THE PREDICTIVE ROLE OF RESPIRATORY MUSCLE FUNCTION ON POSTOPERATIVE PULMONARY COMPLICATIONS AFTER LUNG RESECTION

O PAPEL DA FUNÇÃO DOS MÚSCULOS RESPIRATÓRIOS COMO PREDITOR DE COMPLICAÇÕES PULMONARES PÓS-OPERATÓRIAS DE RESSECÇÃO PULMONAR

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ABSTRACT

Background: Preoperative evaluation before pulmonary surgery typically do not include the assessment of respiratory muscle function, which might be a predictor of postoperative pulmonary complications (PPC). **Objectives:** To ascertain whether preoperative respiratory muscle function predicts PPC in patients submitted to pulmonary resection by thoracotomy. **Methods:** Beyond pulmonary and respiratory muscle functions assessments, physical fitness was evaluated with the 6-minute walking test. We registered PPC occurring up to 30 days after hospital discharge. Discriminant function analysis was carried out to identify which variables were the best predictors of PPC. Logistic regression was used to analyse associations between variables of respiratory muscle function and PPC. **Results:** Patients with PPC (n=20), compared to those without PPC (n=85), had significant heavy smoking habits (t=-2.412; p=0.027; d=0.547), decreased forced expiratory volume in the first second (FEV_1; t=-2.932; p=0.004; d=0.703), peak expiratory flow (PEF; t=-2.412; p=0.018; d=0.586), diffusion capacity for carbon monoxide (DLCO; t=2.183; p=0.039; d=0.673). Regarding respiratory muscle function, maximal expiratory pressure was significantly reduced in patients with PPC (MEP; t=3.116; p=0.002; d=0.744). Discriminant function structural coefficients showed that MEP % (-0.519), FEV_1 % (-0.488), DLCO % (-0.465), PEF % (-0.402) and cigarettes pack-year (0.374) were the most important factors to discriminate groups with and without PPC. Results from logistic regression indicate that those patients with lower MEP (%) have an increased risk of PPC (OR=7.440; 95% CI= 1.228 – 19.471). **Conclusion:** Preoperative maximal expiratory pressure was the strongest predictor of PPC and should be considered for risk assessment in surgical candidates.

Key words: *Pulmonary surgery; Pulmonary function; Respiratory muscle function; Physical Activity; Postoperative pulmonary complications.*

RESUMO

Introdução: A avaliação pré-operatória para cirurgia pulmonar geralmente não inclui a avaliação da função muscular respiratória, a qual pode ser um preditor de complicações pulmonares pós-operatórias (CPP). **Objetivos:** Verificar se a função muscular

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respiratória pré-operatória prediz CPP em doentes submetidos a ressecção pulmonar por toracotomia. **Métodos:** Além das avaliações das funções musculares pulmonares e respiratórias, a aptidão física foi avaliada através do teste de marcha de 6 minutos. Foram registadas as CPP até 30 dias após a alta hospitalar. A análise da função discriminante foi realizada para identificar quais as variáveis que atuam como melhores preditores de CPP. Foi utilizada regressão logística para analisar a associação entre as variáveis da função muscular respiratória e a CPP. **Resultados:** Doentes com CPP (n = 20), em comparação com aqueles que não desenvolveram CPP (n = 85), apresentaram hábito tabágico pesado significativo (t = –2,412; p = 0,027; d = 0,547), diminuição do volume expiratório forçado no primeiro segundo (FEV_1; t = –2,932; p = 0,004; d = 0,703), do pico de fluxo expiratório (PEF; t = –2,412; p = 0,018; d = 0,586) e da capacidade de difusão de monóxido de carbono (DLCO; t = 2,183; p = 0,039; d = 0,673). Em relação à função muscular respiratória, a pressão expiratória máxima estava significativamente reduzida nos doentes com CPP (PEmáx; t = 3,116; p = 0,002; d = 0,744). Os coeficientes estruturais da função discriminante mostraram que a pressão expiratória máxima (MEP%; –0,519), o FEV_1 % (-0,488), a DLCO% (-0,465), o PEF% (-0,402) e os maços de cigarros por ano (0,374) foram os fatores mais importantes para discriminar os doentes que desenvolveram CPP. Os resultados da regressão logística indicaram que os doentes com menor PEmáx (%) apresentam risco aumentado de CPP (OR = 7,440; IC 95% = 1,228 – 19,471). **Conclusão:** A pressão expiratória máxima pré-operatória foi o preditor mais forte de CPP e deverá ser considerado para avaliação de risco em candidatos cirúrgicos.

