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Effectiveness of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease after lobectomy due to non-small cell lung cancer — a single-center retrospective study

Abstract

Introduction: The procedure of lung parenchyma resection may result in impairment of physical capacity and quality of life. In patients with operable non-small cell lung cancer (NSCLC), lobectomy is an elective procedure. Chronic obstructive pulmonary disease (COPD) is a common coexisting condition in patients with NSCLC. Effectiveness of post-operative pulmonary rehabilitation (PR) in patients who underwent lobectomy due to NSCLC and suffering from COPD as compared to individuals without COPD has not been determined yet. The aim of the study was to compare effectiveness of post-operative PR in patients with COPD after lobectomy due to NSCLC (COPD(+) L(+)) with individuals with COPD without lung parenchyma resection (COPD(+) L(-)) and those who underwent lobectomy due to NSCLC and not suffering from COPD (COPD(-) L(+)).

Material and methods: Thirty-seven patients with non-small cell lung cancer (21 patients with and 16 patients without COPD) who underwent lobectomy and 29 subjects with COPD referred to the Lung Diseases Treatment and Rehabilitation Centre in Lodz in 2018–2019 were included in this retrospective analysis. The patients participated in a 3-week inpatient pulmonary rehabilitation (PR) program which included breathing exercises, physical workout, relaxation exercises, education, psychological support and nutrition consulting. The evaluation included lung function measurements, six-minute walking test (6MWT) and the St. George's Respiratory Questionnaire (SGRQ) score. The results obtained before the rehabilitation were compared to those achieved after the 3-week PR program and compared between the study groups.

Results: A significant increase in the distance covered during 6MWT was observed in all the three groups studied: COPD(+) L(+) ($\Delta = 62.52 \pm 14.58$ m); COPD(-) L(+) ($\Delta = 73.67 \pm 11.58$ m); and COPD(+) L(-) ($\Delta = 59.93 \pm 10.02$ m) ($p < 0.001$ for all). Similarly, a statistically and clinically significant improvement in the total SGRQ score was recorded: COPD(+) L(+) $\Delta = -12.05 \pm 3.96$ points; $p < 0.05$ and COPD(-) L(+) $\Delta = -12.30 \pm 4.85$ points; $p < 0.01$ and COPD(+) L(-) $\Delta = -14.07 \pm 3.36$ points ($p < 0.001$). No significant differences in the outcome improvement between the study groups were identified.

Conclusions: The results of the study show that COPD(+) L(+) patients gained benefits from post-operative PR comparable to COPD(+) L(-) and COPD(-) L(+) subjects by improving their physical capacity and quality of life.

Key words: lobectomy, pulmonary rehabilitation, lung cancer, chronic obstructive pulmonary disease, 6MWT

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Introduction

The major risk factor for chronic obstructive pulmonary disease (COPD) and lung cancer is tobacco smoking and for this reason, these two conditions often coexist [1, 2].

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend pulmonary rehabilitation (PR) in symptomatic patients with a chronic respiratory disease [3].

The general goal of rehabilitation is alleviation of symptoms of the disease, recovery of

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maximum physical fitness by the patient, quality of life improvement, as well as anxiety and depression prevention.

Effectiveness of pulmonary rehabilitation in patients with COPD has been reported in many studies [4, 5]. It demonstrates itself by decreased severity of symptoms, a lower frequency of exacerbations and hospital stays, higher tolerance of physical effort, alleviation of anxiety and depression symptoms and improved quality of life.

A vast majority of studies on efficacy of pulmonary rehabilitation in patients who underwent thoracic surgery due to lung cancer referred to preoperative rehabilitation. It has been shown that preoperative exercise-based training improves pulmonary function before surgery, reduces length of hospital stays and post-operative complications after lung resection surgery for lung cancer [6].

