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ORIGINAL ARTICLE

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

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Abstract

OBJECTIVES: Peak VO_2, as measure of physical performance is central to a correct preoperative evaluation in patients with both non-small-cell lung cancer (NSCLC) and chronic obstructive pulmonary disease (COPD) because it is closely related both to operability criteria and the rate of postoperative complications. Strategies to improve peak VO_2, as a preoperative pulmonary rehabilitation programme (PRP), should be considered favourably in these patients. In order to clarify the role of pulmonary rehabilitation, we have evaluated the effects of 3-week preoperative high-intensity training on physical performance and respiratory function in a group of patients with both NSCLC and COPD who underwent lobectomy.

METHODS: We studied 40 patients with both NSCLC and COPD, age < 75 years, TNM stages I–II, who underwent lobectomy. Patients were randomly divided into two groups (R and S): Group R underwent an intensive preoperative PRP, while Group S underwent only lobectomy. We evaluated peak VO_2 in all patients at Time 0 (T0), after PRP/before surgery in Group R/S (T1) and 60 days after surgery, respectively, in both groups (T2).

RESULTS: There was no difference between groups in peak VO_2 at T0, while a significant difference was observed both at T1 and T2. In Group R, peak VO_2 improves significantly from T0 to T1: 14.9 ± 2.3–17.8 ± 2.1 ml/kg/min ± standard deviation (SD), $P < 0.001$ (64.5 ± 16.5–76.1 ± 14.9% predicted ± SD, $P < 0.05$) and deteriorates from T1 to T2: 17.8 ± 2.1–15.1 ± 2.4, $P < 0.001$ (76.1 ± 14.9–64.6 ± 15.5, $P < 0.05$), reverting to a similar value to that at T0, while in Group S peak VO_2 did not change from T0 to T1 and significantly deteriorates from T1 to T2: 14.5 ± 1.2–11.4 ± 1.2 ml/kg/min ± SD, $P < 0.00001$ (60.6 ± 8.4–47.4 ± 6.9% predicted ± SD, $P < 0.00001$).

CONCLUSIONS: PRP was a valid preoperative strategy to improve physical performance in patients with both NSCLC and COPD and this advantage was also maintained after surgery.

Keywords: Lung cancer • Chronic obstructive pulmonary disease • Preoperative risk assessment • Rehabilitation • $VO_{2\ max}$

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 VO_2 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 VO_2 peak, which is an indicator of physical performance, has proved to be the best independent predictor of the surgical complication rate [9]. Increasing the VO_2 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 VO_2 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. All the patients enrolled in the study were treated with long-term bronchodilators (beta-2 agonists and/or anticholinergic) or with an association of beta-2 agonists/inhaled corticosteroids; the therapy was not modified at the enrolment and remained unchanged for the period of the study in order not to influence the results of the PRP. The patients in Group S were excluded from the PRP, despite the evidence of a favourable effect on postoperative morbidity and mortality, because they were within the operability criteria.

The inclusion and exclusion criteria are 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 VO_2 measure.

Table 1: Inclusion and exclusion criteria

Inclusion criteria
Male or female
Age <75 years
Diagnosis of NSCLC stage I–IIA
Concomitant diagnosis of COPD according to the GOLD guidelines
Exclusion criteria
Diabetes
Cardiovascular disease
Chronic renal failure
Liver failure
Respiratory failure (PaO_2 <60 mmHg, breathing room air at rest)
SpO_2 <90% during the 6-min walking test
BMI > 30

Pulmonary rehabilitation program

The PRP was divided into 15 3-h sessions, from Monday to Friday, for 3weeks. 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 ergometric bicycle. The exercise work load 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 ergometric bicycle (ergoline ergoselect, Sensor Medics, Milan, Italy) connected to computerized analyser V_{max} 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 SO_2 by means of pulse oximeter; continuous 12 lead EKG; exhaled gas O_2 and CO_2 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 O_2 at exercise peak (VO_2 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 (V_{max} 22, Sensor Medics, Milan, Italy). The spirometer was interfaced with a computer equipped with the specific software for the analysis of respiratory function tests (V_{max}, 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 peakVO_2 (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 VO_2 value after PRP at T1: [Group R vs S peak VO_2, 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 VO_2, 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 VO_2 improved significantly after PRP and significantly deteriorated after surgery, going back to a similar value to that at baseline: peak VO_2, 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 VO_2 did not change from T0 to T1 and significantly deteriorated after surgery: peak VO_2, 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,