Palavras-chave: *Cirurgia pulmonar; Função pulmonar; Função muscular respiratória; Atividade física; Complicações pulmonares pós-operatórias.*

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INTRODUCTION

Surgical resection is the gold-standard treatment for the early stages of non-small cell lung cancer (NSCLC).[1] Postoperative pulmonary complications (PPC) are a concern in pulmonary surgery,[2,3] especially in thoracotomy approach, when compared to video-assisted thoracoscopic surgery (VATS). Ceppa et al.[4] analysed data from Society of Thoracic Surgeons and observed that PPC ocorred in 21.7% patients submitted to anatomic resections (lobectomy or segmentectomy) by thoracotomy and 17.8% in VATS approach. Postoperative pulmonary complications are associated with postoperative morbidity and mortality, thus leading to loss of quality of life (QoL) and prolonged length of hospital stay (LOS), adding economic costs.[5-8]

There are several generic tools to assess surgical risk, as the American Society of Anesthesiologists (ASA) classification, or the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk index,[9] that might be useful to support surgical decisions and identify patients that most likely would benefit from preoperative risk reduction interventions. In NSCLC patients, the ERS/ESTS [10] recommends the identification of surgical candidates by following an algorithm that starts with cardiac assessment and follows with the evaluation of pulmonary fuction, with special attention to the forced expiratory volume in the first second (FEV_1), and diffusion capacity for carbon monoxide (DLCO). If FEV_1 and DLCO >80 % predicted, patients are considered to be at low risk of death or PPC and thus may proceed to surgery. If FEV_1 or DLCO <80 %, patients will need further lung function calculations (predicted postoperative FEV_1 and DLCO) and exercise tests to assist in the decision.

While this preoperative assessment protocol is undoubtedly a powerful tool to evaluate the risk of morbidity and mortality in surgical NSCLC candidates[10,11], PPC still occur in 12 – 40% of patients submitted to lung resections, wich also included low-risk patients.[7] This raises the question wether preoperative optimization programms should be applied to all surgical candidates, and not only to those considered to be at higher risk of PPC as currently in practice.[12]. Moreover, there is the concern that the current assessment algorithm might need to be updated, for instance by considering other lung function variables currently overlooked. For instance, a retrospective analysis of data on anatomic lung resections deposited in the European Society of Thoracic Surgeons (ESTS) database showed that predicted postoperative forced expiratory volume in 1 s (ppo-FEV_1) was reliably associated with mortality after logistic regression analysis[13]. In addition, to our best knowledge, the association between preoperative respiratory muscle function and the risk of PPC in NSCLC surgical candidates remains unknow. However, there is indirect data pointing for its relevance, with a recent meta-analysis showing that inspiratory muscle training in patients submitted to major surgery (cardiac, abdominal and pulmonary) significantly reduces PPC and LOS, especially in older and higher risk patients.[2] The authors have argued that inspiratory muscle training lead to a lower decline of maximal inspiratory pressure (MIP) in the immediate postoperative period, and therefore might reduce PPC risk, and LOS.[2]

Thus, it seems clear that respiratory function holds potential to improve surgical risk stratification and patient selection for surgery and/or for preoperative optimization in NSCLC patients. We hypothesize that respiratory muscle function could be an independent predictor of PPC in patients selected to pulmonary resections by posterolateral thoracotomy.

