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Respiratory Muscle Training with an App-Based Device Improves Persistent Shortness of Breath in Patients after SARS-CoV-2 Infection – a Randomized Controlled Trial

Atemmuskulaturtraining mit einem App-basierten Trainingsgerät verbessert Kurzatmigkeit nach SARS-CoV-2 Infektion – eine randomisiert kontrollierte Studie

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Summary

› **Background:** Post-acute sequelae of SARS-CoV-2 infection (PASC) is defined as persistent or newly experienced symptoms after the disease. Shortness of breath is a common symptom reported by individuals with PASC. Respiratory muscle training (RMT) to strengthen respiratory muscles (e.g diaphragm, intercostal muscles) can improve symptoms in various diseases. The aim of the study therefore was to investigate the effectiveness of RMT for the reduction of PASC-related shortness of breath by a daily home-based app-guided training intervention.

› **Methods:** Sixteen patients (age 32.0±16.1 years (Mean±SD), female N=9) suffering from persistent shortness of breath after SARS-CoV-2 infection were randomized to either an Intervention-first-group (IfG) starting with RMT immediately or an Intervention-second-group (IsG) receiving RMT after a control period of one month. RMT was conducted using a commercially available training device and daily app-based RMT instructions. Severity of respiratory symptoms was measured using the St. Georges Respiratory questionnaire (SGRQ). Ventilation parameters and peak oxygen consumption (VO_{2peak}) were assessed by cardio pulmonary exercise testing (CPET).

› **Results:** Fifteen patients completed the study. The RMT intervention led to a significant improvement of subjective symptoms (SGRQ reduction: -11.41±8.28, p<0.001, d=-1.38, 95% CI [-0.65, -2.08], Subjective health: 12.43±11.51%, p=0.001, d=1.08, 95% CI [0.40, 1.73]) and improved maximum ventilation (8.94±9.23 l/min, p=0.003, d=0.97, 95% CI [0.31, 1.59]). Exercise capacity and VO_{2peak} significantly increased in a subgroup of patients with low VO_{2peak} values at study inclusion ($relP_{max}$: 0.24±0.26 W/kg, p=0.022, d=0.95, 95% CI [1.13, 1.72]), $relVO_{2peak}$: 2.98±5.79 ml/min*kg, p=0.013, d=1.10 95% CI 0.21,1.89]). During the control period (only IsG) symptoms, maximum power output and VO_{2peak} remained unchanged with only maximum ventilation significantly decreasing.

› **Conclusions:** Patients with persistent shortness of breath after SARS-CoV-2 infection benefit from intense, regular RMT over one month. Patients reported an increase in overall health status and an improvement in VO_{2peak} and exercise capacity was reached in those with low VO_{2peak} values at the beginning.

KEY WORDS:
Rehabilitation, Covid-19, Dyspnea, Symptom Management

Zusammenfassung

› **Hintergrund:** Langzeitfolgen einer SARS-CoV-2-Infektion (Post-Covid-Syndrom, PCS) sind werden als anhaltende oder neu auftretende Symptome nach der Krankheit definiert. Kurzatmigkeit ist ein häufiges Symptom bei Personen mit PCS. Atemmuskeltraining (RMT) zur Verbesserung der Funktion der Atemmuskulatur (z. B. Zwerchfell, Zwischenrippenmuskulatur) kann bei verschiedenen Erkrankungen zu einer Symptomverbesserung führen. Ziel der Studie war es daher, die Wirksamkeit von RMT zur Reduzierung von PCS-bedingter Atemnot durch eine tägliche, app-gesteuerte Trainingsintervention zu Hause zu untersuchen.

› **Methoden:** Sechzehn Patienten (Alter 32,0±16,1 Jahre, weiblich N=9) mit anhaltender Kurzatmigkeit nach SARS-CoV-2-Infektion wurden in 2 Gruppen randomisiert. Eine Gruppe begann sofort mit dem Atemmuskeltraining (IfG) die 2. Gruppe begann das Training nach einer Kontrollphase von einem Monat (IsG). Das Atemmuskeltraining wurde mit einem kommerziell erhältlichen Trainingsgerät und app-basierten Trainingsplänen durchgeführt. Die Schwere der Atemwegssymptome wurde mit dem St. Georges Respiratory Questionnaire (SGRQ) gemessen. Ventilationsparameter und maximale Sauerstoffaufnahme (VO_{2peak}) wurden mittels kardiopulmonalem Belastungstest (CPET) erfasst.

