# Post-lobectomy Pulmonary Rehabilitation on Peak Oxygen Consumption in Old Age Lung Cancer Patients

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# 노인 폐암 환자에서 폐엽 절제술 후 호흡재활이 최대산소섭취량에 미치는 효과

김문정, 전형은, 남훈, 좌경림

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### Abstract

**Objective:** We aimed to evaluate how cardiopulmonary exercise test (CPET)-based treadmill training could affect cardiopulmonary function, especially peak oxygen consumption ($VO_2$peak) in old age post-lobectomy patients with lung cancer.

**Materials:** Four weeks after lobectomy, 31 post-lobectomy patients were assigned to the pulmonary rehabilitation group (N=22) and control group (N=9). Exercise capacity, including $VO_2$ peak and the 6-min walking test, and psychological symptoms, including depression, anxiety, fatigue, sleep quality, and quality of life, were measured before and after the intervention.

**Results:** The pulmonary rehabilitation group showed greater improvement in the cardiopulmonary function, especially $VO_2$peak, than the control group ($p < 0.0001$). Psychological and quality of life parameters didn't show statistically significant differences between groups.

**Conclusion:** This study provided evidence that individualized, tailored pulmonary rehabilitation training is effective in improving cardiopulmonary function, especially $VO_2$peak, in old-age lung cancer patients who underwent lobectomy.

### Key Words

Lung cancer, Lobectomy, Treadmill, Rehabilitation, $VO_2$peak, Old age

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## Introduction

Lung cancer is one of the most common causes of cancer-related deaths, with 1.8 million deaths worldwide in 2020, resulting in 18% of all cancer-related deaths.[1] The treatment depends on the tumor type, stage, and patient-specific factors. Among the treatments, surgical resection is the key treatment modality, and lobectomy is associated with a better long-term prognosis.[2] Although surgical resection improves survival, several patients experience postoperative complications such as a decline in physical function and decreased health-related quality of life (HRQoL). Exercise training is an intervention that has improved exercise capacity and HRQoL in cancer patients.[3-5] The recent international consensus on oncology-related exercise prescription found strong evidence of the benefits of exercise on depression, anxiety, cancer-related fatigue, and physical function during and after cancer treatment.[3] The expert panel found that most of these symptoms were improved by performing moderate-intensity aerobic exercise for 30 min three times a week.[3]

Patients with lung cancer are often deconditioned and may have poor cardiopulmonary functions.[6] Lung resection surgery further reduces cardiopulmonary functions,[7] which could be more severe in old-age patients. Pulmonary rehabilitation may improve cardiopulmonary functions, which are associated with quality of life and mortality rate. However, there is still a lack of research on old-age patients. Therefore, we aimed to evaluate how individualized, tailored pulmonary rehabilitation could affect the cardiopulmonary function, psychological function, and HRQoL in old age patients with lung cancer who underwent lobectomy.

## Materials and Methods

### 1) Study design and patients

This prospective, parallel-group trial was designed to determine the effectiveness of pulmonary rehabilitation in old-age patients with lung cancer who underwent lobectomy. This clinical trial was approved by the Institutional Review Board of Inha University (IRB No. 2020-03-007). Written informed consent was obtained from all the participants.

Old-age patients aged > 65 years, with pathologically verified non-small cell lung cancer (NSCLC) stage I-IIIa after lobectomy, were included in this study. The exclusion criteria included postoperative complications that would prevent the patient from performing a submaximal exercise test after 4 weeks of surgery, a previous history of thoracic surgery, other cardiovascular diseases (e.g., chronic obstructive pulmonary disease, ischemic heart disease, etc.), and neurological and/or musculoskeletal comorbidities that prevented the patients from undergoing study protocol. Participant recruitment was conducted between February 2021 and January 2022. A total of 31 patients were enrolled; among them, 22 patients who agreed to get pulmonary rehabilitation were allocated to the pulmonary rehabilitation group, and 9 patients who didn't want to get pulmonary rehabilitation were assigned to the control group.