There are only a few studies on efficacy of post-operative PR in patients who underwent lobectomy due to non-small cell lung cancer (NS-CLC). Additionally, their results are inconsistent and they exclude or do not provide characteristics of specific groups of patients with COPD who underwent the procedure of lung parenchyma resection [7–9].

The objective of the study was to assess the impact of post-operative PR on lung function, physical effort tolerance and quality of life in COPD patients who underwent lung resection for lung cancer as compared to those without COPD and patients with COPD who did not undergo a thoracic surgery.

Materials and methods

Thirty-seven patients with non-small cell lung cancer (21 patients with and 16 patients without COPD) who underwent lobectomy and 29 subjects with COPD referred to the Lung Diseases Treatment and Rehabilitation Centre in Lodz in 2018–2019 were included in the retrospective analysis. The reasons for referral were the following: reduced exercise tolerance, inability to perform activities of daily living, and dyspnea on exertion despite optimal pharmacological treatment. All patients undergoing lobectomy due to lung cancer were at stage I and did not receive any additional anticancer treatment (neo-adjuvant or adjuvant chemotherapy and radiotherapy).

The patients participated in a 3-week unified pulmonary rehabilitation program, 6 days a week,

44.89 (6.48) weeks following thoracic surgery. The program included:

- breathing exercises (8–12 repetitions): active exercises strengthening the diaphragm and assisted by movement of the upper and lower limbs, exercises based on different patterns of breathing, exercises expanding the external intercostal muscles, exercises related to the expiration phase, exercises improving the strength of the inspiratory muscles, the pectoral girdle and the abdominal muscles;
- physical workout (20–30 min): interval resistance training on cycloergometers and rotors for the upper and lower limbs exercises;
- airway hygiene: mucolytic agents inhalation, respiratory drainage (drainage positions, vibration massage), positive expiratory pressure (PEP), effective coughing technique, forced expiration technique “Huff”;
- relaxation exercises: music therapy, colour therapy, phototherapy;
- education (developing the correct breathing pattern, learning the right body posture during breathing, learning the technique of correct medication inhalation, nutrition advice, tips on quitting smoking).

Effects of PR were evaluated using lung function measurements, a six-minute walking test (6MWT) and the St. George’s Respiratory Questionnaire (SGRQ).

Lung function was evaluated by means of spirometry with forced expiratory volume in 1st second (FEV₁) and forced vital capacity (FVC) measurements. Spirometry was conducted in compliance with the recommendations of the American Thoracic Society (ATS) and European Respiratory Society (ERS) [10]. 6MWT was performed in compliance with the recommendations of the Polish Respiratory Society [11]. In short, the patients were asked to walk the longest distance they were able to cover in 6 minutes. They could walk at their own pace and have some rest when they got tired. Before and after the march, pulse, arterial blood pressure and pulse oximetry (SatO₂) were measured and dyspnea level was assessed according to the Borg scale. An increase in the distance by > 54 m following the completion of the pulmonary rehabilitation program was considered as clinically significant [12].

Both, before and after the completed PR, the patients filled in SGRQ including 76 questions classified into three components: symptoms, activity and impact. The global score ranges from 0 to 100 points, with 0 corresponding to

the smallest impact on life and 100 meaning the most significant one, thus a higher score means a poorer quality of life [13]. A change in the SGRQ score by at least 4 points after the completion of the pulmonary rehabilitation program was regarded as clinically significant.

The study was institutional review board (Ethics Committee of Medical University of Lodz) exempt due to its retrospective nature.

Statistical analysis

Data is presented as mean \pm standard error of mean (SEM) or median (interquartile range, IQR) unless stated otherwise. The data distribution was assessed using the Shapiro-Wilk test. The data was analyzed using a 1-way ANOVA with the Dunnett post hoc test or the Kruskal-Wallis test with Dunn's post hoc test and a 2-way ANOVA with the Bonferroni post hoc test, if appropriate. The Chi₂ test or Fisher exact test were used to compare the proportion of subjects, when appropriate. $P < 0.05$ was considered as significant. Analyses were performed using GraphPad Prism 6 (GraphPad Prism Software Inc., CA, USA).

