Physiology International 108 (2021) 4, 427–439
DOI: 10.1556/2060.2021.00185

AKADÉMIAI KIADÓ

The use of near-infrared spectroscopy for the evaluation of a 4-week rehabilitation program in patients with COPD

BOTOND SZUCS[1], MATE PETREKANITS[2], MONIKA FEKETE[3] and JANOS T VARGA[4*]

[1] PharmaFlight Research and Training Center, Debrecen, Hungary

[2] Institute of Exercise Physiology and Sport Medicine, University of Physical Education, Budapest, Hungary

[3] Department of Public Health, Faculty of Medicine, Semmelweis University, Budapest, Hungary

[4] Department of Pulmonology, Semmelweis University, Budapest, Hungary

Received: July 5, 2020 • Accepted: August 28, 2021
Published online: October 14, 2021

ABSTRACT

Background: Near-infrared spectroscopy (NIRS) technology can evaluate muscle metabolism and oxygenation. NIRS-based oximeters can measure skeletal muscle oxygen delivery and utilization during static and dynamic work non-invasively. Our goal was to assess the value and usability of NIRS technology in chronic obstructive pulmonary disease (COPD) rehabilitation program. *Methods:* Forty patients with COPD participated in a 4-week inpatient rehabilitation program that included breathing exercises and personalized cycle/treadmill training adjusted to the functional capacity, physical activity and comorbidities of the patients. A NIRS muscle oxygen monitor was used to measure tissue oxygenation and hemoglobin levels. Total hemoglobin index, average muscle oxygenation, minimal and maximal muscle oxygenation were recorded before and after the rehabilitation program. *Results:* Rehabilitation resulted improvement in 6 min walking distance (6MWD:335.3 ± 110. vs. 398.3 ± 126.2 m; $P < 0.01$), maximal inspiratory pressure (MIP: 57.7 ± 22.7 vs. 63.6 ± 18.0 cmH_2O; $P < 0.01$), chest wall expansion (CWE: 2.84 ± 1.26 vs, 4.00 ± 1.76 cm; $P < 0.01$), breath hold time (BHT: 25.8 ± 10.6 vs. 29.2 ± 11.6 s; $P < 0.01$) and grip strength (GS: 24.9 ± 11.9 vs. 27.0 ± 11.4 kg; $P < 0.01$). Quality of life improvement was monitored by COPD Assessment Test (CAT: 17.00 ± 8.49 vs. 11.89 ± 7.3, $P < 0.05$). Total hemoglobin index (tHb: 12.8 ± 1.3% vs. 12.8 ± 1.4), average muscle oxygenation (SmO_2: 67.5 ± 14.4% vs. 65.2 ± 20.4%) showed a tendency for

* Corresponding author. Tel: +36 1 459 1500; fax: +36 1 214 2498. E-mail: varga.janos_tamas@med.semmelweis-univ.hu

improvement. Maximal muscle oxygenation decreased (SmO_2 max: 98.0 ± 20.5% vs. 90.1 ± 14.3%; $P < 0.01$). Minimal muscle oxygenation increased (SmO_2 min: 42.6 ± 12.6% vs. 54.8 ± 14.3%; $P < 0.01$). *Conclusions:* NIRS results showed that muscle oxygenation and microcirculation can be described as a high-risk factor in COPD patients. The 4-week rehabilitation improves functional parameters, quality of life and tissue oxygenation levels in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous clinical syndrome found in 6–8% of the population [1]. COPD patients experience functional and structural changes of the respiratory system that deeply influence cardiovascular function [2].

The main part of COPD patient's rehabilitation is physical therapy, the goal is to get the patients' functional capacity back. Long term effect of physical rehabilitation is lower usage rate of medication, fewer exacerbations and if exacerbations occur, their impact is milder [3]. Exercise training also causes changes in muscle perfusion, peripheral muscle activity and function [4].

Muscle oximetry, based on near-infrared spectroscopy (NIRS), is able to non-invasively provide information about these changes in oxygenation and hemodynamics in muscle tissue based on the oxygen-dependent characteristics of near-infrared light. NIRS has been utilized to investigate local muscle oxidative metabolism at rest and during different exercise modalities since the end of the 1980s. Reviews of NIRS methodology, medical applications and potential limitations have been previously published in detail [5]. NIRS technology has been used to evaluate blood flow and muscle oxygen availability in COPD patients during exercise [6]. During our study our goal was to measure the resting oxygenation levels, as this might contribute to a better understanding of individual differences in physical rehabilitation and exercise tolerance.