Four weeks after discharge, the cardiovascular function of the participants was assessed using the CPET and 6-Minute Walking Distance Test (6MWD). In addition, questionnaires on psychological function for assessment of depression using the Patient Health Questionnaire (PHQ-9),[9] for assessment of anxiety using Generalized Anxiety Disorder Screener (GAD-7),[10] for assessment of fatigue using the Fatigue Severity Scale (FSS),[11] for assessment of sleep problem using Pittsburgh Sleep Quality Index–Korean version (PSQI-K),[12] and for assessment of HRQoL using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer (EORTC QLQ-LC13),[13] and Functional Assessment of Cancer Therapy-General (FACT-G)[14] were conducted. After the successful completion of the baseline assessments, the pulmonary rehabilitation group was scheduled for immediate supervised treadmill training. During the intervention, the blood pressure, heart rate, and electrocardiogram (ECG) were monitored by the physician. In addition, the patients were asked to report their rated perception exercise (RPE). On the contrary, the control group didn't receive pulmonary rehabilitation. Instead, after underwent CPET, they were instructed to exercise at an intensity using 11-13 RPE at the follow-up outpatient clinic. Outpatient pulmonary rehabilitation was performed 2-3 times per week for 12 weeks. After a period of 12 weeks, all the assessments were performed again.

## 2) Measurements

### (1) Cardiopulmonary function (CPET, 6MWD)

The CPET was conducted to measure the $VO_2$peak.[15] CPET was performed on a treadmill using a modified Bruce protocol. The blood pressure, heart rate, electrocardiogram (ECG), $VO_2$peak, and respiratory exchange ratio were measured during CPET. In addition, the exercise intensity felt by the patient during exercise was assessed using the Borg rating of perceived exertion (RPE). The CPET was terminated when the patient requested to stop the test for reasons such as leg fatigue or dyspnea. The test was also discontinued when abnormal ECG or abnormal hemodynamic problems, such as blood pressure decrement, were present with increasing exercise intensity. The 6MWD test was performed indoors along a long, flat, straight corridor by a trained technician according to the ATS guidelines.[16]

### (2) Patient Health Questionnaire (PHQ-9)

The PHQ-9 consists of 9 items for the diagnosis of major depressive disorder. For each question, the patients answered on a scale of 0 to 3, depending on the severity of their symptoms. A score of 10 out of 27 points is considered as the cut-off point for depressive symptoms.[9]

### (3) Generalized Anxiety Disorder Screener (GAD-7)

The GAD-7 consists of seven questions, and patients respond on a scale of 0 to 3, depending on the severity of their anxiety symptoms. The sum was calculated, and a score of 8 or higher on the GAD-7 is a reasonable cut-off point for representing anxiety.[10]

### (4) Fatigue Severity Scale (FSS)

The FSS is a 9-item questionnaire examining the degree of fatigue in various situations over the previous week. The patients were requested to select a score from 1 to 7 to indicate the degree of consent. A higher number indicates stronger agreement. The mean was calculated, and a score of 4 was set as the cut-off point for fatigue.[11]

### (5) Pittsburgh Sleep Quality Index-Korean version (PSQI-K)

The PSQI-K consists of 18 questions related to the quality of sleep (sleep onset latency, duration, disturbance, and daytime dysfunction) over the past month. In addition, the bedpartner assessed 5 questions. The score for each question ranged from 0-3. A higher score is indicative of poor sleep quality. A mean score > 8.5 indicated poor sleep quality.[12]

### (6) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer (EORTC QLQ-LC13)

The EORTC QLQ-LC13 covers 13 symptoms related to lung cancer, including cough, dyspnea, and pain. The patients chose a score from 0-4 according to the severity of their symptoms. A higher score indicated that the patient had more severe symptoms.

