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ORIGINAL ARTICLE

Preoperative respiratory muscle endurance training improves ventilatory capacity and prevents pulmonary postoperative complications after lung surgery

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ABSTRACT

BACKGROUND: Resection surgery is the main treatment for non-small cell lung cancer (NSCLC). Postoperative complications and mortality are mostly linked to respiratory failure consecutive to respiratory muscle overload.
AIM: We aimed to evaluate the effect of preoperative respiratory muscle endurance training (RMET) on respiratory muscle capacity and postoperative complications in patients undergoing NSCLC resection.
DESIGN: Randomized controlled trial.
SETTING: French university hospital.
POPULATION: Patients eligible for NSCLC resection.
METHODS: The training group (T group) performed a 3-week preoperative RMET added to usual chest physical therapy while the control group (C group) had only the latter. The primary outcome was the change in respiratory muscle endurance. Secondary outcomes were postoperative complications and mortality. Assessments were performed similarly at baseline and after the intervention. We conducted multivariable analyses with analysis of covariance (ANCOVA) taking into account baseline values for isocapnic hyperpnoea endurance test, exercise capacity and pulmonary function tests. The number of pulmonary postoperative complication was analyzed by Fisher-exact test.
RESULTS: We included 26 patients with NSCLC (14 in the T group and 12 in the C group). Respiratory muscle endurance significantly increased in the T group after the RMET compared with C group (+229±199 *vs*. -5±371 sec, P=0.001). This increase was associated with a significantly lower number of pulmonary postoperative complications (2 *vs*. 10, P=0.037).
CONCLUSIONS: Preoperative RMET improved respiratory muscle endurance and decreased pulmonary postoperative complications after surgery for NSCLC. These positive results obtained after RMET may help improve the perioperative course for such patients. These results should be confirmed in larger randomized controlled trials, including higher number of patients especially with altered respiratory muscle function.
CLINICAL REHABILITATION IMPACT: Low-cost and easy to perform, RMET training could serve as complementary tool to usual chest physical therapy, before lung resection surgery.

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KEY WORDS: Work of breathing; Lung neoplasms; Muscle fatigue; Respiratory insufficiency.

Resection surgery is the main curative treatment for non-small cell lung cancer (NSCLC). However, mortality and morbidity are still high, partly due to respiratory failure consecutive to respiratory muscle overload occurring in the immediate postoperative phase.[1-5] Indeed, the respiratory work increases by about 93% on day 3 postoperatively.[6] Moreover, some patients could present deconditioning due to comorbidities such as chronic obstructive

pulmonary disease (COPD), which increases the postoperative complication risk leading to respiratory failure.[7, 8]

Respiratory muscle strength training demonstrated its effect in population other than NSCLC. In COPD patients, respiratory muscle strength and endurance are impaired.[7, 8] Meta-analyses[9-11] confirmed that resistance inspiratory muscle training can increase the strength and endurance of inspiratory muscles and also ameliorate dyspnea at rest and exercise tolerance of these patients.

In patients eligible for cardiothoracic and abdominal surgery, inspiratory muscle training reduced pulmonary postoperative complications and hospital length of stay.[12] Inspiratory and expiratory muscle strengths were significantly improved after a 14-day preoperative resistance training in patients undergoing pulmonary resection.[13] Also, respiratory muscle strength, respiratory complications and hospital length of stay were improved after resistance inspiratory muscle training and incentive spirometry in patients undergoing coronary bypass surgery.[14]

From a conceptual point of view, respiratory endurance could not be predicted precisely from maximal strength measurements.[15] Respiratory endurance is associated with resistance to fatigue.[15] Moreover, respiratory muscle endurance training (RMET) involves both inspiratory and expiratory muscles, which represents a more physiological way to improve respiratory muscle function.[15] Randomized controlled trials (RCTs) showed significant improvements in respiratory muscle endurance, exercise capacity, dyspnea and quality of life in COPD patients, after RMET.[16, 17] But, to our knowledge, no study evaluated RMET in the setting of preoperative NSCLC.

Therefore, we performed an RCT to evaluate the effect of a 3-week preoperative RMET program on respiratory muscle capacity and postoperative complications in patients undergoing NSCLC resection.

