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Peak oxygen consumption measurement and postoperative outcome in patients with early-stage lung cancer

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Abstract:

INTRODUCTION: In early-stage lung cancer (LC) patients, the best survival rates are achieved when the patient undergoes surgical resection. Cardiopulmonary exercise testing is an important preoperative test because of its ability to detect disturbance in the oxygen transport system, which is, in turn, related to the development of postoperative complications.

OBJECTIVES: The aim of the study is to investigate the value of peak oxygen consumption (peakVO_2) to determine postoperative pulmonary complications (PPCs) in LC patients with surgical resection.

MATERIALS AND METHODS: LC patients who were candidates for surgery between February 2015 and 2017 were included in this prospectively conducted study. PeakVO_2 measurement was performed by utilizing cycle ergometry during incremental exercise. All patients were on follow-up for PPCs for a period of 30 days postoperatively.

RESULTS: The study included 41 patients (mean age: 63.9 ± 9.7 years) who had undergone surgical resection (28 lobectomies/13 pneumonectomies). There was no mortality, but 8 (19.5%) PPCs were observed. Mean peakVO_2 values were not different in patients with and without PPCs. When the patients were divided into two groups based on absolute forced expiratory volume 1 second (FEV_1) (≤1.5 L and >1.5 L) and ppo FEV_1% (≤30% and >30%); mean peakVO_2, mean stay days in intensive care unit and hospital, and PPC rates were similar between groups. Fourteen patients with FEV_1 ≤1.5 L and 11 patients with ppo FEV_1 ≤30% underwent successful surgical resections.

CONCLUSION: PeakVO_2 measurement prevents patients to be deprived of a surgical resection, which is an important treatment modality for LC. PPCs were in acceptable limits in patients with a value of peakVO_2 ≥15 ml/kg/min.

Keywords:

Cardiopulmonary exercise testing, lung cancer, peak oxygen consumption, postoperative complications, preoperative pulmonary evaluation

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Introduction

Lung cancer (LC) is the leading cause of cancer-related death among men and women.[1] It is estimated that there are annually 1.6 million deaths due to LC worldwide.[2] The annually detected new LC cases were 20,467 in men and 3368 in women.[3] Nonsmall cell LC (NSCLC) accounts for the majority of cases with a ratio of 85%.[1] In spite of advances in modern diagnostic, staging, and therapeutic modalities, 5-year survival rate is overall 18% in NSCLC cases. Such a low survival rate is mainly due to diagnosis in advanced stages, since the 5-year survival rates can be as high as 92% in clinically staged IA1 and no survival in Stage IVB.[4] The best survival rates are achieved in early stage LC patients who had undergone surgical resection. Certainly, only 15%–20% of NSCLC cases can be diagnosed at early stages.[1,3]

Another problem halting surgical resections is smoking-related comorbidities such as chronic obstructive pulmonary disease, which causes poor pulmonary functions and atherosclerotic cardiovascular diseases. In a retrospective analysis of NSCLC patients who are potential surgical candidates, severe pulmonary function impairment was identified as the reason for surgical inoperability in more than one-third of the patients.[5] In order not to deprive a patient from a potentially curable surgical resection, the assessment of preoperative pulmonary functions is critically important.

Cardiopulmonary exercise testing (CPET) is an important preoperative test because of its ability to detect disturbance in the oxygen transport system which is, in turn, related to the development of postoperative complications.[6] Brunelli *et al*. suggested the liberal use of CPET before lung resection, since this test can help stratify the surgical risk and optimize perioperative care.[7] The aim of this study is to present the value of peak oxygen consumption (peakVO$_2$) measurement in the evaluation of LC patients who are surgical candidates and to compare peakVO$_2$ values of patients with and without postoperative pulmonary complications (PPCs).

