High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy

Francesco Stefanelli, Ilermando Meoli, Raffaele Cobuccio, Carlo Curcio, Dario Amore, Dino Casazza, Maura Tracey and Gaetano Rocco

INTRODUCTION

Respiratory function has always been considered crucial for preoperative evaluation of patients with non-small-cell lung cancer (NSCLC). On the other hand, despite improvements in surgical techniques and perioperative care, the reduction of respiratory function after surgery is inevitable. Therefore, the preoperative evaluation of respiratory lung function is one of the most important factors to determine operability, particularly in patients with chronic obstructive pulmonary disease (COPD) [1–4].

Until 2007, surgical candidates with NSCLC were evaluated according to the guidelines of the British Thoracic Society [5], and the recommendations of the American College of Chest Physicians [6, 7]. Cardiopulmonary exercise test (CPET) was performed only in selected cases. More recently, the guidelines of the European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) [8] strongly recommended the evaluation of patients’ physical performance. These guidelines suggest the extensive use of VO2 peak evaluation by means of CPET even in the presence of a slight functional alteration detected by basal tests (forced expiratory volume in one second (FEV1) and/or diffusion lung capacity of CO (DLCO) < 80% of the predicted value). Indeed, the VO2 peak, which is an indicator of physical performance, has proved to be the best independent predictor of the surgical complication rate [9].

Increasing the VO2 peak value and the patient’s tolerance to exercise should be the most important preoperative goal. The latter can be achieved by means of optimal medical treatment and rehabilitation, which should both be used to add to their synergic beneficial effects. It has long been known that preoperative respiratory rehabilitation ameliorates the physical performance of patients with...
COPD [10]. Similarly, the possibility of reducing the perception of dyspnoea and increasing exercise tolerance and quality of life (the impact of morbidity and mortality has yet to be defined) in patients with emphysema undergoing lung volume reduction surgery has been recognized [11, 12]. Instead, only a few studies evaluated the effects of preoperative respiratory rehabilitation in patients with both COPD and NSCLC [13–15].

The aim of this study was the evaluation of the effects of a preoperative pulmonary rehabilitation program (PRP) on peak VO2 as measure of physical performance in a group of COPD patients with NSCLC undergoing lobectomy. The secondary goal was the evaluation of the postoperative impact of PRP on physical performance up to 60 days after surgery.

MATERIAL AND METHODS

Patients

Forty COPD patients (23 males—17 females; age 65 ± 7 years) with a Stage I/II NSCLC undergoing lobectomy were enrolled in the study from February 2010 until December 2011. The criteria for operability and resectability were based on the preoperative staging test and the recommendations of the ERS/ESTS guidelines [8]. The lobectomy was performed by means of open thoracotomy. All patients signed informed consent before enrolling in the study. The inclusion and exclusion criteria are listed in Table 1.

Table 1: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>Male or female</td>
<td>Diabetic</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Diagnosis of NSCLC stage I–IIA</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Concomitant diagnosis of COPD according to the GOLD guidelines</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Respiratory failure (PaO2 &lt;60 mmHg breathing room air at rest)</td>
<td>Respiratory failure (PaO2 &lt;60 mmHg breathing room air at rest)</td>
</tr>
<tr>
<td>SpO2 &lt;90% during the 6-min walking test</td>
<td>BMI &gt; 30</td>
</tr>
</tbody>
</table>

The inclusion and exclusion criteria were listed in Table 1.

Study design

Patients were randomly assigned to two groups. The patients in the first group (rehabilitation, R) underwent a 3-week preoperative outpatient intensive PRP based on high-intensity training of both upper- and lower-limb muscles. Conversely, the patients in the second group (surgery, S) did not participate in the preoperative PRP and underwent only surgery according to the normal standard preoperative protocol.

All patients had a baseline evaluation at the time of enrolment in the study (T0), an intermediate evaluation (T1) at the end of the PRP for Group R and immediately before surgery for Group S, respectively. The final evaluation (T2) was performed 60 days after lobectomy for both groups. We studied: respiratory function, by means of FEV1, FVC and DLCO; dyspnoea by means of Borg scale; physical performance by means of CPET peak VO2 measure.