Materials and methods

Setting, registration and ethics

This prospective open-label RCT was conducted in a French university hospital, in accordance with the CONSORT recommendations for non-pharmacological trials.[18, 19] The study protocol was approved by the French regulatory authority for research (Agence Nationale de Sécurité du Médicament et des produits de santé, registration no.: 2012-A00189-34) and the research ethics committee/institutional review board (Comité de Protection des Personnes Sud-Est VI France, human research ethics approval no.: AU958).This study was conducted in accordance with the Helsinki Declaration. All patients received an information form and gave their written consent before inclusion.

Eligibility

We included adult patients who were eligible for NSCLC resection (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy), affiliated to the French health insurance and who gave their written consent. Exclusion criteria were tracheotomy, myasthenia gravis, recurrent paralysis or unstable coronary artery disease. Moreover, we did not include patients who were unable to perform the isocapnic hyperpnoea endurance test or the RMET after the first habituation sessions.

Intervention

Training group

Over 3 weeks, the training group (T group) performed 12 sessions of preoperative RMET consisting of isocapnic hyperpnoea, added to usual chest physical therapy. The training program used the Spirotiger® device (Idiag, Fehraltorf, Switzerland) (Figure 1). The RMET program was adapted from an endurance training protocol using this tool and described previously.[20-23] To standardize the isocapnic hyperventilation, maximal voluntary ventilation (MVV) and vital capacity (VC) were measured during the preintervention pulmonary function test (PFT, see below). The volume of the rebreathing bag corresponded to 50% of VC. The patient had to perform a 30-min training session per day. The training started at 30% of MVV, after 3

Figure 1.—Spirotiger® device.

learning sessions to ensure its feasibility when performed at home. The participants performed RMET on 2 consecutive days and rested for 1 day. The respiratory rate was increased every session by 1 cycle per minute if the previous session lasted 30 minutes. The RMET was supervised once a week by the same physical therapist. The patients completed a notebook during their training.

Adherence was considered when 9/12 sessions (75%) were completed.

The T group also had usual preoperative chest physical therapy (CPT) (see below).

Control group

The control group (C group) performed 12 usual preoperative CPT sessions consisting of 30-min sessions performed for 3 weeks.[24] Sessions were standardized by means of written instructions and included airway clearance techniques, deep breathing exercises emphasizing inspiration and thoracic stretching.

Outcomes measures and assessment time-points

The design and outcomes are presented in Figure 2. Assessments were performed 1 month before surgery (preintervention visit) and the day before surgery (postintervention visit). Mortality, morbidities and hospital length of stay were recorded until month 3 after surgery (postoperative visit). Isocapnic hyperpnoea endurance test was performed in a standardized way by two trained physical therapists (HL and SA, see below), who were not aware of pulmonary function tests (PFT) or maximal exercise capacity results. PFT, including MVV and maximal respiratory pressures measurements, maximal exercise test were performed by the same physiologist, independently of IHET assessors. Postoperative course including complications was recorded by the referent surgeon.

Primary outcome

The primary outcome was the effect of 3-week preoperative RMET program in patients eligible for NSCLC resection surgery. The RMET was evaluated with the isocapnic hyperpnoea endurance test. It was standardized by adapting a protocol described previously.[15, 20, 21, 25] The test started at 30% of the measured MVV. Then minute ventilation (VE) was increased by 10% every 3 min. The test ended when the patient was unable to sustain the targeted VE. Endurance time (ET) corresponded to the total time of hyperventilation.

Secondary outcomes

Secondary outcomes were pulmonary function and MVV, maximal respiratory pressures, maximal exercise test, and the postoperative course including complications.

Pulmonary function test and maximal voluntary ventilation

Tests were performed in accordance with international recommendations by using a body plethysmograph (Bodybox Jaeger Care Fusion, USA).[15, 26, 27] The alveolar-capillary diffusion capacity for carbon monoxide (DLCO) was measured by the apnea method. MVV was measured in duplicate, and the best value was recorded.