› **Ergebnisse:** Fünfzehn Patienten beendeten die Studie. Die RMT-Intervention führte zu einer signifikanten Verbesserung der subjektiven Symptome (SGRQ-Reduktion: -11,41±8,28, p<0,001, d=-1,38, 95% CI [-0,65, -2,08], subjektive Gesundheit: 12,43±11,51%, p=0,001, d=1,08, 95% CI [0,40, 1,73]) und verbesserte die maximale Ventilation (8,94±9,23 l/min, p=0,003, d=0,97, 95% CI [0,31, 1,59]). Die Belastungsfähigkeit und VO_{2peak} nahmen signifikant bei einer Untergruppe von Patienten zu, die zu Studienbeginn niedrige VO_{2peak}-Werte hatten ($relP_{max}$: 0,24±0,26 W/kg, p = 0,022, d = 0,95, 95% CI [1,13, 1,72]), $relVO_{2peak}$: 2,98±5,79 ml/min*kg, p=0,013, d=1,10 95% CI [0,21, 1,89]). Während der Kontrollperiode (nur IsG) blieben Symptome, maximale Leistung und VO_{2peak} unverändert.

› **Schlussfolgerungen:** Patienten mit anhaltender Kurzatmigkeit nach SARS-CoV-2-Infektion profitieren von intensivem, regelmäßigem Atemmuskeltraining über einen Monat.

SCHLÜSSELWÖRTER:
Rehabilitation, Covid-19, Atemnot, Symptomkontrolle

Introduction

Long COVID is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation (18). The prevalence of long COVID (also known as post-acute sequelae of SARS-CoV-2 infection (PASC)) cannot yet be accurately estimated or determined. Studies have reported varying estimates of the proportion of individuals who experience persistent symptoms after recovering from acute SARS-CoV-2, ranging from a few percent to over 50% in some populations (9, 15). ›

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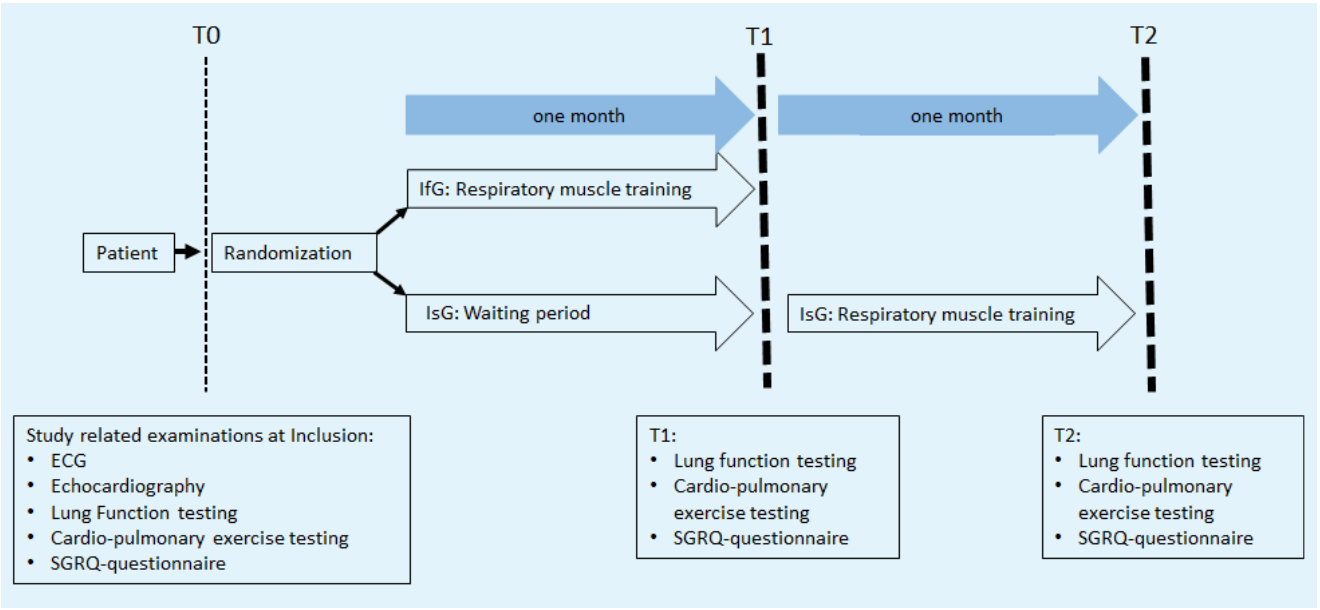

Figure 1

Study design and examinations at the respective time points. T0:study inclusion and randomization; T1:one month control (both groups); T2: two month control (IsG). IfG=Intervention first group, IsG=Intervention second group, SGRQ=St. Georges respiratory questionnaire.