Results

The characteristics of the patients who completed the PR program are presented in Table 1. The values of the evaluated parameters in the study groups, before and after PR, are presented in Table 2.

6-minute walking test

The distance covered in the 6MWT improved significantly after the completed PR

program in the COPD(+) L(+) ($\Delta = 62.52 \pm 14.58$ m), COPD(-) L(+) ($\Delta = 73.67 \pm 11.58$ m) and COPD(+) L(-) ($\Delta = 59.93 \pm 10.02$ m) ($p < 0.001$) for all groups.

As for the SatO₂ value measured before and after the 6MWT following the completion of the rehabilitation program, a significant improvement was recorded in the COPD(+) L(+) ($\Delta = 1.76 \pm 0.66\%$) and the COPD(+) L(-) ($\Delta = 1.77 \pm 0.58\%$) groups. A $\geq 4\%$ decrease in SatO₂ at the end of 6MWT was noted in 4 and 1 patient in the COPD(+) L(+) group before and following PR, respectively; 1 and 0 patients in the COPD(-) L(+) group before and following PR, respectively; and 3 and 2 patients in the COPD(+) L(-) group before and following PR, respectively.

Exercise-induced dyspnea assessed by means of the Borg dyspnea scale was alleviated significantly in the COPD(+) group (median of difference -1, $p < 0.05$). COPD(+) L(+) group (median of difference -1, $p < 0.05$) and COPD(+) L(-) group (median of difference -1, $p < 0.001$).

SGRQ

A statistically and clinically significant improvement was recorded in the symptom category after the completion of PR in the COPD(+) L(+) ($\Delta = -16.39 \pm 5.15$ points; $p < 0.01$) and COPD(-) L(+) ($\Delta = -19.37 \pm 6.31$ points; $p < 0.05$) and the COPD(+) L(-) group ($\Delta = -29.66 \pm 4.37$ points; $p < 0.001$).

A statistically and clinically significant improvement in activity was recorded in the COPD(-) L(+) group ($\Delta = -9.65 \pm 4.4$ points; $p < 0.05$) and the COPD(+) L(-) group ($\Delta = -9.22 \pm 3.08$ points; $p < 0.05$).

Table 1. Characteristics of the patients

	COPD[+] L[+]	COPD[-] L[+]	COPD[+] L[-]	P
Age [years]	67.81 [1.79]	66.50 [1.83]	71.50 [1.81]	0.12
Sex [no. F/M]	9/12	8/8	12/16	0.88
BMI [kg/m ²]	28.66 \pm 1.04	30.09 \pm 1.52	26.61 \pm 1.02	0.32
Period of time after surgery [in weeks]	44.85 \pm 9.92	44.94 \pm 8.05	NA	0.35
Arterial hypertension [% of patients]	38	31	50	0.48
Heart failure [% of patients]	24	25	40	0.43
Ischemic heart disease [% of patients]	19	19	21	0.96
LABA [% of patients]	38	NA	25	0.32
LAMA [% of patients]	29	NA	11	0.14
LABA + LAMA [% of patients]	33	NA	64	0.03
ICS [% of patients]	43	NA	32	0.44

ICS — Inhaled corticosteroids; LABA — long-acting β -receptor agonist; LAMA — long-acting muscarinic antagonist

Table 2. The parameters assessed before and after the completion of the pulmonary rehabilitation program in the study groups