NIRS cannot differentiate between oxyhemoglobin (O_2Hb) and oxymyoglobin (O_2Mb) or deoxyhemoglobin (HHb) and deoxymyoglobin (HMb) [7]. This means that NIRS signals are the result of the weighted average of oxygen saturations of the heme group of hemoglobin (Hb) in the vascular bed (small arteries, arterioles, capillaries, venules and small veins) and the heme group of myoglobin (Mb) in the muscle fibers [8]. Considering that capillaries contribute to 90% of the total blood volume in the muscle [9], and, under normal conditions, all regions of the muscle receive nearly fully oxygenated arterial blood, oxygenation changes would mostly reflect changes in capillary (Hb related) and intracellular (Mb-related) oxygen levels. Direct comparisons are difficult and usually limited to trends in the derived signal because these units are relative in nature. To increase the robustness of the relative values, it is often recommended to use a saturation in a percentage using the following equation [10]:

$$SmO_2 = \frac{O_2Hb}{O_2Hb + HHb} \times 100.$$

In SmO_2, the m indicates that the saturation is intended to be isolated to the muscle layer. This is important because the spot of the measurement, the subcutaneous fat layers might have serious impact on data quality and actual values [11].

Muscle oximetry has been successfully and reliably used in both laboratory and applied sport settings, with specific measures such as muscle oxygenation level, deoxygenation rate, and

reoxygenation rate being utilized for assessing muscle oxidative function, following specific training interventions [12]. The objective of our measurement was to investigate the possibility of using NIRS technology during resting measurements to assess actual muscle oxygenation and local oxidative condition of COPD patients participating in pulmonary rehabilitation. Our hypothesis was that the data provided by NIRS technology and collected during a resting measurement and not in an active state such as exercise will correlate with the results and changes in classic clinical parameters on an individual level. If our hypothesis is correct, the low cost and easy to use NIRS sensors can be used as a valuable tool to monitor COPD patients' rehabilitation progress even during a resting measurement.

MATERIALS AND METHODS

Study subjects

Forty patients with COPD (FEV_1: 45 ± 20% pred, age: 65.4 ± 7.4 years (51–78), BMI: 26 ± 5 kg m^{-2}, male/female: 21:19) participated in this study. The pharmacotherapy of patients was based on the international GOLD guideline, mostly patients were on dual bronchodilator therapy, 5 of them were on ICS+LABA+LAMA combination.

The treatment of co-morbidities, such as atherosclerosis, hypertension and diabetes was based on international guideline, too. The study protocol was approved by the Ethical Committee of the National Korányi Institute for Pulmonology with 25/2017 registration number, and the study was registered at ISRCTN registry with ISRCTN13019180 ID.

It was an observational study using general management in the Department of Pulmonary rehabilitation as a non-interventional study. All patients gave consent for participation in the study.

Patients' characteristics including blood gas analysis are presented in Table 1. Inclusion criteria were the following: age 40 or above, forced expiratory volume in one second (FEV_1) < 70%pred

Table 1. Patients' characteristics

Characteristics (n = 40)	
Age (years)	65.47 ± 7.39
Male: female	21:19
BMI (kg m^{-2})	27.99 ± 6.98
FEV_1 (%pred)	45.43 ± 20.2
Hypertension	35 (87.5%)
Diabetes	12 (30%)
Atherosclerosis	30 (75%)
Pulmonary hypertension	10 (25%)
pH	7.43 ± 0.06
pO_2 (mmHg)	63 ± 8
pCO_2 (mmHg)	39 ± 3

BMI: body mass index; FEV_1: forced expiratory volume in one second, pO_2: partial pressure of the oxygen, pCO_2: partial pressure of carbon-dioxide.

and FEV_1/forced vital capacity (FVC) < 0.7, more than 10 years of smoking in their anamnesis with COPD diagnosis, symptomatic patients in terms of dyspnea and reduction in exercise tolerance, absence of type II respiratory failure and good compliance of the patient. Exclusion criteria were the following: any condition which did not allow the participation in a training program because of joint disease, coronary disease, heart failure or not a good compliance in the previous treatment of COPD or absence of motivation to be on the rehabilitation program.

Training program

Patients took part in an inpatient, complex pulmonary rehabilitation program with chest wall-stretching, controlled breathing techniques and training, as well as personalized exercise training by cycling and treadmill 2–3 times for 20–30 min a day for 4 weeks. Six-minute walking distance (6MWD) [13], lung function [14], chest wall expansion (CWE) [15], grip strength [16], maximal inspiratory pressure (MIP) [17] and breath holding time (BHT) [18] were measured at the start and at the end of the rehabilitation program. The quality of life and dyspnea were evaluated by CAT [19] and mMRC [20].

The breathing exercises were performed on an open-air corridor to take advantage of the special microclimate of the Hospital [21]. The patients learned controlled breathing and stretching technics, chest and spine mobilization exercises and muscle strengthening techniques. The personalized training was performed on exercise bicycles and treadmills with continuous or interval training [22]. The training set was according to the patients' requirements. The protocol was defined considering the stage of COPD, the actual status of the heart, comorbidities and blood gas value. At the beginning and at the end of the program, the different functional parameters were measured.

