committee of Henan Provincial People's Hospital approved, with written informed consent obtained from all participants. The Ethics Committee of Henan Provincial People's Hospital approved this research study (2021 Ethical Approval No. 21).

Consent for publication
The authors declare that the contents of this article has not been published previously. All the authors have contributed to the work described, read and approved the contents for publication in this journal. All the authors have no conflict of interest with the funding entity and any organization mentioned in this article in the past three years that may have influenced the conduct of this research and the findings.

Competing interests
The authors declare no competing interests.

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