### (7) Functional Assessment of Cancer Therapy-General (FACT-G)

The FACT-G is a 27-item questionnaire with 4 subscales. There are seven items in the physical domain, six in the emotional well-being domain, seven in the social/family domain, and seven in the functional domain. It uses a five-point scale, and patients select a score based on their quality of life over the past week. In the social and functional domains, a higher score indicated a better quality of life. In the physical and emotional domains, a lower score indicated a better quality of life.

## 3) Pulmonary rehabilitation by treadmill training

The treadmill-based aerobic exercise program was tailored to each patient individually. All the exercise training sessions were supervised by an exercise specialist in the pulmonary rehabilitation outpatient clinic. The patients worked continuously at an intensity of 65-85% of the maximal heart rate and $VO_2$peak. The exercise training consisted of warm-up (10 min), treadmill training (40 min), and a cool-down period (10 min). The patients participated in treadmill training 2-3 times a week for 12 weeks, with an average of 28 times. The intensity of the exercise was gradually increased from 65% of $VO_2$max, usually a 5% increment per week, to 85% of $VO_2$max at 4 weeks after initiation. The patient's ability to cope with dyspnea, a feeling of fatigue, and individual differences in improvement were considered during the exercise sessions.

### 4) Statistical analysis

Values are presented as mean ± standard deviation. Two-way analysis of variance (ANOVA) was used to analyze whether the mean change across time at baseline and post-treadmill training was significantly different. A 2-sided alpha of 0.05 was used for all tests. All statistical tests were conducted using the SPSS software ver. 19.0 (SPSS Inc., Chicago, IL, USA).

## Results

### 1) Participant characteristics

The baseline characteristics of the patients are shown in Table 1. All the patients underwent lobectomy; 17 patients underwent right lobectomy, and 14 patients underwent left lobectomy. All patients had NSCLC; In the pulmonary rehabilitation group, 14 patients had stage IA, 2 patients had stage IB, 5 patients had stage IIB, 1 patient had stage IIIB. In control group, 8 patients had stage IA,1 patient had stage IIB. Demographic and clinical differences between both groups were not statistically significant. No adverse events

**Table 1.** Demographic and Clinical Variables of the Patients

| | Pulmonary rehabilitation (N=22) | Control (N=9) | p-value |
|---|---|---|---|
| Age, mean (years) | 69.15 ± 7.52 | 68.90 ± 8.92 | 0.89 |
| Sex male/female (%male) | 11 (50%) | 5 (55%) | 0.78 |
| Current smoker yes/no (%yes) | 3/19 (14%) | 1/8 (11%) | 0.59 |
| BMI (kg/m$^2$) | 26.1 ± 4.0 | 25.9 ± 3.5 | |
| Baseline $VO_2$peak | 22.46 ± 4.67 | 22.07 ± 5.54 | 0.91 |

BMI: Body mass index, $VO_2$peak: peak oxygen consumption

**Table 2.** Mean Changes in the Cardiopulmonary Function

| Variable | Pulmonary rehabilitation | | Control | | f-value | p-value |
|---|---|---|---|---|---|---|
| | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | | |
| $VO_2$peak (mL/kg/min) | 22.46 ± 4.67 | 27.92 ± 4.28 | 22.07 ± 5.54 | 23.41 ± 5.34 | 15.00 | < 0.001 |
| 6MWD (M) | 486.82 ± 52.5 | 558.68 ± 51.50 | 468.00 ± 78.80 | 513.67 ± 99.45 | 2.845 | 0.102 |
| Maximal SBP (mmHg) | 122.45 ± 17.16 | 121.73 ± 21.54 | 122.33 ± 17.27 | 131.00 ± 19.27 | 1.110 | 0.301 |
| Maximal DBP (mmHg) | 80.13 ± 10.33 | 81.64 ± 11.83 | 75.00 ± 10.11 | 74.33 ± 11.31 | 0.237 | 0.630 |
| Maximal HR (/min) | 97.23 ± 23.08 | 93.32 ± 14.23 | 102.89 ± 28.10 | 88.89 ± 11.10 | 1.534 | 0.225 |

Data are presented as mean ± standard deviation.
$VO_2$peak: peak oxygen consumption, 6MWD: 6-minute walking distance, SBP: systolic blood pressure, HR: heart rate

were observed during the CPET and treadmill training.

