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CORRESPONDENCE

Correlation of respiratory muscle function and cardiopulmonary exercise testing in post-acute COVID-19 syndrome

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To the editors,

We read the paper published by Hennigs et al. [1] with great interest and thank the authors for shifting the focus to studying respiratory muscle function in Post-COVID-19 patients. The authors report striking pathological findings of mouth occlusion pressure (MOP) measurements in previously hospitalized but also non-hospitalized patients presenting with post-acute COVID-19 syndrome (PACS). In their study, Hennigs and co-authors found a high proportion of patients, more frequently females, with decreased maximum inspiratory pressure (MIP, or PImax), suggesting impairment of respiratory muscle strength. Additionally, their data indicate that increased neuroventilatory or central ventilatory drive (P0.1) may have a role in perceived respiratory distress in patients suffering from Post-COVID-19 fatigue. With this letter, we would like to share complementary data from a case series correlating MIP and P0.1 with cardiopulmonary exercise testing (CPET) in patients with PACS. Furthermore, we aim to elaborate on the limitations of MOP measurements, particularly MIP.

Methods: To better understand the effects of respiratory muscle dysfunction, we selected patients from our ongoing PACS observational study cohort to perform CPET. Additionally, MOP and pulmonary function tests (PFT) were compared between patients and a control group of healthy volunteers without history of SARS-CoV-2 infection. For PFT and MOP, we used identical methodology as described in the study by Hennigs et al. [1]. CPET was performed on a bicycle ergometer using a ramp protocol according to recommendations published by the German Respiratory Society [2]. Blood gas analyses and flow-volume curves were obtained at the beginning, at ventilatory threshold and towards the end of exercise. Statistical analyses were performed using SPSS version 28 (IBM Corporation). For normally distributed data, one-sample *t*-test and Pearson correlation analysis were used, for nonparametric data Mann–Whitney and Spearman correlation, respectively. Normally distributed data is presented as mean ± standard deviation, nonparametric data in median ± interquartile range (Q1; Q3).

Results: Fourteen patients were evaluated at a median of 160 days (range 47–310 days) after PCR-confirmed diagnosis of acute SARS-CoV2 infection. All patients were female and reported fatigue, varying degrees of dyspnea and several other PACS symptoms (Online Resource, Fig. S1). None of the patients had been hospitalized for COVID-19 and none had pre-existing cardiopulmonary comorbidities except for two patients with mild, controlled asthma. Two patients were active cigarette smokers. Electrocardiogram and laboratory investigations, including Troponin T, NT-pro-BNP and D-Dimer were normal in all patients.

Twelve out of 14 patients (85.7%) had decreased MIP < 7.0 kPa and 5/14 patients (35.7%) had increased P0.1 > 0.30 kPa. In the control group, 13/20 participants (65.0%) had decreased MIP and 6/20 participants (30.0%) had increased P0.1 values. Statistically, there were no significant differences between the two groups (**Table 1**).

On PFT, no patient had a FEV1/FVC ratio below the lower limit of normal (LLN), only one patient with known asthma showed slightly increased airway resistance (SReff 158%). None of the patients had ventilatory restriction (TLC 106 ± 15% predicted). Three patients showed abnormal DLCO/VA (< 80%). Details are shown in Table 1.

During CPET, only 5/14 patients reached ≥ 90% of predicted maximum heart rate and only one patient reached respiratory exchange rate (RER) > 1.16. All patients reached > 80% predicted work rate (mean 143 ± 38 W) and 8/14 reached > 85% predicted peak oxygen uptake

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Table 1 Mean values (±SD) or median values (IQR) of age, body mass index (BMI), pulmonary function tests and mouth occlusion pressure measurements in patients (PACS) and healthy controls (Non-COVID-19)

	PACS ($n=14$)	Non-Covid-19 ($n=20$)	p-value
Age	34.4 ± 12.8	38.6 ± 11.5	0.320
BMI	23.20 ± 3.42	26.61 ± 6.10	0.069
MIP [kPa]	5.51 (3.82; 5.99)	6.25 (5.05; 7.85)	0.292
p0.1 [kPa]	0.17 (0.12; 0.34)	0.26 (0.20; 0.31)	0.276
p0.1/MIP [%]	3.96 (2.64; 5.76)	4.37 (3.29; 5.31)	0.530
SReff [%]	80 ± 30	47 ± 20	< 0.001
TLC [%]	106 ± 15	105 ± 12	0.801
FVC [L]	3.83 ± 0.68	3.74 ± 0.59	0.644
FEV1 [L]	3.20 ± 0.53	3.14 ± 0.5	0.761
FEV1/FVC	0.84 ± 0.07	0.84 ± 0.06	0.942
DLCO/VA [%]	91.3 ± 16.5	103 ± 11	0.016