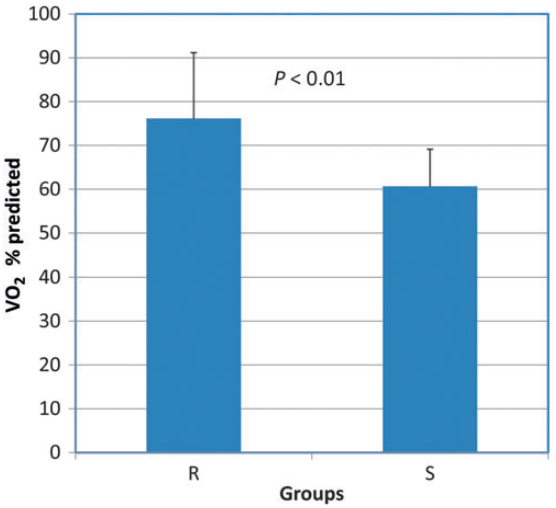

Figure 1: Inter-group comparison at T1: VO_2% predicted values.

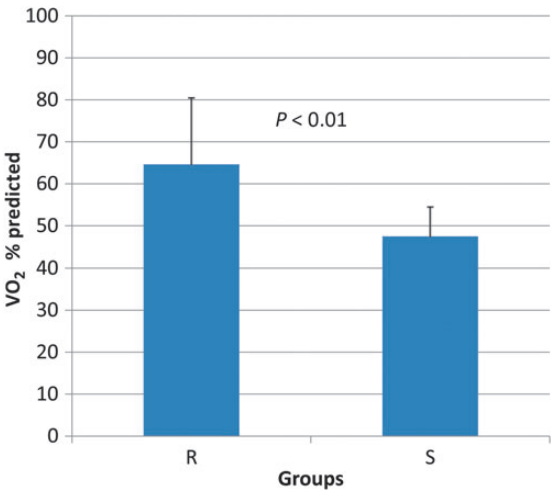

Figure 2: Inter-group comparison at T2: VO_2% predicted value.

Table 2: Inter-group comparison for respiratory function and physical performance at baseline (T0), T1 and T2

	T0			T1			T2		
	Group R	Group S	*P*-value *	Group R	Group S	*P*-value*	Group R	Group S	*P**
FEV1% predicted	57.4 ± 19.1	57.6 ± 16.9	NS	59.8 ± 19.2	57.5 ± 17.0	NS	44.1 ± 17.5	46.4 ± 15.5	NS
VO_2 ml/kg/min	14.9 ± 2.3	14.8 ± 1.4	NS	17.8 ± 2.1	14.5 ± 1.2	<0.001	15.1 ± 2.4	11.4 ± 1.2^	<0.01
% predicted	64.5 ± 16.5	60.8 ± 8.7	NS	76.1 ± 14.9	60.6 ± 8.4	<0.05	64.6 ± 15.5	47.4 ± 6.9*	<0.05

*The *t*-test for independent samples.

Table 3: Intragroup analysis, Group R: respiratory function, dyspnoea and physical performance