	COPD(+) L(+)		COPD(-) L(+)		COPD(+) L(-)	
	Pre PR	Post PR	Pre PR	Post PR	Pre PR	Post PR
FEV ₁ , n (%)	49.75 ± 3.86; 49.50 (22.75)	52.50 ± 3.69; 55.50 (18.00)	72.53 ± 5.14; 72.00 (27.00) ^a	73.47 ± 4.57; 73.00 (20.00) ^a	42.52 ± 2.41; 44.00 (15.00)	44.15 ± 2.99; 41.00 (20.00)
FEV ₁ (l)	1.47 ± 0.12; 1.46 (0.77)	1.55 ± 0.11; 1.56 (0.83)	1.81 ± 0.22; 1.59 (1.09)	1.83 ± 0.22; 1.64 (1.02)	1.07 ± 0.05; 1.01 (0.23) ^b	1.11 ± 0.07; 1.06 (0.46) ^b
FVC (%N), n (%)	54.52 ± 2.47; 58.10 (20.81)	56.56 ± 2.39; 57.42 (15.53)	71.60 ± 5.13; 77.00 (29.00) ^c	77.14 ± 4.84; 80.09 (21.00) ^{a, d}	59.13 ± 3.20; 64.00 (24.00)	62.17 ± 4.02; 69.00 (34.00)
FVC (l)	2.68 ± 0.18; 2.52 (1.12)	2.75 ± 0.18; 2.71 (1.09)	2.29 ± 0.29; 2.21 (1.13)	2.49 ± 0.30; 2.34 (1.38) [*]	2.29 ± 0.10; 2.43 (0.92)	2.38 ± 0.15; 2.46 (1.56)
FEV ₁ %FVC	54.52 ± 2.47; 58.10 (20.81)	56.56 ± 2.39; 57.42 (15.53)	78.65 ± 1.40; 79.49 (6.65) ^a	73.17 ± 1.64; 75.16 (12.97) ^a	47.60 ± 1.29; 48.15 (8.93)	47.73 ± 1.47; 47.78 (13.27)
Distance covered in 6MWT [m]	339.00 ± 21.50; 365.00 (114.5)	401.50 ± 19.54; 400.00 (155.5) ^d	368.00 ± 31.65; 373.00 (165.00)	441.70 ± 32.77; 450 (201.00) ^d	314.30 ± 16.57; 280 (129.00)	374.23 ± 16.27; 368.00 (140.00) ^d
SatO ₂ before 6MWT (%)	92.95 ± 0.69; 93.00 (3.50)	94.71 ± 0.63; 96.00 (3.50)	95.20 ± 0.87; 97.00 (4.00)	96.73 ± 0.44; 97.00 (2.00)	93.19 ± 0.53; 94.00 (5.00)	94.70 ± 0.60; 95.00 (4.00)
SatO ₂ after 6MWT (%)	92.95 ± 1.05; 93.00 (3.50)	94.71 ± 0.91; 96.00 (3.50) ^e	93.73 ± 1.44; 96.00 (5.00)	95.67 ± 0.83; 96.00 (3.00)	92.48 ± 0.55; 93.00 (5.00)	94.26 ± 0.60; 95.00 (3.00) ^e
Borg scale before 6MWT (points; median [min–max])	0 [0–3]	0 [0–4]	0 [0–3]	0 [0–1]	1 [0–5]	0 [0–3] ^e
Borg scale after 6MWT	2 [0–5]	1 [0–3] [*]	2 [0–3]	1 [0–3]	3 [0–7] ^b	1 [0–4] ^d
SGRQ — symptoms	50.11 ± 3.97; 45.12 (25.22)	33.31 ± 4.49; 26.90 (21.51) ^f	45.91 ± 6.98; 42.03 (46.01)	26.55 ± 7.87; 26.28 (46.99) ^e	68.54 ± 2.44; 71.70 (19.10)	38.88 ± 5.77; 34.37 (53.21) ^d
SGRQ — activity	69.21 ± 2.74; 69.32 (19.34)	60.67 ± 4.69; 59.46 (19.20)	64.71 ± 5.37; 66.19 (17.72)	55.05 ± 4.40; 55.17 (21.62) ^e	77.74 ± 2.29; 78.96 (14.2)	68.52 ± 3.46; 66.19 (28.52) ^e
SGRQ — impact	45.07 ± 4.33; 44.45 (21.30)	34.26 ± 4.60; 33.83 (22.03)	38.82 ± 4.43; 37.25 (27.01)	30.94 ± 4.47; 29.33 (21.04)	59.04 ± 3.88; 61.46 (27.26) ^b	45.67 ± 4.79; 41.49 (43.80) ^f
SGRQ — total	54.80 ± 2.69; 54.48 (14.20)	36.64 ± 4.69; 40.01 (18.63) ^e	49.81 ± 4.95; 45.10 (25.74)	28.13 ± 5.28; 37.86 (26.24) ^e	65.60 ± 2.76; 67.57 (23.08)	51.53 ± 4.26; 50.88 (36.73) ^d