METHODS

Study design, recruitment, and procedures in data collection

This is a prospective, observational and analytical study conducted in the Cardiothoracic Surgery Department at the Hospital São João (Porto, Portugal). Inclusion criterion were patients submitted to pulmonary resection by posterolateral thoracotomy, due to lung cancer. The study was conducted from February 2011 to February 2015. Exclusion criteria were the following: patients submitted to pneumonectomy or previous thoracic surgery, mental disorders, diagnosis of cardiac, or neurologic, or renal failure, and ambulation impairments.

The present study was approved by the Ethical Committee for Health of São João Hospital on October 19th, 2010.

Eligible patients were recruited in the first appointment before surgery. Patients who agreed to participate signed an informed consent form. All participants were followed by the same surgical team and received the same anaesthetic and analgesic protocol. During hospital stay, all patients underwent chest physiotherapy intervention, twice a day, encompassing deep breathing exercises, incentive spirometry, bronchial hygiene, postural correction, early deambulation, improving shoulder range of motion and strength.

Patients' demographic data, health status information, and anthropometric measurements were collected preoperatively. Also, an independent and blinded assessor evaluated patients' pulmonary function and physical fitness one to two weeks before surgery.

Postoperative pulmonary complications were registered up to 30 days after hospital discharge. The PPC diagnostic was established by a surgeon and a pulmonologist, who were blinded for the study design and procedures, according to European Perioperative Clinical Outcome definition.[14]

Assessments

Demographic and clinical data included information about smoking habits, and medication.

Anthropometrics included the assessment of height, weight, and calculation of body mass index (BMI).

Dyspnoea was assessed using the Portuguese version of the *Medical Research Council Dyspnoea Questionnaire* (MRC).[15,16]

Pulmonary function tests using body plethysmography (MasterScreen™; Jaeger, Germany) were conducted according to the ATS/ERS guidelines.[17,18] The measured variables included forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), Tiffeneau index (TI), peak expiratory flow (PEF), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO), diffusing capacity of the lung for carbon monoxide per unit of alveolar volume (DLCO/VA), respiratory muscle function [maximum voluntary ventilation (MVV), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)].

Physical fitness was assessed by the 6 minute walking distance test (6-MWD) according to the American Thoracic Society (ATS) guidelines.[19] During the test, heart rate and oxygen saturation were monitored using the PULSO X-3i (Konica Minolta). According to the recommendations, only patients with ppo-FEV_1 or ppo-DLCO lower than 30% should be submitted a cardiopulmonary exercise test.

Statistical Procedures – Statistical Analysis

Continuous variables are presented as mean and standard deviation, while categorical data are presented as counts and/or relative frequency. Before analysis, normal distribution of continuous variables was examined with Shapiro-Wilk test. For all variables in which distributions were skewed, square root transformation was performed. However, for the sake of clarity and comprehensiveness of data and results, the descriptive statistics is presented with the raw values (please, check notes in tables results for more details).

To accomplish the study aim, data analysis started by the identification of the number of cases with and without PPC after surgery. Data analysis proceeded by dividing participants into two groups: with and without PPC. Student's *t*-test for independent samples and Chi-Square ($\times^2$) test were performed to analyse differences between groups for the data gathered before surgery regarding demographics, anthropometrics, clinical conditions, pulmonary function, physical fitness, and perceived health status. Pearson coefficients (Pearson's r) were calculated to analyse correlations between variables.

Discriminant function analysis (DFA) was carried out to identify which variables from pulmonary function would be considered the best predictors of PPC. Discriminant function structural coefficients were considered major indicators of the relative contribution of independent variables to discriminate groups with and without PPC. Structural coefficients must be interpreted as linear correlations between independent variables (predictors) and the discriminant function (outcome). A minimum of ±0.3 for structural coefficients is considered significant.[20]

Finally, logistic regression was calculated to analyse associations between MEP and PPC. Tertiles for MEP were calculated and the *odds ratio* for manifesting PPC were determined assuming the third (high MEP) tertile as the reference group.

All analyses were carried out in IBM SPSS Statistics version 21.0. Statistical significance was set at 5% ($P<0.05$) for all tests.

