Respiratory Muscle Dysfunction in COVID-19 Patients with Persistent Symptoms

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Abstract

In a cross-sectional analysis, we have identified a high prevalence of respiratory muscle dysfunction in persistently symptomatic patients after COVID-19 ('Long COVID'). Respiratory muscle impairment in these patients was associated with exercise-induced deoxygenation, impaired exercise tolerance, activity and functional outcomes after COVID-19.

Main Text

While lung, kidney, and venous system appear to be the main sites of acute SARS-CoV-2-related complications [1, 2], sequelae of COVID-19 are reported by the vast majority of convalescent patients [3-5], a condition now referred to as "Long COVID". Most commonly reported symptoms include persistent dyspnea and fatigue in up to 51% and 63% of cases, respectively [3, 6, 7], which are also among the longest lasting sequelae [7, 8]. As recently reported in the *Journal*, fatigue, exertional intolerance and dyspnea can also be observed in Long COVID patients with preserved lung function [9]. In this light, besides the growing body of evidence regarding pulmonary parenchymal and cardiac sequelae [10-14], fatigue and dyspnea in convalescent COVID-19 patients might have additional causes related to respiratory muscular dysfunction.

In a cross-sectional approach, we have therefore prospectively investigated respiratory drive and effort in convalescent COVID-19 patients presenting to our outpatient department (OPD) with persisting respiratory symptoms.

Sixty-seven adult convalescent COVID-19 patients (30 female, 37 male, mean age: 49 yrs, baseline characteristics are given in Table 1) after mild to critical disease (according to WHO classification) completed general symptom, activity and productivity (modified WPAI score) questionnaires before undergoing complete pulmonary function testing (PFT) including spirometry, body plethysmography, capillary blood gas analyses (CBG) at rest and after performing a six-minute walk test (6MWT) including assessment of dyspnea intensity at rest and during 6MWT using the Modified BORG Dyspnea Scale (Borg CR10). In addition, respiratory muscle testing to assess respiratory drive and effort was conducted following current guidelines, which also defined pathological cut-off values [15, 16]. PRISM 9 (GraphPad Inc, San Diego, CA) and R for macOS version 3.6.3 (https://cran.r-project.org) with RStudio 1.3 (RStudio, Boston, MA) was used for the following statistical analyses: One-sample t-test and Pearson correlation analysis for normally distributed data (D'Agostino-Pearson Test); Mann-Whitney, Spearman correlation and Fisher's exact test for non-parametric data.

At time of presentation to our OPD (median of 152 days, IQR: 65 - 260), convalescent patients which initially had to be hospitalized due to COVID-19 (55% of cohort) showed reduced PFT parameters compared with non-hospitalized COVID-19 patients. In addition, initially hospitalized COVID-19 patients walked 92.3 m (15.2%) less in 6MWT and showed a more pronounced decrease in P_aO_2 during 6MWT (median: +1.5 mmHg vs. -7.8 mmHg). No differences were found in dyspnea perception, functional

impairment, daily activity or productivity. While hospitalized patients were older, had a higher Body-Mass-Index and more co-morbidities, history of lung disease was rare and did not differ between hospitalized and non-hospitalized patients (Table 1).

Most frequently reported symptoms after COVID-19 were persistent exertional dyspnea (95.5%) and fatigue (83.6%, Figure 1A). These symptoms were associated with alterations in respiratory drive and effort. Both, hospitalized and non-hospitalized patients, had increased total respiratory muscle strain (= $P_{0.1}/PI_{max}$ >0.02, [16]); 97.2% vs. 87.1%, $P_{0.1}/PI_{max}$ range: 3%-25%,p=0.0005 and p=6.6E-08, Figure 1B) at time of presentation to the OPD. Inspiratory muscle strength (as determined by $PImax_{peak}$ RV = PI_{max}) was decreased below sex- and age-specific cut-offs (from: [15]) in 88% of patients (figure 1B, vertical bar), predominantly in patients previously hospitalized due to COVID-19 (p=0.0108, female and p=0.0079, male; Figure 1C). Inspiratory muscle weakness was more frequent in women (96.4% vs 79.3%,p=0.0088, Fisher's exact test). Patients also showed elevated neuroventilatory activity as determined by $P_{0.1}$>0.3 kPa (~ 3.1 cmH_2O, [16]) which was independent of hospitalization status (mean $P_{0.1}$: 0.36 and 0.37 kPa,p=0.0291 and p=0.0029, non-hospitalized and hospitalized, respectively, Figure 1D). Consistent with respiratory pump impairment, patients with elevated inspiratory $P_{0.1}$ (> 0.3 kPa) also showed a significant increase in the $P_{0.1}$/Minute Ventilation ratio ($P_{0.1}$/MV,p=0.0145).

