Effects of a high-intensity pulmonary rehabilitation program on the minute ventilation/carbon dioxide output slope during exercise in a cohort of patients with COPD undergoing lung resection for non-small cell lung cancer

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ABSTRACT

Objective: Preoperative functional evaluation is central to optimizing the identification of patients with non-small cell lung cancer (NSCLC) who are candidates for surgery. The minute ventilation/carbon dioxide output ($V_{E}/V_{CO2}$) slope has proven to be a predictor of surgical complications and mortality. Pulmonary rehabilitation programs (PRPs) could influence short-term outcomes in patients with COPD undergoing lung resection. Our objective was to evaluate the effects of a PRP on the $V_{E}/V_{CO2}$ slope in a cohort of patients with COPD undergoing lung resection for NSCLC. Methods: We retrospectively evaluated 25 consecutive patients with COPD participating in a three-week high-intensity PRP prior to undergoing lung surgery for NSCLC, between December of 2015 and January of 2017. Patients underwent complete functional assessment, including spirometry, DLCO measurement, and cardiopulmonary exercise testing. Results: There were no significant differences between the mean pre- and post-PRP values (% of predicted) for FEV\(_1\) (61.5 ± 22.0% vs. 62.0 ± 21.1%) and DLCO (67.2 ± 18.1% vs. 67.5 ± 13.2%). Conversely, there were significant improvements in the mean peak oxygen uptake (from 14.7 ± 2.5 to 18.2 ± 2.7 mL/kg per min; \(p < 0.001\)) and $V_{E}/V_{CO2}$ slope (from 32.0 ± 2.8 to 30.1 ± 4.0; \(p < 0.01\)). Conclusions: Our results indicate that a high-intensity PRP can improve ventilatory efficiency in patients with COPD undergoing lung resection for NSCLC. Further comprehensive prospective studies are required to corroborate these preliminary results. Keywords: Carcinoma, non-small-cell lung; Pulmonary disease, chronic obstructive/rehabilitation; Carbon dioxide/metabolism; Oxygen consumption/physiology; Risk assessment.

INTRODUCTION

Risk stratification has always been considered crucial in patients with non-small cell lung cancer (NSCLC) undergoing lung resection. The decline in the respiratory function after surgery remains a noteworthy drawback despite the advances in surgical techniques and perioperative care. The current guidelines of the European Respiratory Society and the European Society of Thoracic Surgery\textsuperscript{(1)} strongly suggest the assessment of patients’ physical performance by a functional-based algorithm. Peak oxygen uptake ($VO_{2peak}$) has shown to be the best independent predictor of surgical complication rates\textsuperscript{(2-7)} and, for this reason, cardiopulmonary exercise testing (CPET) is recommended when preoperative FEV\(_1\) and/or DLCO are < 80% of the predicted values.\textsuperscript{(5)} Therefore, preoperative evaluation of respiratory function is one of the most important factors to determine operability, especially in patients with COPD.\textsuperscript{(1,3-8)} Although $VO_{2peak}$ is certainly the most widely used variable, CPET provides various other direct and indirect indicators that change in response to incremental workloads. Consistent data are emerging about the relationship between minute ventilation ($V_{E}$) and carbon dioxide output ($V_{CO2}$), also called the ventilatory efficiency slope. Patients with lung disease have increased ventilatory requirements for a given level of exercise.\textsuperscript{(9)} In two independent studies that involved patients undergoing lung resections, a higher $V_{E}/V_{CO2}$ slope showed to be a predictor of surgical complications and increased mortality.\textsuperscript{(3,8)} A few studies reported the impact of preoperative pulmonary rehabilitation programs (PRPs) on exerctional parameters in cohorts of NSCLC patients undergoing radical surgery.\textsuperscript{(10-12)} Therefore, the

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aim of the present study was to evaluate the effects of a preoperative high-intensity PRP on the \( V_{E}/V_{CO_2} \) slope in a cohort of patients with COPD undergoing lung resection for NSCLC.