RESULTS

We were able to include 105 patients, 64.8% were male, with a mean age of 61.7 ± 9.8 years old and a mean BMI of 26.2 ± 3.5. Taking into account the extension of lung resections, it was registered 4 bilobectomies, 25 right inferior lobectomies, 14 left inferior lobectomies, 7 middle lobectomies, 33 right upper lobectomies, 20 left upper lobectomy, and 2 segmentectomies. We observed the presence of PPC in 20 patients (19,04%) and no deaths occurred. Five patients presented more than one PPC: 1 with respiratory infection and prolonged air leak, 2 with prolonged air leak and pleural effusion, 1 with empyema and respiratory infection, and 1 with respiratory infection and pleural effusion. The remaining 15 patients present single PPC: respiratory infection (4 patients), chylothorax (2 patients), prolonged air leak (6 patients), pneumonia (1 patient), empyema (1 patient), atelectasis (1 patient).

Descriptive data and comparisons between patient's without and with PPC

In the patients' group with PPC, compared with the group without PPC, the male frequency (85%) was significantly higher, and the frequency of patients with normal pulmonary function was lower (40.0 %; see Table 1).

Table 2 shows the preoperative descriptive data for age, anthropometrics, clinical conditions, pulmonary function, physical fitness, and perceived health status for the total sample and the comparisons between patients with and without PPC. Patients with PPC were taller (t=-2.857; P=0.005; d=-0.687), had a significant higher mean number of cigarettes pack-year (t=-2.245; p=0.027; d=-0.547), decreased FEV_1 (%) (t=2.932; p=0.004; d=0.703), PEF (%) (t=2.412; P=0.018; d=0.586), MEP (%) (t=3.116; p=0.002; d=0.744), DLCO (%) (t=2.183; p=0.039; d=0.673), and increased TLC (t=-3.450; p=0.001; d=-0.816).

Further, discriminant function analysis estimated a significant canonical function (Wilk's Lambda=0.741; Canonical Correlation=0.509; P=0.027), indicating that groups with and without PPC could be effectively discriminated by variables of pulmonary function and physical fitness.

Table 1 – **Descriptive data from gender, pulmonary medication and patients with normal pulmonary function in percentage for each group**

	All (n=105)	Without PPC (n=85)	With PPC (n=20)	χ^2	p-value
Gender (Male %)	64.8 %	60.0 %	85.0 % *	4.434	0.035
Bronchodilators (yes, %)	21.0 %	21.2 %	20.0 %	0.014	0.907
Corticosteroids (yes, %)	10.5 %	10.6 %	10.0 %	0.006	0.938
Other anti-asthmatic drugs (yes, %)	1.0 %	1.2 %	0.0 %	0.238	0.626
Pulmonary function (normal, %)	63.8 %	69.4 %	40.0 %*	20.401	0.001