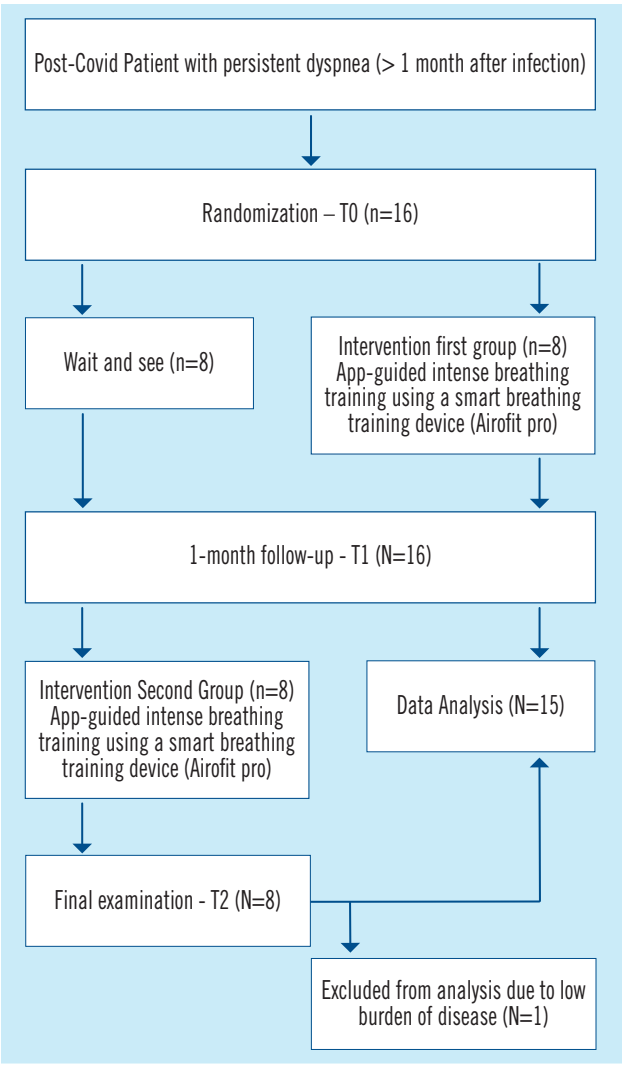

Figure 2

CONSORT-diagram of the progress through the study.

However, the true prevalence of PASC may be underestimated, as many individuals with persistent symptoms may not seek medical attention or may not be included in studies.

Shortness of breath is a common symptom reported by individuals with PASC and can have a significant impact on their quality of life (15). There is evidence that suggests that organic dysfunction can contribute to shortness of breath in individuals with PASC: Lung changes such as inflammation, fibrosis, and decreased lung function (one second capacity – FEV1, vital capacity – VC) may occur in people with PASC, contributing to shortness of breath. (3, 5, 16). Also cardiovascular changes, such as myocarditis, have been found (4, 12). However, in the majority of patients suffering from persistent shortness of breath in PASC, there is no pulmonary or cardiac damage attributable for the symptom. (1). Therefore, there is a lack of therapy recommendations based on pathophysiology.

Potential treatments for shortness of breath in PASC may include (12): 1) Lung rehabilitation: Exercise programs designed to improve lung function and reduce dyspnea; 2) Oxygen therapy: Supplementing the body with oxygen to improve breathing and reduce dyspnea; 3) Medications: Prescription drugs such as bronchodilators, corticosteroids, and antibiotics may be used to address underlying medical conditions that contribute to shortness of breath; 4) Psychological interventions: Counseling and other psychological interventions may be useful for addressing psychological factors, such as anxiety and stress, that contribute to shortness of breath; 5) Respiratory muscle training (RMT).

RMT is a type of exercise aimed at strengthening the muscles used for breathing, including the diaphragm and intercostal muscles and improving its function and efficiency. Training typically involves performing exercises that put specific demands on the respiratory muscles, such as deep breathing, coughing, or using devices that resist inhaling or exhaling.

A number of studies have demonstrated that RMT can improve breathing function and reduce symptoms of shortness of breath in patients with various respiratory conditions, such as chronic obstructive pulmonary disease (COPD), asthma, and