Materials and Methods

Patients

The study was carried out prospectively and approved by the Local Ethics Committee (GO 15/494-30). Informed consent was obtained from all the patients. Newly diagnosed early-stage LC patients, who are candidates for surgery between February 2015 and 2017, were included in this study. All patients were older than 18-year-old and did not have any contraindications for performing CPET. All patients underwent preoperative cardiovascular evaluation before performing CPET. Exclusion criteria were disapproval of participating in the study, neoadjuvant chemotherapy or radiotherapy, unstable clinical conditions such as uncontrolled hypertension (systolic pressure ≥200 mmHg and diastolic pressure ≥110 mmHg), recent myocardial infarction, severe aortic stenosis, suspicious or documented dissection of aorta, severe pulmonary hypertension (≥50 mmHg), hypoxemia (pulse O$_2$ saturation ≤85% in room air), and orthopedic problems precluding cycling.

A study form including demographic data, smoking history, comorbidities, medications, LC data (pathological stage, histological subtype, and resection type), pulmonary funtion tests, CPET analysis, and postoperative follow-up data was filled for each patient. Eight edition of tumor-node-metastasis classification was used for pathological staging.[8]

All study patients were followed up for 30 days postoperatively. Postoperative follow-up data included: intensive care unit and hospital stay days, mechanical ventilation needs and PPCs (prolonged mechanical ventilation >48 h, respiratory failure, pneumonia, empyema, atelectasis, acute respiratory distress syndrome, and pulmonary edema). The study participants were divided into two groups based on preoperative absolute forced expiratory volume 1 second (FEV$_1$) values (≤1.5 L, >1.5 L) and anatomically calculated ppoFEV$_1$ values (≤30%, >30%). These groups were compared for postoperative morbidity and mortality.

Cardiopulmonary exercise testing

CPET was performed to patients with the Fitmate-MED (Cosmed) CPET device. All patients underwent symptom-limited cycle ergometry exercise with a facemask (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas City, MO, USA) fixed on face. After 3-min baseline resting period records, a 3-min warm-up period (60 rpm was the maintenance pedaling rate) was started and then incremental work (10 W elevation for each minute) was applied.[6] The maximum work rate for half a minute was saved. During CPET, electrocardiography, blood pressure, and pulse oxygen saturation were monitored. Symptoms such as leg pain, chest pain, fatigue, dizziness, or dyspnea were also noted. peakVO$_2$ (peakVO$_2$ ml/kg/min) was determined. As preoperative peakVO$_2$ of >15 ml/kg/min is associated with no appreciable increase in perioperative mortality and complications according to the British Thoracic Society (BTS) guideline,[9] patients with peakVO$_2$ ≥15 ml/kg/min were referred for surgery.

Statistical analysis

Statistical analyses were performed with SPSS Statistics Version 22.0. (Armonk, NY: IBM Corp). Data obtained were indicated as frequencies or mean ± standard deviation. For comparison of study groups Mann–Whitney U-test was used for continuous parameters; Chi-square test was used for discrete parameters. $P < 0.05$ was considered as statistically significant.

Results

CPET was performed to 69 patients during the 2 years study period. As shown in the flowchart, 28 patients were excluded due to several reasons [Figure 1]. At the end, 41 (36 males/5 females) newly diagnosed early-stage LC patients who had undergone surgical resection in the Department of Chest Surgery, Hacettepe University School of Medicine, were analyzed. The mean age was 63.9 ± 9.7 years and all patients had a peakVO_2 higher than 15 ml/kg/min. The characteristics of patients and pulmonary function tests (PFT), CPET parameters are seen in Tables 1 and 2, respectively.

The study participants were divided into two groups based on preoperative absolute FEV_1 values (≤1.5 L, >1.5 L) and anatomically calculated ppoFEV_1 values (≤30%, >30%). The comparison of these groups based on PFT and CPET parameters are seen in Table 3. The groups were similar based on mean age and smoking history. As expected, the PFT parameters (FEV_1, forced vital capacity [FVC], FEV_1/FVC, FEF 25%–75%, maximal voluntary ventilation %) were significantly lower in the study groups with preoperative absolute FEV_1 ≤1.5 L and anatomically calculated ppoFEV_1 ≤30%. However, the groups were similar based on CPET parameters such as peakVO_2, heart rate reserve, and O_2 pulse. Respiratory reserve was significantly lower in the study group with preoperative absolute FEV_1 ≤1.5 L ($P = 0.04$) [Table 3].