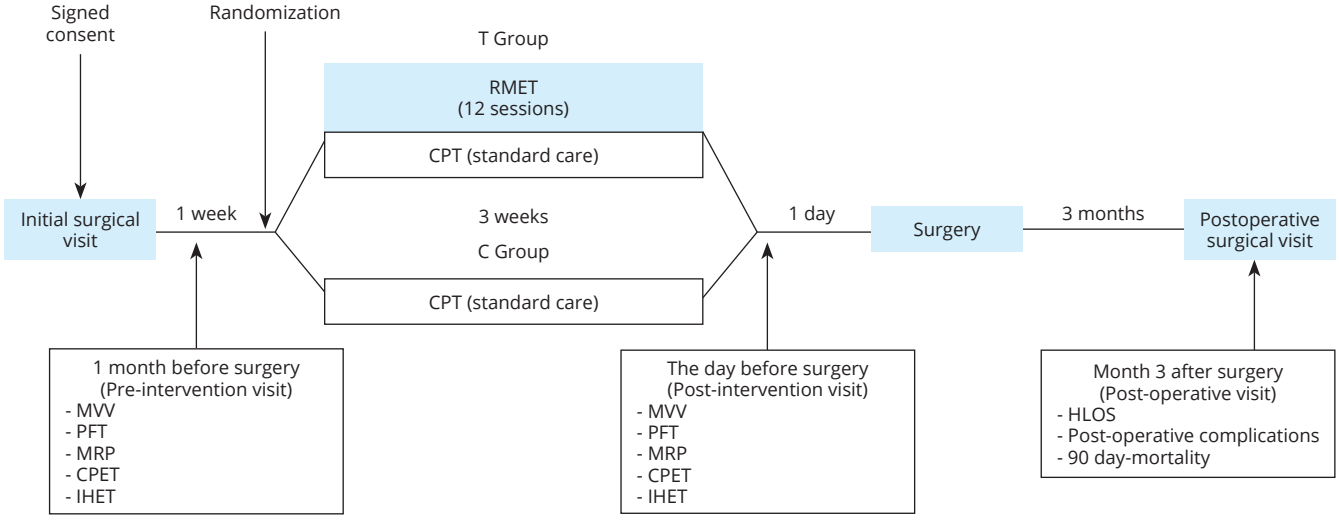

Figure 2.—Design and outcomes.

Maximal respiratory pressures

Maximal respiratory pressures (inspiratory and expiratory pressures at mouth, and nasal inspiratory pressure) were measured in accordance with international recommendations.[15] They were measured at residual volume and total lung capacity, in triplicate to ensure the reproductibility. The maximal value was considered for analysis.

Cardio-pulmonary exercise test

The patient performed a standardized incremental test following international recommendations.[28] The test was performed on a cycloergometer until exhaustion, with continuous recording by 12-lead electrocardiography and breath-by-breath expired gas analysis (CPX MedGraphics, St Louis, MO, USA). The ventilatory threshold was determined by the Beaver method. Maximal power output (Wmax) and peak oxygen consumption (VO_{2peak}) were measured at the end of the last exercise level maintained for at least 30 sec. Symptoms were rated on a 10-point Borg scale.

Postoperative course

Postoperative complications were defined according to the literature and classified as pulmonary and non-pulmonary: cardiovascular, infectious, and others[1, 2] (Table I). Their severity was graded by the Clavien-Dindo classification.[3, 5] Mortality was recorded until month 3 after surgery.

Hospital length of stay was defined as the time between the day of surgery and the day of discharge.

Patient's selection, randomization, allocation procedure and blinding

Patient's selection was performed by the referent surgeon at first medical visit. The randomization was performed electronically after recruitment, by a clinical research associate who was independent of the assessors. Allocation was transmitted by emails send to assessors and therapists. As this is the case in rehabilitation medicine, the physical evaluation and intervention could not be blinded. We limited the bias by performing the evaluations by two trained

TABLE I.—*Definitions of postoperative complications (according[1, 2]).*

Type of complications	Definitions
Respiratory atelectasis	Systematized ventilatory disorder objectified by chest radiography requiring enhanced management such as additional physical therapy sessions, bronchoscopy associated or not with non-invasive ventilation (NIV), maintenance or transfer to an Intensive Care Unit (ICU)
Significant bronchial congestion	Difficult or spontaneous expectoration of bronchial secretions requiring enhanced management such as additional physical therapy sessions, bronchoscopy with or without NIV, maintenance or transfer to an ICU
Bronchospasm	Occurrence or aggravation of dyspnea, wheezing at auscultation requiring a specific treatment
Respiratory failure	Requirement for management in an ICU for NIV or intubation
Prolonged chest tube duration	>7 days
Tracheobronchial infection	Tracheobronchial infection requiring antibiotic treatment, temperature >38.5 °C, dirty sputum, hyperleucytosis >10,000/mm^3, dubious radiological image, absence of pathogenic germs after culture of sputum and/or endobronchial samples
Postoperative pneumopathy	Pulmonary infection requiring specific antibiotic treatment because of the presence of a pathogenic germs found after culture of sputum and/or endobrochial samples, associated with at least 2 other signs (temperature>38.5 °C, dirty sputum, hyperleucytosis >10,000/mm^3, dubious radiological image)
Nosocomial pneumopathy	Pneumopathy occurring after postoperative day 5
Cardiovascular	
Pulmonary embolism proven by angio-CTscan	
Acute coronary syndrome	
Circulatory failure	Requirement for specific inotropic treatment
Rhythm disorder	Requirement for specific treatment
Infectious	
Pleurisis requiring punction or redrainage for lobectomies	
Other	
Empyema	
Bronchopleural fistula	
Recurrent paralysis	
Bleeding	