(VO2peak). Mean VO2peak was 25.7 ± 5.4 ml/min/kg, resulting in a normal mean exercise capacity in the cohort (mean VO2peak/$VO2peak_{predicted}$ = 93 ± 21%). Exercise testing was terminated due to muscular exhaustion ($n=7$), dyspnea ($n=4$) or both ($n=3$). Breathing frequency (BF) and minute ventilation (VE) increased adequately throughout exercise and tidal volume (Vt) reached at least 70% of inspiratory capacity (IC) in all fourteen participants. Twelve out of 14 patients had preserved breathing reserve (BR) > 30%. Two patients with decreased MIP (3.1 and 3.44 kPa) showed depleted BR but reached VO2peak > 110% predicted and work rate > 120% predicted, indicating that depleted BR in these cases reflects excellent exercise capacity rather than ventilatory limitation.

No correlation was found between MIP and TLC, FVC or any CPET parameter (Table 2, Online Resource Fig. S2.A). P0.1 showed significant negative correlations with oxygen uptake VO_2 (−0.589; $p=0.027$), carbon dioxide output VCO_2 (−0.644; $p=0.013$), peak PaO_2 (−0.556; p = 0.039) and O_2 pulse (−0.648; $p=0.012$) (Table 2, Online Resource Fig. S2.B). P0.1/MIP ratio showed several significant correlations with PFT and CPET. There was a positive correlation with DLCO/VA (0.572; $p=0.033$), PaO2 at rest (0.620; $p=0.018$), and tidal

Table 2 Correlation between P0.1, MIP, P0.1/MIP and variables of pulmonary function testing and variables of cardiopulmonary exercise testing, respectively

	Mean ± SD	Correlation					
		P0.1		MIP		P0.1/MIP	
		r-value	p-value	r-value	p-value	r-value	p-value
sReff [%]	80 ± 30	0.020	0.946	0.499	0.069	−0.160	0.548
FVC [L]	3.83 ± 0.68	−0.105	0.733	0.484	0.094	−0.440	0.133
FEV1 [L]	3.20 ± 0.53	−0.077	0.802	0.363	0.223	−0.324	0.280
TLC [%]	106 ± 15	−0.110	0.707	0.275	0.341	−0.389	0.169
DLCO/VA [%]	91.3 ± 16.5	0.440	0.115	−0.022	0.940	0.572	**0.033***
Work [W]	143 ± 38	−0.463	0.095	−0.009	0.976	−0.542	**0.045***
VO2 [l/min]	1.70 ± 0. 42	−0.589	**0.027***	−0.002	0.994	−0.635	**0.015***
VO2/kg [ml/min/kg)	25.7 ± 5.4	−0.467	0.092	0.108	0.714	−0.490	0.075
VCO2 [l/min]	1.8 ± 0.5	−0.644	**0.013***	−0.174	0.553	−0.596	**0.025***
RER	1.06 ± 0.11	−0.020	0.946	−0.007	0.982	0.070	0.811
HR [1/min]	155 ± 18	−0.283	0.327	0.165	0.572	−0.458	0.099
O_2 pulse [ml/beat]	10.9 ± 2.1	−0.648	**0.012***	−0.121	0.681	−0.635	**0.015***
VE [l/min]	60 ± 17	−0.379	0.181	−0.393	0.164	−0.182	0.533
Bf [1/min]	30 ± 7	−0.034	0.907	−0.374	0.188	0.135	0.646
BR [%]	48 ± 22	0.258	0.373	0.354	0.214	0.035	0.905
VE/VO2 Slope	24.5 ± 3.8	0.151	0.639	0.119	0.713	0.210	0.513
VE/VCO2 at VT	29.2 ± 3.5	0.309	0.283	−0.187	0.523	0.398	0.159
PaO2rest	95 ± 7	0.418	0.137	−0.090	0.759	0.620	**0.018***
PaCO2rest	36 ± 3	0.265	0.360	−0.097	0.742	0.442	0.113
PaO2max	94 ± 7	−0.556	**0.039***	0.125	0.670	−0.732	**0.003***
PaCO2max	36 ± 4	−0.362	0.204	−0.029	0.923	−0.358	0.208
VTpeak	2.1 ± 0.5	0.213	0.465	−0.345	0.226	0.557	**0.038***
ICpeak	2.3 ± 0.5	0.101	0.730	−0.202	0.488	0.352	0.217

*$p < 0.05$

Bold values indicate statistical significance

volume (Vt) at peak exercise (0.557; $p = 0.038$). Negative correlations were found between p0.1/MIP and work rate (−0.542; $p = 0.045$), VO_2 (−0.635; $p = 0.015$), VCO_2 (−0.596; $p = 0.025$), O_2 pulse (−0.614; $p = 0.015$) and peak PO_2 (−0.732; $p = 0.003$) (Table 2, Online Resource Fig. S2.C). There were no statistically significant correlations between MIP or P0.1 and VE, BF, BR, IC at peak exercise or VE/VCO_2-Slope (Table 2).

