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The interaction effect of COVID-19 infection and hypoxia at high altitudes on the physiological functions of multiple systems- A cross-sectional study based on people at high altitudes

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Research Article

Keywords: Plateau hypoxia, COVID-19, CPET, interaction effect

Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10902992/v1

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Additional Declarations: No competing interests reported.

Abstract

Backgroud:

Both the low-oxygen environment at high altitudes and COVID-19 infection can independently cause cardiopulmonary dysfunction. There are multiple intersections at the pathophysiological level between the two, but their synergistic effects and long-term impacts remain unclear.

Methods

This study adopted a cross-sectional design and included 290 Han residents from Lhasa City, who were divided into a COVID-19 recovery group (COVID-19) and an uninfected control group(N-COVID).Demographic characteristics and psychological behavior data were collected through standardized questionnaires. CPET, muscle strength and balance tests were used to assess cardiopulmonary and muscle neuropsychological functions between the two groups. The aim was to reveal the functional recovery characteristics and potential mechanisms of COVID-19 recovered patients in high-altitude hypoxic environments.

Result

VO_2peak/kg,VE/VCO_2,VE/VCO_2slope and RER in COVID-19 were significantly increased ($P < 0.05$); The grip strength, balance ability, SDS, SAS and FACIT-F fatigue scores of the subjects with N-COVID were significantly higher than those with COVID-19 ($P < 0.05$). Regression analysis after adjusting for confounding factors showed that: COVID-19 infection and VO_2peak/kg [B(95%CI): 1.796 (0.292–3.301)], VE/VCO_2slope[B(95%CI): 1.886(0.207–3.565)], RER[B (95%CI): 0.035 (0.017–0.052)], balance left/right [B(95%CI):14.869(19.807–9.932)/14.959(9-10.149-19.76)] have an independent correlation effect ($P < 0.05$), The cumulative length of residence on the plateau (every 10 years) has an impact on VD/VT[B(95%CI): 0.006 (0.002–0.01)], SAS [B (95%CI) : 1.827 (0.949–2.705)], SDS[B (95%CI):1.353 (0.457–2.249)] and FACIT-F [B (95%CI):0.935(0.046–1.824)] had an independent correlation effect ($P < 0.05$). Both COVID-19 infection and the cumulative length of residence at high altitudes (per 10 years) were negatively correlated with grip strength ($P < 0.05$), and the effect size of COVID-19 infection was approximately 2.46 times that of the cumulative length of residence at high altitudes (per 10 years). There was no interaction effect between the cumulative length of residence in the plateau (every 10 years) and COVID-19 ($P > 0.05$).

Conclusions

During the long-term recovery from COVID-19 at high altitude, the reduction of VE/VCO_2 slope persists, and its sensitivity to recognizing cardiopulmonary dysfunction is superior to that of VO_2peak. Meanwhile,

the hypoxic environment at high altitude has a significant independent impact on VD/VT. The resulting pattern of functional dimension separation constitutes the specific pathophysiological phenotype of recovered COVID-19 patients at high altitude.

Trial registration:

All subjects signed the informed consent form at the time of inclusion. This study was approved by the Medical Ethics Committee, with the approval number 2021(53).

Background

Coronavirus Disease 2019 (COVID-19) is a systemic multi-system disease with the lungs as the main target organ[1], and its pathological damage may last for months or even years[2, 3]. Studies show that approximately 70% of COVID-19 patients still experience symptoms such as fatigue and muscle weakness half a year after recovery[4]. Cardiopulmonary exercise tests indicate a decline in exercise endurance and lung function. Severe cases can lead to acquired neuromuscular disease, resulting in a significant decline in limb muscle function[5]. Additionally, more than 20% of those who have recovered report anxiety and depression. And the incidence rate is positively correlated with the severity of the acute phase[4]. Meanwhile, the hypoxic environment at high altitudes can independently induce pathological changes such as cardiopulmonary dysfunction, ventilation-perfusion mismatch, mitochondrial oxygen utilization disorder, and autonomic nerve dysfunction, affecting multiple systems including cardiopulmonary, skeletal muscle, and neuro-psychiatric systems[6–9]. Given that both of the above two exposures can independently cause multi-system damage, this study hypothesized that the low-oxygen environment at high altitude might reshape the pathophysiological recovery trajectory of COVID-19 recoveries. There may be interactions between the two in terms of cardiopulmonary function, muscle endurance and psychological behavior, and they may also show relatively independent separation effects. Based on this, this study aims to systematically explore the multi-system functional change characteristics of COVID-19 recoveries in a hypoxic environment at high altitudes and reveal their potential pathophysiological association mechanisms.

Methods

Participants

This study adopted a cross-sectional design and recruited 290 non-disease-stricken Han subjects who had resided in the Lhasa area from Dec. 6.2022 to Nov.26.2024. The inclusion criteria were as follows Aged 18 to 65 years, Han and/or those who had lived in Lhasa for more than 3 months and/or had turned negative for COVID-19, basically normal physical examination, Signed the informed consent form. Exclusion criteria There are other neurological, muscular, skeletal or rheumatic diseases that may be aggravated by exercise, Major surgery (excluding body surface surgery) has been performed within half

a year, ▯ Those with breathing difficulties, pain, limb dysfunction, etc., who are unable to complete the CPET test, ▯ Those with acute and chronic heart, lung, and skeletal system diseases such as diabetes, hypertension, coronary heart disease, Chronic Obstructive Pulmonary Disease(COPD), and variant cardiovascular diseases, ▯ Those with severe mental or psychological disorders, ▯ those who can not accept or have no time to cooperate with the test.

All the subjects were tested at the Lhasa Plateau Health Promotion Center of the Xizang Office in Chengdu. Including demographic information such as height, age, gender, weight and length of residence at high altitudes, and static physiological indicators [including Resting Heart Rate (HRrest), Systolic Blood Pressure (SDP), Diastolic blood pressure (Diastolic Blood Pressure (DBP), Oxygen Saturation (SpO_2), cardio-pulmonary exercise testing (CPET), muscle strength test and psychological behavior questionnaire survey.