physical therapists (IHET) and a trained physiologist (PFT and exercise test) who worked independently one from the other.

Statistical analysis

Sample size estimation was determined to highlight a difference between randomized groups concerning the VE obtained at the end of the isocapnic hyperpnoea endurance test. According to studies of healthy individuals,[22, 23] we aimed to include 14 patients per group, with two-tailed type I error at 5% and power greater than 80%. Finally, we aimed to include 28 patients.

Statistical analyses involved Stata v 13 (StataCorp, College Station, TX, USA). The tests were two-sided, with $P<0.05$ considered statistically significant. Continuous data are expressed as mean±SD. The assumption of normality was assessed by the Shapiro-Wilk test. Quantitative data, were compared by means of Student's *t*-test or the Mann-Whitney test otherwise (normality and homoscedasticity analyzed by the Fisher-Snedecor test). To evaluate the effect of a 3-week preoperative RMET program in patients eligible for NSCLC resection surgery, we conducted multivariable analyses with analysis of covariance (ANCOVA) taking into account baseline values. The normality of residuals from these models was examined by the Shapiro-Wilk test. The statistical analysis was performed as intent to treat. Categorical data were compared by Fisher Exact test.

TABLE II.—*Baseline characteristics.*

	TG (N.=14)	CG (N.=12)	P value
Age (years)	64±7 [44-73]	62±9 [45-73]	NS
Sex			NS
Women	5 (36%)	3 (25%)	
Men	9 (64%)	9 (75%)	
BMI (kg/m²)	25.8±5.9 [19.0-39.7]	25.8±6.2 [19.5-38.1]	NS
Resections			NS
RLL	2 (14%)	4 (33%)	
RML	0 (0%)	1 (8%)	
RUL	6 (43%)	1 (8%)	
LUL	2 (14%)	3 (25%)	
LP	3 (21%)	1 (8%)	
S	1 (7%)	2 (17%)	
Number of removed segments	4.9±2.4 [3.0-9.0]	4.3±2.1 [1.0-9.0]	NS
Anatomopathology			NS
Adenocarcinoma	10 (71%)	6 (50%)	
Epidermoid	2 (14%)	3 (25%)	
Benign	1 (7%)	0 (0%)	
Metastasis	1 (7%)	2 (17%)	
Inflammatory	0 (0%)	1 (8%)	
Oncologic stage			NS
IA-2	0 (0%)	1 (8%)	
IA-3	1 (7%)	0 (0%)	
IB	2 (14%)	1 (8%)	
IIA	1 (7%)	2 (17%)	
IIB	3 (21%)	3 (25%)	
IIIA	3 (21%)	0 (0%)	
IIIB	2 (14%)	2 (17%)	
IV	0 (0%)	0 (0%)	
NA	2 (14%)	3 (25%)	
Neoadjuvant chemotherapy	7 (50%)	5 (42%)	

Mean±SD [range] or frequency and percentage.
BMI: Body Mass Index; CG: control group; NA: not applicable; NS: not significant; LP: left pneumonectomy; LUP: left upper lobectomy; RLL: right lower lobectomy; RML: right middle lobectomy; RUL: right upper lobectomy; S: segmentectomy; TG: training group

Results

Population

We included in the analysis 26 patients, 14 in the T group and 12 in the C group, due to 2 drop-outs during the hyperventilation learning sessions in the C group. All the patients were recruited by the staff of one surgical tertiary hospital ward.

Baseline characteristics presented in Table II, did not significantly differ between groups. Mean age was 63±8 years and mean Body Mass Index (BMI) was 25.8±5.9 $kg.m^{-2}$. The sex ratio favored men (8 women and 18 men). Twenty patients were ex-smokers and 3 were current smokers. Mean tobacco use was 34±18 pack-years.