Clinically, alterations in respiratory drive and effort after COVID-19 were associated with reduced distance (6MWD) in the 6MWT ($P_{0.1}$: 595.5 vs. 529.3 m,p=0.0219; PI_{max}: 600.1 vs. 537.6 m,p=0.0599; $P_{0.1}/PI_{max}$: 659.3 vs. 548.5 m,p=0.0162; Figure 1E).

While no patient was hypoxemic at rest, convalescent COVID-19 patients with elevated $P_{0.1}$ showed a significant decrease in arterial oxygen partial pressure (P_aO_2) during 6MWT (DP_aO_2: -6.6 mmHg,p=0.0134; Figure 1F). In all patients with exertional deoxygenation pulmonary thromboembolic disease was ruled out by subsequent V/Q scans.

Patients with elevated $P_{0.1}$ after COVID-19 reported increased dyspnea during 6MWT as informed by a larger difference (D) in BORG scores at rest and upon exercise (+1.3 vs. +2.1,p=0.0299; larger = worse, Figure 1G). In addition, patients with elevated $P_{0.1}$ >0.3 kPa also reported less daily activity and productivity due to persisting symptoms (modified WPAI score, 6.3 vs. 9.8,p=0.0471; higher = larger impairment, Figure 1H) as well as increased overall functional impairment as determined by Post-COVID Functional Status (PCFS, [17]) scale (1 vs. 2, p=0.0058; higher = larger impairment, Figure 1I).

In a principal component analysis-based correlation matrix $P_{0.1}$ and $P_{0.1}/PI_{max}$ clustered with Age, BMI, number of co-morbidities, FEV1/FVC, Time from diagnosis and CBG. Further associations were found between $P_{0.1}$ and $P_{0.1}/PI_{max}$ (r=0.51,p=1.5E-05) and $P_{0.1}$/MV (r=0.44,p=0.001); PI_{max} and $P_{0.1}/PI_{max}$ (r=-0.51,p=1.5E-05), FVC (r=0.25,p=0.043) and DLCO (r=0.37,p=0.003); FVC and FEV1 (r=0.92,p=1.6E-28), TLC (r=0.77,p=7.4E-14), DLCO (r=0.65,p=6.2E-09) and FRC (r=0.48,p=5.0E-05) (Figure 1J).

In our cross-sectional pilot study of convalescent COVID-19 patients with persistent exertional dyspnea and fatigue we have identified a high prevalence of impaired respiratory muscle function at ~5 months after diagnosis. Functionally, this was associated with impaired exercise tolerance and daily activity/productivity in connection with exercise-induced deoxygenation.

Recently published PFT data of COVID-19 patients show mildly reduced TLC and DLCO at discharge, three- or six-months convalescence mostly in patients with severe disease [12, 18]. This is in line with our data showing patients initially hospitalized for COVID-19 had significantly lower PFT parameters including TLC and DLCO up to 5 months after infection. This was also associated with reduced exercise capacity in hospitalized patients after COVID-19 as measured by 6MWD.

Our study extends these findings as we newly report a high prevalence of increased respiratory drive and impaired respiratory muscle capacity in convalescent, persistently symptomatic COVID-19 patients. In our cohort, patients requiring hospitalizations including ICU treatment also had impaired respiratory muscle strength consistent with recently reported findings of fibrotic diaphragm remodeling in patients deceased due to COVID-19-related ARDS [14]. Even though central dyspnea processing shows high interindividual variability [19], in line with our results, elevated $P_{0.1}$ is strongly associated with heightened dyspnea perception [20]. This was also the case in our cohort as shown by elevated BORG-CR scores and everyday activity, productivity and COVID-related functional impairment (PCFS). In keeping with persistent respiratory pump impairment convalescent yet persistently symptomatic COVID-19 patients with elevated $P_{0.1}$ also featured an increase in $P_{0.1}$/MV supporting our findings of clinically relevant inspiratory muscle weakness. Prevalence of elevated $P_{0.1}$ in our Post-COVID-19 cohort was comparable to that in acutely ill COVID-19 patients on ICU [21] possibly pointing towards a persistent COVID-19-associated phenomenon.