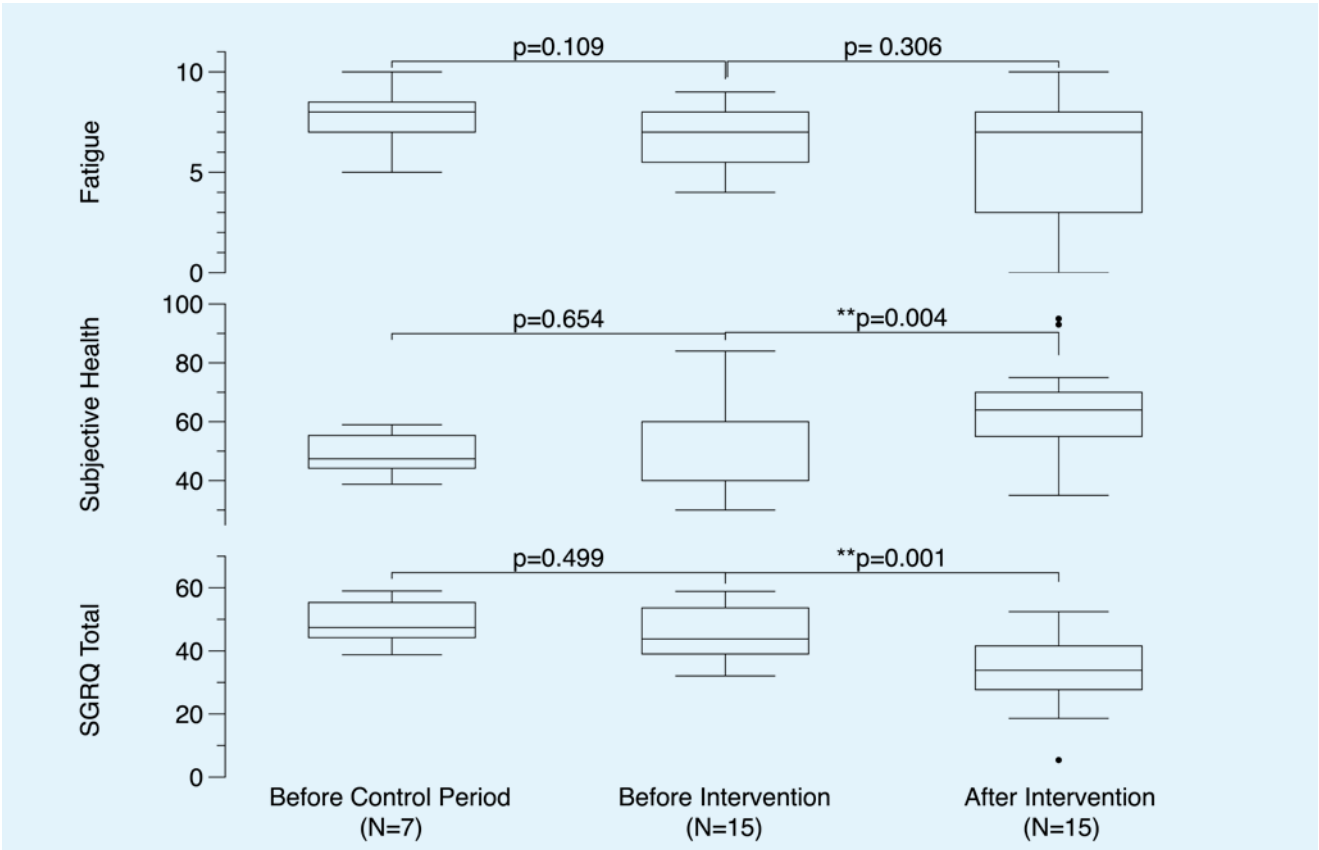

Figure 3

Results of the questionnaire data. Fatigue assessed by a visual analogue scale (VAG) ranging from 0 to 10. Subjective health status assessed by a VAG ranging from 0 to 100. SGRQ Total=Total points reached in the St. Georges respiratory questionnaire.

heart failure (2, 14). The evidence base for respiratory muscle training as a treatment for shortness of breath in PASC is still developing with first studies showing a positive effect on symptom severity and functional parameters like 6-minute-walk test, (6, 13) but more research is needed to determine its effectiveness in this population (7, 14).

The aim of this study was to investigate the subjective and objective change in PASC-related shortness of breath with one month of daily RMT. The participants were randomized in two groups using a cross-over design. Based on the first studies conducted (6, 13) reduction in subjective and objective symptoms is expected.

Material and Methods

Study Design
Participants

Study participation was offered to all patients referring to the department of the Division of Sports- and Rehabilitation medicine of Ulm University hospital, with persistent shortness of breath more than 30 days after PCR- proven infection with SARS-CoV 2, after exclusion of infection related heart (ECG, Echocardiography) or lung damages (Bodyplethysmography) explaining the symptom. Decision for study inclusion was made by the treating physician. The treating physicians, the authors were aware of the identity of the individual patients during and after data collection. CONSORT reporting guidelines according to (17) were used. The study design as well as the examinations at the respective time points: are shown in figure 1.

Patients were randomized into two groups (allocation ratio 1:1). The Intervention-first-group (IfG) immediately started RMT after randomization at T0. The Intervention-second-group (IsG) underwent an additional month without RMT as a control period and started RMT after a second examination at T1.