Pulmonary rehabilitation program

The PRP was divided into 15 3-h sessions, from Monday to Friday, for 3 weeks. The programme consisted of respiratory exercises on the bench, mattress pad and wall bars, respectively, followed by a high intensity training of the upper limbs with the rowing ergometer and the lower limbs by means of the treadmill and the ergonomic bicycle. The exercise workload for each patient was set according to the results of the CPET, starting with 70% of the maximum score reached at the CPET and increased by 10 W when the patient was able to tolerate the set load for 30 min.

Cardiopulmonary exercise test and evaluation of dyspnoea

CPET was performed at T0, T1 and T2 by means of the loading ramp test with the ergonomic bicycle (ergoline ergoselect, Sensor Medics, Milan, Italy) connected to computerized analyser Vmax encore 29c (Sensor Medics, Milan, Italy), with the breath-by-breath method. In brief, the patient was monitored measuring the blood pressure every 2 min; the SO2 by means of pulse oximeter; continuous 12 lead EKG; exhaled gas O2 and CO2 breath-by-breath at the mouth of the patient. The test started with a 2 min evaluation of the patient at rest followed by a warm-up period during which the patient cycled freely for 2 min. Then, the intensity of the cycling was increased with ramp loading of the preset watts, lasting 8–10 min until the end of the test. The loading ramp was planned according to the predicted patient workload resulting from patient’s age, sex, weight, and diet besides the grade of obstruction diagnosed at spirometry. The CPET was interrupted when the patient reached the maximum predicted cardiac rate or the occurrence of other kinds of limitations. At the end of the test, the grade of dyspnoea was measured with the BORG scale. The maximum consumption of O2 at exercise peak (VO2 peak) was recorded measuring the absolute value expressed in ml/kg/min and the percentage of the predicted values.

Respiratory function tests

The respiratory function tests were performed using a plethysmograph box (V6200 Autobox, Sensor Medics, Milan, Italy) connected to a dry spirometer (Vmax 22, Sensor Medics, Milan, Italy). The spirometer was interfaced with a computer equipped with the specific software for the analysis of respiratory function tests (Vmax, Sensor Medics Milan, Italy). All respiratory function tests and measurements were performed according to American Thoracic and European Respiratory Societies [7]. FEV1, FVC, and...
FEV1/FVC ratio were all expressed as absolute (ml) and percentage values according to predicted values for age, sex, weight and height of the patients. Diffusion lung of CO was expressed as ml/mmHg/min.

**Statistical analysis**

The inter-groups analysis was performed at T0, T1 and T2 by a t-test for independent samples while the intragroup analysis was performed by a t-test for dependent samples for all the different parameters evaluated at T0, T1 and T2: comparisons were performed between T0 and T1, T0 and T2 and T1 and T2 and a P-value of <0.05 was considered statistically significant.

**RESULTS**

**Inter-group comparisons**

At T0, the two groups did not significantly differ in age (years ± SD, Group R vs S: 65.5 ± 7.4 vs 64.8 ± 7.3, P = NS), BMI (Group R vs S: 25.6 ± 4.5 vs 27.6 ± 3.5, P = NS), FEV1 and peakVO2 (Table 2).

No difference between groups was observed in pulmonary function, by means FEV1, also at T1 and T2 (Table 2), while a significant difference was evident in peak VO2 value after PRP at T1: [Group R vs S peak VO2, ml/kg/min ± SD (% predicted value ± SD): 17.8 ± 2.1 vs 14.5 ± 1.2 (76.1 ± 14.9 vs 60.6 ± 8.4), P < 0.0001 (<0.05), Fig. 1, Table 2] and this difference was maintained also 60 days after surgery at T2: [peak VO2, ml/kg/min ± SD (% predicted value ± SD): 15.1 ± 2.4 vs 11.4 ± 1.2 (64.6 ± 15.5 vs 47.4 ± 6.9), P < 0.05 (<0.05), Fig. 2, Table 2].

