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ORIGINAL ARTICLE

# Preoperative pulmonary rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease

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## Abstract

**OBJECTIVES**: Impaired cardiopulmonary reserve is the main cause of inoperability in non-small-cell lung cancer (NSCLC). This study aims to evaluate the role of a preoperative pulmonary rehabilitation (PPR) programme in the improvement of functional parameters, which can enable an increase in the number of patients eligible for surgery.

**METHODS**: From January 2008 to June 2011, we observed a uniform group of 27 patients with NSCLC and chronic obstructive pulmonary disease (COPD). It showed: (i) a body mass index of 21.5 ± 2 kg/m$^2$; (ii) forced expiratory volume in 1 s ($FEV_1$) of 1.14 ± 0.7 l; (iii) maximal peak of oxygen consumption ($VO_2$max) of 12.9 ± 1.8 ml/kg/min; (iv) carbon monoxide diffusing capacity (DLCO) of 72 ± 3% predicted; (v) stage IB of lung cancer. All patients underwent a 4-week PPR programme, 6 days a week and were re-evaluated before inclusion for surgery.

**RESULTS**: The rehabilitation programme was completed by all patients and extended by 2 weeks in nine patients, in order to obtain a further functional improvement. A statistically significant increase has been in the values of $PaO_2$ (60 ± 10 vs 82 ± 12 mmHg), of $VO_2$max (12.9 ± 1.8 vs 19.2 ± 2.1 ml/kg/min, $P = 0.00001$) and of $FEV_1$ (1.14 ± 0.7 vs 1.65 ± 0.8 l, $P = 0.02$). All patients underwent a lobectomy, with a postoperative morbidity of 15%.

**CONCLUSIONS**: A 4 to 6-week PPR programme prepares the NSCLC and COPD patients properly for the surgical approach, reducing the functional limitations of inoperability.

**Keywords:** Non-small-cell lung cancer • Chronic obstructive pulmonary disease • Respiratory insufficiency • Pulmonary rehabilitation • Surgical resection

## INTRODUCTION

Ninety percent of patients with non-small-cell lung cancer (NSCLC) are smoke addicted and ∼75% of them display a chronic obstructive pulmonary disease (COPD) [1]. Loganathan *et al*. [2] showed a clinically active COPD in 73% of men and 53% of women with lung cancer. Cardiopulmonary insufficiency, which determines the functional limit of resection, is the main cause of inoperability. In fact, only 15–25% of patients with NSCLC can be surgically treated when diagnosed [3]. COPD patients display increased cardiac and respiratory work and progressive physical disability. The clinical appearance is a consequence of pulmonary parenchyma destruction, which is linked to tissue hyper-insufflation, bronchial hyper-reactivity and bronchospasm. These characteristics explain the small reduction in pulmonary function after a resection for lung cancer as well as the poor postoperative functional reserve [4]. Therefore, some regional functional differences can invalidate the indication of NSCLC excision in COPD patients even though cancer resection is anatomically possible. Preoperative pulmonary rehabilitation (PPR) improves the functional parameters responsible for inoperability [5, 6], but the selection criteria are still controversial. Varela *et al*. [7] highlighted, in 125 patients who underwent a pulmonary lobectomy, that the measured forced expiratory volume in 1 s ($FEV_1$) increased from 1 to 6 days postoperatively and the values were not related to the predicted postoperative (ppo) $FEV_1$. These results were confirmed by a subsequent study of 198 patients submitted to a lobectomy or pneumonectomy [8] and the authors concluded that the observed $FEV_1$ on day 1 after intervention was a better predictor of complications. Brunelli *et al*. [9], in 200 patients undergoing major resection, showed a direct correlation between the postoperative peak of oxygen consumption ($VO_2$ peak) and the preoperative $VO_2$ peak, and the postoperative $FEV_1$ and the carbon monoxide diffusing capacity (DLCO). The ERS/ESTS functional guidelines [10], arising from the different experiences in the literature, established the new cut-off values of operability and led to establishing the objectives of PPR. The purpose of our study is the evaluation of the effectiveness of the preoperative multidisciplinary rehabilitative programme, aiming to obtain the increase in surgical eligibility in functionally inoperable patients without anatomical restriction. This is a short-term rehabilitation, as a delay in

excision can negatively influence the curative intent of intervention and survival. To achieve uniform results, a group of patients selected for age, body mass index (BMI), pulmonary function testing (PFT), cardiopulmonary exercise testing (CPET), NSCLC stage and type of lung resection was enrolled.