Mean intensive care unit and hospital stay days of the study participants were 2.36 ± 2 (range: 1–10) and 13.9 ± 9.8 (range: 5–60) days, respectively. There was no mortality, but 8 (19.5%) PPCs (prolonged mechanical ventilation in 7 patients and empyema in 1 patient) were observed. The comparison of patients with and without PPCs is depicted in Table 4. Including mean peakVO_2 values, there was not any statistically significant difference.

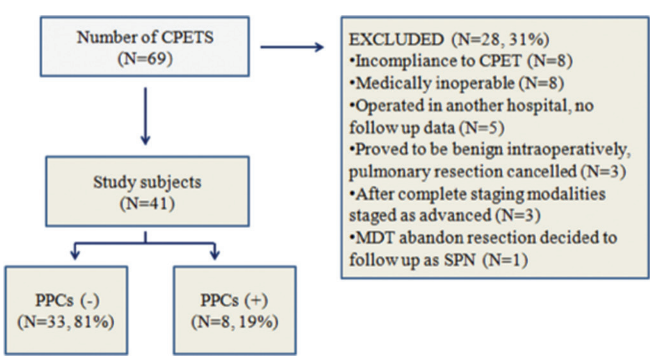

Figure 1: The flowchart of the study participants. CPET: Cardiopulmonary exercise testing, MDT: Multidisciplinary team, PPCs: Postoperative pulmonary complications, SPN: Solitary pulmonary nodule

When the patients were divided into two groups based on absolute FEV_1 (≤1.5 L and >1.5 L) and ppo FEV_1% (≤30% and >30%) values, mean intensive care unit, and hospital stay days, PPC rates were similar between groups [Table 5]. Fourteen patients who had an absolute FEV_1 ≤1.5 L with peakVO_2 higher than 15 ml/kg/min and 11 patients who had a ppoFEV_1 ≤ 30% with peakVO_2 higher than 15 ml/kg/min underwent successful surgical resections.

Discussion

In this study, our aim was to present the importance of peakVO_2 measurement in the evaluation of LC patients who are surgical candidates and its relation with PPCs. We prospectively performed CPET and determined peakVO_2

Table 1: The characteristics of the study patients

Parameters	Values
Number of study patients	*n*=41
Mean age (years)	63.6±9.7 (range: 27-82)
Gender, *n* (%)	
Male	36 (87.8)
Female	5 (12.2)
Smoking history, *n* (%)	
Ever smoker	36 (87.8)
Never smoker	5 (12.2)
Mean smoking history (pack-years)	42.9±14.4 (range: 10-100)
Comorbidities	
Absent	10 (24.4)
COPD	23 (56)
CAD	5 (12.2)
Other	7 (17)
Type of pulmonary resection, *n* (%)	
Lobectomy	28 (68.3)
Right pneumonectomy	7 (17.1)
Left pneumonectomy	6 (14.6)
Histological subtypes, *n* (%)	
Squamous cell	20 (48.8)
Adenocarcinoma	16 (39.2)
Large-cell carcinoma	2 (4.8)
Carcinoid tumor	2 (4.8)
Small-cell carcinoma	1 (2.4)
Pathological stages, *n* (%)	
IA1	3 (7.3)
IA2	3 (7.3)
IA3	3 (7.3)
IB	8 (19.5)
IIA	6 (14.7)
IIB	9 (22)
IIIA	8 (19.5)
IIIB	1 (2.4)

COPD: Chronic obstrcutive pulmonary disease, CAD: Coronary artery disease in 41 early-stage LC cases during 2 years of the study period. All of the patients had a peakVO$_2$ ≥15 ml/kg/min. Fourteen patients who had an absolute FEV$_1$ ≤1.5 L and 11 patients who had an anatomically calculated ppoFEV$_1$ ≤30% underwent successful surgical resections. In these patients, peakVO$_2$ measurement prevented patients to be deprived of a surgical resection, which is an important treatment modality for LC. Within the context of the study, we also followed the patients up postoperatively for 30 days for the onset of mortality and PPCs. While there was no mortality, there were eight patients (19.5%) with PPCs, which were easily managed. Mean peakVO$_2$ values were not significantly different among patients with and without PPCs. PPCs were not significantly different among patients who underwent lobectomy or pneumonectomy.