Discussion: MIP is the maximum pressure that can be generated by a subject trying to inhale through a blocked mouthpiece after a full exhalation. MIP reflects inspiratory muscle strength, but optimal patient cooperation and maximum effort are essential. P0.1 denotes MOP at 100 ms of inspiration during calm breathing and is considered a marker of central ventilatory drive. In patients with inspiratory muscle weakness, minute ventilation and arterial pCO_2 at rest are maintained at normal levels, implying that central ventilatory drive is increased for compensation. In patients with underlying chronic pulmonary diseases, such as COPD, P0.1/MIP ratio is considered to represent respiratory muscle strain.

The advantage of MIP assessment is that normal values can safely rule out IMW. The high proportion decreased MIP and elevated P0.1 in healthy controls indicates poor test specificity for the detection of clinically relevant inspiratory muscle weakness (IMW), which is a well-known problem in pulmonary medicine. The clinical relevance of decreased MIP must be validated by pulmonary function (TLC, FVC) and exercise testing. When combined test results are still indicative of IMW, invasive testing is warranted, such as transdiaphragmatic twitch pressure measurement and electromyography, which represent the gold standard for assessing respiratory muscle function.

Investigation of ventilatory response to exercise in CPET in patients with respiratory muscle dysfunction is a subject of ongoing research. Bonnevie et al. studied CPET in 14 patients with uni- and bilateral diaphragm paresis and observed a relationship between respiratory muscle function and exercise capacity (VO2peak), VEpeak and, Vtpeak. Moreover, ventilatory limitation was evident in pathological breathing patterns with low Vt, excessive BF and abolished BR [3]. Similar findings were reported by Berton et al. who examined CPET parameters in 23 patients with dyspnea due to IMW in the pre-COVID era. Patients with IMW by definition showed decreased MIP values, but also reduced FVC and TLC compared to healthy controls. On CPET, these patients exhibited reduced work rate, oxygen uptake and lower VEpeak (in association with high BF and low Vtpeak). Declining IC and lower peak IC during exercise were also found in IMW patients [4].

In the case series presented here, no relationship between MIP and ventilatory limitation in CPET was found. P0.1 and P0.1/MIP ratio were negatively correlated with oxygen uptake, carbon dioxide output and peak PaO_2. Additionally, P0.1/MIP was also correlated with reduced work rate.

These findings support the hypothesis by Hennigs and co-authors, who speculated that in a subset of PACS patients with previous mild COVID-19, dysregulation of central ventilatory drive may contribute to respiratory distress, but may not be secondary to IMW, despite a high proportion of low MIP readings in these patients.

Other pathophysiological mechanisms have recently been suggested to cause overshooting respiratory response in dyspneic patients after mild COVID-19, such as disturbance of skeletal muscle metabolism and autonomic dysfunction [5]. The latter may also explain the negative correlation between P0.1 and O_2 pulse in our data, as both ventilatory drive and ventricular stroke volume are subject to the influence of autonomic nervous regulation.

We do not know if the detected changes are the consequence of SARS-CoV-2-infection, as our control group did not perform CPET. Also, the small number of patients in this series is a major limitation and all results should be interpreted with caution. Larger scale studies are needed to further characterize the relationship between respiratory muscle function and CPET in patients with PACS.

Our data nonetheless suggest that decreased MIP may overestimate the extent of IMW and demonstrate an association between central ventilatory drive and exercise capacity in these patients.

Therefore, we unequivocally agree with the conclusion of Hennigs and co-authors who advocate the inclusion of respiratory muscle function tests in the diagnostic workflow in PACS patients with dyspnea. Both the evidence of significant IMW and dysregulated central respiratory drive due to other factors may inform therapeutic consequences by indicating the need for physical therapy and rehabilitation.

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article. No funding was received to assist with the preparation of this manuscript.

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Consent to participate and consent to publish Informed consent was obtained from all individual participants included in the study.

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