**Intragroup analysis: Group R**

Peak VO2 improved significantly after PRP and significantly deteriorated after surgery: peak VO2, ml/kg/min ± SD (% predicted value ± SD), T0 vs T1: 14.9 ± 2.3 vs 17.8 ± 2.1, P < 0.001 (64.5 ± 16.5–76.1 ± 14.9, P < 0.05); T1 vs T2: 17.8 ± 2.1–15.1 ± 2.4, P < 0.001 (76.1 ± 14.9–64.6 ± 15.5, P < 0.05), Fig. 3, Table 3. Dyspnoea, measured by the modified BORG scale and respiratory function did not change significantly after PRP and deteriorated significantly after surgery (Table 3).

**Intragroup analysis: Group S**

Peak VO2 did not change from T0 to T1 and significantly deteriorated after surgery: peak VO2, ml/kg/min ± SD (% predicted value ± SD), T0 vs T1: 14.8 ± 1.4 vs 14.5 ± 1.2, P = NS (60.8 ± 8.7 vs 60.6 ± 8.4, P = NS); T1 vs T2: 14.5 ± 1.2 vs 11.4 ± 1.2, P < 0.00001 (60.6 ± 8.4 vs 47.4 ± 6.9, P < 0.00001), Fig. 4, Table 3. Dyspnoea, measured by the modified BORG scale and respiratory function did not change significantly after PRP and deteriorated significantly after surgery (Table 3).

<table>
<thead>
<tr>
<th>T0</th>
<th>T1</th>
<th>T2</th>
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<tbody>
<tr>
<td>Group R</td>
<td>Group S</td>
<td>Group R</td>
</tr>
<tr>
<td>FEV1% predicted</td>
<td>57.4 ± 19.1</td>
<td>57.6 ± 16.9</td>
</tr>
<tr>
<td>VO2 ml/kg/min % predicted</td>
<td>14.9 ± 2.3</td>
<td>14.8 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>64.5 ± 16.5</td>
<td>60.8 ± 8.7</td>
</tr>
</tbody>
</table>

*The t-test for independent samples.
measured by the modified BORG scale and respiratory function did not change significantly from T0 to T1 and deteriorated significantly after surgery (Table 3).

The differences between different time points in both groups are listed in Table 4.

**DISCUSSION**

On the basis of the data obtained, it is possible to state that preoperative high-intensity PRP improves the degree of physical performance of patients with COPD and NSCLC undergoing surgical resection compared with similar surgical patients who did not undergo preoperative PRP. These differences were not present at the baseline evaluation and became obvious after PRP, and continued to be observed after surgery. In fact, the possibility of improving the physical performance of patients with COPD by means of preoperative PRP has long been known [16]. Similarly, preoperative PRP reduced the perception of dyspnoea and increased both exercise capacity and quality of life of patients with pulmonary emphysema undergoing lung volume reduction surgery, even if the impact of preoperative PRP on morbidity and mortality needs to be better clarified in this subset of patients [11, 12]. On the other hand, there were no data on the beneficial effects of preoperative PRP on patients with COPD and NSCLC undergoing surgery. Actually, despite the scarce data in the literature, the results of our study show that preoperative PRP is an important strategy, together with optimization of the pharmacological therapy and quitting smoking, in order to improve the surgical outcome of this subset of patients. This approach seems to be even more crucial since preoperative PRP increases the number of these patients eligible for surgery. In this regard, it is important to underline the role of CPET in risk stratification [9]. CPET is performed according the current ERS/ESTS guidelines when the first-level respiratory functional test (FEV1 and DLCO) shows some anomalies [8]. This test (more than the respiratory functional tests performed with the patient at rest) measures the maximal oxygen consumption, or peak VO2 oxygen, which represents the sum of the integrate functions of different organs and apparatus involved in the muscular oxygenation [17, 18].

The clinical importance of this test is based on the observation that the cardiorespiratory functional evaluation at rest does not often correlate with the maximal exercise capability of the patient. On the other hand, the evaluation of the stress test is more reliable
than the functional respiratory tests at rest like spirometry and echocardiography. The results of this study clearly demonstrated the central role of CPET in the preoperative evaluation of patients with COPD and NSCLC, according to ERS/ESTS guidelines.