**METHODS**

**Patients**

We retrospectively evaluated the electronic medical records of 32 consecutive COPD patients attending a preoperative high-intensity PRP prior to undergoing lung surgery for NSCLC, between December of 2015 and January of 2017. Inclusion criteria were having been previously diagnosed with clinical stage I-IIIa NSCLC; being deemed fit for surgery according to the European Respiratory Society/European Society of Thoracic Surgery guidelines; being < 80 years of age; having a body mass index of 18-34 kg/m\(^2\); and presenting with a postbronchodilator fixed FEV1/FVC ratio < 0.70. Exclusion criteria were contraindications to surgery based on baseline CPET; cardiovascular or musculoskeletal disorders limiting training; use of oxygen therapy or noninvasive ventilation for chronic lung failure; cognitive impairment or psychiatric disorders; and pregnancy. The PRP was offered to patients with COPD who had a \( VO_2_{peak} \) ≤ 15.0 mL/kg per min or an FEV1 ≤ 50% of the predicted value and were awaiting surgical resection. The inclusion of patients in the PRP was not a reason for postponing surgical resection in any case. Patients who were deemed fit for surgery underwent open thoracotomy or video-assisted lobectomy three weeks after the beginning of PRP. COPD treatment was not modified during the observation period. Complete functional assessment, including spirometry, DLCO measurement, and CPET, was carried out, in accordance with our routine practice, before and after the PRP, both prior to surgery.

**CPET and evaluation of dyspnea**

Before and after the PRP, CPET was performed using a ramp protocol and breath-by-breath measurements on a cycle ergometer (Ergoline Ergoselect; SensorMedics, Milan, Italy) connected to computerized analyzer (Vmax encore 29C; SensorMedics). Hemodynamic and respiratory parameters were monitored during the test, including blood pressure, \( SpO_2 \), heart rate (HR), electrocardiogram, exhaled \( O_2 \), and exhaled \( CO_2 \).

The test started with a 2-min evaluation of the patient at rest, followed by a 2-min warm-up period during which the patient cycled freely. Exercise intensity was gradually increased based on the predicted workload for each patient. The test was interrupted when the patient reached the maximum predicted HR or whether other limitations occurred. At the end of the CPET, the reasons for exercise limitation and the perception of dyspnea, determined by the Borg scale, were registered.

**PRP**

A PRP, in daily 3-h sessions from Monday to Friday, was carried out for 3 consecutive weeks. In brief, the program consisted of respiratory exercises on a bench, on a mattress pad, and using wall bars. Subsequently, high-intensity training for the upper limbs (on a rowing ergometer) and the lower limbs (on a treadmill or cycle ergometer) were carried out. For rowing and walking, training was conducted at a perceived exertion rating of 15-17 (hard to very hard) on the Borg Rating of Perceived Exertion scale. For cycling, the exercise workload was set according to CPET results for each patient, starting with 70% of the maximum score reached in CPET and increased by 10 W when the patient was able to tolerate that workload for 30 min. High-intensity exercises lasted for 10-15 min. In the presence of physical exhaustion or severe dyspnea, the exercise was prematurely interrupted. The training sessions were supervised by an experienced physical therapist.

**Statistical analysis**

Data are reported as frequencies, means, and standard deviations; for respiratory parameters, absolute and percentage of the predicted values were considered. Intragroup analysis was performed using a t-test for dependent variables. The level of significance was set at 5%.

**RESULTS**

Of the 32 patients evaluated, 7 were excluded because of incomplete PRP or lack of post-PRP assessment: 5 patients (15.6%) underwent surgery at other hospitals; and 2 (6.2%) abandoned the PRP after less than one week. Therefore, the sample comprised 25 patients (17 males and 8 females) diagnosed with resectable NSCLC (stage I-IIIA). The mean age was 62.3 ± 6.0 years. The baseline characteristics of the patients are summarized in Table 1, whereas Table 2 shows the comparison of characteristics between included and excluded patients. All of the patients had a baseline \( VO_2_{peak} \) ranging from 10 to 20 mL/kg per min (mean, 14.7 ± 2.5 mL/kg per min). Three patients (12%) had a previous diagnosis of chronic heart failure, and 16 (64%) had systemic hypertension. Table 3 compares spirometry and CPET parameters before and after the 3-week PRP. As expected, the major spirometry variables showed no significant differences between the pre- and post-PRP values. Conversely, the \( VO_2_{peak} \) improved significantly after the PRP (14.7 ± 2.5 mL/kg per min vs. 18.2 ± 2.7 mL/kg per min; \( p < 0.001 \)), as did the \( V_{E}/V_{CO_2} \) slope (32.0 ± 2.8 vs. 30.1 ± 4.0; \( p < 0.01 \)).