Our data support that, pathophysiologically, elevated $P_{0.1}$ might be a function of exercise-induced deoxygenation in convalescent, persistently symptomatic COVID-19 patients. While pulmonary thromboembolic disease was not detected by V/Q scan (as described above), six patients showed signs of ground-glass opacity and (mostly minor) fibrotic changes. Systematic analysis of these changes, however, was out of the scope of the present study which is a limitation. Also, due to unavailability of data in some patients, we cannot exclude pre-existing changes in respiratory drive and effort sustained from before SARS-CoV-2 infection. Additional limitations include a putatively biased patient selection as most patients reported to our OPD with persistent symptoms after COVID-19 with very few patients referred for a routine follow-up after COVID-19. Patients and staff were also not blinded to the overall testing, possibly inserting additional bias in the measurement as does lack of historical PFT data. We also cannot specifically attribute the detected changes in respiratory drive and inspiratory muscle function to SARS-CoV-2 as we cannot rule out a general effect of viral infections. Although it is not possible to differentiate inspiratory muscle impairment from generalized muscle weakness or post-infection myopathy, in our cohort, creatine kinase and myoglobin serum levels did not differ between patients with normal or abnormal respiratory muscle function (p=0.202 and p=0.075, respectively). Regardless of SARS-CoV-2 specificity, high prevalence in our pilot study points towards a relevant healthcare burden given the pandemic nature of COVID-19.

Thus, in our cohort respiratory drive ($P_{0.1}$) was most likely increased due to impaired inspiratory muscle function (PI_{max}) which was present in approx. 90% of patients. In addition, to deoxygenation-triggered central chemoreceptors, there might be other explanations for increased neuromuscular activity in Long COVID patients such as dysfunctional thoracic receptors or altered cortical and emotional central feedback loops (as reviewed in [22]). The latter would also be in line with Long COVID patients reporting heightened stress and anxiety levels [23] which is another well characterized trigger of respiratory drive [24].

As there is strong evidence that chronic fatigue syndrome (CFS) is associated with COVID-19 [7, 8, 25], it is compelling to speculate to what extend heightened neuroventilatory activity as documented by $P_{0.1}$ in our cohort contributes to COVID-19-CFS. Particularly, as incapability to adequately increase respiratory effort upon increased respiratory drive is known to worsen respiratory distress [26]. Therefore, more invasive techniques such as twitch interpolation might help to further characterize dysregulation of respiratory drive and effort in Long COVID patients.

Conclusion

We were able to detect increased respiratory drive as well as inspiratory muscle dysfunction in persistently symptomatic patients months after COVID-19. Notwithstanding the small sample size, our findings reveal a previously unidentified neuromuscular component of COVID-19 sequelae.

Given the wide accessibility of respiratory muscle testing as a relatively low-cost approach (in particular in comparison with imaging and immunological laboratory studies), we strongly advocate for systematic respiratory muscle testing in the diagnostic workup of persistently symptomatic, convalescent COVID-19 patients.

Abbreviations

ARDS: Acute Respiratory Distress Syndrome, BMI: Body-Mass-Index, CBG: capillary blood gas, *D*: Difference between Rest and Exercise, CR: category ratio, Dx: Diagnosis, DLCO: Diffusion capacity for carbon monoxide, FEV1: Forced expiratory volume in 1 second, FRC: Functional residual capacity, FVC: Forced vital capacity, IQR: Inter-Quartile Range, $P_{0.1}$: Airway occlusion pressure at 100 ms, PI_{max}: Maximum inspiratory mouth pressure, $PImax_{peak}$ RV: Peak value of maximum inspiratory mouth pressure measured from residual volume, PCFS: Post-COVID-19 Functional Status, PFT: Pulmonary Function Test, RV: Residual volume, 6MWT: 6-minute walk test, 6MWD: 6-minute walking distance, TLC: Total lung capacity, WPAI: Work Productivity and Activity Index

Declarations

Ethics approval and consent to participate

Ethics committee of the Hamburg Chamber of Physicians (Hamburger Ärztekammer) approved of data

collection (PV7298 and PV7343). Informed consent was obtained from the participants.

Consent for publication

Not applicable.

Availability of data and materials.
Data analyzed during this study are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Conceptualization, oversight and design: J.K.H., S.K., H.K. Data acquisition: J.K.H., M.H., A.H., T.O., M.S., S.S., J.SzW. Contribution of data/analysis tools: L.H., J.K., M.M.A., H.K. Data Analysis: J.K.H., M.H., T.O. Writing of manuscript: J.K.H. All authors read and approved the manuscript.