Our patients performed respiratory training in the morning, chest wall mobilization, learning controlled breathing techniques (it lasted 30 min), inhalation, expectoration, smoking cessation and a personalized training were part of the whole rehabilitation program. The personalized training was based on continuous or interval type of cycle- and/or treadmill training for 10–30 min, 2–3 times a day at a level of 60–80% of peak work rate [23, 24]. The duration was 4 weeks. The intensity was between 60 and 80% of peak work rate and it was progressive keeping Borg dyspnea scale breathlessness and leg fatigue on grade No. 7.

Clinical measurements

6-minute walking distance (6MWD). The 6MWD was measured in the corridor of the National Korányi Institute for Pulmonology, according to the international guidelines [13]. Oxygen saturation and heart rate were measured as supportive data before, during and after executing the task, and the exertion of the patients was evaluated with a modified Borg-scale. Patients had to walk as fast as possible [13].

Pulmonary function. All patients underwent post-bronchodilator pulmonary function tests including spirometry measurements, which were carried out according to ATS/ERS guidelines (V_{max} 229 and Autobox 6,200, Sensormedics) [14]. COPD patients inhaled 400 µg salbutamol 20 min before testing.

Chest wall expansion (CWE). Chest wall expansion measures the difference of chest circumferences between deep inspiration and expiration. It is measured at the level of processus xyphoideus [15].

Grip strength measurement (GS). Kern hand grip dynamometer (2016 Kern & Sohn GmbH – Germany) was used to determine the power of peripheral muscles [16].

Maximal inspiratory pressure (MIP). Power Breathe K1 (POWERbreathe International Limited) was used to measure MIP. The calculation of diaphragmatic force was based on the patient's height, weight, age and sex. Patients were asked to inhale suddenly with maximal force after a maximal exhalation [17].

Breath holding time (BHT). The severity of COPD was assessed with BHT. In this task the subjects were asked to hold their breath as long as possible with closed nostrils and mouth after a maximal inhalation [18].

Resting measurements. We used a standardized protocol for every patient. This way we tried to eliminate different causes of individual lifestyle and activity patterns. The NIRS measurements were performed at the same time between 9 and 11 in the morning. Patients were asked not to do any physical activity on days of measurements, the assessing room was separated, quiet and temperature controlled (maintained around 24 °C). The patients had rested quietly in supine position for 15 min before the NIRS measurements. The NIRS monitor was placed on the vastus lateralis of the patients as this is a usual measurement area of NIRS measurements [25]. The location is recommended by the SENIAM project 35 for electromyography measurements. The emitter and detectors were aligned in the direction of muscle fibers, and body hair was removed from the sensor sites. The sensors were fixed in place using medical adhesive tape (Hypafix; BSN Medical, DE) and were then covered with the compatible commercially available light shield to eliminate possible ambient light intrusion.

The timing and makeup of our measurements can be seen in Fig. 1.

NIRS monitor, Moxy Monitor. The Moxy Monitor (Fortiori Design LLC) is an NIRS device that propagates to provide an a priori 0%–100% scale with a reasonable accuracy for everyday

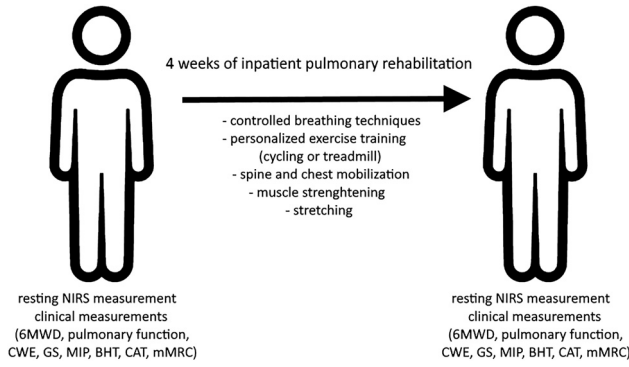

Fig. 1. Timing and makeup of our measurements

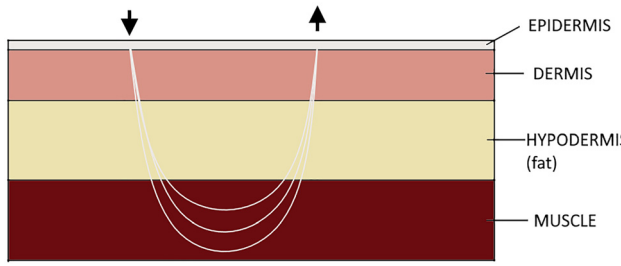

Fig. 2. The measurement site and layers of human tissue the Moxy monitor measures

applications. The device measures the amount of light reaching two detectors from one emitter at four wavelengths in a diffuse reflectance configuration for a total of eight measurements. The device detectors are spaced at 12.5 and 25 mm from the emitter. The default sampling rate cycles through the four wavelengths 80 times every 2 s and averages out the readings for an output rate of 0.5 Hz.