**DISCUSSION**

In the present study, we found that a high-intensity PRP in patients with COPD undergoing lung resection for NSCLC might influence exertional parameters by increasing \( VO_2_{peak} \) and reducing the \( V_{E}/V_{CO_2} \) slope. The risk of lung cancer is approximately five times greater in patients with COPD than in smokers without COPD, regardless of age and smoking history. In patients in the early stages of NSCLC, the
Despite the small number of patients, our study offers novel insights in this field of research. However, the present study has some limitations. First, because of the retrospective design of the study, we were unable to report the 1-year survival rate of the patients studied, which would be an interesting long-term observation. Second, the number of patients who were unable to complete the postoperative training, are also under investigation in two clinical trials (NCT00363428 and NCT02887521). The effects of pulmonary rehabilitation in COPD patients undergoing NSCLC surgery are currently under investigation in two clinical trials (NCT00363428 and NCT02887521). The effects of a longer PRP, including preoperative and postoperative PRPs, the few such studies having produced inconsistent results. The effects of pulmonary rehabilitation in COPD patients undergoing NSCLC surgery has yet to be clarified. Mainini et al., (26) in an elegant systematic review, emphasized that PRPs should be better studied due to the scarcity of randomized clinical trials regarding preoperative and postoperative PRPs, the few such studies having produced inconsistent results. The effects of pulmonary rehabilitation in COPD patients undergoing NSCLC surgery are currently under investigation in two clinical trials (NCT00363428 and NCT02887521). The effects of a longer PRP, including preoperative and postoperative training, are also under investigation (NCT02405273).

Table 1. Baseline characteristics of the patients (N = 25).*  

| Characteristic        | Result            |
|-----------------------|-------------------|
| Age, years            | 62.3 ± 6.0        |
| Gender, male          | 17 (68)           |
| Smoking history, pack-years | 37.2 ± 8.0       |
| BMI, kg/m²             | 26.1 ± 3.4        |
| FEV₁, L               | 1.67 ± 0.7        |
| FEV₁, % predicted     | 61.5 ± 22.0       |
| FEV₁/FVC              | 54.1 ± 13.1       |
| TLC, % predicted      | 108.7 ± 28.6      |
| IC, % predicted       | 84.4 ± 14.3       |
| IC/TLC                | 38.5 ± 12.1       |
| RV, % predicted       | 130.0 ± 39.4      |
| DLCO, % predicted     | 67.2 ± 18.1       |
| VO₂peak, mL/kg per min | 14.7 ± 2.5      |
| VO₂peak, % predicted  | 64.1 ± 19.2       |
| COPD staging          |                   |
| I                     | 4 (16)            |
| II                    | 9 (36)            |
| III/IV                | 12 (48)           |
| COPD treatment        |                   |
| LAMA                  | 3 (12)            |
| LABA                  | 1 (4)             |
| LABA/LAMA             | 16 (64)           |
| LABA/LAMA/ICS         | 5 (20)            |
| TNM staging           |                   |
| Ia                    | 6 (24)            |
| Ib                    | 8 (32)            |
| Iia                   | 7 (28)            |
| Iib                   | 4 (16)            |

BMI: body mass index; IC: inspiratory capacity; VO₂peak: peak oxygen uptake; LABA: long-acting β₂ agonists; LAMA: long-acting muscarinic antagonists; ICS: inhaled corticosteroids; and TNM: tumor-lymph node-metastasis. *Values expressed as n (%) or mean ± SD.
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In conclusion, our results underscore the influence of a high-intensity PRP on ventilation efficiency. Further comprehensive prospective studies are required in order to corroborate these preliminary results.