The study period lasted from March 2022 (first patient in) till December 2022 (last patient out). The approval for this study was obtained from the ethical board of Ulm University (86/22). Written informed consent was obtained from all subjects before the enrollment in the study. This trial was registered in the German register of clinical trials (DRKS00028645) and was carried out according to the declaration of Helsinki.

St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire (SGRQ) is a widely used patient-reported outcome measure (PROM) designed to assess health-related quality of life (HRQoL) in individuals with respiratory diseases. The SGRQ is a self-administered questionnaire that measures three dimensions of HRQoL related to respiratory disease: symptoms, activity, and impact.

The SGRQ consists of 50 items, which are answered on a 5-point scale from "very much" to "not at all." The scores from the questionnaire are used to generate an overall score, which ranges from 0 to 100, with higher scores indicating a lower quality of life and more severe respiratory symptoms. The SGRQ has been validated for use in individuals with a range of respiratory diseases, including chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung disease (11). The SGRQ is available in german.

Considering the assessment of treatment efficacy in obstructive airway disease a change of score of 4 points is considered slightly efficacious, a change of 8 points moderately efficacious and 12 points highly efficacious (10). ›

Table 1

Patients baseline results and differences after the control and intervention period. Differences after control derived from Intervention-second-group only (IsG) Δ T1-T0. Differences after Intervention are Intervention-first-group (IfG): Δ T1-T0, IsG: Δ T2-T1. Data are Mean±standard deviation. Signifcant differences indicated by * p< 0.05, ** p < 0.01(Wilcoxon-test). CPET= Cardiopulmonary exercise testing; $relP_{max}$=maximum power output per body mass; $relVO2_{peak}$=maximum oxygen uptake per body mass; RQ_{max}=respiratory quotient at maximum; VE_{max}=maximum ventilation, VT_{max}=maximum tidal volume; BF_{max}=maximum breathing frequency; HR_{max}=maximum heart rate.

	T0	DIFFERENCES AFTER CONTROL (ISG) (T1)	DIFFERENCE AFTER INTERVENTION (ISG AND IFG) (T1/T2)
Age [y]	32.0±16.1		
Height [cm]	175.0±9.6		
Weight [kg]	76.5±16.6		
Subjective health [%]	49.6±16.9	-7.3±17.3	12.5±11.5 **
Fatigue	6.7±1.5	-1.1±1.9	0.9±3.3
SGRQ Scores			
Total	47.12±8.0	-3.1±11.6	-11.4 ±8.3 **
Symptoms	50.8±14.7	-2.4±16.5	-10.14±13.8**
Activity	56.2±11.1	-1.2±12.8	-15.1±12.7**
Impacts	40.0±9.3	-4.5±13.5	-9.4±8.2**
CPET			
$relP_{max}$ [W/kg]	2.8±0.7	0.16±0.8	0.15±0.29 *
$relVO_{2peak}$ [ml/kg*min]	29.8±5.7	-2.6±3.9	3±5.8 *
RQ_{max}	1.13±0.09	0.03±0.07	0.01±0.07
VE_{max} [l/min]	76.8±18.4	-9.6±11.2*	8.9±9.3 *
VT_{max} [l]	2.1±0.8	-0.04±0.27	0.17±0.28 *
BF_{max} [1/min]	39.3±10.1	-6.2±8.23*	0.2±4.77
HR_{max} [1/min]	166±16.3	-6.5±13.2	4.7±8.3 *

Other Questionnaires

Patients subjective fatigue was assessed using a visual analogue scale (VAS) ranging from 0 to 10. Patients perception of actual health status on the day of examination was assessed using a VAS ranging from 0 to 100.

Cardiopulmonary Exercise Testing (CPET)

All patients underwent CPET to assess their Aerobic Capacity and the breathing patterns, combined with electrocardiogram (AMEDTEC Cardiopart 12B, AMEDTEC Medizintechnik Aue GmbH, Aue, Germany) on a cycle ergometer (Lode Excalibur Sport, Lode B.V., Groningen,The Netherlands). A ramp wise incremental test protocol (25 W + 15 W/min) till voluntary exhaustion was used to assess respiratory parameters during CPET utilizing a breath-by-breath metabolic analyzer (Quark, Cosmed, Rome, Italy).

Respiratory Muscle Trainer

Airofit Pro is a respiratory training device (Airofit, Copenhagen, Denmark). The device is designed to help individuals improve their breathing and respiratory muscle strength through resistance training. The device allows users to adjust the level of resistance during inspiration and exspiration through adjustable valves, which can be further adjusted as their breathing and respiratory muscles become stronger. A flowmeter which connects to the smartphone is build into the device, allowing real time feedback. The Airofit app allows users to connect their Airofit respiratory training device to their smartphone, which enables them to track progress, set goals, and monitor their breathing and respiratory muscle strength during exercise. The application provides users with personalized training programs (based on testing results within the app) and feedback on their progress, and also allows them to share their results with healthcare professionals. Within the app videos are provided for the correct execution of the exercises. The app was set to offering two sessions a day, each lasting 3-6 minutes depending on the session content. The use of the device and app were explained at the start of the intervention. The guidance within the intervention period was provided by the app by giving daily training recommendations and push messages as a reminder. We aimed for at least one daily session between 3 and 6 minutes as suggested by the manufacturer of the device.

