RESPIRATORY MUSCLE STRENGTH IN PATIENTS AFTER COVID-19

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Respiratory muscles (RM) are a very important part of the respiratory system that enables pulmonary ventilation. This study aimed to assess the post-COVID-19 strength of RM by estimating maximum static inspiratory (MIP or PImax) and expiratory (MEP or PEmax) pressures and to identify the relationship between MIP and MEP and the parameters of lung function. We analyzed the data of 36 patients (72% male; median age 47 years) who underwent spirometry, and body plethysmography, diffusion test for carbon monoxide (DLCO) and measurement of MIP and MEF. The median time between the examinations and onset of COVID-19 was 142 days. The patients were divided into two subgroups. In subgroup 1, as registered with computed tomography, the median of the maximum lung tissue damage volume in the acute period was 27%, in subgroup 2 it reached 76%. The most common functional impairment was decreased DLCO, detected in 20 (55%) patients. Decreased MIP and MEP were observed in 5 and 11 patients, respectively. The subgroups did not differ significantly in MIP and MEP values, but decreased MIP was registered in the second subgroup more often (18%). There were identified no significant dependencies between MIP/MEP and the parameters of ventilation and pulmonary gas exchange. Thus, in patients after COVID-19, MIP and MEP were reduced in 14 and 31% of cases, respectively. It is reasonable to add RM tests to the COVID-19 patient examination plan in order to check them for dysfunction and carry out medical rehabilitation.

Keywords: respiratory muscle strength, spirometry, body plethysmography, diffusion test, post-COVID-19, new coronavirus infection

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ИССЛЕДОВАНИЕ СИЛЫ ДЫХАТЕЛЬНЫХ МЫШЦ У БОЛЬНЫХ, ПЕРЕНЕСШИХ COVID-19

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Дыхательные мышцы (ДМ) — важнейшее звено респираторной системы, обеспечивающее легочную вентиляцию. Целью исследования было оценить силу инспираторных (MIP) и экспираторных (MEP) ДМ после COVID-19 и выявить взаимосвязь показателей MIP и MEP с функциональными показателями системы дыхания. Проанализированы данные 36 пациентов (72% мужчин; медиана возраста — 47 лет), которым проводили спирометрию и бодиплетизмографию, определяли диффузионную способность легких (DLCO) и измеряли MIP/MEP. Медиана срока проведения исследований от начала COVID-19 составила 142 дня. Пациенты были разделены на две подгруппы. Медиана максимального объема поражения легочной ткани в острый период заболевания по КТ в подгруппе 1 составила 27%, в подгруппе 2 — 76%. Наиболее частым функциональным нарушением было снижение DLCO (выявлено у 20 (55%) пациентов). Снижение MIP и MEP было отмечено у 5 и 11 пациентов соответственно. Статистически значимых различий по показателям MIP и MEP между подгруппами выявлено не было, однако частота снижения MIP во второй подгруппе была выше (18%). Статистически значимых связей показателей MIP и MEP с параметрами вентиляции и легочного газообмена выявлено не было. Таким образом, у пациентов, перенесших COVID-19, обнаружено снижение MIP и MEP в 14 и 31% случаев соответственно. Исследование силы ДМ целесообразно включать в план обследования пациентов, перенесших COVID-19, для выявления их дисфункции и проведения медицинской реабилитации.

Ключевые слова: сила дыхательных мышц, спирометрия, бодиплетизмография, диффузионный тест, пост-COVID-19, новая коронавирусная инфекция, SARS-CoV-2

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COVID-19 is a highly contagious infectious disease caused by the new coronavirus SARS-CoV-2. The virus attacks respiratory system as one of its main targets, and this attack is the main reason that brought such patients to the hospital. The research efforts focused on COVID-19 mainly aimed to investigate the pathogenesis of the disease and find ways to treat it at the acute phase in order to minimize mortality. However, with the accumulation of knowledge, it became clear that COVID-19 is a multisystem disease, the consequences of which are currently not well understood.

From the point of view of damage to the respiratory system, the main functional disorder in the post-COVID period is the reduced lung diffusion capacity; less common are restrictive ventilation disorders, and even less so are obstructive ventilation disorders [1–3]. The data obtained are taken into account when drawing up individual post-disease medical rehabilitation programs for COVID-19 patients. However, it is not just the respiratory system that needs medical rehabilitation after COVID-19 but also the cardiovascular system, as well as the peripheral skeletal muscles, which grow weak and fatigued in severe and extremely severe COVID-19 cases.