Data is presented as mean ± SEM; median (IQR) unless stated otherwise.

^avs COPD(+) L, p < 0.00; ^bvs COPD(+) L, p < 0.05; ^cvs COPD(+) L, p < 0.01; ^dPre PR vs post PR, p < 0.001; ^ePre PR vs post PR, p < 0.05; ^fPre PR vs post PR, p < 0.01

A significant improvement in the life impact category was recorded only in the COPD(+) L(-) group ($\Delta = -13.37 \pm 4.07$ points; $p < 0.01$).

Nevertheless, the SGRQ total score improved significantly in all the groups after the completed rehabilitation program (COPD(+) L(+)) $\Delta = -12.05 \pm 3.96$ points; $p < 0.05$ and COPD(-) L(+)) $\Delta = -12.30 \pm 4.85$ points; $p < 0.01$ and COPD(+) L(-)) $\Delta = -14.07 \pm 3.36$ points; $p < 0.001$).

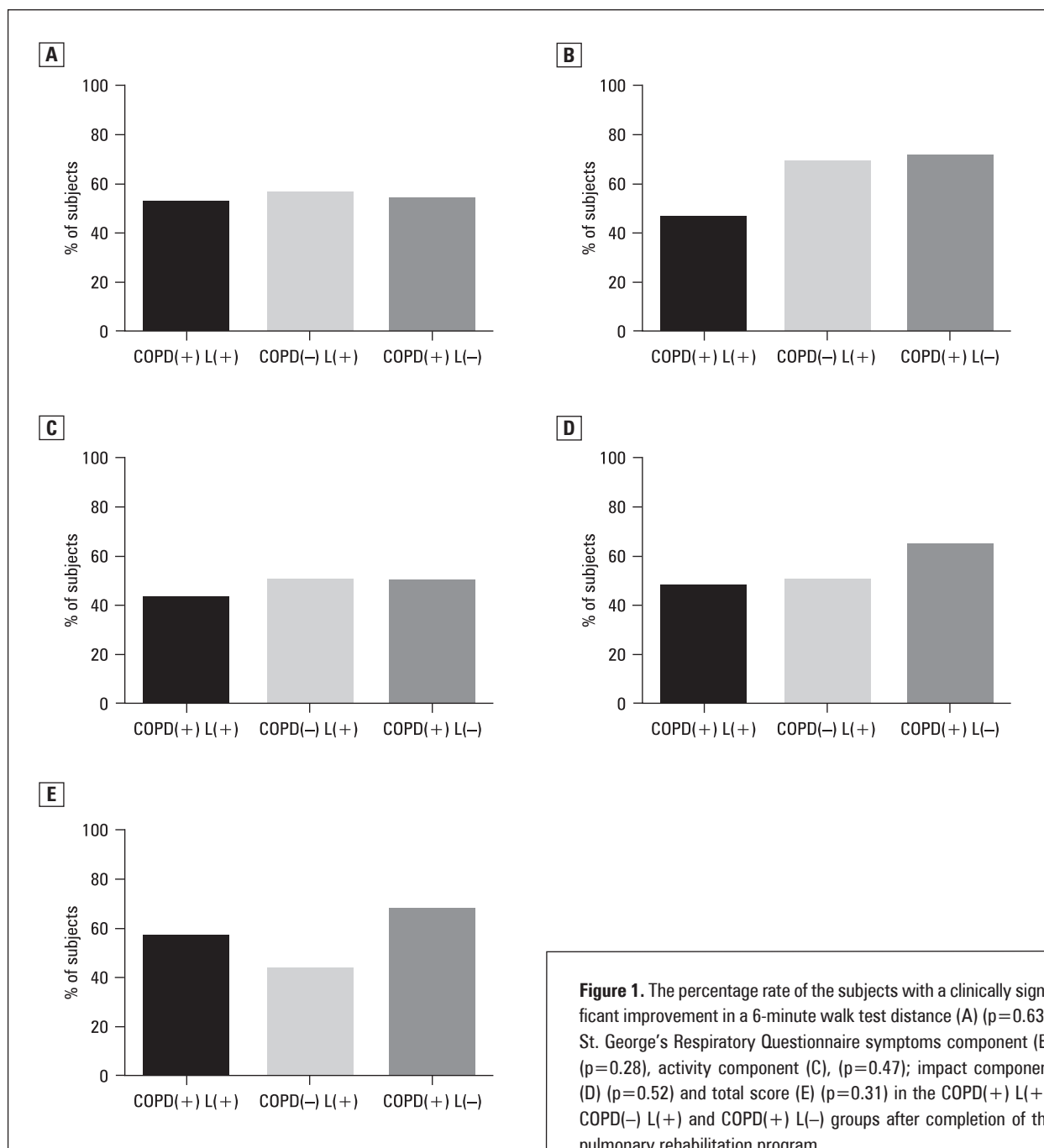
Spirometry

No significant changes in FEV₁ were recorded in any of the groups.

In the COPD(-) L(+) group, an improvement in FVC absolute values ($\Delta = 198 \pm 34$ mL; $p < 0.05$) as well as in the percentage rate of predicted normal values ($\Delta = 9.87 \pm 1.77\%$; $p < 0.001$) was recorded.

Comparison of changes in the 6MWT distance and SGRQ score between the groups

There was a trend towards greater improvement in the SGRQ symptoms component in the COPD(+) L(-) group as compared to the other groups ($p = 0.07$).



No statistically significant differences were recorded in the other assessed parameters (data not shown).

The percentage rate of the patients who showed a clinically significant improvement in the covered 6MWT distance was comparable in all the groups (Figure 1A).