In the last 10 years, complex algorithms and better predictors of perioperative and/or postoperative complications have been developed with the objective of improving the risk stratification of patients with NSCLC eligible for surgery. The results of a large meta-analysis published in 2007 showed that there is an inverse relationship between the perioperative and/or postoperative complication rates and the VO2 peak measured by means of cardiopulmonary exercise stress test [19]. Therefore, the risk stratification by means of the measurement of the physical performance has become crucial to the point that the ERS/ESTS Task Force concluded that the exercise capability has a reverse correlation with the postoperative complications rate (Grade 1+) [8]. Other tests used for the evaluation of the physical performance, like the 6-min walking test, the shuttle walking test, and the stair-climbing test have proved to be less reliable with respect to CPET, which should then be considered the gold standard [20, 21]. The shuttle walking test correlates only partially with the VO2 values. Patients with lung cancer eligible for surgery who are unable to walk <250 m on two different occasions are considered at high risk for both perioperative and/or postoperative complications and mortality since the estimated VO2 is <10 ml/kg/min [22, 23].

In the stair climbing test the patient climbs one or more ramps of stairs. This test has proved to be the best alternative to CPET since it is a good predictor of both perioperative and/or postoperative complications. Those patients who are able to climb five flights of stairs are good surgical candidates since the estimated value of VO2 will be >20 ml/kg/min. However, this test has some limitations which affect its reproducibility and repeatability (height and numbers of steps, speed of climbing etc.) [22–25]. The studies which used the 6-min walking test did not show univocal results and therefore this is not recommended for patients with NSCLC who are surgical candidates [24].

The results of this study highlighted that the beneficial effects obtained by means of a high-intensity preoperative PRP persist even after surgery; those patients who underwent preoperative respiratory rehabilitation had a better physical performance with respect to the group of patients who did not undergo preoperative PRP on both pre- and post-surgical evaluation. Currently, other studies are needed to demonstrate that the patients who undergo preoperative PRP could have also a better quality of life, less postoperative complications and a longer survival after surgery.

### Table 4: Differences between time points; in Group R, peak VO2 significantly rises from T0 to T1 and declines from T1 to T2 at a value similar to that at T0 while in Group S, peak VO2 does not change from T0 to T1 and significantly declines from T1 to T2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group R</th>
<th></th>
<th></th>
<th>Group S</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1–T0</td>
<td>T2–T1</td>
<td>T2–T0</td>
<td>T1–T0</td>
<td>T2–T1</td>
<td>T2–T0</td>
</tr>
<tr>
<td>FEV1 ml (% predicted value)</td>
<td>+2.09</td>
<td>−4.32</td>
<td>−2.23</td>
<td>+3.0</td>
<td>−3.12</td>
<td>−3.09</td>
</tr>
<tr>
<td>DLCO ml/min/mmHg /±SD (% predicted value ±SD)</td>
<td>+0.3</td>
<td>−0.7</td>
<td>−0.34</td>
<td>+0.3</td>
<td>−0.35</td>
<td>−0.2</td>
</tr>
<tr>
<td>BORG grades ± SD</td>
<td>−0.8</td>
<td>+1.1</td>
<td>+0.3</td>
<td>−0.2</td>
<td>−1.4</td>
<td>−0.2</td>
</tr>
<tr>
<td>VO2 ml/kg/min ± SD (% predicted value ± SD)</td>
<td>+2.9</td>
<td>−2.7</td>
<td>−0.2</td>
<td>−0.3</td>
<td>−3.1</td>
<td>−3.4</td>
</tr>
<tr>
<td></td>
<td>+11.6</td>
<td>−11.5</td>
<td>+0.1</td>
<td>−0.2</td>
<td>−13.2</td>
<td>−13.6</td>
</tr>
</tbody>
</table>

### Funding

**Conflict of interest:** none declared.

### REFERENCES