Lung resections performed were 19 lobectomies, 4 pneumonectomies and 3 segmentectomies. The T group and C group did not differ in type of resection performed, number of removed segments (4.7±2.2), surgical enlargement (5 patients) or anatomic-pathology and oncologic stage considering the last classification for lung cancer staging.[29]

The adherence to the RMET program was good: all but 2 (14%) patients completed the training. Reasons for not reaching the minimal number of required sessions were paraneoplastic syndrome and tiredness.

Primary outcome

VE and ET during the isocapnic hyperpnoea endurance test before and after RMET are presented in Table III and Figure 3. The groups did not significantly differ in VE and ET before RMET. VE and ET increased significantly after RMET in only the T group (+15±16 *vs*. -2±17 $l.min^{-1}$ and +229±199 *vs*. -5±371 sec, respectively; and P=0.004 and P=0.001, respectively).

TABLE III.—*Results for the isocapnic hyperpnoea endurance test, pulmonary function and exercise capacity before (pre) and after (post) respiratory muscle endurance training.*

	Pre		Post		ANCOVA P value
	T group	C group	T group	C group	
IHET					
VE (L.min^{-1})	85 [77-92]	81 [66-96]	99** [87-112]	80 [63-96]	0.018
ET (sec)	1114 [937-1290]	1244 [981-1508]	1343** [1131-1554]	1239 [910-1569]	NS
PFT and MVV					
VC (L)	3.83 [3.27-4.38]	3.90 [3.37-4.44]	3.91 [3.41-4.40]	3.95 [3.34-4.56]	NS
VC (%predicted)	107 [98-116]	106 [92-120]	109 [103-116]	107 [93-121]	NS
FEV1 (L)	2.49 [2.24-2.74]	2.54 [2.06-3.02]	2.49 [2.23-2.75]	2.49 [1.99-3.00]	NS
FEV1 (%predicted)	93 [83-102]	90 [72-107]	92 [84-100]	88 [69-106]	NS
FRC (L)	3.87 [3.38-4.37]	3.94 [3.25-4.62]	3.91 [3.25-4.57]	4.02 [3.31-4.73]	NS
FRC (%predicted)	121 [108-133]	120 [105-135]	121 [105-137]	124 [104-147]	NS
MVV (L.min^{-1})	100 [86-113]	87 [70-104]	97 [84-110]	91 [71-110]	NS
MVV (%predicted)	95 [84-106]	81 [65-97]	94 [81-106]	84 [66-102]	NS
MRP					
MEP (cmH_2O)	89* [70-109]	122 [103-142]	105 [81-128]	111 [88-134]	NS
MIP (cmH_2O)	65* [53-77]	70 [60-81]	68 [57-80]	73 [54-91]	NS
SNIP (cmH_2O)	75 [60-91]	75 [57-94]	77 [62-91]	83 [59-107]	NS
CPET					
VO_{2peak} (mL.min^{-1}.kg^{-1})	18.3 [15.4-21.1]	17.2 [13.7-20.8]	18.2 [15.2-21.2]	17.1 [13.7-20.5]	NS
VO_{2peak} (%predicted)	82 [68-96]	72 [57-88]	83 [70-97]	72 [59-86]	NS
W_{max} (watt)	87 [68-105]	87 [56-117]	88 [72-104]	89 [63-114]	NS
W_{max} (%predicted)	73 [55-90]	66 [49-83]	78 [63-94]	68 [49-88]	NS
HR_{max} (%predicted)	89 [81-97]	86 [75-97]	89 [83-96]	86 [77-95]	NS

Mean [95%CI].
C group: control group; CPET: cardio-pulmonary exercise test; ET: endurance time; FEV1: forced expiratory volume in one second; FRC: functional residual capacity; HR_{max}: maximal heart rate; IHET: isocpanic hyperpnoea endurance test; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MRP: maximal respiratory pressures; MVV: maximal voluntary ventilation; NS: not significant; PFT: pulmonary function test; SNIP: sniff inspiratory pressure; T group: training group; VC: vital capacity; VE: minute ventilation; VO_{2peak}: peak oxygen consumption; W_{max}: maximal power output.
*Intergroup difference before (pre) intervention with P<0.05; **intragroup difference after (post) intervention with P<0.05.

Secondary outcomes

Postoperative course

The number of pulmonary postoperative complications was significantly lower in the T group than C group (2 *vs*. 10, P=0.037) (Figure 4). The incidence of overall, cardiovascular and other complications did not differ between T group and C group. No infectious complication was observed in both groups. The severity of complications according to Clavien-Dindo classification did not differ between the groups.