Respiratory muscles (RM), which are the most important component of the respiratory system that enabled pulmonary ventilation, also belong to the skeletal muscles. Pathological changes in the respiratory muscles that occur after community-acquired pneumonia (CAP) [4, 5] and thoracic interventions [6] have been studied well. A comparative analysis of the strength of RM in CAP cases of varying severity of endogenous intoxication showed that, causing local inflammation and damaging myofibrils [5], this intoxication is the dominant extrapulmonary mechanism triggering RM dysfunction. In addition, there is hyperventilation syndrome caused by arterial hypoxemia that also contributes to RM fatigue. Moreover, glucocorticosteroids may also be the reason of weakness [7, 8]. However, there are just a few publications that investigate respiratory muscles strength after COVID-19 [9, 10].

The most common method for assessing RM strength is measurement of the maximum static mouth pressure when the person's airways are closed. This pressure may be expiratory (MEP) and inspiratory (MIP). Thus, this study aimed to assess the post-COVID-19 strength of RM and identify the relationship between MIP and MEP and other lung function parameters.

METHODS

The observational cross-sectional study included 36 patients (26 of them male, median age 47 years) admitted to hospitals with a diagnosed interstitial lung disease caused by the new coronavirus infection (J98.4). The inclusion criteria were: confirmed recovery from moderate or severe case of COVID-19, bilateral viral lung damage. In all patients the diagnosis was confirmed by polymerase chain reaction. The exclusion criterion was a recorded history of chronic lung disease. In the context of a single visit, all participants of this study underwent functional examinations of the respiratory system, including spirometry, body plethysmography, diffusion test and RM strength measurement. The system used for the examinations was the MasterScreen Body/Diff system (Viasys Healthcare / ErichJager, Vyaire Medical / ErichJager; Germany).

All procedures were carried out in accordance with national and international standards [11–14] and recommendations of the Russian Respiratory Society for conducting lung function tests during the COVID-19 pandemic [15].

The lung diffusing capacity was assessed for carbon monoxide measured by means of the single-breath test through the use of rapidly responding gas analyser (RGA).

Analyzed parameters:

1) spirometry (forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), FEV_1/FVC, maximal mid-expiratory flow between 25% and 75% of the FVC expiration ($MMEF_{25-75}$));

2) body plethysmography (slow vital capacity (VC), total lung capacity (TLC), residual volume (RV) and its ratio to TLC (RV/TLC), thoracic gas volume (TGV), inspiratory capacity (IC), total airways resistance (Raw_{tot}));

3) diffusion test (transfer factor CO (DLCO) adjusted for hemoglobin value and its ratio to alveolar volume (VA) — DLCO/VA);

4) MIP and MEP.

The analyzed data were presented as a percentage of the predicted values ($\%_{pred}$), which were calculated using the equations of the European Coal and Steel Community [16] for patient's gender, age and height. The predicted MIP and MEP values were calculated by the equations recommended the European Respiratory Society [17]. Values greater than $75\%_{pred}$ were considered normal [18].

As registered with high-resolution chest computed tomography (CT), there was post-inflammatory damage of varying severity in the lungs of the patients at the time of the study. The cohort was divided into two subgroups depending on the maximum area of lung damage caused by SARS-CoV-2 in the acute period of the disease. Patients whose lungs had ≤ 50% of tissue damaged were included in subgroup 1, those with lung damage exceeding 50% made up subgroup 2.

Sixteen (44%) patients had concomitant diseases: 7 patients — hypertension, 4 patients — hypertension and type 2 diabetes mellitus, one patient each — type 1 diabetes, varicose veins, myocarditis, psoriasis, iron deficiency anemia.

We employed STATISTICA 10.0 software (StatSoft Inc.; USA) for statistical analysis and Shapiro–Wilk test to assess the normality of distribution of the variables. Quantitative variables, the distribution of which differed from normal, were presented as medians (Me) and interquartile range (Q_1–Q_3), nominative variables — number of patients (*n*). Comparison of nonparametric quantitative indicators of the two groups relied on the nonparametric Mann–Whitney *U* test, that of qualitative variables — Fisher's exact test. Correlation analysis was performed using Spearman's rank correlation. The differences were considered significant at $p < 0.05$.

RESULTS

The median duration of the lung function examination from the onset of COVID-19 was 142 (108–186) days.

Table 1 presents characteristics of all the patients participating in the study and their characteristics by subgroups.

There were no significant differences established between the subgroups by age, gender, height, body mass index.

The majority of patients in both subgroups were nonsmokers; only subgroup 1 had a small number of smokers.