The device itself propagates to provide an a priori 0%–100% scale with reasonable accuracy, a clearer picture of the technical process involved to isolate and investigate the muscle layer and generate an SmO_2 output is provided. Moxy uses a four-layered tissue model consisting of epidermis, dermis, fat and muscle (Moxy monitor e-book) (Fig. 2).

SmO_2 min and max levels were identified as continuous 3-second sections in SmO_2 values. As Moxy Monitor has a data collection frequency of 2 Hz, this means 6 identical SmO_2 levels. The lowest value provided the SmO_2 min and the highest value provided the SmO_2 max level.

Statistical analysis

Patient characteristics, SmO_2 levels were compared by a paired *t*-test, a non-parametric sign test and a Wilcoxon test. Significance was accepted at $P < 0.05$ level. The distribution around the mean was expressed as ± SD in tables. Scatterplot distribution was observed in figures. Distributions were tested for normality by the Kolmogorov-Smirnov test.

To calculate sample size, we used a sample size calculator with the probability of type-I error set at 0.05 and the probability of type-II error set at 0.2, the primary endpoint was set as continuous. We selected SmO_2 average as the parameter used with a level of 75 ± 20% and an expected change of 12%. The calculated study subject size was 39, and we enrolled 40 subjects in our study.

RESULTS

Functional and quality of life parameters before and after of the rehabilitation program are presented in Table 2. Pulmonary function did not show improvement after the rehabilitation period (Table 2).

Table 2. Functional and quality of life marker parameters

Parameter	before treatment	after treatment	*P* value
FEV_1 (l)	45.43 ± 20.2	45.06 ± 18.2	n.s.
FVC (l)	75.81 ± 22.71	74.78 ± 17.37	n.s.
mMRC	1.86 ± 0.71	1.63 ± 0.6	<0.01
MIP (cmH_2O)	57.72 ± 22.69	63.63 ± 18.01	<0.001
CWE (cm)	2.84 ± 1.26	4 ± 1.76	<0.001
BHT (sec)	25.77 ± 10.63	29.21 ± 11.60	<0.001
GS (kg)	24.87 ± 11.88	27.03 ± 11.43	<0.001
6MWD (m)	335.32 ± 110.43	398.32 ± 126.21	<0.001
CAT	17 ± 8.49	11.89 ± 7.31	<0.001

FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; mMRC: modified Medical Research Council Dyspnea Scale; MIP: maximal inspiratory pressure; CWE: chest wall expansion; BHT: breath holding time; GS: grip strength; 6MWD: 6-min walking distance; CAT: COPD assessment test.

Table 3. NIRS parameters

Parameter	before treatment	after treatment	*P* value
tHB (%)	12.76 ± 1.3	12.82 ± 1.4	n.s.
SmO_2 avg (%)	67.47 ± 14.39	65.21 ± 20.39	n.s.
SmO_2 min (%)	42.6 ± 12.60	54.8 ± 14.32	<0.01
SmO_2 max (%)	98 ± 20.51	90.1 ± 14.33	<0.01

tHB: total hemoglobin index; SmO_2 avg: average muscle oxygenation; SmO_2 min: minimal muscle oxygenation; SmO_2 max: maximal muscle oxygenation.

Significant changes were detected in CWE, BHT, GS, 6MWD, CAT, mMRC (Table 2). MIP results showed significant increment, but the values are still under the physiologic values (Table 2).

The parameters measured by MOXY are presented in Table 3. tHb and SmO_2 average do not show clear, significant improvement. Considering changes on an individual level all SmO_2 levels show an improving tendency (Table 3).

Minimal muscle oxygenation levels increased and maximal muscle oxygenation levels decreased, both changes achieved clinical significance. These changes show a clear tendency of normalization in the peripheral oxygen usage ability and capacity of patients as a result of the rehabilitation program (Table 3).

No correlation was found between the calculated change of the NIRS parameters and health status markers.

DISCUSSION

Evaluating oxidative skeletal muscle performance in sports and physical rehabilitation is an emerging area. We conducted clinical research for determining the peripheral oxygen consumption, capillarization of muscles in COPD patients and the effects of a 4-week rehabilitation program on the physiological phenomena measured by NIRS technology during resting. In our

clinical tests significant changes were detected in CWE, BHT, GS, 6MWD, CAT and mMRC. MIP results showed significant increment, but the values were still under the physiologic values. FEV_1 and FVC results did not change as a result of the rehabilitation program. The 4-week rehabilitation program resulted improvement in SmO_2 min, SmO_2 max levels. On an individual level more than 50% of the patients had better NIRS results after the rehabilitation period.