### 2) Cardiopulmonary function

Pulmonary rehabilitation improved $VO_2$peak in the rehabilitation group compared with the control group. Table 2 shows the mean $VO_2$peak in the pulmonary rehabilitation group increased by 24% from 22.46 mL/kg/min to 27.92 mL/kg/min with a difference of 5.5 mL/kg/min, while in the control group, the mean $VO_2$peak increased by 6% from 22.07 mL/kg/min to 23.41 mL/kg/min with a difference of 1.3 mL/kg/min. Other variables, such as the 6MWD, maximal heart rate, and maximal systolic blood pressure, showed no significant changes between the groups.

### 3) Psychological function and HRQoL

Table 3 shows the changes in the psychological aspects and HRQoL endpoints. The PHQ-9, GAD-7, FSS, PSQI-K, EORTC QLQ-LC13, and FACT-G physical, and emotional domain decreased in both pulmonary rehabilitation and control groups. On the contrary, FACT-G functional domain increased in both pulmonary rehabilitation and control groups. The FACT-G social domain decreased in the pulmonary rehabilitation group but increased in the control group. On PHQ-9, GAD-7, FSS, PSQI-K, EORTC QLQ-LC13, and FACT-G showed no significant difference between the two groups.

## Discussion

The principal finding of this study was that CPET-based individualized pulmonary rehabilitation resulted in significant improvements in $VO_2$peak in old-age patients. The results indicated that the improvement of $VO_2$peak

**Table 3.** Mean Changes in the Psychological Function and HRQoL

| Variable | Pulmonary rehabilitation | | Control | | f-value | p-value |
|---|---|---|---|---|---|---|
| | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | Pre-treatment Mean ± SD | Post-treatment Mean ± SD | | |
| PHQ-9 | 15.41 ± 6.19 | 11.05 ± 2.36 | 14.89 ± 6.27 | 11.78 ± 2.68 | 0.268 | 0.609 |
| GAD-7 | 9.91 ± 3.66 | 7.82 ± 1.56 | 8.78 ± 3.11 | 7.33 ± 0.71 | 0.346 | 0.561 |
| FSS | 22.45 ± 13.05 | 15.59 ± 9.55 | 17.71 ± 9.46 | 13.14 ± 3.29 | 0.129 | 0.722 |
| PSQI-K | 7.68 ± 4.54 | 4.68 ± 2.80 | 9.44 ± 3.84 | 6.33 ± 3.12 | 0.006 | 0.939 |
| EORTC QLQ-LC13 | 22.05 ± 3.84 | 17.86 ± 4.09 | 19.75 ± 3.24 | 16.50 ± 2.33 | 0.635 | 0.432 |
| FACT-G physical | 13.00 ± 4.58 | 8.91 ± 2.54 | 10.38 ± 3.16 | 7.75 ± 0.71 | 1.015 | 0.322 |
| FACT-G social | 25.18 ± 5.57 | 24.86 ± 6.45 | 25.78 ± 5.31 | 26.44 ± 4.00 | 0.212 | 0.649 |
| FACT-G emotional | 12.27 ± 5.34 | 9.82 ± 2.95 | 10.38 ± 3.11 | 8.13 ± 2.75 | 0.016 | 0.901 |
| FACT-G functional | 24.45 ± 6.55 | 27.68 ± 5.58 | 27.56 ± 7.18 | 28.33 ± 6.23 | 0.869 | 0.359 |