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Tables

Table 1. Baseline Characteristics of Study Cohort at Time of Presentation to Outpatient Department

Hospitalization during COVID-19:		*no*	*yes*	*P value*
		n = 30	*n = 37*	
Age (*Years*)		*41.1 ± 10.7*	*55.9 ± 12.5*	*<0.001*
Mean ± SD				
Sex (**n**, %)	*Female*	*17 (56.7)*	*13 (35.1)*	*0.130*
BMI (**kg/m^2**)		*25.3 ± 4.5*	*28.6 ± 5.3*	*<0.001*
Mean ± SD				
Time from Dx (**days**)		*123.6 ± 69.4*	*147.5 ± 70.8*	*0.170*
Mean ± SD				
Smoking Status (**n**, %)				0.322
	Active	*4 (13.3)*	*2 (5.4)*	
	Former	*8 (26.7)*	*16 (43.2)*	
	Never	*18 (60.0)*	*18 (48.6)*	
	Unknown	*0 (0.0)*	*1 (2.7)*	
Disease Severity (**n**, %)				*<0.001*
WHO class	*Mild*	*20 (66.7)*	*2 (5.4)*	
	Moderate	*10 (33.3)*	*12 (32.4)*	
	Severe	*0 (0.0)*	*7 (18.9)*	
	Critical	*0 (0.0)*	*16 (43.2)*	
ARDS (**n**, %)	yes	*0 (0.0)*	*15 (40.5)*	*<0.001*
Co-Morbidities (**n**)		*0 (0 – 1)*	*2 (0 – 3)*	*<0.001*
Median (IQR)				
PFT (**%**)				
Mean ± SD	*FVC*	*98.2 ± 12.4*	*83.7 ± 21.5*	*0.002*
	FEV1	*97.2 ± 11.9*	*87.3 ± 18.0*	*0.012*
	FEV1/FVC	*99.3 ± 8.0*	*105.7 ± 8.6*	*0.003*
	RV	*107.4 ± 28.3*	*91.4 ± 28.4*	*0.025*
	TLC	*103.5 ± 14.5*	*87.5 ± 18.9*	*<0.001*
	FRC	*96.3 ± 21.6*	*82.2 ± 21.9*	*0.012*
	DLCO	*83.0 ± 12.6*	*68.8 ± 17.7*	*0.001*
6MWT				
Mean ± SD	*6MWD (m)*	*607.0 ± 53.7*	*514.7 ± 127.2*	*<0.001*
CBG (mmHg)				
Median (IQR)	*DP_aO_2*	*1.5 (-7.8 – 5.2)*	*-7.8 (-12.10 – -0.38)*	*0.021*
	DP_aCO_2	*0.8 (-0.8 – 2.4)*	*-0.5 (-1.1 – -2.2)*	*0.406*
Dyspnea (Borg CR10)				
Median (IQR)	*Difference*	*1.00 (0.62 – 3.00)*	*2.00 (0.50 – 2.25)*	*0.984*

Mean ± SD	*at Rest*	*0.4 ± 0.8*	*0.6 ± 1.1*	*0.462*
	Exercise	*2.2 ± 1.7*	*2.3 ± 1.7*	*0.829*
Productivity (modified WPAI)				
Median (IQR)		*5.5 (3.0 – 11.5)*	*10.0 (4.0 –15.25)*	*0.104*
PCFS Scale				
Median (IQR)		*2 (1 – 3)*	*2 (1 –3)*	*0.698*

BMI: Body-Mass-Index, Dx: Diagnosis, IQR: Inter-Quartile Range, ARDS: Acute Respiratory Distress Syndrome, PFT: Pulmonary Function Test, 6MWT: 6-minute walk test, CBG: capillary blood gas, *D*: Difference between Rest and Exercise, CR: category ratio, WPAI: Work Productivity and Activity Index, PCFS: Post-COVID-19 Functional Status