## PATIENTS AND METHODS

Between January 2008 and June 2011, we observed 151 patients with NSCLC at stage I and COPD. After Ethical Committee approval, 27 of these showed the clinical characteristics for inclusion in the 4-week PPR programme. According to the ERS/ESTS recommendations [10], the ppo $FEV_1$ and ppo DLCO <30% predicted, associated to a $VO_2$ peak <10 ml/kg/min were the criteria leading to exclusion from the rehabilitative programme and surgery. The study was conducted under informed consent from each patient. The patients were 20 men (74%) and 7 women (26%) with an average age of 55 ± 1 year (range: 50–61 years), height of 172 ± 3 cm, weight of 65 ± 1 kg and BMI ($kg/m^2$) of 21.5 ± 2. Nineteen patients showed a squamous carcinoma (70%) and 8 showed an adenocarcinoma (30%). COPD was classified at Stage IIB of the GOLD criteria [11] with increased dyspnoea, cough accentuation and reduction in physical activity, despite an oral theophylline therapy with 600 mg per day. All patients showed addiction to smoking for at least 10 years, smoking 15 pack-years. No patient displayed comorbidities. Clinical data of the patients concerning blood gas analysis, spirometry and CPET are expressed in Tables 1–3. Six-minute walk distance (6MWD) test was 220 ± 30 m. The BODE index calculated according to Celli *et al*. [12] was 4.5 ± 1. Functional parameters were repeated at the end of the 4-week PPR for the evaluation of the eligibility to excision. The threshold values to undergo a muscle-sparing axillary minithoracotomy consisted of $PaO_2$ >70 mmHg, $PaCO_2$ <30 mmHg, $FEV_1$ ≥1.5 l or >60% predicted, $FEV_1$/FVC and DLCO over 70% predicted and maximal peak of oxygen consumption ($VO_2$max) ≥15 ml/kg/min.

**Table 1:** Blood gas analysis before and after completion of the PPR programme

| Parameters | Data pre-PPR | Data post-PPR | *P*-value |
|---|---|---|---|
| $PaO_2$ (mmHg) | 60 ± 10 | 82 ± 12 | 0.00001 |
| $PaCO_2$ (mmHg) | 39 ± 7 | 26 ± 3 | 0.00001 |
| $SaO_2$ (%) | 84 ± 3 | 91 ± 5 | 0.00001 |

**Table 2:** PFT before and after completion of the PPR programme

| Parameters | Data pre-PPR | Data post-PPR | *P*-value |
|---|---|---|---|
| $FEV_1$ (l) | 1.14 ± 0.7 | 1.65 ± 0.8 | 0.02 |
| $FEV_1$ (% pred.) | 41 ± 9 | 61 ± 13 | 0.00001 |
| FVC (l) | 1.98 ± 1 | 2.12 ± 1.3 | 0.5 |
| FVC (% pred.) | 69 ± 5 | 71 ± 1 | 0.06 |
| $FEV_1$/FVC (% pred.) | 65 ± 3 | 79 ± 4 | 0.00001 |
| PEF (l s) | 2.09 ± 1 | 3.15 ± 1.1 | 0.001 |
| PEF (% pred.) | 30 ± 6 | 43 ± 8 | 0.00001 |
| DLCO (% pred.) | 72 ± 3 | 75 ± 5 | 0.09 |