Lung resection provides the greatest likelihood of cure for patients with early-stage LC but is associated with a risk of mortality, decreased postoperative lung function, and other complications. Despite of the advances in anesthetic and surgical technique, 30-day mortality of 2.3% for lobectomy and 5.8% for pneumonectomy have been reported.[9,10] Lung resection induces a significant stress to the cardiopulmonary system, so it is important to identify patients who can tolerate surgery. The objectives of preoperative pulmonary evaluation in a lung resection candidate are to assure that the remnant lung can provide adequate respiratory function to allow the patients weaned off mechanical ventilation after surgery, maintain the candidate's vital needs after recovery, and provide a reasonable quality of life.[11]

Pulmonary function testing using spirometry, diffusing capacity for carbon monoxide (DLCO), and determining peakVO$_2$ with CPET help predict the risk of mortality and PPCs. Foreseeing postoperative lung function using the proportion of lung segments to be resected by anatomical methods or radionuclide scanning is also important for assessing surgical risk. The American College of Chest Physicians (ACCP), the European Respiratory Society/European Society of Thoracic Surgeons (ERS/ESTS), and the BTS guidelines provide detailed algorithms for preoperative risk assessment, but their recommended approaches differ somewhat. The ACCP guideline recommends the calculation of ppoFEV$_1$ and predicted postoperative carbonmonoxide diffusion capacity (ppoDLCO) in the first step, low technology exercise tests in the second, and CPET at the end.[12] BTS guideline again recommends the calculation of ppoFEV$_1$ and ppoDLCO at first and directly proceeds to CPET if not adequate.[9] ERS/ESTS guideline recommends performing spirometry and diffusion capacity for carbon monoxide at the beginning and proceeds with CPET if either one is <80%.[13]

Table 2: Pulmonary funtion test and cardiopulmonary exercise testing parameters of the study patients

Parameters	Mean	Range
FEV$_1$ (L)	2.1±0.58	0.86-3.1
FEV$_1$ (%)	70.63±20.4	32-109
FVC (L)	2.9±0.66	1.12-3.95
FVC (%)	78±16.8	37-117
FEV$_1$/FVC	69.6±10.8	37-88
FEF 25-75 (%)	49.6±25.2	12-107
MVV (%)	69.2±28.5	13-145
Peak VO$_2$ (ml/kg/min)	17.8±2.4	15.0-23.1
Heart rate reserve (pulse/min)	23±13	0-56
Respiratory reserve (L/min)	36.5±23.2	5-93
O$_2$ pulse	0.1±0.03	0.09-0.23

FVC: Forced vital capacity, FEV$_1$: Forced expiratory volume in 1 second, MVV: Maximum voluntary ventilation, FEF: Forced expiratory flow, VO$_2$: Oxygen consumption

Table 3: The comparison of pulmonary function test and cardiopulmonary exercise testing parameters in study patients divided into two groups based on preoperative absolute forced expiratory volume in 1 second values (≤1.5 L, >1.5 L) and anatomically calculated ppoFEV1 values (≤30%, >30%)