Figures

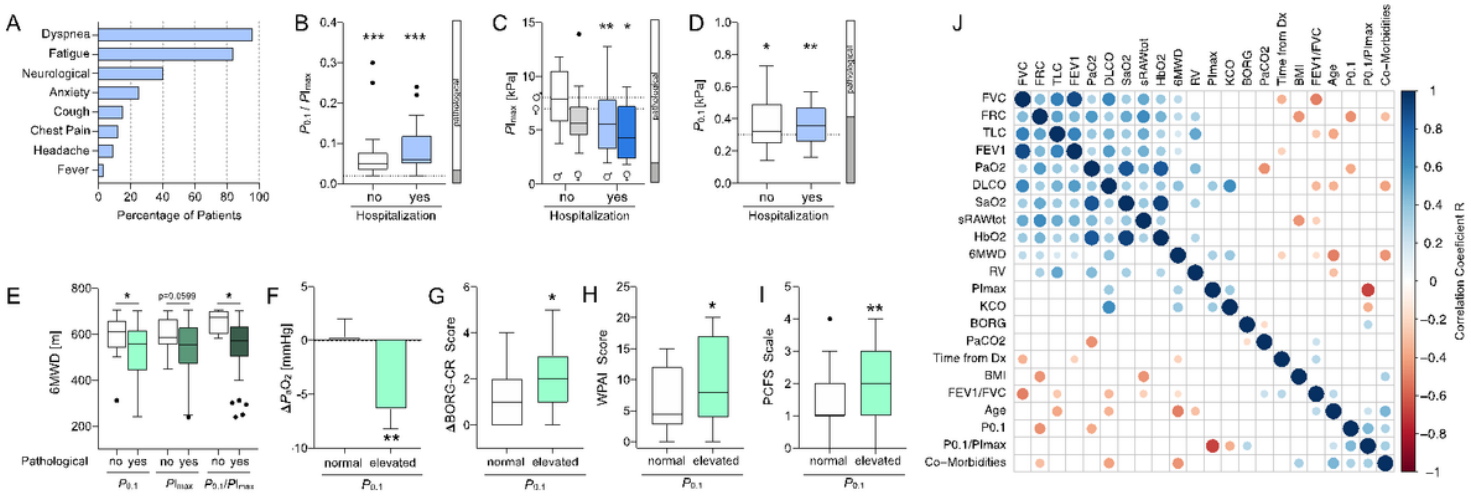

Figure 1

Respiratory Muscle Impairment after COVID-19 is associated with impaired exercise tolerance, exercise-induced deoxygenation, activity and functional outcome: (A) Persisting symptoms of convalescent COVID-19 patients at time of presentation to Outpatient Department (OPD) (mean: 152 days after diagnosis, Dx, n=67). (B) Respiratory muscle strain P0.1/PImax at OPD presentation after COVID-19 by hospitalization status of acute COVID-19 (***p=6.0E-08 and ***p=5.8E-11, respectively; one-sample Wilcoxon test, cut-off: 0.02). (C) Inspiratory muscle strength PImax by sex and hospitalization status (non-hospitalized: male (□), p=0.83 and female (□), p=0.10; hospitalized: male, **p=0.0079; female, *p=0.0269; one-sample Wilcoxon cut-off: 8 kPa, male and 7 kPa, female). Fraction of sex- and age-corrected pathological tests results are given in the adjacent vertical bar. (D) Airway occlusion pressure at 0.1s, P0.1 per same patients as in (B) (*p=0.0291, **p=0.0027, one-sample t-test, cut-off: 0.3 kPa) and fraction of pathological test results (adjacent bar). (E) Six-minute walking test (6MWT) distance (6MWD) in meters (m) by P0.1 (*p=0.0219), PImax (p=0.0599) and P0.1/PImax (p=0.0162), Mann-Whitney test. (F) Difference in arterial partial pressures for oxygen (ΔPaO2) by P0.1 (**p=0.0134, unpaired, 2-sided t-test)

(G) Difference in self-reported dyspnea perception (BORG-CR score) immediately before and after 6MWT by P0.1 (ΔBORG-CR, *p=0.0299, Mann-Whitney test). (H) Self-reported activity and productivity impairment (modified WPAI score) in the last seven days before presentation to the OPD by P0.1 (*p=0.0471, Mann-Whitney test). (I) Self-reported Post-COVID-19 Functional Status (PCFS) scale at time of presentation to OPD by P0.1 (**p=0.0058, Mann-Whitney test). (J) Matrix of significantly ($p<0.05$) correlated variables from study cohort (Pearson or Spearman R values) sorted by first principal component. Box-and-Whiskers showing medians + inter-quartal range (IQR) and outliers (Tukey method). In (F) normally distributed data are given as mean±standard error of the mean. Dashed lines in (G), (H) and (I) represent pathological (sex-specific) cut-off values. Vertical bars in (B), (C) and (D) represent fraction of pathological (open) and normal (grey) values from total cohort