The NIRS is a lightweight technology that represents a quick, non-invasive and continuous measurement. The use of wireless and miniaturized NIRS sensors in pulmonary rehabilitation has the potential to further increase the understanding how peripheral muscles respond to cumulative exercise bouts and could help in the creation of evidence-based, individualized training regimens.

The relative novelty of the NIRS technology produces a lot of questions regarding the usability and reliability of these devices. Some of these have already been answered: there is a good correlation with in vitro assessed oxidative capacity via muscle biopsy analysis [26]. Some NIRS studies have shown that muscle reoxygenation rate after either static or dynamic [27] exercises can be important determinants of both individual muscle performance and training status. Still a lot of questions remain: it is unclear whether the responses in NIRS for one muscle site (a few cm_2) could be representative enough to quantify internal (i.e., physiological responses to training activities) loading and guide training. Clarification of the interrelationship between muscle oxygenation, pulmonary exchange ratio, HR, and muscle activation (as measured by electromyography) responses during longitudinal studies is required. Recent studies show that lower effort during exercise helps in preserving muscle oxygenation and reducing metabolic acidosis but the results show that these factors do not determine exhaustion [28] in COPD patients. During high intensity exercise insufficient adjustment in respiratory muscle perfusion associates with greater dyspnea sensation in patients with COPD [29]. It has also been shown that central hemodynamic and leg muscle oxygen availability in COPD can be associated with the intensity of daily physical activity [30]. All the aforementioned studies used NIRS devices during physical activities, in our study we focused on using these devices and the data during a 6-minute resting period. We tried to find correlation between the classic clinical parameters and SmO_2 levels on an individual level monitoring the effectiveness of a 4-week pulmonary rehabilitation program.

Only few NIRS instruments have been clinically validated to date [31, 32]. Moxy Oxygen Monitor and the NIRS device we used in our study is one of these [31]. In addition, Niemeijer et al. [33] confirmed that adipose tissue thickness has a strong effect on NIRS results by either overestimating actual skeletal muscle oxygenation or decreasing its sensitivity for deoxygenation.

As an interpretation of NIRS results, in clinical practice central venous oxygen saturation ($ScvO_2$), and mixed venous oxygen saturation ($ScvO_2$) are usually used to assess oxygen saturation [34]. $ScvO_2$ reflects the transport and metabolism of oxygen [35] and is a surrogate marker of SvO2 but it is simpler to measure [34]. $ScvO_2$ is only an approximation of $ScvO_2$, and this should be remembered when interpreting measurements [36] but it gives an indication of how much oxygen is extracted by the organs before the blood returns to the right side of the heart, showing the balance between oxygen delivery and consumption.

SvO_2 can be used to measure cardiac output, guide clinical practice when using early goal-directed therapy treatment protocols, understand and treat arterial hypoxaemia, rapidly estimate shunt fraction and help identify patients at risk of weaning failure [36]. Tissue hypoxia suggested by SvO_2 can be an early marker of sepsis [37–39] as when oxygen delivery has been

compromised or oxygen consumption has exceeded its supply, subsequent oxygen venous return is diminished [38]. Parameters for SvO_2 levels were set as, 0–70% = hypoxia, 70–89% = normoxia and 90–100% = hyperoxia [38]. McManus highlighted in his work that comparing NIRS-derived values for SmO2 against invasive measures of SvO_2, the SmO_2 values cannot be higher than the measured value for SvO2. SmO_2 should be lower, as SvO2 is a combination of venous blood returning from all tissue layers, including adipose and skin tissue; this is the premise of venous blood contamination [40]. While this does not establish validity of an NIRS-derived SmO_2 value, it does establish thresholds against which measured values can be tested and lends a useful SmO_2 range.

Our results show an elevation in SmO_2 min results, this can be explained by the elevated cardiac output, the improved extraction of oxygen and slightly elevated hemoglobin concentration caused by physical rehabilitation. These results are even more significant on an individual level, NIRS results of 16 of the 40 patients changed from heavy hypoxia SmO_2 levels (40–57% SmO_2) to normoxic levels (74–78% SmO_2). This is even more accentuated since Bracht found that patients with an $ScvO_2$ of 60% or lower on admission to intensive care had a higher 28-day mortality rate than those who had a $ScvO_2$ of greater than 60% on admission [41]. According to Textoris et al. mortality rates were 30% when $ScvO_{2max}$ was less than 80%, and when $ScvO_{2max}$ was over 80%, the mortality rate was 48% in patients treated using early goal-directed therapy [37].

The slight decrease in SmO_2 max levels is also very promising. High levels of $ScvO_2$ and so SmO_2 can mean a very high oxygen delivery in excess of tissue requirements and decreased cellular consumption of oxygen or a large arterio-venous shunt (58). $ScvO_2$ higher than 80% in the first 72 h of resuscitating septic shock patients can increase mortality [39]. However, to make these results more robust, a prospective study should be carried out, as the retrospective design of this study relied upon data already collected.