**Table 3:** CPET before and after the completion of the PPR programme

| Parameters | Data pre-PPR | Data post-PPR | *P*-value |
|---|---|---|---|
| $VO_2$max (ml/kg/min) | 12.9 ± 1.8 | 19.2 ± 2.1 | 0.00001 |
| $VO_2$max (l) | 1.12 ± 0.8 | 1.63 ± 0.4 | 0.009 |
| $VO_2$/AT (ml/kg/min) | 11.5 ± 1.1 | 15.2 ± 1.6 | 0.00001 |
| $VO_2$/AT (l) | 0.91 ± 0.6 | 1.23 ± 0.3 | 0.03 |
| WL (W) | 68 ± 6 | 82 ± 10 | 0.001 |
| $O_2$ pulse (ml/bpm) | 8.4 ± 3.6 | 11.6 ± 4.7 | 0.0004 |
| VE/max (l) | 34 ± 12 | 43 ± 13 | 0.002 |
| BR (%) | 18 ± 14 | 16 ± 8 | 0.6 |
| $VE/VCO_2$ | 33 ± 11 | 29 ± 6 | 0.13 |

### Preoperative pulmonary rehabilitation programme

The PPR consisted daily of 50 min of respiratory physiotherapy and 40 min of aerobic work under electrocardiographic control, 6 days a week.

Respiratory physiotherapy included three sessions: (i) breathing exercises, lasting 20 min, carried out with a Bennett ventilation system (Puritan-Bennett Corporation, Pleasanton, CA, USA), which uses intermittent positive pressure (IPP); (ii) a diaphragmatic breathing exercise, lasting 20 min, was the specific inspiratory muscle training (SIMT); (iii) postural drainage, lasting 10 min.

Aerobic work training was carried out with a cycle ergometer (20 min) and walking (20 min). The first phase consisted of a 5 min warm-up at 20% of the maximal work rate, calculated during CPET, followed by 10 min at 70% of the maximal work rate and 5 min at the maximum effort, precociously interrupted for physical exhaustion if necessary. The second phase included 5 min on a straight route and a further 15 min up to a maximum gradient of 5%, which facilitated improvement in cardiopulmonary work.

The aim was that of ending cigarette smoking during the 4-week PPR programme, using medical and psychological support. Theofillines were suspended and replaced with inhaled bronchodilators exclusively for the first 3 days of the PPR programme, in order to avoid the bronchospasm due to the rapid reduction in the drug circulating levels. The diet was low-salt, low-sugar, hyperlipidic and with normal protein content for 1100–1300 Kcal daily, on 5 meals per day. Water intake was 1.5–2.0 l per day, with diuresis of 1.2–1.6 l per day.

### Statistical analysis

The analysis was performed using SPSS 10.0. Data were entered into a database using SPSS Data Entry II (SPSS Inc., Chicago, IL, USA) and were expressed as the mean ± standard deviation (range 95%). We analysed the different parameters concerning the blood gas, spirometry, cardiopulmonary exercise testing, 6MWD, BMI and BODE index at the beginning and at the end of

the PPR programme. We carried out a univariate analysis of data and the normally distributed variables were compared by Student's *t*-test for paired data. The correlation between different variables was determined by the Spearman rank-sum test. All *P*-values <0.05 were considered to indicate significance and 95% CI.