Notes: Data presented relative group percentage; * for P<0.05 vs Without PPC

Table 2 – **Descriptive data from patients with and without PPC**

	All (n=105)	Without PPC (n=85)	With PPC (n=20)	t	p-value	Cohen's d
Age (years)	61.7 ± 9.8	62.3 ± 9.0	59.4 ± 12.6	1.330	0.186	0.329
Cigarette pack-year	39.6 ± 37.5	35.6 ± 36.4	56.6 ± 38.2 *	-2.245	0.027	-0.547
Height (cm)	166.0 ± 8.8	164.8 ± 8.5	170.9 ± 8.8 *	-2.857	0.005	-0.687
Weight (kg)	72.4 ± 12.1	72.2 ± 12.1	73.0 ± 12.3	-0.254	0.800	-0.063
BMI (kg/m^2)	26.2 ± 3.5	26.5 ± 3.5	25.0 ± 3.7	1.789	0.077	0.440
Dyspnoea (grade 1-5)	1.8 ± 0.6	1.8 ± 0.6	1.9 ± 0.7	-0.428	0.670	-0.107
FVC (L)	3.5 ± 0.9	3.5 ± 0.9	3.8 ± 1.1	-1.464	0.146	-0.362
FVC %	106.8 ± 18.3	108.1 ± 18.0	101.4 ± 19.2	1.481	0.142	0.366
FEV$_1$ (L)	2.5 ± 0.7	2.5 ± 0.6	2.5 ± 0.9	0.002	0.998	0.001
FEV$_1$%	95.0 ± 20.5	97.8 ± 19.6	83.4 ± 20.5 *	2.932	0.004	0.703
PEF (L/s)	6.4 ± 1.9	6.4 ± 2.0	6.2 ± 1.9	0.451	0.653	0.113
PEF%	89.6 ± 20.2	91.8 ± 19.6	80.0 ± 20.4 *	2.412	0.018	0.586
TI (%)	71.7 ± 11.1	72.8 ± 9.1	66.7 ± 16.5	1.011	0.323	0.348
MVV (L/min)	91.8 ± 26.8	91.0 ± 24.3	95.2 ± 35.9	-0.394	0.695	-0.098
MVV%	88.4 ± 18.6	89.6 ± 17.3	83.3 ± 23.1	1.155	0.259	0.341
MIP (cmH$_2$O)	74.0 ± 22.0	73.7 ± 21.3	75.0 ± 25.1	-0.238	0.812	-0.060
MIP%	69.5 ± 21.2	69.2 ± 20.7	70.8 ± 23.5	-0.297	0.767	-0.074
MEP (cmH$_2$O)	100.7 ± 30.4	101.1 ± 29.3	98.9 ± 35.6	0.478	0.634	0.119
MEP%	94.7 ± 27.8	98.6 ± 28.0	78.3 ± 20.2 *	3.116	0.002	0.744
TLC (L)	6.4 ± 1.3	6.2 ± 1.2	7.3 ± 1.4 *	-3.450	0.001	-0.816
TLC%	111.3 ± 13.8	110.4 ± 12.2	115.2 ± 19.1	-1.075	0.293	-0.350
DLCO (mmol/min/kPa)	6.2 ± 1.7	6.3 ± 1.6	6.0 ± 2.2	0.620	0.542	0.199
DLCO%	75.9 ± 16.3	77.8 ± 14.8	67.8 ± 19.9 *	2.183	0.039	0.673
DLCO/VA (mmol/min/kPa/L)	1.2 ± 0.3	1.2 ± 0.2	1.1 ± 0.4	1.404	0.174	0.474
DLCO/VA %	83.1 ± 17.9	84.5 ± 15.6	76.9 ± 25.0	1.305	0.205	0.426
6-MWD (m)	451.2 ± 59.8	451.9 ± 54.7	448.4 ± 79.8	0.324	0.746	0.081
Health status (grade 0-100)	69.7 ± 17.9	70.0 ± 18.4	68.8 ± 16.0	0.270	0.788	0.067

Notes: Data presented as Mean ± Standard Deviation. # Although descriptive data is shown for the raw variables, statistical inferences were calculated to variables transformed to their square root; * for P<0.05 vs Without PPC.

Legend: BMI – Body Mass Index; FVC – Forced Vital Capacity; FVC % – Forced Vital Capacity percent of predicted; FEV$_1$ – Forced Expiratory Volume in 1 second; FEV$_1$% – Forced Expiratory Volume in 1 second percent of predicted; PEF – Peak Expiratory Flow; PEF% – Peak Expiratory Flow percent of predicted; TI – Tiffeneau Index; MVV – Maximal Voluntary Ventilation; MVV% – Maximal Voluntary Ventilation percent of predicted; MIP – Maximal Inspiratory Pressure; MIP% – Maximal Inspiratory Pressure percent of predicted; MEP – Maximal Expiratory Pressure; MEP% – Maximal Expiratory Pressure percent of predicted; TLC – Total Lung Capacity; TLC% – Total Lung Capacity percent of predicted; DLCO – Diffusion Lung Capacity for Carbon Monoxide; DLCO% – Diffusion Lung Capacity for Carbon Monoxide percent of predicted; DLCO/VA – Diffusion Lung Capacity for Carbon Monoxide per unit alveolar volume; DLCO/VA % – Diffusion Lung Capacity for Carbon Monoxide per unit alveolar volume percent of predicted; 6-MWD – Six Minute Walking Distance Test.