Clinical perspectives and limitations of our study

Studies with resistive inspiratory loading protocols have shown that respiratory fatigue results in diaphragm ischemia and reduced mechanical efficiency [42]. Patients with chronic heart failure demonstrated reduced oxygen saturation in the intercostal muscle and increased blood lactate during the resistive inspiratory loading protocol. The increase in blood and muscle lactic acidosis facilitates the dissociation of O_2 from hemoglobin, thereby increasing O_2 extraction [43]. The integration of convective (the bulk delivery of O_2) and diffusive (the movement of O_2 from hemoglobin to the mitochondria) components of the O_2 transport pathway mostly determine the muscle metabolism during exercise [44].

Keeping all these issues in mind NIRS has the potential to be used as an objective measure and evaluate individual response to pulmonary rehabilitation not just during exercise but during rest, too. Skeletal muscle status directly contributes to the ability to sustain performance, loadability and fatigue [45], but the objective measurement of cardiovascular strain using heart rate should also be used to accurately measure internal workload. Muscle oxygenation and HR measurements are likely to be differently influenced by external factors (e.g., eccentric muscle actions or thermoregulatory/dehydration disturbances, changes in pH, respiratory exchange ratio). In the future, NIRS-based variables may provide an option for measuring total workload, especially for training and physical rehabilitation.

One of the main limitations of our study was that the duration of the rehabilitation was shorter than most of the rehabilitation programs. To compensate for this the individual training program was intensive, and the patients performed the training 2–3 times per day. This makes it possible to compare our results with previous studies by other colleagues and our group. In the future we may focus on longitudinal studies to measure changes in peripheral oxygenation during a longer period of time and use other physiological parameters during and after training to have a complex understanding of the effect of pulmonary rehabilitation on microcirculation, oxygenation as well as individual responses in COPD patients during pulmonary rehabilitation.

In the future we plan to repeat the study with a larger sample size, using NIRS during and after exercise not just at the start and at the end of the pulmonary rehabilitation program. This would provide an even better understanding of the acute changes in muscle oxygenation during and after exercise on patients with different stages of COPD.

Considering the short rehabilitation period our findings and the measured improvements show a promising trend. Increased oxygen supply and oxygenation responses support the beneficial effect of training on muscle function in patients with COPD. NIRS technology seems appropriate for use in determining exercise training intensity, volume and efficiency. Although the use of NIRS is relatively new even to sports science, it has proven to be a viable noninvasive tool to determine peripheral muscle oxygenation as an effect of a pulmonary rehabilitation program.

Consent for publication: Not applicable.

Funding: The authors have not received any financial support for the research or the publication of this article.

Conflict of interest: None of the authors reported conflict of interest.

ACKNOWLEDGMENTS

The Authors would like to thank Dr. Maria Kerti PhD and Blanka Toth as physiotherapist for their work in the pulmonary rehabilitation program.

REFERENCES

1. Murray CJ, Lopez AD, Alternative projections of mortality and disability by cause 1990–2020. Global Burden Disease Study. Lancet 1997; 349: 1498–504. https://doi.org/10.1016/S0140-6736(96)07492-2.
2. Szucs B, Szucs C, Petrekanits M, Varga JT. Molecular characteristics and treatment of endothelial dysfunction in patients with COPD: a review article. Int J Mol Sci 2019; 20(18): 4329. https://doi.org/10.3390/ijms20184329.
3. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997; 155(5): 1541–51. https://doi.org/10.1164/ajrccm.155.5.9154855.