## RESULTS

All patients concluded the 4-week PPR programme. Nine patients (33%) needed 2 weeks more of exercises, in order to improve their $FEV_1$ (l) from 1.35 ± 0.1 to 1.68 ± 0.1 as well as the $VO_2$max (ml/kg/min) from 13.4 ± 1.5 to 18.3 ± 3.4. COPD was re-classified in all patients at Stage IIA of GOLD [11], despite the $FEV_1$/FVC ≥75% and the absence of chronic symptoms. A statistical significance was showed by the blood gas analysis (Table 1), spirometry (Table 2) and cardiopulmonary exercise testing (Table 3) improvements. The BMI ($kg/m^2$) increased from 21.5 ± 2 in the previous evaluation to 22.1 ± 3 ($P = 0.21$) at the end of the PPR programme. The 6MWD improved from 220 ± 30 to 390 ± 20 m ($P < 0.00001$), while the BODE index from 4.5 ± 1 to 1 ± 0.5 ($P < 0.00001$). Spearman's rank analysis found a highly significant correlation between $FEV_1$(l) vs DLCO (% predicted) before ($r = 0.850$; $P < 0.0001$) and after ($r = 0.71$; $P < 0.0001$) the PPR programme. No correlation has been found between $VO_2$max (ml/kg/min) and other indicators. The 27 patients were considered eligible for the surgical approach and underwent a lobectomy, associated to hilar and mediastinal lymph-node dissection. The excisions carried out were: (i) 12 upper lobectomies (44.5%), eight to the right side and four to the left side; (ii) 10 lower lobectomies (37%), six to the right side and four to the left side; and (iii) 5 middle lobectomies (18.5%). A patient showed an atrial fibrillation 24 h after surgery, solved with pharmacological treatment. Three patients displayed an atelectasis of the parenchyma needing respiratory physiotherapy and aspiration with a fiberoptic bronchoscope, resolved on the second day after surgery. The average time of hospitalization was 10 ± 1 days. All patients are alive after 30 ± 3 months and have been revaluated. Five patients used bronchodilators by inhalation every day. Seven patients resumed cigarette smoking with a daily consumption of 6 ± 2 cigarettes. Blood gas analysis and PFT parameters are expressed in Table 4.

**Table 4:** Blood gas analysis and pulmonary function testing follow-up at 30 ± 3 months

| Parameters | Data | Parameters | Data |
|---|---|---|---|
| $PaO_2$ mmHg | 82 ± 8 | $FEV_1$ (l) | 1.50 ± 0.1 |
| $PaCO_2$ mmHg | 30 ± 1 | $FEV_1$ (% pred.) | 59 ± 4 |
| $SaO_2$% | 96 ± 3 | FVC (L) | 2.00 ± 0.9 |
| | | FVC (% pred.) | 68 ± 3 |
| | | $FEV_1$/FVC (% pred.) | 73 ± 1 |
| | | PEF (l s) | 2.03 ± 0.8 |
| | | PEF (% pred.) | 39 ± 3 |
| | | DLCO (% pred.) | 71 ± 1 |

## DISCUSSION

Our study highlights that a PPR programme, based on the functional cardiopulmonary performance of each NSCLC and COPD patient, facilitated an increase in candidates to surgery and an improvement of surgical results. In fact, a blood gas analysis and spirometry evaluation at 30 months after intervention showed the parameters equivalent to those after 4–6 weeks of rehabilitation, previous to the lobectomy. A shunt effect reduction, attributable both to the PPR programme and to the lung excision, remains invariable in time, showing an improvement in normal personal life habits, like cigarette smoking. Baser *et al.* [13], in a retrospective study on 206 patients with lung cancer, revealed 108 patients (52.4%) surgically inoperable in which pulmonary insufficiency affected 37% (40 patients on 108). McGarry *et al.* [14], analysing 128 NSCLC patients at I/II stage, considered 14% patients not eligible for excision due to a limited pulmonary reserve. Despite similar assumptions, the role and type of PPR are controversial. Jones [15] examined the efficiency of a preoperative training programme, consisting of five cycle ergometer sessions a week done at 60–65% of the work previously developed, in 20 patients with lung cancer and afterwards undergoing surgery. Although an improvement of 21% in the peak of $VO_2$ and of 13% in 6MWT was seen, no variation of the pulmonary function was observed after 4–6 weeks. Bobbio *et al.* [16] obtained analogous results in 12 patients with NSCLC and included in a 4-week PPR programme. In fact, the authors verified that the PFT parameters remained unchanged, but there was an increase in $VO_2$/max of 2.8 ml/kg/min ($P = 0.001$), of $VO_2$ at AT of 3.3 ml/kg/min ($P = 0.016$), of WL of 14 ($P = 0.001$) and of $O_2$ pulse of 1.9 ml/bpm ($P = 0.007$). However, in both studies, it was not highlighted that cardiopulmonary performance development positively influenced the results of surgery. Cesario *et al.* [17] recruited eight patients in a rehabilitation programme, whose reduced spirometric indexes did not allow the pulmonary neoplasm excision. This programme lasted for 4 weeks, for 5 days a week, consisting of 3 h of training and included, unlike our personal experience, the use of abdominal muscle electrical stimulation. The FVC (0.44 ± 0.2 l; 12.9 ± 2.8% predicted), $FEV_1$ (0.12 ± 0.06 l; 5.5 ± 1.6% predicted), 6MWD (79.0 ± 30.4 m) and the $PaO_2$ (7.2 ± 3.8 mmHg) improvement ensured cancer surgical resection, with a 25% postoperative morbidity positively treated. We believe that a targeted rehabilitation should actively implement diaphragmatic mobility and aerobic work without the support of electrical devices for passive stimulation, as we are dealing with patients inclined to adapt to scarce physical performance. In our experience, the preoperative rehabilitation programme guaranteed air flow optimization, improving the functional status of patients and the related quality of life, preventing possible hypoxia and infections consequent to the surgery. A careful examination of the preoperative functional parameters avoided postoperative complications. The British Thoracic Society [18] and the American College of Chest Physician (ACCP) [19] recommend a preoperative $FEV_1$ superior to 1.5 l for a lobectomy and to 2 l for a pneumonectomy. According to the ACCP, CPET with a $VO_2$max lower than 15 ml/kg/min is predictive of an increased risk of perioperative complications. The ERS/ESTS guidelines [10] proposed a $VO_2$ peak >20 ml/kg/min or >75% predicted, and $FEV_1$ and DCLO >80% as the values of operability without the risk. In a study on 237 patients, Ferguson *et al.* [20] highlighted that the DCLO lower than 60% predicted is associated to an increase in postoperative mortality; the risk of pulmonary complications was two or three times higher with a DLCO lower to the 80% predicted. In our study, we included patients with a reduced $FEV_1$ in the PPR programme