The median value of the maximum lung damage area (CT_{max}.) in the acute period of the disease was 27% in the 1st subgroup and 76% in the 2nd subgroup, which is a significant difference. The length of hospital stay for COVID-19 was significantly longer in subgroup 2.

Table 2 summarizes the functional examination data analysis overall and by subgroups.

For all the patients, the medians of all analyzed lung function parameters were within normal range, apart from the decreased DLCO in 20 (55%) patients. In addition, 5 (14%) patients had impairment of TLC, one patient had impairment of VC and FEV_1/VC (FEV_1/VC < 0.7), 5 (14%) and 11 (31%)

Table 1. Patient characteristics

Parameter	Overall *n* = 36	Subgroup 1 *n* = 14	Subgroup 2 *n* = 22	*p**
Gender, men, *n* (%)	26 (72)	8 (57)	18 (82)	NS
Age, years	47 (40–58)	46 (39–59)	48 (42–57)	NS
Height, cm	174 (165–181)	170 (165–183)	174 (165–179)	NS
BMI, kg/m^2	29 (26–32)	30 (25–32)	29 (27–31)	NS
Tobacco smoking, no/ex-smoker/smoker, %	69/28/3	72/21/7	68/32	–
Length of hospital stay for COVID-19	18 (13–25)	14 (8–16)	23 (15–27)	0,01

Note: the data are presented as quantity (n) or median (lower quartile — upper quartile). BMI — body mass index; * — subgroups 1 and 2 compared with Mann–Whitney test; NS — no significant differences found between subgroups 1 and 2.

patients had impairment of MIP and MEP, respectively. It should be noted that decreased TLC was found mainly in patients of subgroup 2, with only one such case registered in subgroup 1. Eight patients had the RV decreased, and 3 of them had the RV decreased isolated without impairment of TLC.

We found significant differences in TLC and DLCO values between the subgroups, these values being lower in subgroup 2. The subgroups did not differ significantly in MIP and MEP values, but decreased MIP was registered in the second subgroup more often (18%), while the frequency of decreased MEP was similar.

Correlation analysis did not reveal significant dependencies between MIP/MEP and the studied parameters of ventilation and pulmonary gas exchange.

DISCUSSION

Observation of COVID-19 convalescents indicates that after discharge from the hospital they do not fully recover functionally for a long time. Patients continue to experience shortness of breath, general weakness, increased fatigue and deteriorating quality of life. Besides, there are functional impairments of the respiratory system, cardiovascular system, as well as neuropathy and myopathy registered, which are primarily caused the extremely severe course of COVID-19 that required intensive care.

At the same time, even mild and moderate COVID-19 course brings the same symptoms with varying intensity of manifestation. The reduced RM strength is part of COVID-19-induced neuropathy and myopathy, which indicates the need for medical rehabilitation interventions to remedy the symptoms.

The Experts Consensus concerning respiratory techniques which are recommended for inclusion in post-COVID-19 medical rehabilitation programs draws special attention to training of inspiratory muscles aimed at improving ventilation-perfusion ratios and oxygenation [19]. However, this study shows that the reduced MEP registers twice as often as reduced MIP, that points out to justify breathing techniques in the context of training expiratory RM.

At the same time, physiotherapy methods such as electrical stimulation, chest massage with correction of muscle triggers and myofascial release, infrared laser therapy and magnetic therapy in the chest zones, help improve microcirculation and functional state of both inspiratory and expiratory RM.

Among the other findings of this study that draw attention is the lack of significant differences in MIP and MEP values between the subgroups, i.e., lack of confirmation the changes in these parameters depend on the lung damage severity during the acute period of the disease. The results obtained are consistent with those reported in the previously published studies [9, 10], which allows considering other factors, possibly biochemical, including those affecting the central mechanisms of respiration regulation and, accordingly, the functional state of RM after COVID-19.

The median duration of this study from the onset of COVID-19 was 142 days, and the most common functional impairment registered was decreased diffusion capacity (55% of cases), mainly found in patients who had over 50% of their lungs damaged by the disease (subgroup 2), and restrictive ventilation disorders were diagnosed in 5 (14%) patients, 4 of whom (18%) were also in subgroup 2, while airways obstruction was only discovered in 1 patient. The meta-analysis that covered early post-COVID-19 period (1 to 3 months) showed that the prevalence of decreased diffusion capacity is 39% (CI: 24–56%; $p < 0.01$; heterogeneity index (I^2) — 86%), whereas restrictive ventilation disorders is 15% (CI: 9–22%; $p = 0.03$; $I^2 = 59\%$), airways obstruction — 7% (CI: 4–11%; $p = 0.31$; $I^2 = 16\%$) [3].