Similarly, there was no difference in the percentage rate of the patients who showed a clinically significant improvement in specific components and the SGRQ total score in the studied groups (Figure 1B-E).

Discussion

The results of this retrospective study show that post-operative PR may be beneficial in COPD subjects undergoing lobectomy due to NSCLC. Completion of PR course resulted in this group of patients in clinically significant improvement in physical capacity and quality of life. Moreover, the percentage of COPD(+) L(+) patients gaining clinical benefits from post-operative PR is comparable to COPD(+) L(-) and COPD(-) L(+) groups.

One of nonpharmacological methods of COPD treatment is pulmonary rehabilitation which should be considered as an integral part of therapy in symptomatic patients. The benefits some patients with COPD gain from this type of therapy include alleviation of symptoms, improvement in physical activity and quality of life as well as less frequent hospital admissions and decreased mortality [5, 14, 15]. Our results showing beneficial impact of PR in COPD(+) L(-) stay in line with the above mentioned previous findings.

Among all primary lung cancers, NSCLC accounts for 80–90% of cases. NSCLC management depends on advancement of the disease upon diagnosis and includes the option of surgical treatment. Lobectomy is a therapy of choice in patients who qualify for resection [16]. Lung parenchyma resection leads to a reduction in the breathing reserve and, in consequence, in a decrease in physical capacity. In extreme cases, it may result in respiratory failure [17].