Discriminant function structural coefficients (Table 3) showed that MEP (%) (-0.519), FEV1 (%) (-0.488), DLCO (%) (-0.465), PEF (%) (-0.402) and cigarettes pack-year (0.374) contributed the most to discriminate groups with and without PPC. Estimated group centroids for the discriminant function were –0.28 ± 0.91 for the group without PPC and 1.21 ± 1.31 for the group with PPC. Discriminant function analysis indicated significant differences between groups centroids (t=-4.817; P<0.001; d=-1.284). Finally, the relative individual distance for group centroids in the discriminant function was used to reclassify subjects as with or without PPC. In this analysis, 78.1% of original grouped cases were correctly classified, indicating a good fit of the discriminant model. Physical fitness did not discriminate groups with and without PPC.

Since MEP (%) showed to be the strongest independent predictor of PPC, it was transformed in tertiles to analyse the *odds ratio* of having PPC as MEP (%) values decreased. In comparison with the third tertile of MEP (%) (reference category), those patients with lower MEP (%) (first tertile) have and increased and significant risk of PPC (OR=7.440; 95% CI= 1.228 – 19.471). In comparison with the third tertile of MEP (%) (reference category), those patients with moderate MEP (%), i.e. in the second tertile, the odds *ratio* for PPC was not significant (OR=3.792; 95% CI= 0.505 – 9.639).

Pearson correlation coefficients are presented in table 4. As can be seen MEP, correlate significantly with cigarette pack-year (r=-0.462; P=0.000), with pulmonary function FVC (%) (r=0.288; P=0.003), FEV_1 (%) (r=0.446; P=0.000), PEF (%) (r=0.372; P=0.000), IT (r=0.316; P=0.001), MVV (%) (r=0.316; P=0.001).

Table 3 – **Discriminant function coefficients**

Independent	Unstandardized Coefficients	Standardized Coefficients	Structural Coefficients
BMI(kg/m²)	-0.068	-.238	-0.298
Cigarette pack-year	-0.008	-.030	0.374*
FVC%	0.036	.659	-0.247
FEV1%	-0.066	-1.313	-0.488*
PEF%	-0.010	-.197	-0.402*
TI	0.772	.965	-0.234
MVV%	0.015	.284	-0.230
MIP%	0.015	.315	0.049
MEP%	-0.389	-.531	-0.519*
TLC%	0.055	.752	0.235
DLCO%	-0.843	-.773	-0.465*
DLCO/VA%	0.032	.560	-0.288
6 MWD (m)	-0.035	-.051	-0.054
(Constant)	9.850		

Notes: * A minimum discriminant function structural coefficient of ±0.3 is considered significant.

Legend: BMI – Body Mass Index; FVC % – Forced Vital Capacity percent of predicted; FEV_1% – Forced Expiratory Volume in 1 second percent of predicted; PEF% – Peak Expiratory Flow percent of predicted; TI – Tiffeneau Index; MVV% – Maximal Voluntary Ventilation percent of predicted; MIP% – Maximal Inspiratory Pressure percent of predicted; MEP% – Maximal Expiratory Pressure percent of predicted; TLC% – Total Lung Capacity percent of predicted; DLCO% – Diffusion Lung Capacity for Carbon Monoxide percent of predicted; DLCO/VA % – Diffusion Lung Capacity for Carbon Monoxide per unit alveolar volume percent of predicted; 6-MWD – Six Minute Walking Distance Test.