In the T group, the complications were pneumopathy (N.=1), prolonged chest tube duration (N.=1), rhythm disorder (N.=1), haemothorax (N.=2), and distended bladder (N.=1). In the C group, the complications were ventilatory disorder requiring bronchoscopy (N.=1), respiratory failure (N.=1), pneumopathy (N.=4), prolonged chest tube duration (N.=2), pulmonary embolism (N.=1), arterial hypertension (N.=1), empyema (N.=1), chest wall hematoma (N.=1) and recurrent paralysis (N.=2).

The T group and C group did not differ in hospital length of stay (7.6±3.3 *vs*. 8.5±4.7 days), ICU length of stay (2.6±2.4 *vs*. 4.7±3.8 days), or chest tube duration (5.2±2.8 *vs*. 4.9±3.9 days).

We recorded only one death in the C group.

Pulmonary function tests and exercise capacity

Before RMET, the T group and C group did not differ in all PFT parameters or exercise capacity, except for maximal expiratory pressure which was lower in the T group than C group (Table II). After RMET, the groups did not differ in any parameter.

Discussion

We show for the first time that preoperative RMET significantly increased respiratory endurance during isocapnic hyperpnoea endurance test in patients eligible for NSCLC surgery. Moreover, it allows to decrease pulmonary postoperative complications.

The preoperative characteristics of our patients (age, BMI, PFT, MRP) agreed with those previously reported

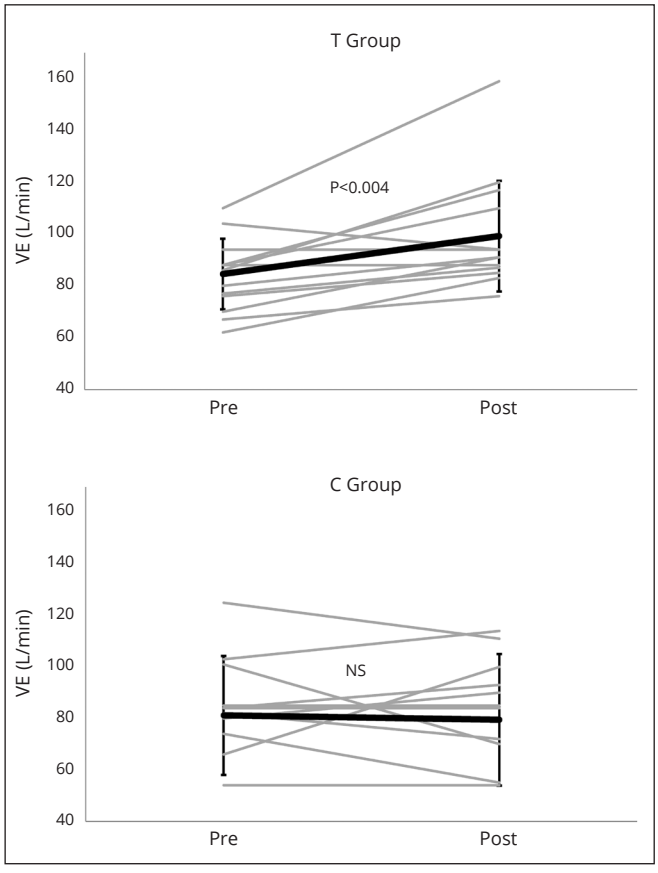

Figure 3.—Results of the isocapnic hyperpnoea endurance test.

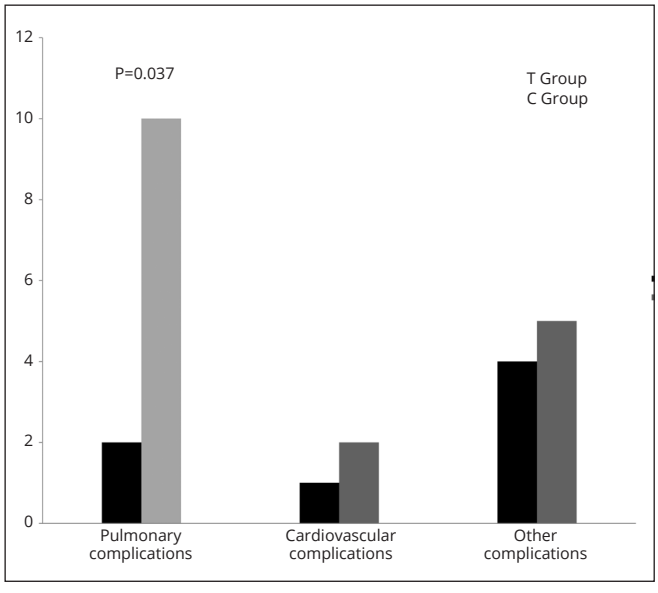

Figure 4.—Number of postoperative complications.