After the test was completed, Peak Oxygen Uptake (VO_2peak), Anaerobicthreshold (AT), and Ventilatory Equivalent for carbon dioxide(VE/VCO_2,VE/VCO_2slope) were collected. Heart Rate Reserve (HRR), Heart Rate Recovery at 1 minute (HRR1), oxygen pulse, muscle strength, balance.And calculate the Functional Assessment of Chronic Illness Therapy- Fatigue Scale (FACIT-F), International Physical Activity Questionnaire-Long Form (IPAQ-LF), Self-Rating Anxiety Scale(SAS), Self-Rating Depression Scale (SDS), and Pittsburgh Sleep Quality Index (PSQI) were used to compare the differences in cardiopulmonary function, muscle strength, and psychological behavior between the two groups.

Measurement of CPET

CPET test: German Cotex Metalyzer 3B was used. The indoor temperature was maintained at 22–25℃ and the humidity at 45%-55%. Before each test, turbine and standard gas calibrations were carried out. All subjects underwent lung function tests first, including slow lung capacity and fast lung capacity. After the test is completed, take a 5-minute break, then put on the 12-lead electrocardiogram electrode and mask. Once the mask shows no air leakage and the electrocardiogram is normal, start the cardiopulmonary exercise test. The test adopts the power bicycle ramp protocol, which is divided into a 3-minute rest stage, a 3-minute no-power warm-up stage, and a 10W/min Ramp protocol from the 7th minute. In the final powerless recovery stage, the termination criteria for the exercise endurance test are: RER ≥ 1 or RPE ≥ 7, and blood pressure higher than 220/120mmhg.

Measurement of Muscle Strength and balance test

Muscle Strength and balance test: Grip strength(left/right,GSL/GSR) was tested using the Camry electronic grip strength meter (model EM101) for left and right grip strength. Each side was tested twice, recorded and the peakimum value was taken. The upper limb muscle strength is measured by push-ups (kneeling position for women), and the number of standard tests completed is recorded. The lower limb muscle strength is measured by doing a static squat against the wall, and the duration is recorded. Balance was performed using the left/right-Leg Stance Test With Eyes Open (LLS-EO/RLS-EO), and the duration on each side was recorded.

Statistical analysis

In this study, SPSS 26.0 was used for relevant data analysis. Quantitative data such as cardiopulmonary function and muscle strength were analyzed by t-test and expressed as M ± SD. Qualitative data such as questionnaires were analyzed using chi-square analysis. The effects of hypoxia at high altitudes and COVID-19 infection were analyzed using general linear regression. The correlation between pulmonary ventilation function and quantitative indicators such as muscle strength was analyzed using Pearson and partial correlation analysis. A $P < 0.05$ was considered significant. Some of the missing data in the study (with a peakimum accurate proportion of approximately 11%) were due to non-health-related external factors (such as business trips and time conflicts). To assess the potential impact of the missing data, 10 sets of imputed data were generated for analysis using the fully defined condition prediction mean matching PMM method for the original data. All regression analyses were conducted simultaneously in the interpolated data, and the interpolation was combined as a sensitivity analysis.

To explore the independent and interactive effects of cumulative length of residence at high altitudes and COVID-19 infection on multiple system physiological indicators, general regression analysis was first used to identify the affected indicators. Confounding factors were included for all indicators with baseline $P < 0.1$, including age, gender, BMI, cumulative length of residence at high altitudes, smoking history, drinking history, exercise habits, and group. Given that BMI is highly correlated with waist circumference (VIF > 5), to avoid multicollinearity, BMI was ultimately included as an indicator of body shape. Secondly, a multiple linear regression model was constructed by using an interactive analysis of the separation and interaction of the effects of high altitude and COVID-19 on differential outcome indicators. In the model, the outcome variables are each continuous physiological indicator, and the independent variables include the COVID-19 grouping, the duration of residence at high altitudes after centralization, and the interaction term of the product of the two. All models strictly follow the hierarchical principle, the interaction term and the two main effects that constitute the interaction term must be retained in the model simultaneously. Age, gender, BMI, smoking history, drinking history and exercise habits were forcibly included in the model as prior covariates without stepwise screening. Multicollinearity was evaluated by the variance inflation factor (VIF), and the VIF < 5, indicating that there was no significant collinearity problem in the model.

For each outcome indicator, the following linear regression model is constructed:

$$Y = beta_0 + beta_1.COVID + beta_2.Altitudecentered + beta_3.\ (COVID * Altitudecentered) + beta_4.Age + beta_5.Sex + beta_6.Smoking + beta_7.Alcohol + beta_8.Exercise + beta_{10}.BMI + \mathcal{E}$$

Results

Basic Characteristics and Exposure Distribution of the Subjects

There were no statistically significant differences in age, gender, height, weight, exercise habits, occupation, income and the duration of residence at high altitude between the COVID group and the N-COVID group ($P > 0.05$), while there were significant statistically significant differences in smoking history, drinking history and BMI ($P < 0.05$). 77.5% have been infected with COVID-19 for more than 6 months, 59.5% have experienced a decline in physical fitness, and 42.5% have asthma after activity (see Table 1).