Table 4 – **Pearson's *r* correlations between pulmonary and respiratory muscles function, physical fitness and daily physical activity**

	FVC%	FEV1%	PEF%	IT	MVV%	MIP%	MEP%	TLC%	DLCO%	DLCOVA%	6 –MWD (m)
	r	r	r	r	r	r	r	r	r	r	r
Cigarette pack-year	-0.108	-0.401*	-0.117	-0.468**	-0.183	0.278*	-0.462**	0.176	-0.172	-0.164	-0.003
BMI (kg/m2)	-0.123	0.039	-0.024	0.098	0.035	-0.050	0.161	-0.056	0.300*	0.385**	-0.105
FVC%	1.000	0.723**	0.419**	-0.100	0.279*	0.024	0.288*	0.569**	0.080	-0.259*	0.069
FEV1%	0.723**	1.000	0.564**	0.565**	0.510**	-0.005	0.446**	0.217*	0.377**	0.080	-0.036
PEF%	0.419**	0.564**	1.000	0.260*	0.608**	0.266*	0.372**	0.091	0.345**	0.120	0.156
TI	-0.100	0.565**	0.260*	1.000	0.373**	-0.052	0.316*	-0.284*	0.339**	0.286*	-0.126
MVV%	0.279*	0.510**	0.608**	0.373**	1.000	0.318*	0.316*	-0.113	0.394**	0.266*	0.133
MIP%	0.024	-0.005	0.266*	-0.052	0.318*	1.000	0.178	-0.106	0.151	0.131	0.276*
MEP%	0.288*	0.446**	0.372**	0.316*	0.316*	0.178	1.000	0.047	0.076	-0.089	0.010
TLC%	0.569**	0.217*	0.091	-0.284*	-0.113	-0.106	0.047	1.000	-0.137	-0.468**	-0.070
DLCO%	0.080	0.377**	0.345**	0.339**	0.394**	0.151	0.076	-0.137	1.000	0.805**	0.118
DLCO/VA%	-0.259*	0.080	0.120	0.286*	0.266*	0.131	-0.089	-0.468**	0.805**	1.000	0.124
6-MWD (m)	0.069	-0.036	0.156	-0.126	0.133	0.276*	0.010	-0.070	0.118	0.124	1.000

* $p \leq 0.05$; ** $p \leq 0.001$

Legend: BMI – Body Mass Index; FVC % – Forced Vital Capacity percent of predicted; FEV_1% – Forced Expiratory Volume in 1 second percent of predicted; PEF% – Peak Expiratory Flow percent of predicted; TI – Tiffeneau Index; MVV% – Maximal Voluntary Ventilation percent of predicted; MIP% – Maximal Inspiratory Pressure percent of predicted; MEP% – Maximal Expiratory Pressure percent of predicted; TLC% – Total Lung Capacity percent of predicted; DLCO% – Diffusion Lung Capacity for Carbon Monoxide percent of predicted; DLCO/VA % – Diffusion Lung Capacity for Carbon Monoxide per unit alveolar volume percent of predicted; 6-MWD – Six Minute Walking Distance Test.

DISCUSSION

This study aimed to evaluate whether pulmonary function (including respiratory muscle function) and physical fitness are independent predictors of PPC, in patients selected to pulmonary resections by posterolateral thoracotomy.

The main findings indicate that pulmonary and respiratory muscle functions are predictors of PPC, as well as smoking habits, being MEP the strongest predictor of PPC. Indeed, patients with lower MEP (%) had an increased and significant risk of PPC. Physical fitness did not predict PPC, although correlate significantly with MIP.

The finding that MEP significantly predicts PPC is interesting and possibly highly relevant, since the expiratory muscle strength is deeply related to mucus clearance efficiency.[21] Additionally, surgery-induced respiratory muscle weakness, which is proportional with the surgical incision [22,23], might also contribute to a greater cough ineffectiveness, and therefore empowering PPC development.[24] Cough ability is dependent of both inspiratory and expiratory muscles strength and coordination; normal cough consists of four phases: inspiratory, compressive, expulsive, and relaxation.[18,23,25] Mucus clearance depends on the inspiratory capacity and apnoea (in the end of inspiration, especially for the small airways),[26,27] the expiratory flow rate (to promote the equal pressure point), and cough (for more proximal secretions).[27] Beyond the aforementioned, the relevance of our finding is reinforced by the results of the logistic regression analysis, which showed that patients in the lower tertile of MEP had an *odd ratio* for PPC seven fold higher than patients in the third tertile.