	FEV$_1$ ≤1.5 L	FEV$_1$>1.5 L	*P*	ppoFEV$_1$ ≤30%	ppoFEV$_1$>30%	*P*
Number of patients	14	27	-	11	30	-
Mean age (years)	64.5±5.9	63.2±11.3	0.64	64.3±6.3	63.4±10.8	0.83
Smoking (pack-years)	41±27	36±14	0.1	32.8±18.1	39.4±20.1	0.36
FEV$_1$ (L)	1.31±0.21	2.38±0.39	<0.001*	1.46±0.42	2.2±0.54	0.001*
FEV$_1$ (%)	45.9±12.2	80.7±13.9	<0.001*	48.3±12.6	76.1±18.6	<0.001*
FVC (L)	2.31±0.52	3.24±0.48	<0.001*	2.53±0.6	3.07±0.63	0.034*
FVC (%)	62.7±14.0	85.9±12.0	<0.001*	66.1±14.5	82.4±15.5	0.005*
FEV$_1$/FVC	58.3±10.5	73.1±7.4	<0.001*	57.9±10.1	71.8±8.9	<0.001*
FEF 25-75 (%)	30.6±17.7	59.4±22.9	<0.001*	26.4±9.6	58.1±23.8	<0.001*
MVV (%)	46.9±16.9	80.7±26.5	<0.001*	54±18.2	74.8±29.8	0.02*
Peak VO$_2$ (ml/kg/min)	18.0±2.4	17.7±2.5	0.73	18.3±2.2	17.7±2.27	0.32
Heart rate reserve (pulse/min)	20.7±8.7	24.2±14.8	0.3	23.9±14.2	22.7±12.8	0.91
Respiratory reserve (L/min)	22.8±15.9	40.8±23.7	0.04*	24.1±16	39.8±23.9	0.09
O$_2$ pulse	0.13±0.03	0.13±0.028	0.64	0.15±0.04	0.13±0.02	0.11

*P < 0.05 is significant. FVC: Forced vital capacity, FEV$_1$: Forced expiratory volume in 1 second, MVV: Maximum voluntary ventilation, FEF: Forced expiratory flow, VO$_2$: Oxygen consumption, ppoFEV$_1$: predicted postoperative forced expiratory volume in 1 second

In the present study, we directly perform spirometry and CPET to all the study participants who are candidates for lung resection. We used a unique cutoff level for peakVO_2 ≥15 ml/kg/min and performed all planned resections. This cutoff level was also defined as a threshold for increased risk in other studies.[14,15] After 30 days follow-up, there was no mortality; there were 8 patients (19.5%) with PPCs, which were easily managed. Mean peakVO_2 values were not significantly different among patients with (18.5 ml/kg/min) and without PPCs (17.8 ml/kg/min).

As a comprehensive physiologic evaluation, exercise testing is dependent on the interactions among pulmonary function, cardiovascular function, and oxygen utilization by peripheral tissues. It is obvious that the higher the exercise tolerance, the more likely an individual patient will be able to tolerate thoracic surgery.[16] Therefore, it is a comprehensive way of identifying suitable surgical candidates. Exercise testing can be performed by low technology exercise tests (ex: 6-min walk, stair climbing, shuttle walk,) or CPET.[12] CPET is useful when the results of ppoFEV_1, ppoDLCO, and/or low technology exercise testing do not clearly define the patient's risk as either high or low. CPET predicts a patient's ability to elevate metabolism, cardiac output, and oxygen consumption for a prolonged period without requiring anaerobic respiration and thus attempts to predict a patient's risk of postoperative morbidity and mortality. During the last 20 years, CPET has become an integral part of the preoperative pulmonary evaluation of lung resection candidates. It is particularly important in patients with poor pulmonary function testing. However, CPET is not used in a widespread manner in clinical practice, as it is a time-consuming procedure, which requires equipment and educated staff, and there are more than one contraindications for applicability. After incorporating peakVO_2 in the evaluation of patients, we securely allowed our patients to lung resection. Fourteen patients who had an absolute FEV_1 ≤1.5 L and 11 patients who had an anatomically calculated ppoFEV_1 ≤30% underwent successful surgical resections. Mean peakVO_2 values, mean intensive care unit, and hospital stay days, PPC rates were not significantly different between patients with FEV1.