Table 1 Demographic baseline characteristics and exposure distribution of recovered COVID-19 patients and non-infected populations

	n(COVID-19 /N-COVID)	COVID-19 (M±SD)	N-COVID (M±SD)	*P*
Sex(Male n,%)	89/201	51(57.30%)	125(62.19%)	0.432
Age(y)	80/198	37.94±8.82	38.62±9.13	0.569
Heighte(cm)	88/197	166.48±8.32	166.49±7.48	0.994
Weight(kg)	87/197	62.74±11.23	65.15±11.73	0.108
BMI	87/197	22.51±2.82	23.40±3.33	0.031
Occupation(n)	80/196			0.820
Heavy physical		2	3	
Light physical		27	63	
Sedentary		51	130	
Education(n)	79/196			0.209
Primary and below		0	4	
Junior high school		3	13	
High school		13	45	
Bachelor's and above		63	134	
Income(CNY)(n)	79/178			0.062
≤3000		6	3	
3000-6000		5	8	
6000-9000		16	29	
≥9000		52	138	
Family history (n)	79/195			0.821
Yes		25	59	
No		54	136	
Smoking (n)	78/195			0.019
Never smoker		64	127	
Former smoker		5	18	
Current smoker		9	50	
Alcohol(n)	78/196			0.000

Never drinker		51	65	
Former drinker		1	11	
Current drinker		26	120	
Physical activity (n)	79/196			0.082
Never exercises		9	16	
Occasional physical activity		54	114	
Regular exercise		16	66	
Waist circumference (cm)	87/197	80.51±10.05	83.10±11.11	0.063
Hip circumference (cm)	87/197	94.51±6.36	95.22±6.61	0.398
Duration of current high-altitude residence (months)	80/193	18.09±56.31	12.43±45.46	0.691
Cumulative high-altitude residence (per 10 years)	80/194	1.149±0.96	1.41±1.17	0.061
COVID-19 infection status (n,%)				
Infection duration > 6 months	80	66 (77.5%)		
Decreased physical activity	79	47 (59.5%)		
Post-exertional dyspnea	80	34 (42.5%)		

The multiple interpolation aggregated data are consistent with the original analysis in terms of statistical effect direction and significance.

Regression analysis of the independent association effect of COVID-19 infection and low-oxygen environment at high altitudes on multiple system physiological indicators

Baseline analysis of multi-system outcome indicators for subjects

There were no significant differences in VO_2peak, VO_2/HR, HRrest, SBP, HRR, upper limb, lower limb and core muscle endurance, IPAQ-LF, and PSCI between the COVID-19 infected and non-infected populations (P>0.05). There were significant differences in VO_2peak/kg, Mets, RER, SpO_2, FEV_1, FEV_1/FVC, VE/VCO_2, VE/VCO_2slope, VD/VT, HRR_1, grip strength, balance, DBP, FACIT-F, SDS, and SAS (P<0.05). Among them, the differences in FEV_1 and VD/VT were weak (P=0.048). In the COVID-19 recovery group, VO_2peak/kg, Mets, RER, SpO_2, FEV_1, FEV_1/FVC, VE/VCO_2, VE/VCO_2slope, and HRR_1 were higher than those in the non-infected group. FACIT-F, SDS and SAS were significantly lower than those in the non-infected population (see Table 2).

Table 2 Basic characteristics of outcome indicators in various systems for recovered COVID-19 patients and non-infected populations

	n(COVID-19 /N-COVID)	COVID-19 (M±SD)	N-COVID (M±SD)	*P*
FVC(ml)	84/182	4.51±1.194	4.48±1.018	0.814
FEV1(ml)	84/182	3.38±0.83	3.17±0.78	0.048
FEV1/FVC(%)	84/182	75.33±8.99	71.19±12.41	0.007
VE/VCO2	84/181	43.20±4.67	40.41±4.32	0.000
VE/VCO_2slope	84/179	42.72±6.01	40.45±5.53	0.003
Oues	84/179	1739.29±469.30	1798.32±529.84	0.383
ΔVO_2/ΔWR	84/179	11.86±1.22	11.70±1.74	0.445
VO_2/HR(ml)	84/181	10.65±2.34	8.3±11.07	0.476
VD/VT	84/181	0.07±0.04	0.08±0.03	0.048
VO_2peak(ml/mim)	84/181	1.59±0.39	1.51±0.48	0.167
VO_2peak/kg(ml/mim/kg)	84/181	25.73±5.85	23.64±7.02	0.018
Mets	84/181	7.70±1.67	7.01±1.99	0.006
AT	84/180	0.81±0.26	0.83±0.34	0.696
RER	84/181	1.07±0.06	1.04±0.06	0.000
VO_2/HR(ml)	84/181	10.65±2.34	8.3±11.07	0.476
SpO_2	87/197	92.93±2.82	91.67±3.60	0.004
GSL(kg)	87/194	29.36±11.91	32.75±10.25	0.016
GSR(kg)	87/194	31.07±13.03	35.09±10.80	0.007
Upper limb muscular endurance(reps)	87/194	13.62±11.46	13.37±12.27	0.87
Lower limb muscular endurance (s)	87/194	46.49±21.39	45.42±25.85	0.737
Trunk muscular endur ance (reps)	87/194	11.54±9.93	9.14±9.94	0.063
LLS-EO(s)	87/194	33.72±12.11	48.36±19.30	0.000
RLS-EO(s)	87/194	34.13±12.43	48.86±18.85	0.000
SBP(mmhg)	87/197	119.85±15.94	121.10±18.16	0.579

DBP(mmhg)	87/197	81.13±11.61	84.14±13.39	0.07
HRrest(beat/min)	87/197	75.51±12.40	75.32±9.98	0.893
HRR(beat)	84/181	8.3±11.07	9.03±10.57	0.604
HRR1(beat)	83/181	23.34±8.49	20.94±8.88	0.04
IPAQ-LF	74/182	2935.29±4705.15	3211.11±4261.46	0.649
PSCI	79/196	5.73±3.19	6.41±3.46	0.136
SDS	79/196	37.23±7.54	39.91±8.63	0.016
SAS	79/197	30.52±6.314	32.53±6.69	0.022
FACIT-F	78/197	30±6.98	31.77±6.38	0.045

In the multiple interpolation aggregated data, there was no statistical difference in **FEV1**(*P*=0.05)**,**VD/VT(*P*=0.05), and FACIT-F(*P*=0.065), while the others remained consistent with the original analysis in terms of the direction and significance of statistical effects.