Regarding inspiratory muscle strength, it was somehow surprising that MIP was not a predictor of PPC in our sample. Several meta-analysis support the efficacy of IMT to reduce PPC,[2,28,29], suggesting that preoperative inspiratory muscle strength has an important role to avoid PPC. However, despite our sample showed on average a MIP value below the cut-off for clinically important inspiratory muscle weakness in adults (- 80cm H_2O)[18], no differences were detected between groups, which might explain the lack of power to predict PPC.

Other significant respiratory function predictors were FEV_1%, DLCO%, and PEF (in a descendent order). Apart from PEF, neither FEV_1% nor DLCO%, bring new relevant information, as they are already accepted as independent PPC predictors.[11,30,31] Peak expiratory flow add value to measure the air-flow limitation, and might be reduced by impairements at multiple levels as: the force generated by the expiratory muscles, the thoracic compliance, the airways obstruction, the power of expiratory muscles, and pulmonary compliance.[32] Yutian et al.[33] in a prospective study found that PEF is an independent predictor of PPC after lobectomy. Moreover the authors stated that patients with a PEF below 300L/min have a 8 fold increase risk of develop PPC.[33]

Patients with PPC presented a poor preoperative pulmonary function, as shown by the significantly lower MEP%, FEV_1%, DLCO%, PEF%, and a highest absolute value of TLC. These findings might be related with the pulmonary repercussion of their heavy smoking habits. Tobacco consumption is a risk factor not only for lung cancer, but also for other pulmonary and cardiac diseases.[11,34] Therefore, it is frequent that lung cancer patients also have COPD, adding two important issues; first the chronic mucus hypersecretion,[35] and second patients might have respiratory muscle impairment.[36] According to Terzano et al.[36] both inspiratory and expiratory muscles lose strength in COPD patients; the inspiratory muscles strength decrease even at the early stages, while expiratory muscle strength decrease occurs later on, especially in severe airway obstruction. Ramírez-Sarmiento et al.[37] observed that expiratory muscles in COPD patients show endurance decrease. Vilaró et al.[38] observed that peripheral and respiratory muscle dysfunction in COPD patients is associated with exacerbations and hospitalisations. Corroborating with this fact, in the present study it was observed a negative correlation between heavy smoking habits with lower values of both MEP%, MIP% and FEV1%.

Previous studies support the use of the 6-MWD to discriminate patients at risk of poor postoperative outcomes[39]. In the current study, we did not found differences between patients with and without PPC for the 6-MWD, wich explain why it was not a predictor of PPC. Moreover, the average distance walked by patients from our study, including those who developed PPC, was above the cut off point (>400m) reported in a recent study were this test was shown to a predictor of PPC[39].

We are aware of the study limitations, starting on the PPC definition which is not universally established, and we agree with Miskovic et al.[14] that PPC are defined heterogeneously, which might be a source of misunderstanding.[14] In our opinion, this subject deserves attention and discussion in order to reduce the literature bias. Our sample size could also be considered a limitation but it was suficient to highlight the importance of the preoperative respiratory muscle assessment to predict PPC. While the predictive role of preoperative maximal expiratory pressure should be submitted to external validation, our data highlights the need to include preoperative respiratory muscle assessment in the typical assessment model. Future studies should examine the effect of preoperative expiratory muscle training in PPC reduction. Finally, it would also be relevant to compare the eficcacy of expiratory muscle training and inspiratory muscle training in reducing PPC and LOS.

CONCLUSIONS

Preoperative respiratory muscle function and smoking are associated with PPC in patients with NSCLC submitted to pulmonary surgery by post-lateral thoracotomy. Preoperative maximal expiratory pressure is a stronger predictor of PPC and should be considered for the risk assessment in surgical candidates.

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The authors have no conflicts of interest to declare.

Authors' contribution

All authors have contributed for the conception of the problem, theorizing, and/or interpreting data as well as for drafting the article or revising it critically, approving the final version.

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