The results of this study are consistent with the data of the meta-analysis, however, the present study addressed later post-COVID-19 recovery periods, which may indicate that, after this disease, the functions of the respiratory system recover slowly.

No statistically significant correlations were found between the maximum static mouth pressure and the lung function parameters, which once again confirms the importance of measuring RM strength, especially in patients who experience shortness of breath and rapid fatigue while having the traditional pulmonary functional tests return normal values.

The effect COVID-19 has on RM strength should be investigated further in order to uncover the relationship between MIP/MEP values and the quantitative assessment of muscle strength by the MRC Weakness scale, as well as the severity of dyspnea by the mMRC scale.

Particular attention to RM strength should be paid when COVID-19 takes extreme form and causes post-intensive care syndrome (PICS), including general muscle weakness, decreased muscle mass, reduced physical performance and muscle strength, and reduced strength of the inspiratory muscles that may result in diaphragm atrophy and dysfunction. Measurement of the MIP and MEP values over time in such patients will allow adjustment of the medical rehabilitation program and prediction of the outcomes of identified impairments.

Table 2. Spirometry, body plethysmography, diffusion test, respiratory muscle strength test data

Parameter	Overall *n* = 36	Subgroup 1 *n* = 14	Subgroup 2 *n* = 22	*p*
VC, $\%_{pred}$	106 (95–120)	111 (103–123)	104 (92–112)	NS
VC < $80\%_{pred}$, *n*	1	0	1	NS
FVC, $\%_{pred}$	109 (99–123)	116 (106–125)	107 (96–114)	NS
FEV_1, $\%_{pred}$	105 (98–125)	119 (102–128)	103 (97–116)	NS
FEV_1 < $80\%_{pred}$, *n*	1	0	1	NS
FEV_1/VC, %	82 (78–84)	82 (78–84)	83 (78–86)	NS
FEV_1/VC < 0.7, *n*	1	0	1	NS
FEV_1/FVC, %	83 (80–85)	82 (80–84)	83 (80–86)	NS
$MMEF_{25–75}$, $\%_{pred}$	109 (93–123)	110 (103–121)	105 (92–125)	NS
TLC, $\%_{pred}$	100 (90–109)	108 (98–114)	97 (85–105)	NS
TLC < $80\%_{pred}$, *n*	5	1	4	NS
TGV, $\%_{pred}$	87 (75–101)	93 (75–105)	85 (75–95)	NS
IC, $\%_{pred}$	114 (102–126)	114 (109–137)	114 (95–125)	NS
RV, $\%_{pred}$	88 (81–97)	89 (81–97)	85 (73–89)	0.03
RV < $80\%_{pred}$, *n*	8	0	8	0.011
RV/TLC, $\%_{pred}$	83 (78–89)	108 (98–119)	82 (79–86)	NS
Raw_{tot}, kPa·s/L	0.22 (0.17–0.29)	0.23 (0.19–0.30)	0.2 (0.17–0.29)	NS
DLCO, $\%_{pred}$	77 (68–89)	87 (76–95)	72 (67–83)	0.014
DLCO < $80\%_{pred}$, *n*	20	5	15	0.058
DLCO/VA, $\%_{pred}$	90 (82–98)	96 (86–103)	87 (79–93)	NS
MIP, $\%_{pred}$	108 (89–135)	114 (91–137)	102 (85–129)	NS
MIP decreased, *n*	5	1	4	NS
MEP, $\%_{pred}$	87 (72–105)	86 (74–108)	87 (71–103)	NS
MEP decreased, *n*	11	4	7	NS

Note: data are presented as median (lower quartile — upper quartile); * — Mann–Whitney test applied to comparison of subgroups 1 and 2; NS — no significant differences found between subgroups 1 and 2.

In addition, given that muscle strength directly depends on protein metabolism, it is advisable to analyze the relationship of total blood protein with MIP and MEP values, and in case of their decrease, consider nutritional support for the patients.

Thus, RM strength test is an important addition to the traditional pulmonary function tests in terms of information concerning the functional state of the RM that can be used in the context of prevention of pathological conditions and adequate clinical treatment.

CONCLUSIONS

Patients that recovered from COVID-19 of varying severity exhibit decreased maximum static mouth pressure, specifically, expiratory pressure in 31% of cases and inspiratory pressure in 14% of cases. There were identified no significant dependencies between MIP/MEP values and the parameters of ventilation and pulmonary gas exchange. It is reasonable to add RM tests to the COVID-19 patient examination plan in order to detect their dysfunction and timely initiate a medical rehabilitation intervention.

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