Analysis of the Interaction Effects of COVID-19 Infection and Low-oxygen Environment at High Altitudes on Multiple Systems

After adjusting for confounding factors, COVID-19 had independent positive association effects on FEV_1, RER, VE/VCO_2slope, VE/VCO_2, VO_2peak/kg, Mets, grip strength left, and balance. The low-oxygen environment on the plateau has independent effects on VD/VT, FACIT-F, SAS and SDS. The combined effect of COVID-19 and the hypoxic environment at high altitudes on grip strength ($P<0.05$), with the effect size of COVID-19 being approximately 2.46 times that of the duration of residence at high altitudes. FEV_1/FVC, HRR1, and SpO_2 had no association effect with COVID-19 and high-altitude hypoxic environment ($P>0.05$)(see Table 3).

Table 3 Independent effect Analysis of COVID-19 and high-altitude hypoxic environment on outcome indicators of various systems

Characteristic	Variable	Cumulativehigh-altitude residence (per 10 years)		COVID-19 vs. N-COVID-19	
		Multivariable-adjusted B(95%CI)	*P*	Multivariable-adjusted B(95%CI)	*P*
Static pulmonary function	**FEV_1(ml)**	-0.027(-0.115-0.061)	0.548	0.190(0.011-0.368)	0.037
	FEV_1/FVC	-0.139(-1.803-1.524)	0.869	3.268(-0.115-6.651)	0.058
Exercise pulmonary function	**VE/VCO_2slope**	-0.363(-1.199-0.473)	0.393	1.886(0.207-3.565)	0.028
	VE/VCO_2	-0.609(-1.249-0.031)	0.062	2.357(1.073-3.641)	0.000
	VD/VT	0.006(0.002-0.01)	0.004	-0.008(-0.016-0.001)	0.052
Metabolic parameters	**VO_2peak/kg (ml/mim/kg)**	-0.544(-1.294-0.206)	0.154	1.796(0.292-3.301)	0.020
	Mets	-0.172(-0.393-0.049)	0.126	0.571(0.127-1.014)	0.012
	RER	-0.004(-0.013-0.005)	0.408	0.035(0.017-0.052)	0.000
	SpO_2	-0.089(-0.542-0.364)	0.699	0.763(-0.178-1.704)	0.134
	HRR1(beats)	-0.299(-1.718-1.121)	0.679	2.266(-0.591-5.123)	0.120
Muscle strength and balance ability	**GSL(kg)**	-1.018(-2.296-0.259)	0.118	-2.736(-5.354--0.118)	0.041
	GSR(kg)	-1.493(-2.870--0.116)	0.034	-3.673(-6.495--0.851	0.011
	LLS-EO(s)	-0.499(-2.909-1.91)	0.684	-14.869(-19.807--9.932)	0.000
	RLS-EO(s)	-1.507(-3.854-0.840)	0.207	-14.959(-19.769--10.149)	0.000
Psychological and behavioral factors	**FACIT-F**	0.935(0.046-1.824)	0.039	-1.075(-2.924-0.774)	0.253
	SDS	1.353(0.457-2.249)	0.003	-1.753(-3.617-0.111)	0.065

	SAS	1.827(0.949-2.705)	0.000	-1.365(-3.191-0.461)	0.142

The regression analysis of multiple imputed aggregated data show that low-oxygen environment on the plateau has independent effects on in **VE/VCO_2**(*P*=0.043) and COVID-19 had independent positive association effects on VD/VT(*P*=0.044),**FEV_1/FVC**(*P*=0.044),while the others remained consistent with the original analysis in terms of the direction and significance of statistical effects.

Analysis of RER and HRR Indicators in the Context of COVID-19 Infection and Low-oxygen Environment at High Altitudes

Compared with those who recovered from COVID-19, the frequency and proportion of RER < 1 in the non-infected population were 11(13.09%) VS 38(20.99%), respectively. The overall tendency of those who recovered from COVID-19 was to the right (see Figure 2), while there was no significant difference in HRR between the two groups (see Figures 3)

Analysis of the interaction effect between the cumulative duration of high altitude (every 10 years) and the effect of COVID-19 infection on multi-system outcomes

Interaction effect analysis shows that the cumulative duration of high altitude and the interaction term of COVID-19 infection have a significant impact on VD/VT:B(95%CI) -0.007(-0.015-0.001),*P*=0.067, and grip strength left: B(95%CI)1.800(-0.618-4.219), right grip strength B(95%CI) 2.095(-0.509-4.700). The outcome indicators of each system did not reach statistical differences (*P* > 0.05), and the interaction analysis of each system (see Figure 4).

Discussion

The phenomenon of functional dimension separation, time-variability and decoupling of peripheral gas exchange efficiency in recovered COVID-19 patients at high altitudes

This study observed that recovered COVID-19 patients showed elevated VE/VCO_2slope accompanied by a significant decrease in VD/VT. After adjusting for confounding factors, the statistics showed an independent effect specific to the indicators: COVID-19 still has a significant independent effect on VE/VCO_2slope, while the variation of VD/VT is mainly controlled by the cumulative length of residence at high altitude. The phenomenon of this functional dimension separation in the CPET test suggests that the decline in ventilation efficiency left after COVID-19 infection may more reflect the impairment of ventilation-metabolic coupling efficiency. Rather than structural changes in intrapulmonary gas distribution or dead space ventilation, it is consistent with previously reported patterns of post-infection respiratory dysfunction [10,11]. Fresard [10] found in long COVID patients that respiratory dysfunction can exist independently of traditional gas exchange abnormalities, presenting as irregular breathing patterns accompanied by normal VD/VT. The changes in VD/VT caused by chronic high-altitude exposure may result from hypoxic pulmonary vasoconstriction and adaptive remodeling of V/Q matching[12,13].

It is worth noting that although there was no significant difference in VO_2peak between the two groups, a significant separation of VE/VCO_2slope has occurred. This finding suggests that subclinical abnormalities may be detected in ventilation efficiency indicators before overall exercise endurance is impaired[14,15]. If only VO_2peak is relied upon to assess cardiopulmonary function, the existing ventilation regulation disorders in COVID-19 survivors may be underestimated. The insignificance of the interaction effect further suggests that hypoxia exposure at high altitudes does not significantly modify the degree of impact of COVID-19 infection on ventilation efficiency, that is, this injury does not intensify or alleviate with the extension of the length of residence at high altitudes.