in NSCLC populations.[4, 5, 12, 13] Moreover, preoperatively, maximal exercise capacity and pulmonary function tests results were similar in both groups. Exercise capacity was relatively preserved, which is a prerequisite for lung surgery.[30] The MVV was also around the normal value in both groups.[25] So, RMET in these patients could be considered an add-on treatment. This result reinforces the idea that respiratory muscle training could be beneficial even in patients with preserved respiratory muscle strength and endurance. Although RMET was time-consuming (30 min per session), most of patients completed the required number of sessions (9/12), and none complained of difficulty in handling the device. The training program was supervised only once a week and we could not assess formally the training time and intensity.

Regarding the increase of respiratory muscle capacity to sustain an increased ventilation requirement its beneficial effect was previously shown in other settings that lung resection for NSCLC. In a recent meta-analysis, Ge *et al.*[12] demonstrated that preoperative resistance inspiratory muscle training in patients eligible for cardiothoracic and abdominal surgery increased maximal inspiratory pressure and reduced pulmonary postoperative complications. In healthy individuals, cyclists and obese patients, RMET improved MVV, respiratory muscle endurance, dyspnea and exercise capacity.[20-23] However, such a training modality has never been used before lung surgery for cancer. In the present study, RMET specifically improved respiratory muscle endurance, with no effect on maximal respiratory muscle strength, MVV or exercise capacity. The short duration of the training program could explain why the improved respiratory muscle endurance did not increase exercise tolerance. Because inspiratory muscle training improves maximal exercise capacity and maximal respiratory strength,[9] this conflicting result deserves further investigation. Messaggi-Sartor *et al.* showed recently that a combined aerobic exercise and high-intensity respiratory muscle training program performed 6-8 weeks after lung resection improved exercise capacity and respiratory muscle strength.[31] In the present study, we restricted the intervention to a preoperative respiratory muscle training. Moreover, we included patients with concomitant chemotherapy which could further alter physical status. Although respiratory muscles strength or exercise capacity were not significantly improved, postoperative morbidity was significantly decreased. In light of our results and literature, respiratory muscle training could be included in perioperative programs of rehabilitation for NSCLC patients, as an inter-

esting add-on modality to improve physical status and postoperative course.

Another important issue was the decrease of pulmonary postoperative complications. Lung resection surgery is well known to increase the postoperative respiratory work and induce hypoxia and hyperventilation.[6] Thus, RMET could help the patient deal with this additional physiologic burden occurring in the early postoperative period. This could explain the lower pulmonary postoperative complications we found in T group, representing the most common and fatal postoperative complications. Also, the extent of pulmonary resection was similar in both the T group and C group and could not explain the reduced number of pulmonary postoperative complications in the T group. We acknowledge we found a relatively high mean incidence of pulmonary postoperative complications, but this number remained within the range previously published.[1, 2, 12]

Our study was underpowered to detect a significant reduction in hospital length of stay or ICU length of stay, and we only found a tendency to a reduction of both indices in the T group compared with the C group.

Limitations of the study

Our study contains some limitations. The evaluators were not blinded to allocation groups, which could have biased our results. For practical purposes, evaluators could not be blinded, but they were instructed to stimulate the patients to perform their best during the assessments. A strength is that, the isocapnic hyperpnoea endurance test, learning sessions and RMET were supervised by the same physical therapists (HL and SA), which allowed for standardization of the isocapnic hyperpnea endurance test and RMET. Finally, our sample of patients was rather limited and selected due to the design of the study (pre and postoperative evaluations, learning sessions), which was only suitable for highly motivated patients. However, RMET could be used by physiotherapists in addition to the usual CPT to improve respiratory muscle function.

Conclusions

Preoperative RMET improved respiratory muscle endurance and decreased pulmonary postoperative complications after surgery for NSCLC. These positive results obtained after RMET may help improve the perioperative course for such patients. These results should be confirmed in larger randomized controlled trials, including higher number of patients especially with altered respiratory muscle function.