Endpoints

Primary endpoint: Improvement of dyspnea symptoms through breathing training (SGRQ, visual analog scale for subjective health status). Secondary Endpoints: Physical performance (maximum oxygen uptake, maximum minute ventilation, breathing economy, as calculated by the CPET Interface, Omnia, Cosmed, Rome, Italy).

Statistics

Data analyses were performed using SPSS Version 28 (IBM Corp, NY, USA). To compare intervention-related changes paired Wilcoxon-Tests were conducted. An α-level of 0.05 was considered significant. Data presented in the results are mean±SD if not otherwise indicated. Sample size was determined a priori using G*Power 3.1 (8). Under the assumption of an effect size of d=0.70 of RMT on subjective shortness of breath and an intra-individual standard deviation of 0.6, at a power of 1-ß=0.9, and a significance level of alpha=0.05, N=20 patients are necessary for the study.

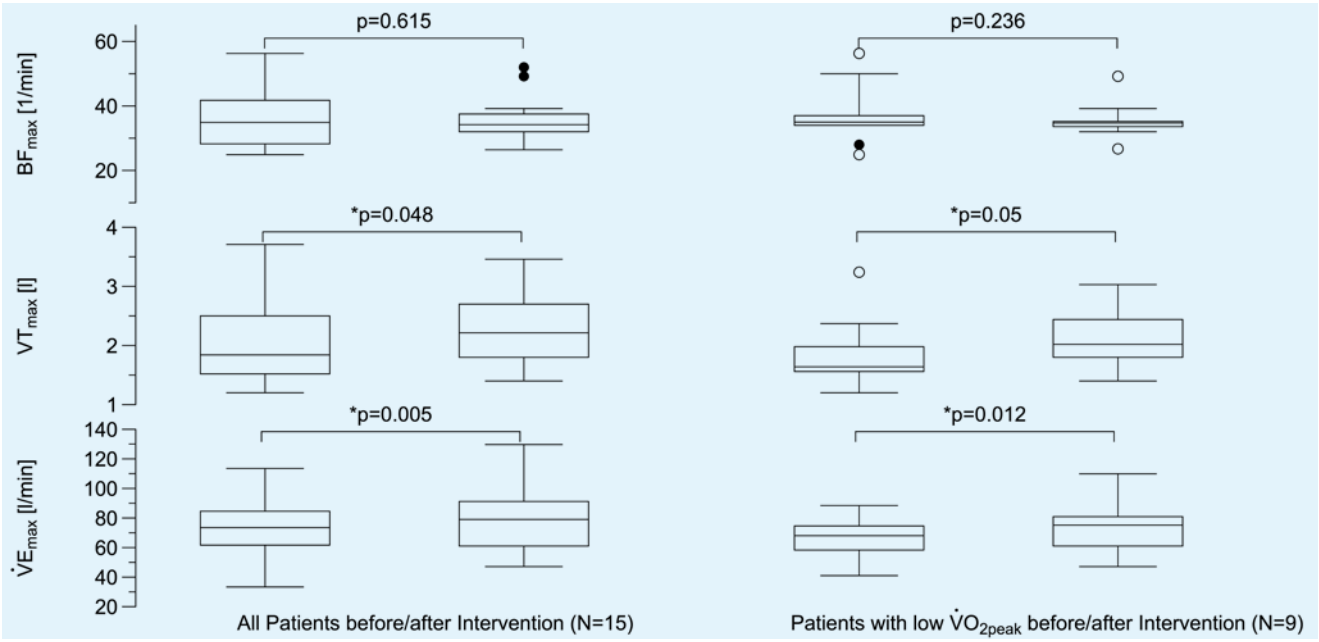

Figure 4

Changes in ventilation parameters during the intervention period. Left column: whole group, right column: patients with maximum oxygen uptake (VO_{2peak}) below the normal values (Wasserman 2012) at T0. Significant differences indicated by * with p-values in the graph (Wilcoxon-test). BF=Breathing frequency, VT=Tidal volume, VE=Ventilation.