In addition, in CPET, recovered COVID-19 patients showed an increased overall respiratory exchange rate (RER), while there was no significant difference in heart rate reserve (HRR) compared with non-infected individuals. This separation phenomenon is accompanied by an increase in VE/VCO_2slope, suggesting that hyperventilation may not be due to insufficient subjective effort. Adjusted regression analysis showed that elevated RER was significantly associated with COVID-19 infection, but not with the duration of exposure to hypoxia at high altitudes. This is consistent with reports that RER tends to stabilize after chronic hypoxia adaptation [20]. This phenomenon may be related to enhanced sensitivity of carotid body chemoreceptors [16] or excessive activation of peripheral muscle metabolic reflexes[17], reflecting that exercise-induced hyperventilation is widespread even in mild COVID-19 infections. This specific physiological drive triggered by COVID-19 It may be related to abnormal respiratory control [18] or excessive respiratory excitation reflex caused by metabolic and autonomic nerve dysfunction of peripheral skeletal muscle [19], but direct neurophysiological evidence is still needed for verification.

Effects of COVID-19 Infection and exposure to High-altitude Environments on Cardiopulmonary indicators and muscle strength

In the baseline comparison, the absolute values of FVC and FEV1 in the COVID-19 recovery group were both higher than those in the non-infection group, and the FEV1/FVC ratio also significantly increased. However, both groups were greater than 70%, which was within the normal range. However, after adjusting for confounding factors, the independent effect of COVID-19 infection on FEV1/FVC was no longer significant. The physiological mechanism was that FEV1 was strongly positively correlated with FVC, and both were positively correlated with weight and height, and negatively correlated with age [21]. It also indicates that the increase in FEV1 observed in the limit mainly exists along with the synchronous increase of FVC, which is essentially a volume-dependent phenomenon. When FEV1 is standardized by FVC, the differences between groups disappear. This result is consistent with reports that resting lung function can return to the normal range [22] after mild to moderate COVID-19 infection, and also with studies that peakimize the retention of lung function and diffusion capacity in young COVID-19 survivors[23], supporting the core inference of this study: The resting pulmonary function changes in mild COVID-19 survivors are mainly manifested as subtle changes in lung volume, rather than fixed airway obstruction (such as chronic obstructive pulmonary disease) or significant restrictive ventilation disorders.

However, normalization of resting lung function does not rule out ventilation abnormalities during dynamic movement. The CPET dynamic test in this study showed that the VE/VCO_2slope and VE/VCO_2 ratios of COVID-19 survivors were significantly increased, suggesting that the dynamic ventilation efficiency could still be impaired in the context of static pulmonary function normalization. This "resting-motor dissociation" phenomenon is consistent with the 34-month longitudinal follow-up direction of Dorelli [24] on COVID-19 survivors, indicating that low ventilation efficiency can persist as a long-term sequela of COVID-19.

At the metabolic and muscle strength levels, COVID-19 survivors present a phenotype of elevated VO_2peak/kg, Met and RER, accompanied by a significant decrease in grip strength. This high-power-high-cost mode may indicate a decline in the oxygen extraction efficiency of peripheral skeletal muscle, requiring the body to consume more oxygen and produce more CO_2 to maintain the same exercise output, rather than a true enhancement of the central cardiopulmonary pumping capacity [24,25]. Mayer[25] found that the activity of mitochondrial complexes and in skeletal muscle of severely recovered COVID-19 patients was decreased, providing cytological evidence for peripheral oxygen utilization disorders. The coexistence of decreased grip strength and increased ventilation efficiency in this study may jointly point to compensatory respiratory enhancement driven by impaired peripheral muscle function.

The cumulative duration at high altitudes was only correlated with the grip strength on the right side, while no significant association was observed on the left side. Given that the vast majority of the subjects are right-handed, the grip strength on the right side usually has a larger absolute value and a wider range of variation, and is more likely to achieve statistical significance under the same effect size. Therefore, this laterality result is more likely to reflect the difference in statistical power rather than the biologically specific damage to the right muscle group caused by high-altitude hypoxia. In light of the fact that COVID-19 has a significant impact on bilateral grip strength, it can be inferred that the damage to muscle strength caused by COVID-19 infection has a broader peripheral basis, while the independent effect of cumulative exposure to high altitudes on muscle strength may be relatively weak and unstable in clinical practice.

The Independent Driving Effect of Plateau environment exposure on Psychological Behavior

In the baseline comparison, the anxiety, depression and fatigue indices of the non-infection group were significantly higher than those of the COVID-19 recovery group. However, after adjusting for confounding factors, multivariate regression showed that COVID-19 infection had no significant independent effect on the above psychological indicators, while the cumulative duration of high altitude was significantly positively correlated with them. This result indicates that the psychological advantage observed in the COVID-19 recovery group at baseline mainly stems from the confounding factor that the non-infected group has a longer period of residence at high altitudes, rather than the non-infection itself having a protective effect on the psychological state.

It is worth noting that the psychological indicators showed a correlated directional reversal in both baseline and regression analyses. This phenomenon clearly indicates that cumulative hypoxia exposure is the dominant factor driving emotional disorders and fatigue among people at high altitudes, and its effect intensity is sufficient to cover and mask the potential impact of COVID-19 infection. After stripping away the influence of the duration at high altitudes, COVID-19 infection did not leave detectable independent psychological sequelae among people who have lived at high altitudes for a long time. This discovery supports the hypothesis that the cumulative damage to the central nervous system caused by chronic hypoxia takes precedence over the psychological impact of viral infections.