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**Table 2. Spirometry and cardiopulmonary exercise test parameters before and after the three-week pulmonary rehabilitation program.**

| Parameter                        | Before  | After   | p   |
|----------------------------------|---------|---------|-----|
| FEV1, % predicted                | 61.5 ± 22.0 | 61.9 ± 21.1 | ns  |
| VC, % predicted                  | 81.1 ± 19.0 | 82.0 ± 17.8 | ns  |
| FEV1/VC                          | 54.1 ± 13.1 | 54.5 ± 14.1 | ns  |
| DLCO, % predicted                | 67.2 ± 18.1 | 67.5 ± 13.2 | ns  |
| VO2peak mL/kg per min            | 14.7 ± 2.5  | 18.2 ± 2.7   | < 0.001 |
| VO2peak % predicted              | 64.0 ± 19.2 | 81.1 ± 18.0  | < 0.001 |
| VE/VCO2 slope                    | 32.0 ± 2.8  | 30.1 ± 4.0   | < 0.01 |
| Peak HR, % predicted             | 92.1 ± 1.8  | 92.3 ± 2.0   | ns  |
| Peak RER                         | 1.2 ± 0.3   | 1.3 ± 0.2    | ns  |
| Breathing reserve, %             | 24.3 ± 6.1  | 24.7 ± 6.4   | ns  |

ns: not significant; VO2peak: peak oxygen uptake; VE: minute ventilation; VCO2: carbon dioxide output; and RER: respiratory exchange ratio.

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**Table 3. Baseline characteristics of included and excluded patients.**

| Characteristic | Included patients | Excluded patients | p   |
|----------------|-------------------|-------------------|-----|
| Age, years     | 62.3 ± 6.0        | 60.4 ± 5.1        | 0.45|
| Gender         |                   |                   |     |
| Male           | 17 (68.0)         | 5 (71.4)          | 0.94|
| Female         | 8 (32.0)          | 2 (28.6)          | 0.90|
| Smoking history, pack-years | 37.2 ± 8.0   | 32.2 ± 9.1        | 0.16|
| BMI, kg/m²     | 26.1 ± 3.4        | 27.5 ± 2.9        | 0.33|
| FEV1, L        | 1.67 ± 0.70       | 1.84 ± 0.60       | 0.56|
| FEV1, % predicted | 61.5 ± 22.0 | 63.4 ± 26.2        | 0.84|
| FEV1/FVC       | 54.1 ± 13.1       | 59.1 ± 10.1       | 0.36|
| TLC, % predicted | 108.7 ± 28.6     | 111.1 ± 27.2       | 0.83|
| IC, % predicted | 84.4 ± 14.3       | 87.1 ± 12.9        | 0.64|
| IC/TLC         | 38.5 ± 12.1       | 35.4 ± 15.9       | 0.64|
| RV, % predicted | 130.0 ± 39.4      | 124.5 ± 42.1       | 0.76|
| DLCO, % predicted | 67.2 ± 18.1   | 71.0 ± 16.5        | 0.60|
| VO2peak mL/kg per min | 14.7 ± 2.5     | 15.1 ± 2.8         | 0.73|
| VO2peak % predicted | 64.1 ± 19.2 | 67.8 ± 21.1         | 0.68|
| COPD staging   |                   |                   |     |
| I/II           | 13 (52.0)         | 3 (42.8)          | 0.80|
| III/IV         | 12 (48.0)         | 4 (57.2)          | 0.81|
| TNM staging    |                   |                   |     |
| Ia-b           | 14 (56.0)         | 4 (57.1)          | 0.98|
| Ila-b          | 11 (44.0)         | 3 (42.9)          | 0.97|

BMI: body mass index; IC: inspiratory capacity; VO2peak: peak oxygen uptake; and TNM: tumor-lymph node-metastasis. *Values expressed as n (%) or mean ± SD.

the PRP and were therefore excluded from the final analysis represents a potential limitation of the study. However, no differences were found between the two groups at baseline.

In conclusion, our results underscore the influence of a high-intensity PRP on ventilation efficiency. Further comprehensive prospective studies are required in order to corroborate these preliminary results.
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