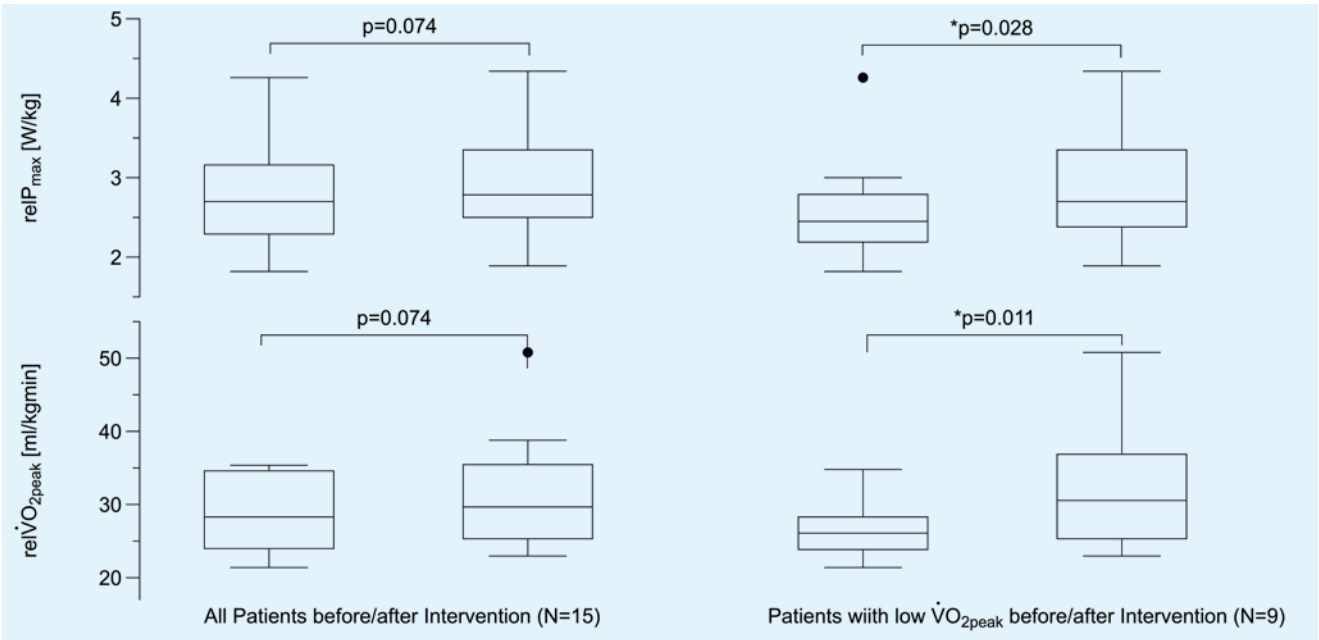

Figure 5

Changes in relative power output (relPmax) and relative oxygen uptake ($relVO_{2peak}$) during the intervention period. Left column: whole group, right column: patients with VO_{2peak} below the normal values (19) at T0. Significant differences indicated by with p-values in the graph (Wilcoxon-test).

Results

A total of 16 patients were randomized and completed the study between May and December 2022, the intended study end. One patient was excluded from analysis due to very low level of symptom severity corresponding to a healthy individual in the SGRQ at T0 (figure 2). There were no adverse events during the study.

From the 15 patients (6 male, 9 female) included in the analysis 8 (3 male, 5 female) were randomized into the Intervention first group and 7 (3 male, 4 female) in the Intervention second group. There were no significant differences between the two groups at baseline. Patients baseline characteristics at randomization (T0) are shown in table 1.

Control Period

The patients randomized into the IsG (N=7) were examined again one month after T0 (T1) to assess the spontaneous development of symptoms and alterations in CPET. Although there was a significant change in subjective health (14.14±10.25, p=0.011, d=1.38, 95% CI [0.29, 2.42]), neither fatigue (-1.14±1.86, p=0.156, d=-0.61, 95% CI [-1.41, 0.22]) nor the results measured by ›

the SGRQ (Total: -3.1±11.64, p=0.51, d=-0.27 95% CI [-1.01, 0.50], Symptoms: -2.38±16.50, p=0.72, d=-0.14, 95% CI [-0.88, 0.43], Activity: -1.15±12.77, p=0.82, d=-0.09, 95% CI [-0.83, -0.67], Impacts: -4.53±13.50, p=0.41, d=-0.34, 95% CI [-1.09, 0.44]) changed during the control-period. There was a significant decrease in maximum ventilation ($\dot{V}E_{max}$) (-9.56±11.23 l/min, p=0.033, d=-0.85 95% CI [-1.71, 0.05]) during that time. All other CPET parameters showed no significant differences after the control-period (table 1).

Intervention Period

Fifteen patients completed the training intervention. The number of sessions and total training duration varied non-significantly between the patients and adherence to the app-based training was very high (total duration 163 ±74 minutes, number of training sessions 49±19). The results of control period and intervention period are shown in table 1.