This study observed that the cumulative length of residence on the plateau was independently and positively correlated with the scores of anxiety, depression and fatigue. Meta-analysis shows that the prevalence of depressive symptoms among residents at high altitudes is as high as 17.9%. The prevalence of moderate to severe depression among people exposed to high altitudes for a long time can reach 38.9%[26], and 18.8% have anxiety symptoms [27]. The studies have confirmed that hypoxia at high altitude can trigger the HPA axis stress response by activating CRF/CRFR1 receptors, thereby inducing anxiety-like behavioral changes in a time-dependent manner,the cumulative dose-effect characteristics of this study show that the longer the residence at high altitudes, the higher the score[28,29].which is highly consistent with the above time-dependent mechanism model. This supports that the continuous impact of chronic hypoxia exposure on the neuroendocrine system is an important pathophysiological basis for emotional disorders in people who have lived at high altitudes for a long time.

The physiological mechanism of the missing interaction effect between COVID-19 infection and exposure to high-altitude environments

This study found no significant interaction between COVID-19 infection and exposure to high-altitude environments in the dimensions of static lung function, dynamic lung function, metabolic muscle strength, and psychological behavior, suggesting that the two may exert their effects through relatively independent and non-interacting physiological pathways.

At the pulmonary function level, hypoxia at high altitudes may act on the gas exchange interface through local vascular reactions such as hypoxic pulmonary vasoconstriction[12,13], while COVID-19 infection may act on neuroregulatory pathways through carotid body sensitization and abnormal respiratory center drive[16]. At the skeletal muscle and metabolic levels, direct viral invasion or persistent inflammatory damage leads to an increase in mitochondrial SIL2R, resulting in a decrease in mitochondrial complex III protein levels [25] and mitochondrial respiratory function [30]. This kind of damage can occur without muscle damage [31]. Chronic hypoxia enhances the interaction between E3 van der ligase Mdm2 and Sirt1, triggering Sirt1 degradation and leading to mitochondrial dysfunction and skeletal muscle atrophy [32]. In terms of psychological indicators, mental health problems of people who have lived in high-altitude areas for a long time are mainly attributed to chronic hypoxia exposure itself, which may be related to the continuous activation of the CRF system[28]. However, a history of mild COVID-19 infection

in this group did not leave any detectable independent or superimposed psychological sequelae.At the pathophysiological level, the core pathway of COVID-19 is that the virus directly invades cells through the ACE2 receptor, triggering endodermatitis, microthrombi and cytokine storm [33]. The core pathway of the plateau is hypoxia-activated hypoxia-inducible factor HIF-1 signaling activation[34]. The activation of HIF-1α may inhibit the expression of ACE2, a key receptor for the invasion of COVID-19 [35].

Based on multi-level evidence, COVID-19 infection and exposure to hypoxia at high altitudes may affect the body through parallel and independent pathways, and no synergistic effect has been produced between the two. This means that among COVID-19 survivors in plateau areas, improving hypoxia exposure at high altitudes mainly alleviates elevated VD/VT and psychological and emotional problems. For the rehabilitation of post-COVID-19 syndrome, the focus is on improving ventilation efficiency, peripheral metabolism and muscle strength. The intervention targets of the two are different and cannot be substituted for each other.

Conclusion

This study systematically revealed the characteristics of functional dimension separation and indicator-specific independent effects of COVID-19 infection and high-altitude hypoxia exposure in multiple system indicators of the human body: COVID-19 infection mainly affects the ventilator-metabolic coupling efficiency and peripheral muscle strength, while high-altitude hypoxia exposure mainly affects the gas distribution in the lungs and psychological behavior. Although each of them imposes a significant physiological load on the body, there are differences in their target sites and functional dimensions, and no synergistic amplification effect is shown. This discovery provides a theoretical basis for the precise stratified assessment and differentiated rehabilitation strategies of COVID-19 survivors in plateau areas.

Abbreviations

COVID-19	Coronavirus Disease 2019
HRrest	Resting Heart Rate
DBP	Diastolic Blood Pressure
SpO_2	Oxygen Saturation
CPET	cardio-pulmonary exercise testing
VO_2peak	Peak Oxygen Uptake
AT	Anaerobicthreshold
HRR	Heart Rate Reserve

HRR1	Heart Rate Recovery at 1 minute
FACIT-F	Functional Assessment of Chronic Illness Therapy- Fatigue Scale
IPAQ-LF	International Physical Activity Questionnaire-Long Form
SAS	Self-Rating Anxiety Scale
SDS	Self-Rating Depression Scale
PSQI	Pittsburgh Sleep Quality Index
GSL/GSR	Grip strength left/right,
LLS-EO/RLS-EO	left/right-Leg Stance Test With Eyes Open
COPD	Chronic Obstructive Pulmonary Disease

Declarations

Acknowledgments

We would like to express our sincere gratitude to all the participants who volunteered for this study. We are grateful to Guo Caiying, Zhao Liming, Cao Yuting, Cai Zhengyao, Zhou Mingshuang, Zhang Jie, Tao Yang, Chen Jinzi, and Liu Jianping for their generous help with subject recruitment and laboratory analyses. We thank Hao Doudou and Li Hongwei for their invaluable assistance with specific data collection and sample processing.

Author Contributions

CL was the first author of the paper and made important contributions to the acquisition, analysis, and interpretation of the data and the drafting of the paper. FYX, WYH, and YHX contributed to the revision of the manuscript. XL and DW contributed to the data collection. PYL and LLX contributed to the study design. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by the Central-guided Local Project of China : The Impact of Remote Personalized Exercise Intervention on Cardiovascular Function and Bone Metabolic System of Han Residents at High Altitudes XZ202202YD0011C.the funder had no role in study

Data availability

The data set for this study abtained by applying to the corresponding author for reasonable reason.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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Central-guided Local Project: The Impact of Remote Personalized Exercise Intervention on Cardiovascular Function and Bone Metabolic System of Han Residents at High Altitudes XZ202202YD0011C