	Group R			Group S		
	T0	T1	T2	T0	T1	T2
FEV1 ml ± SD (% predicted value ± SD)	1519 ± 770 57.4 ± 19.1	1728 ± 790 59.8 ± 19.2	1296 ± 790* 44.1 ± 17.5*	1462 ± 325 57.6 ± 16.9	1465 ± 336 57.5 ± 17.0	1153 ± 280* 46.4 ± 15.5*
DLCO ml/min/mmHg /±SD (% predicted value ±SD)	16.0 ± 4.8 64.0 ± 17.6	16.3 ± 4.6 65.3 ± 16.4	12.6 ± 4.3* 50.2 ± 15.2*	15.6 ± 2.6 70.3 ± 12.5	15.9 ± 2.4 69.9 ± 11.9	12.4 ± 2.1** 55.7 ± 11.9*
BORG grades ± SD	1.7 ± 2.2	0.9 ± 1.0***	2.0 ± 1.2****	1.9 ± 0.6	1.8 ± 0.7	3.1 ± 0.7*
VO_2 ml/kg/min ± SD (% predicted value ± SD)	14.9 ± 2.3 64.5 ± 16.5	17.8 ± 2.1** 76.1 ± 14.9**	15.1 ± 2.4**** 64.6 ± 15.5****	14.8 ± 1.4 60.8 ± 8.7	14.5 ± 1.2 60.6 ± 8.4	11.4 ± 1.2* 47.4 ± 6.9*

The *t*-test for paired data, **P* < 0.01 vs T0 and T1; ***P* < 0.01 vs T0; ****P* < 0.05 vs T0 and *****P* < 0.01 vs T1.

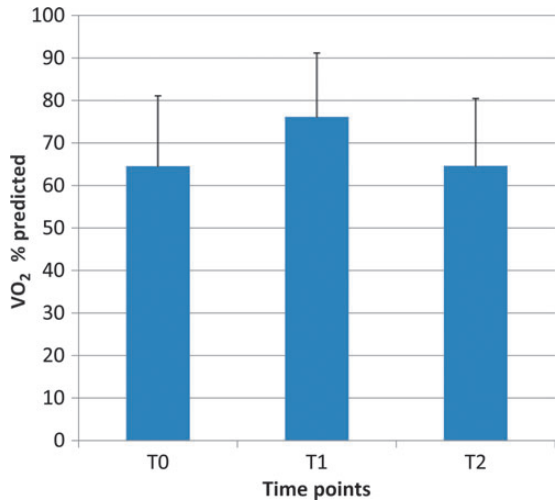

Figure 3: Intragroup analysis at different time points in Group R: VO_2% predicted value.

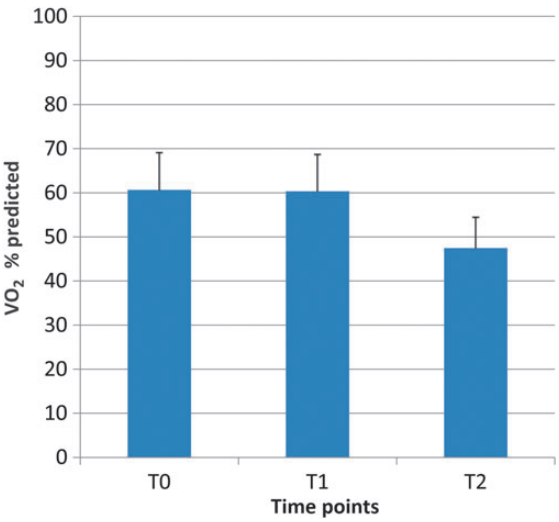

Figure 4: Intragroup analysis at different time points in Group S: VO_2% predicted value.

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 VO_2 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

Table 4: Differences between time points; in Group R, peak VO_2 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 VO_2 does not change from T0 to T1 and significantly declines from T1 to T2

	Group R			Group S		
	T1–T0	T2–T1	T2–T0	T1–T0	T2–T1	T2–T0
FEV1 ml (% predicted value)	+209	−432	−223	+3	−312	−309
	+2.4	−15.7	−13.3	−0.1	−11.1	−11.2
DLCO ml/min/mmHg /±SD (% predicted value ±SD)	+0.3	−3.7	−3.4	+0.3	−3.5	−3.2
	+1.3	−15.1	−13.8	−0.2	−14.2	−14.4
BORG grades ± SD	−0.8	+1.1	+0.3	−0.1	+1.3	+1.2
VO_2 ml/kg/min ± SD (% predicted value ± SD)	+2.9	−2.7	+0.2	−0.3	−3.1	−3.4
	+11.6	−11.5	+0.1	−0.2	−13.2	−13.6

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 VO_2 peak measured by means of cardiorespiratory 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 VO_2 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 VO_2 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 VO_2 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 RPP 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.

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