The training intervention reduced dyspnea symptoms significantly indicated by a significant decrease of total points (-11.41±8.28, p < 0.001, d=-1.38 95% CI [-0.65, -2.08]) as well as in the different dimensions of the SGRQ (Symptoms: -10.14±13.83, p=0.013, d=-0.733, 95% CI [-0.15, -1.30], Activity: -15.07±12.71, p < 0.001, d=-1.19, 95% CI [-0.51, -1.84], Impacts: -9.38±8.22, p<0.001, d=-1.14, 95% CI [-0.47,-1.79]). Subjective health significantly increased during the intervention period (12.43±11.51, p=0.001, d=1.08, 95% CI [0.40, 1.73]), while fatigue remained unchanged (-0.93±3.34, p=0.317, d=0.28, 95% CI [-0.81, 0.26]) (figure 3).

The intervention significantly increased $\dot{V}E_{max}$ (8.94±9.23 l/min, p=0.003, d=0.97 95% CI [0.31, 1.59]) due to a significant increase in tidal Volume (VT_{max}) (0.17±0.28 l, p=0.041, d=0.61 95% CI [0.03, 1.17]) in all patients. There was no significant change in maximum relative power output ($relP_{max}$) (0.15±0.29 W/kg, p=0.075, d=0.52 95% CI [-0.05, 1.01]) or relative peak oxygen consumption ($rel\dot{V}O_{2peak}$) (2.98±5.79 ml/min*kg, p=0.076, d=0.52 95% CI [-0.05, 1.07]) after the training intervention for the whole group (figure 4 and 5).

A subanalysis of N=9 patients within the study who had impaired $\dot{V}O_{2peak}$ values before the intervention (below 100% of the expected normal value (19)) showed a significant increase in $relP_{max}$ (0.24±0.26 W/kg, p=0.022, d=0.95 95% CI [1.13, 1.72]) and $rel\dot{V}O_{2peak}$ (2.98±5.79 ml/min*kg, p=0.013, d=1.10 95% CI 0.21, 1.89]) (figure 5).

Discussion

The results show, that patients complaining about persistent shortness of breath after SARS-CoV-2 benefit from regular RMT over a period of one month. The impact of shortness of breath on overall health, daily life and perceived well-being was significantly reduced, as shown by the results of the St. George's Respiratory Questionnaire. The mean score reduction of 10 points would correspond to a moderately to highly efficacious treatment in the context of obstructive airway diseases (10). The effect was associated with the training intervention since there was no score reduction at all during the control period. Accompanied with the reduction of subjective dyspnea symptoms patients perceived overall health status increased over the intervention period. This is in line with other studies: Del Corral et al. found an increased quality of life in patients with PASC after an 8 weeks intense telerehabilitation program (6). Mc Narry et al reached similar results by an 8 weeks intervention on the perception of breathlessness (13).

The results of CPET showed a significant increase in $\dot{V}E_{max}$ after RMT due to an increase of VT_{max} indicating a strengthening of the respiratory muscles especially the diaphragm due to the training. $rel\dot{V}O_{2peak}$ and $relP_{max}$ did not change significantly in the whole study population. In a subgroup of patients with low $\dot{V}O_{2peak}$ values at study inclusion the training intervention significantly increased $rel\dot{V}O_{2peak}$ and $relP_{max}$.

The use of the Airofit pro as a respiratory muscle trainer was found to be feasible and was associated with high patient adherence to daily exercise recommendations probably due to the simple usage of the device and well executed app-guidance. Straightforward usability of a respiratory training device is of special importance in the context of PASC since the number of patients suffering from the syndrome is high and access to rehabilitation facilities is limited.

Limits and Strengths

The significance of the findings of this study is limited by the small sample size. This was partly addressed by a cross-over study design and the well-defined study cohort. Calculated effect sizes indicated large effect sizes for the main findings. However, larger studies are needed to fully evaluate the efficacy of RMT compared with a control group and especially compared with various proposed alternative intervention strategies.

Conclusion

Patients suffering from persistent shortness of breath after SARS-CoV-2 can benefit from RMT regarding symptom control and economization of the breathing pattern during exercise. Patients suffering from persistent shortness of breath and having $\dot{V}O_{2peak}$ values below age-, weight-, height-, and sex related normal values might even gain an additional benefit by improving their $\dot{V}O_{2peak}$ and therefore their P_{max} by respiratory muscle training. Our results suggest that RMT may be a promising intervention strategy in the clinical context of rehabilitation of patients with persistent shortness of breath after SARS-CoV-2. The efficacy of RMT should be further investigated in larger intervention studies.

Conflict of Interest
The authors have no conflict of interest.

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