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Figures

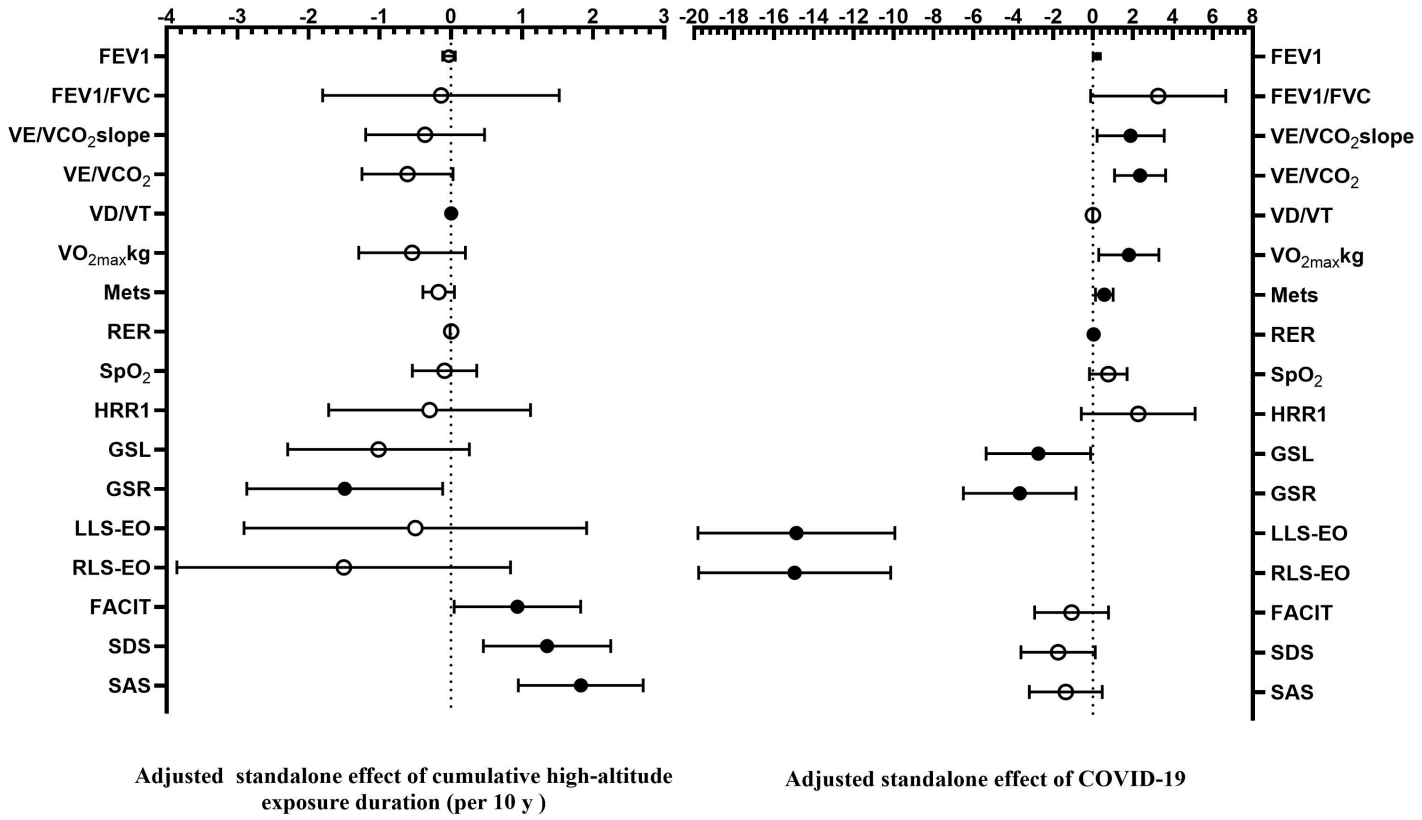


Figure 1

Forest map of the independent effects of COVID-19 and low-oxygen environment in high-altitude areas on multiple systems