Table 4: The comparison of patients with and without postoperative pulmonary complications

	Without PPCs	With PPCs	*P*
Number of patients	33	8	-
Mean age (years)	62.9±10.1	66.7±7.6	0.41
Type of pulmonary resection	Lobectomy=23 Pneumonectomy=10	Lobectomy=5 Pneumonectomy=3	0.69
FEV_1 (L)	2.09±0.62	1.68±0.47	0.11
FEV_1 (%)	71.3±21.6	57.8±15.5	0.97
FVC (%)	78.4±18.1	76.5±9.8	0.66
FEV_1/FVC	70.4±9.5	58.6±12.5	0.16
MVV %	72.2±28.9	56.6±24.8	0.16
PeakVO_2 (ml/kg/min)	17.8±2.2	18.5±2.3	0.42
Heart rate reserve (pulse/min)	24.6±13.1	16.5±11.0	0.12
Respiratory reserve (L/min)	29.1±26.4	24.8±30.4	0.52
O_2 pulse	0.13±0.027	0.14±0.031	0.21

PPCs: Postoperative pulmonary complications, VO_2: Oxygen consumption, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in 1 second, MVV: Maximum voluntary ventilation

This study is valuable since it is carried out prospectively; the patients were operated in the same center and followed up 30 days postoperatively. However, the number of study participants was slightly low. We excluded nearly one-third of the patients that we performed CPET. The major reasons for exclusion were in compliance to cycling, incomplete staging prior to CPET, and the patients preferring another center for surgery. Another limitation might be thought as the lack of DLCO measurement in the present study. CPET was performed to all the study participants; hence, lack of DLCO measurement did not cause a deficiency in surgical assessment. DLCO is used to measure the body's ability to transfer oxygen across the alveolar-capillary membrane.[17] It is widely used in the evaluation of pulmonary parenchymal function. Unfortunately, the interpretation of DLCO test is complicated. It is not only effected by patients' cardiovascular health, hemoglobin and carboxyhemoglobin levels, and respiratory effort, the lung volumes at which DLCO measured, but also the altitude and the laboratory

Table 5: The comparison of mean intensive care unit and hospital stay days, postoperative mechanical ventilation needs, and PPCs in study patients divided into two groups based on preoperative absolute forced expiratory volume in 1 second values (≤1.5 L, >1.5 L) and anatomically calculated ppoFEV_1 values (≤30%,>30%)

	FEV_1 ≤1.5 L	FEV_1>1.5 L	*P*	ppoFEV_1 ≤30%	ppoFEV_1>30%	*P*
Number of patients	14	27	-	11	30	-
Mean ICU stay (days)	13.8±13	14.0±7.3	0.33	15.9±15	13.5±7.1	0.67
Mean hospital stay (days)	2.5±2.2	2.29±1.75	0.83	2.9±2.6	2.1±1.7	0.34
Postoperative MV need (%)	9 (64)	19 (70)	0.96	6 (54)	22 (73)	0.44
PPCs (%)	4 (29)	4 (15)	0.52	3 (27)	5 (16)	0.65

ICU: Intensive care unit, MV: Mechanical ventilation, PPCs: Postoperative pulmonary complications, FEV_1: Forced expiratory volume in 1 second, ppoFEV_1: predicted postoperative forced expiratory volume in 1 second environment.[18] Achieving consistent results between and within laboratories remains a difficult problem. Even when healthy individuals are tested in different laboratories, the results can very widely.[19] CPET is a dynamic test evaluating both cardiovascular and pulmonary health, including the respiratory mechanics and the pulmonary parenchymal function by measuring peakVO_2. Moreover, if either the ppoFEV_1 or ppoDLCO is <30 percent, CPET is indicated with measurement of oxygen consumption. Therefore, CPET is a higher level functional test than DLCO measurement for the risk stratification in lung resection.[20] Consistent with these suggestions, 11 patients who had an anatomically calculated ppoFEV_1 ≤30% with peakVO_2 higher than 15 ml/kg/min underwent successful surgical resections, and no significant differences in terms of PPCs were observed in the present study.

Conclusion

PeakVO_2 measurement prevents patients to be deprived of a surgical resection, which is an important treatment modality for LC. PPCs were in acceptable limits in patients with an adequate peakVO_2 ≥15 ml/kg/min. We suggest the usage of CPET in the second step in a patient with an abnormal spirometry and/or DLCO.

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Conflicts of interest

There are no conflicts of interest.

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