Data are presented as mean±standard deviation.
EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer, FACT-G: Functional Assessment of Cancer Therapy-General, FSS: Fatigue Severity Scale, GAD-7: Generalized Anxiety Disorder Screener, PHQ-9: Patient Health Questionnaire, PSQI-K: Pittsburgh Sleep Quality Index-Korean version

was seen by an increase of 5.5 mL/kg/min or 24% after pulmonary rehabilitation. An improvement of -15% is the generally accepted "clinically important" change in the $VO_2$peak in noncancer populations.[17,18] According to this content, an improvement of 24% in $VO_2$peak in this study in old-age NSCLC patients who received pulmonary rehabilitation is a clinically significant result. The $VO_2$peak is a strong independent predictor of survival in NSCLC, a $VO_2$peak > 0.96 L/min or 13.9 mL/kg/min was associated with a 24% to 61% reduction in the risk of mortality relative to the lowest $VO_2$peak categories. Each 1.0 mL/kg/min increase in $VO_2$peak was associated with a 4% reduction in all-cause mortality in non-resected NSCLC patients.[8] Although the mortality benefit of $VO_2$peak increment was not studied in post-lobectomy NSCLC old-age patients, considering the deconditioning and post-lobectomy states, the improvement of $VO_2$peak in these patients could be more meaningful.

The mechanisms underlying the association between $VO_2$peak and mortality are thought to be mediated by high aerobic capacity (or exercise training-induced changes), established cardiovascular disease risk factors control, and possibly mitochondrial function in non-cancer populations, especially cardiovascular disease patients.[19] The improvements in $VO_2$peak may also impact cancer-specific mortality via other mechanisms.[20] There has been a negative relationship between exercise and cancer progression by modulation of circulating metabolic and sex-steroid hormone concentrations, immune surveillance, and systemic inflammation / oxidative damage.[21]

To our knowledge, only four previous studies[22-25] assessed the exercise capacity after lung resection surgery reporting the $VO_2$peak changes after an exercise intervention. The mean $VO_2$peak changes were 2.8-3.4 mL/kg/min compared to 5.5 mL/kg/min in our study. Several considerations should be noted regarding the differences between previous studies and the present study. Of the four studies, three studies used a cycle ergometer with increments of $VO_2$peak up to 2.1 mL/kg/min (-15% increment). One study used treadmill training with resistance exercise, with a $VO_2$peak increment of 17% (3.4 mL/kg/min). The main difference was seen in the aerobic training method. In a recent meta-analysis study, congestive heart failure patients benefited from better $VO_2$peak gain and longer exercise duration from treadmill training than that from the cycling ergometer.[26] The reason for better gain was attributed to the added upper limb contribution to oxygen consumption and less fatigue in the quadriceps muscles during treadmill exercise. Our results show that post-lobectomy patients who can perform treadmill training could earn better gain in cardiopulmonary function, especially $VO_2$peak.

Although depression, anxiety, fatigue, and QoL are important issues in cancer patients, this study didn't show positive results in the pulmonary rehabilitation group compared to the control group. This might be because the current study included patients who did not have postoperative complications and other comorbidities to undergo pulmonary rehabilitation, and their baseline scores did not reach the minimum cut-off score that indicated the clinically significant symptoms of these instruments, which might be the reason for the results. Future well-designed studies with larger participants are warranted.

There are several limitations to this study. First, the present study aimed to compare the effects of the pulmonary rehabilitation group and control group; however, participants who wanted to receive pulmonary rehabilitation could not be placed in the control group due to ethical issues. Therefore, selection bias may have occurred, although homogeneity among the two groups was verified. In addition, all individuals who did not perform submaximal CPET for various reasons were not included. Second, we expected to find an improvement in psychological or QoL in the pulmonary rehabilitation group. Probably a small number of participants was the reason for this result. Finally, we didn't investigate pulmonary function tests like forced vital capacity and forced expiratory volume in one second. We have planned a prospective randomized controlled trial that is currently underway. In this ongoing trial, the positive results described in this study will be verified.

In conclusion, this study provided evidence that individualized, tailored pulmonary rehabilitation is effective in improving cardiopulmonary function, especially $VO_2$peak, in old-age lung cancer patients who underwent lobectomy.

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