References

1. Agostini P, Naidu B, Cieslik H, Rathinam S, Bishay E, Kalkat MS, *et al.* Comparison of recognition tools for postoperative pulmonary complications following thoracotomy. Physiotherapy 2011;97:278–83.

2. Miskovic A, Lumb AB. Postoperative pulmonary complications. Br J Anaesth 2017;118:317–34.

3. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

4. Thomas PA, Berbis J, Falcoz PE, Le Pimpec-Barthes F, Bernard A, Jougon J, *et al.*; EPITHOR Group. National perioperative outcomes of pulmonary lobectomy for cancer: the influence of nutritional status. Eur J Cardiothorac Surg 2014;45:652–9, discussion 659.

5. Seely AJ, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, *et al.* Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg 2010;90:936–42, discussion 942.

6. Maeda H, Nakahara K, Ohno K, Kido T, Ikeda M, Kawashima Y. Diaphragm function after pulmonary resection. Relationship to postoperative respiratory failure. Am Rev Respir Dis 1988;137:678–81.

7. Orozco-Levi M. Structure and function of the respiratory muscles in patients with COPD: impairment or adaptation? Eur Respir J Suppl 2003;46:41s–51s.

8. Luce JM, Culver BH. Respiratory muscle function in health and disease. Chest 1982;81:82–90.

9. Beaumont M, Forget P, Couturaud F, Reychler G. Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. Clin Respir J 2018;12:2178–88.

10. Lötters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. Eur Respir J 2002;20:570–6.

11. Gosselink R, De Vos J, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? Eur Respir J 2011;37:416–25.

12. Ge X, Wang W, Hou L, Yang K, Fa X. Inspiratory muscle training is associated with decreased postoperative pulmonary complications: evidence from randomized trials. J Thorac Cardiovasc Surg 2018;156:1290–1300.e5.

13. Nomori H, Kobayashi R, Fuyuno G, Morinaga S, Yashima H. Preoperative respiratory muscle training. Assessment in thoracic surgery patients with special reference to postoperative pulmonary complications. Chest 1994;105:1782–8.

14. Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA 2006;296:1851–7.

15. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002;166:518–624.

16. Koppers RJ, Vos PJ, Boot CR, Folgering HT. Exercise performance improves in patients with COPD due to respiratory muscle endurance training. Chest 2006;129:886–92.

17. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease: impact on exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000;162:1709–14.

18. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P; CONSORT Group. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 2008;148:W60-6.

19. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, *et al.* The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235–41.

20. Vergès S, Flore P, Nantermoz G, Lafaix PA, Wuyam B. Respiratory muscle training in athletes with spinal cord injury. Int J Sports Med 2009;30:526–32.

21. Villiot-Danger JC, Villiot-Danger E, Borel JC, Pépin JL, Wuyam B, Vergès S. Respiratory muscle endurance training in obese patients. Int J Obes 2011;35:692–9.

22. Verges S, Renggli AS, Notter DA, Spengler CM. Effects of different respiratory muscle training regimes on fatigue-related variables during volitional hyperpnoea. Respir Physiol Neurobiol 2009;169:282–90.

23. Verges S, Lenherr O, Haner AC, Schulz C, Spengler CM. Increased fatigue resistance of respiratory muscles during exercise after respiratory muscle endurance training. Am J Physiol Regul Integr Comp Physiol 2007;292:R1246–53.

24. Varela G, Novoa NM, Agostini P, Ballesteros E. Chest physiotherapy in lung resection patients: state of the art. Semin Thorac Cardiovasc Surg 2011;23:297–306.

25. Vincent M, Court-Fortune I, Brun C, Camdessanché JP, Vergès S, Costes F. Determination of normal values for an isocapnic hyperpnea endurance test in healthy individuals. Respir Physiol Neurobiol 2016;230:5–10.

26. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, *et al.* Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.

27. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.*; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–38.

28. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211–77.

29. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, *et al.*; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:39–51.

30. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(5 Suppl): e166S-90S.

31. Messaggi-Sartor M, Marco E, Martínez-Téllez E, Rodriguez-Fuster A, Palomares C, Chiarella S, *et al.* Combined aerobic exercise and high-intensity respiratory muscle training in patients surgically treated for non-small cell lung cancer: a pilot randomized clinical trial. Eur J Phys Rehabil Med 2019;55:113–22.

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