but associated to a $VO_2$max higher than 10 ml/kg/min and to a DLCO over 60%. The functional improvement obtained allowed operability, with a total morbidity of 15%. This increase in the pulmonary reserve persists considerably over time, and could be explained by the lung volume reduction effect [21] not being confined only to the immediate postoperative period. Moreover, we observed with the Spearman test, a statistically significant correlation exclusively between the $FEV_1$ and the DLCO. This evaluation involves a double finding. In fact, on the one hand, it confirms the validity of the BODE index as an indicator of the operative risk. The 6MWD can be considered a simple, reliable and safe method, complementary not alternative to the CPET. Cote *et al*. [22] support this hypothesis through a study conducted on 365 patients with COPD. Authors underlined how the survival at over 67 months was 65% in patients able to cover more than 350 m and 39% of those covering less than 350 m. On the other hand, the $VO_2$max can be interpreted as an independent predictive factor of operability, pointing out the aerobic capacity and cardiopulmonary fitness. In the case of an impaired spirometry and DLCO, a pulmonary resection is indispensable, as it is peculiarly correlated to the postoperative morbidity and mortality. Drawing definitive conclusions about the choice of the most significant functional parameters in the selection of surgical candidates is hard, as well as the identification of the timing and duration of the PPR programme. We opine that the time interval between rehabilitation and surgery should not be too long. According to the Swedish Lung Cancer Study Group [23], the ideal length of a PPR programme should be 4–6 weeks, so as not to negatively affect survival. Bozcuk and Martin [24] showed, in 189 patients with NSCLC, that a treatment delay of up to 48 days does not influence survival, independently of the cancer stage. The emphasis should be placed on the carrying out of specific respiratory training, improving the cardiopulmonary reserve and ensuring a curative surgical resection.

In conclusion, a 28 to 42-day preoperative rehabilitation in NSCLC and BPCO patients can be considered a multidisciplinary treatment indispensable for the optimization of cardiopulmonary function. Restoration of a proper lifestyle obtained with psychological support training to the illness both through the agreement to do physical exercise and the association to a targeted diet improves the clinical symptoms. Patients surgically inoperable due to lung function impairment, even if anatomically resectable, become eligible for surgery with a reduction in social and health costs following the radical treatment. Our experience allows us to believe that a PPR programme is fundamental to the achievement of good results, after a rigorous selection of patients.

**Conflict of interest**: none declared.

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