4. Gale NS, Duckers JM, Enright S, Cockcroft JR, Shale DJ, Bolton CE. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? BMC Pulm Med 2011; 11: 20. https://doi.org/10.1186/1471-2466-11-20.
5. Hamaoka T, McCully KK, Quaresima V, Yamamoto K, Chance B. Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. J Biomed Opt 2007; 12(6): 062105. https://doi.org/10.1117/1.2805437.
6. Louvaris Z, Habazettl H, Asimakos A, Wagner H, Zakynthos S, Wagner P D, et al. Heterogeneity of blood flow and metabolism during exercise in patients with chronic obstructive pulmonary disease. Respir Physiol Neurobiol 2017 Mar; 237: 42–50. https://doi.org/10.1016/j.resp.2016.12.013.
7. Jöbsis FF. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 1977; 198(4323): 1264–7. https://doi.org/10.1126/science.929199.
8. McCully KK, Hamaoka T. Near-infrared spectroscopy: what can it tell us about oxygen saturation in skeletal muscle?. Exerc Sport Sci Rev 2000; 28(3): 123–7. PMID: 10916704.
9. Poole DC, Mathieu-Costello O. Skeletal muscle capillary geometry: adaptation to chronic hypoxia. Respir Physiol 1989; 77(1): 21–9. https://doi.org/10.1016/0034-5687(89)90026-1.
10. Grassi B, Quaresima V. Near-infrared spectroscopy and skeletal muscle oxidative function in vivo in health and disease: a review from an exercise physiology perspective. J Biomed Opt 2016; 21(9): 091313. https://doi.org/10.1117/1.JBO.21.9.091313.
11. Bezemer R, Lima A, Myers D, Klijn E, Heger M, Goedhart PT, et al. Assessment of tissue oxygen saturation during a vascular occlusion test using near-infrared spectroscopy: the role of probe spacing and measurement site studied in healthy volunteers. Crit Care 2009; 13(Suppl 5): S4. https://doi.org/10.1186/cc8002.
12. Perrey S, Ferrari M. Muscle oximetry in sports science: a systematic review. Sports Med 2018; 48(3): 597–616. https://doi.org/10.1007/s40279-017-0820-1.
13. Balke B. A simple filed test for the assessment of physical fitness. Rep 63-6. Rep CivAeromed Res Inst US 1963: 1–8. PMID: 14131272.
14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. Eur Respir J Suppl 1993; 16: 5–40. PMID: 8499054.
15. Debouche S, Pitance L, Robert A, Liistro G, Reychler G. Reliability and reproducibility of chest wall expansion measurement in young healthy adults. J Manipulative Physiol Ther 2016; 39(6): 443–9. https://doi.org/10.1016/j.jmpt.2016.05.004.
16. An KN, Chao EY, Askew LJ. Hand strength measurement instruments. Arch Phys Med Rehabil 1980; 61(8): 366–8. PMID: 7406674.
17. Neumeister W, Rasche K, Maas P, Monnerjahn C, Singh B, Schultze-Werninghaus G. Reproduzierbarkeit computergestützter Mundverschlussdruckmessungen [Reproducibility of computer-assisted mouth occlusion pressure measurements]. Med Klin (Munich) 1996; 91(Suppl 2): 73–5. PMID: 8684335.
18. Mirsky IA, Lipman E, Grinker RR. Breath holding time in anxiety states. Fed Proc 1946; 5(1 Pt 2): 74. PMID: 21066398.
19. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD Assessment Test (CAT™) scores. BMC Pulm Med 2011; 11: 42. https://doi.org/10.1186/1471-2466-11-42.
20. Launois C, Barbe C, Bertin E, Nardi J, Perotin JM, Dury S, et al. The modified Medical Research Council scale for the assessment of dyspnea in daily living in obesity: a pilot study. BMC Pulm Med 2012; 12: 61. https://doi.org/10.1186/1471-2466-12-61.