A vast majority of studies on pulmonary rehabilitation in patients who underwent lung parenchyma resection due to NSCLC assessed the effectiveness of the intervention before surgical procedure. Jones *et al.* proved that a 5-day aerobic workout plan before thoracic surgery improves physical performance of patients, which may have an impact on surgical outcome and post-surgical recovery [18]. A similar effect of a short-term preoperative aerobic workout is observed in patients with COPD [19]. Further research showed that preoperative pulmonary rehabilitation in patients with lung cancer and coexisting moderate and severe COPD results in reduction of hospital stay length [20].

On the other hand, there are only a few studies on effectiveness of pulmonary rehabilitation after thoracic surgery. In the study by Edwardsen *et al.*, which included a heterogeneous group of patients (28% of individuals with COPD), it has been showed that pulmonary rehabilitation 5–7 days after various thoracic surgeries, carried out for a period of 20 weeks, improved effort tolerance and muscle strength as compared to the group of patients who, on discharge, received standard recommendations which did not include any rehabilitation exercises [21].

Another study proved that post-operative home-based pulmonary rehabilitation may also bring benefits to patients undergoing lung surgery for NSCLC [7].

In the study which excluded patients with COPD, post-operative PR significantly improved

pulmonary ventilation parameters to the extent of FVC, quality of life and reduced discomfort during post-operative periods in the subjects who underwent lung resection due to lung cancer [8]. Vagvolgyi *et al.* compared the effects of post-operative pulmonary rehabilitation in patients with COPD undergoing lung parenchyma resection due to lung cancer (72% of the participants) and other causes demonstrating that both these methods result in improvement of exercise capacity and quality of life [22].

In our study, pulmonary rehabilitation was implemented in the patients who underwent lobectomy due to lung cancer with concomitant COPD, as well as in those who did not suffer from obstructive pulmonary disease. The obtained results showed improvement in effort tolerance measured based on a 6MWT and improvement in quality of life in all study groups while a significant increase in FVC was seen only in COPD(-) L(+) subjects. It proves the effectiveness of the implemented post-operative PR in the patients who underwent lung parenchyma resection presenting restrictive ventilatory defect and in whom chest expansion exercises after lung parenchyma resection cause an increase in FVC. What is important, the results were achieved although, on average, pulmonary rehabilitation started about one year after the surgery, which is conditioned by access to PR in Lodz, Poland.

Our study has its limitations. At baseline the studied groups differed in terms of pulmonary ventilation parameters, exercise capacity and long-acting bronchodilator use, which might have influenced the comparison of pulmonary rehabilitation effects. The differences, however, cannot be eliminated due to populations of patients qualified for lobectomy (better ventilation parameters) and patients with COPD qualified for PR (symptomatic patients with more advanced COPD). Additionally, the groups of the study subjects might have been too small to demonstrate significant differences in PR effects. Due to this reason, we were also unable to conduct additional analyses on PR benefits dependent on the type of pharmacological treatment.

Conclusions

Pulmonary rehabilitation proved to be effective both in patients with COPD and those who underwent lobectomy due to lung cancer. In all the studied groups, we observed an improvement in physical capacity and quality of life despite lack of improvement in lung function. Notewor-

thy, positive effects of post-operative PR were observed although pulmonary rehabilitation was started about a year after the surgery. Therefore, it is advisable to refer symptomatic patients after lung parenchyma resection due to lung cancer, both those with coexisting COPD and those who do not suffer from the disease, to pulmonary rehabilitation departments if PR prior to thoracic surgery is unfeasible.

Clinical implications/future directions

The results suggest that pulmonary rehabilitation may be effective in patients who underwent lobectomy regardless of whether they suffer from COPD or not. The effects of such an intervention may be similar to the described benefits gained by patients with COPD who completed a pulmonary rehabilitation program. Nevertheless, we have not established whether it affects the course of COPD in these patients in a longer observation period or if it has an impact on their length of life. These issues require further research.

Conflict of interest

The authors declare no conflict of interest.

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