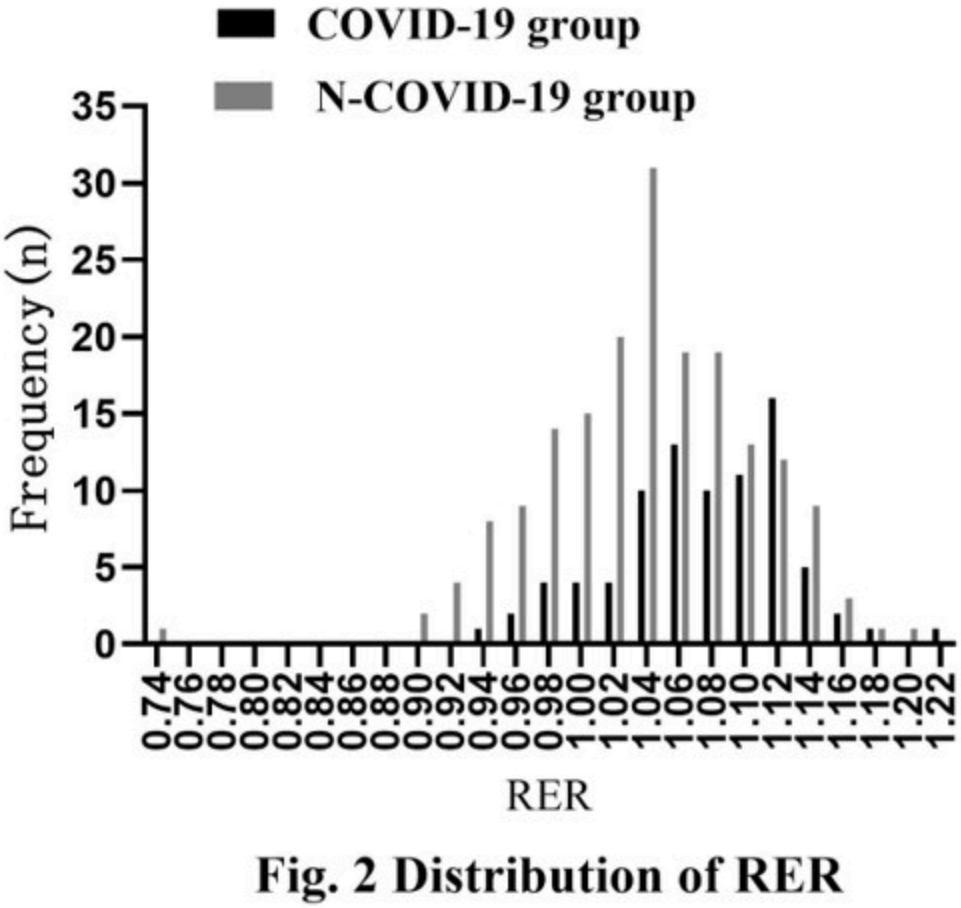


Fig. 2 Distribution of RER

Figure 2

See image above for figure legend

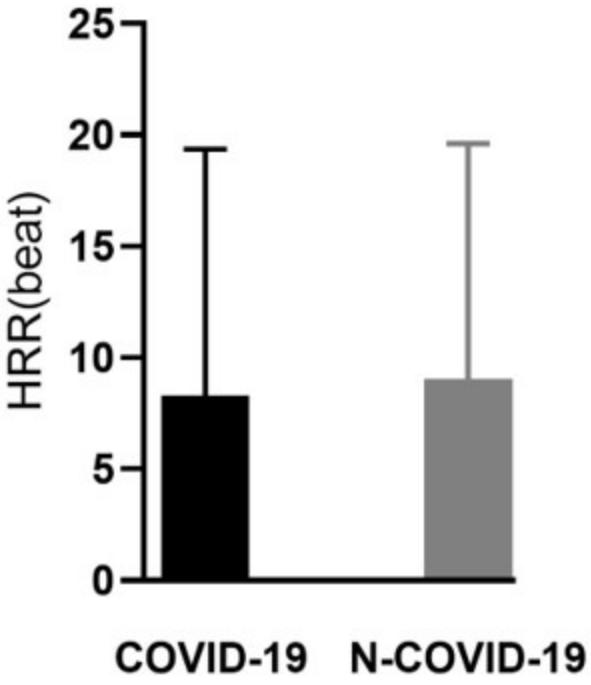


Fig. 3 Bar Chart of HRR

Figure 3

See image above for figure legend

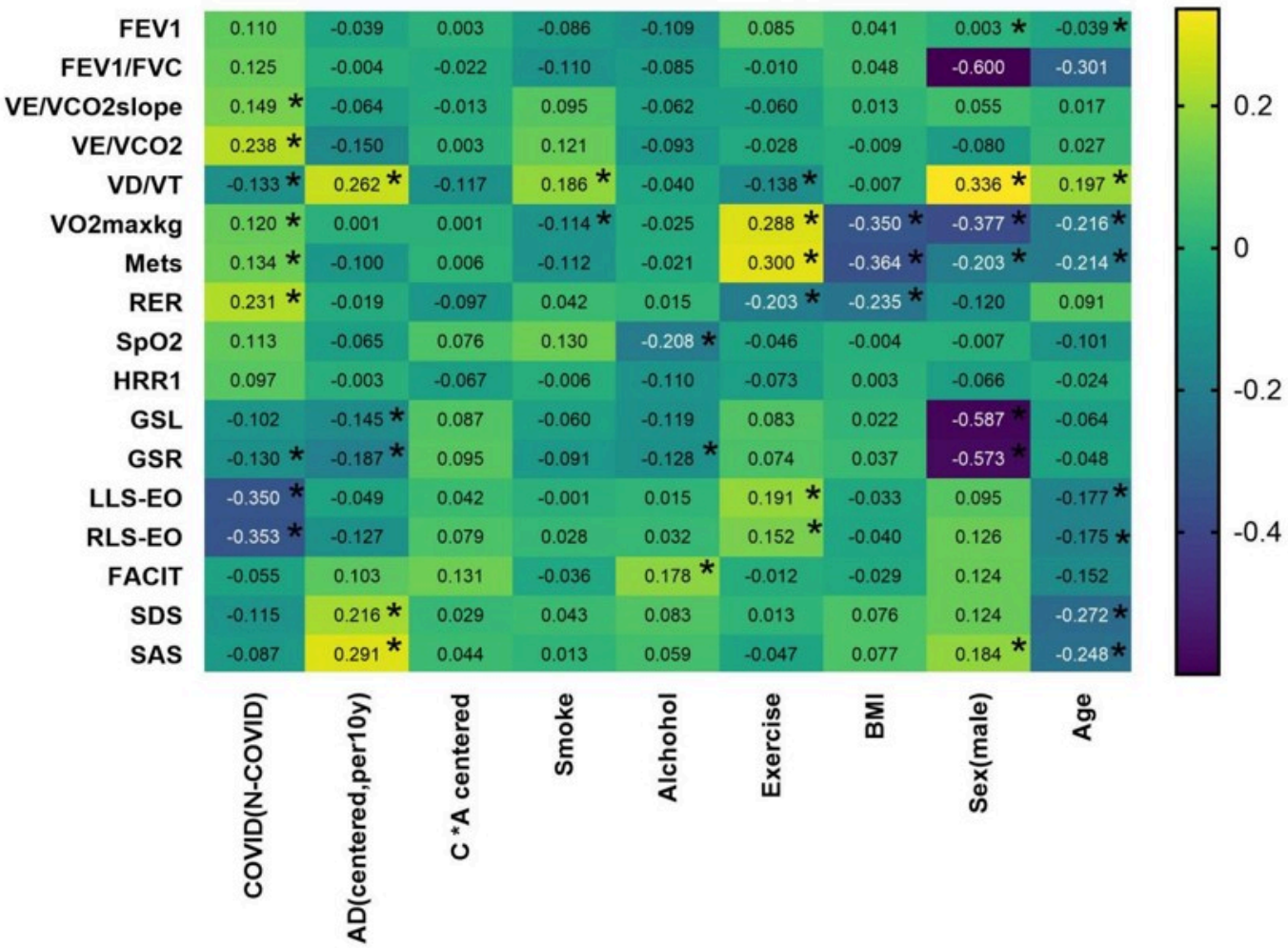


Figure 4

shows the interaction heat map of the cumulative duration of the plateau (every 10 years) and the effect of COVID-19 infection on multi-system outcomes

Supplementary Files

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