21. Kerti M, Balogh Z, Kelemen K, Varga JT. The relationship between exercise capacity and different functional markers in pulmonary rehabilitation for COPD. Int J Chron Obstruct Pulmon Dis 2018; 13: 717–24. https://doi.org/10.2147/COPD.S153525.
22. Varga JT, Munkácsi A, Máthé Cs, Somfay A, Bálint B, Lovász O, et al. The effect of the inspiratory muscles training on physical condition in COPD. [A belégzőizmok tréningjének hatása a betegek fizikai állapotára COPD-ben]. Med Thor 2018; 71: 96–102.
23. Varga J, Porszasz J, Boda K, Casaburi R, Somfay A. Supervised high intensity continuous and interval training vs. self-paced training in COPD. Respir Med 2007; 101(11): 2297–304. https://doi.org/10.1016/j.rmed.2007.06.017.
24. Vagvolgyi A, Rozgonyi Z, Kerti M, Vadasz P, Varga J. Effectiveness of perioperative pulmonary rehabilitation in thoracic surgery. J Thorac Dis 2017; 9(6): 1584–91. https://doi.org/10.21037/jtd.2017.05.49.
25. Jones B, Hamilton DK, Cooper CE. Muscle oxygen changes following sprint interval cycling training in elite field hockey players. PLoS One 2015; 10(3): e0120338. https://doi.org/10.1371/journal.pone.0120338.
26. Ryan TE, Brophy P, Lin CT, Hickner RC, Neufer PD. Assessment of in vivo skeletal muscle mitochondrial respiratory capacity in humans by near-infrared spectroscopy: a comparison with in situ measurements. J Physiol 2014; 592(15): 3231–41. https://doi.org/10.1113/jphysiol.2014.274456.
27. Fryer S, Stoner L, Stone K, Giles D, Sveen J, Garrido I, et al. Forearm muscle oxidative capacity index predicts sport rock-climbing performance. Eur J Appl Physiol 2016; 116(8): 1479–84. https://doi.org/10.1007/s00421-016-3403-1.
28. Louvaris Z, Chynkiamis N, Spetsioti S, Asimakos A, Zakynthynos S, Wagner PD, et al. Greater exercise tolerance in COPD during acute interval, compared to equivalent constant-load, cycle exercise: physiological mechanisms. The Journ of Physiol 2020; 598(17): 3613–29. https://doi.org/10.1113/JP279531.
29. Louvaris Z, Rodrigues A, Dacha S, Giojevic T, Janssens W, Vogiatzis I, et al. High-intensity exercise impairs extradiaphragmatic respiratory muscle perfusion in patients with COPD. J Appl Phisiol 2021; 130(2): 325–41, https://doi.org/10.1152/japplphysiol.00659.2020.
30. Louvaris Z, Kortianou EA, Spetsioti S, Vasilopoulou M, Nasis I, Asimakos A, et al. Intensity of daily physical activity is associated with central hemodynamic and leg muscle oxygen availability in COPD, J Appl Phisiol 2013 Sep; 115(6): 794–802. https://doi.org/10.1152/japplphysiol.00379.2013.
31. Crum EM, O'Connor WJ, Van Loo L, Valckx M, Stannard SR. Validity and reliability of the Moxy oxygen monitor during incremental cycling exercise. Eur J Sport Sci 2017; 17(8): 1037–43. https://doi.org/10.1080/17461391.2017.1330899.
32. Benni PB, MacLeod D, Ikeda K, Lin HM. A validation method for near-infrared spectroscopy based tissue oximeters for cerebral and somatic tissue oxygen saturation measurements. J Clin Monit Comput 2018; 32(2): 269–84. https://doi.org/10.1007/s10877-017-0015-1.
33. Niemeijer VM, Spee RF, Jansen JP, Buskermolen AB, van Dijk T, Wijn PF. Test-retest reliability of skeletal muscle oxygenation measurements during submaximal cycling exercise in patients with chronic heart failure. Clin Physiol Funct Imaging 2017; 37(1): 68–78. https://doi.org/10.1111/cpf.12269.
34. Scott BR, Slattery KM, Sculley DV, Lockie RG, Dascombe BJ. Reliability of telemetric electromyography and near-infrared spectroscopy during high-intensity resistance exercise. J Electromyogr Kinesiol 2014; 24(5): 722–30. https://doi.org/10.1016/j.jelekin.2014.07.008.
35. Reid M. Central venous oxygen saturation: analysis, clinical use and effects on mortality. Nurs Crit Care 2013; 18(5): 245–50. https://doi.org/10.1111/nicc.12028.
36. Haase N, Perner A. Central venous oxygen saturation in septic shock: a marker of cardiac output, microvascular shunting and/or dysoxia? Crit Care 2011; 15: 184–6. https://doi.org/10.1186/cc10314.

37. Textoris J, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, et al. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care 2011; 15(4): R176. https://doi.org/10.1186/cc10325.
38. Walley KR. Use of central venous oxygen saturation to guide therapy, Am J Resp Crit Care Med 2011; 184: 514–20. https://doi.org/10.1164/rccm.201010-1584CI.
39. Maddirala S, Khan A. Optimising hemodynamic support in septic shock using central venous and mixed venous oxygen saturation. Crit Care Clin 2010; 26: 323–33. https://doi.org/10.1016/j.ccc.2009.12.006.
40. McManus CJ, Collison J, Cooper CE. Performance comparison of the MOXY and PortaMon near-infrared spectroscopy muscle oximeters at rest and during exercise. J Biomed Opt 2018; 23(1): 1–14. https://doi.org/10.1117/1.JBO.23.1.015007.
41. Bracht H, Hänggi M, Jeker B, Wegmüller N, Porta F, Tüller D, et al. Incidence of low central venous oxygen saturation during unplanned admissions in a multidisciplinary intensive care unit: an observational study. Crit Care 2007; 11: 1–8. https://doi.org/10.1186/cc5144.
42. Bellemare F, Wight D, Lavigne CM, Grassino A. Effect of tension and timing of contraction on the blood flow of the diaphragm. J Appl Physiol Respir Environ Exerc Physiol 1983; 54: 1597–606. https://doi.org/10.1152/jappl.1983.54.6.1597.
43. Stringer W, Wasserman K, Casaburi R, Pórszász J, Maehara K, French W. Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. J Appl Physiol (1985) 1994; 76(4): 1462–7. https://doi.org/10.1152/jappl.1994.76.4.1462.
44. Wagner PD. Gas exchange and peripheral diffusion limitation. Med Sci Sports Exerc 1992; 24: 54–8. PMID: 1548996.
45. Denis R, Bringard A, Perrey S. Vastus lateralis oxygenation dynamics during maximal fatiguing concentric and eccentric isokinetic muscle actions. J Electromyogr Kinesiol 2011; 21(2): 276–82. https://doi.org/10.1016/j.jelekin.2010.12.006.